

Prevalence of Undetected Genital Tract Pre-malignancy and Malignancy in Hong Kong Women Undergoing Hysterectomy for Uterine Prolapse

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Objective: To determine the prevalence of undetected genital tract malignancy and pre-malignancy in women who underwent hysterectomy for pelvic organ prolapse (POP).

Methods: This was a retrospective study of 497 women who underwent vaginal hysterectomy or laparoscopic-assisted vaginal hysterectomy for POP from 2005 to 2014 at a local hospital. The prevalence of malignancy and pre-malignancy was compared between pre-menopausal and post-menopausal patients as well as between those with symptoms of malignancy and those without.

Results: Of the 497 women studied, 415 (83.5%) were menopausal and only 67 (13.5%) had symptoms suggestive of malignancy. Two (0.5%) uterine malignancies, one (0.2%) cervical cancer, and one (0.2%) borderline ovarian tumour were detected in four asymptomatic patients, two of whom were menopausal. Twelve patients had pre-malignant conditions, including five cases of cervical intraepithelial neoplasia, six cases of endometrial hyperplasia, and one case of vaginal intraepithelial neoplasia. Five of the patients were asymptomatic, and nine were menopausal. The overall risk of missed malignancy and pre-malignancy was 0.8% and 2.4%, respectively, in women who underwent hysterectomy for POP.

Conclusion: Routine histological examination of the hysterectomy specimens is recommended. Comprehensive preoperative examination is important especially in patients with symptoms suggestive of malignancy. Counselling of patients about the risks of missing malignancy is important in those who opt for uterus-preserving surgery.

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Introduction

Pelvic organ prolapse (POP) usually affects parous women, particularly those of advanced age. In the United States, the prevalence of POP in women older than 50 years has been reported to be as high as 40%, and their lifetime risk of having a single operation for POP by 80 years of age was estimated to be 11.1%¹. In Hong Kong, a territory-wide audit in 2009 reported an increasing prevalence of POP over the last decade². POP not only causes vaginal bleeding and a dragging sensation but also is associated with acute retention of urine requiring catheterisation, constipation, and recurrent urinary tract infection in severe cases^{3,4}. The treatment protocol usually starts with conservative treatment such as the use of a vaginal pessary, with >85% of gynaecologists prescribing a ring pessary⁵. However, vaginal pessary is associated with vaginal discharge, a foul odour, vaginal ulceration, and discomfort.

The most common surgical options for POP are vaginal hysterectomy and pelvic floor repair⁵. Both are

minimally invasive with no abdominal wound and can treat POP in the anterior, middle, or posterior compartment. Increasingly more women opt to retain the uterus and cervix, as it may help maintain sexual satisfaction. Uterine-preserving surgery and vaginal hysterectomy achieve a similar functional outcome⁶. Nonetheless, preserving the uterus and cervix may be associated with the risk of missing malignancy of the genital tract⁷. This study aimed to evaluate the prevalence of undetected malignancy in hysterectomy specimens and determine the appropriateness of uterus-preserving surgery for women with POP. The risks of undetected malignancy and pre-malignancy were compared between symptomatic and asymptomatic patients as well as between pre-menopausal and post-menopausal patients.

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Methods

This was a retrospective study of all women who underwent vaginal hysterectomy or laparoscopic-assisted vaginal hysterectomy for POP from 2005 to 2014 by the urogynaecology team at Queen Elizabeth Hospital in Hong Kong. Ethics approval was obtained from the Kowloon Central/Kowloon East Research Ethics Committee. Patient records were retrieved from the Clinical Management System. Demographic data such as age, parity, body mass index, menstrual history, and family history of gynaecological malignancy were obtained. Abdominal and pelvic examination and preoperative POP staging (using the POP quantification system from the International Continence Society) were reviewed. Ultrasonographic results for endometrial thickness, cervical smear results, and endometrial biopsy results were reviewed.

Symptomatic women were defined as those having symptoms suggestive of malignancy such as abnormal uterine bleeding, post-menopausal bleeding, and abdominal masses. Malignancy had been excluded prior to surgery. Women were referred to the gynae-oncology team and excluded if they were diagnosed with a pre-existing genital tract malignancy or pre-malignancy. All hysterectomy specimens were examined histopathologically, and the prevalence of undetected genital tract malignancy or pre-malignancy was determined.

Descriptive statistics such as frequency, mean, and standard deviation were used. Subjects were dichotomised to those with or without symptoms of genital tract malignancy, as well as those who were menopausal or not. Their demographic data, preoperative symptoms, and treatment outcomes were compared. Fisher's Exact test

was used for categorical data. A two-tailed p value of <0.05 was considered statistically significant. Statistical analyses were performed using SPSS (Windows version 24.0; IBM Corp, Armonk [NY], US).

Results

Hysterectomy for POP was performed in 497 women over the 9-year study period (Figure). The mean patient age was 65.0 ± 11.2 years, mean body mass index was 25.15 ± 3.56 kg/m², and mean number of vaginal births was 3.38 ± 1.75 . Of the women, 366 (73.6%) had stage I/II POP and the remaining 131 (26.4%) had stage III/V POP (Table 1). 415 (83.5%) women were menopausal and 430 (86.5%) women were asymptomatic. Among the 67 (13.5%) symptomatic women, 42 (62.7%) had post-menopausal bleeding and 25 (37.3%) had abnormal pre-menopausal uterine bleeding.

Of the 497 women, 439 (88.3%) underwent vaginal hysterectomy and 58 (11.7%) underwent laparoscopic-assisted vaginal hysterectomy. In addition, 47 (9.5%) women underwent concomitant bilateral salpingo-oophorectomy (BSO). All the specimens were examined histopathologically. Two (0.5%) uterine malignancies, one (0.2%) cervical cancer, and one (0.2%) borderline ovarian tumour were identified; these were in four asymptomatic women: two pre-menopausal and two menopausal.

Of the two pre-menopausal women with malignancy, one was 41 years old and referred in 2013 by a private doctor for uterine fibroid and genital prolapse. Cervical smear screening in 2012 was normal. Pathology showed adenocarcinoma and adeno-squamous carcinoma of the cervix. The other patient was 49 years old and also presented with uterine fibroid and genital prolapse.

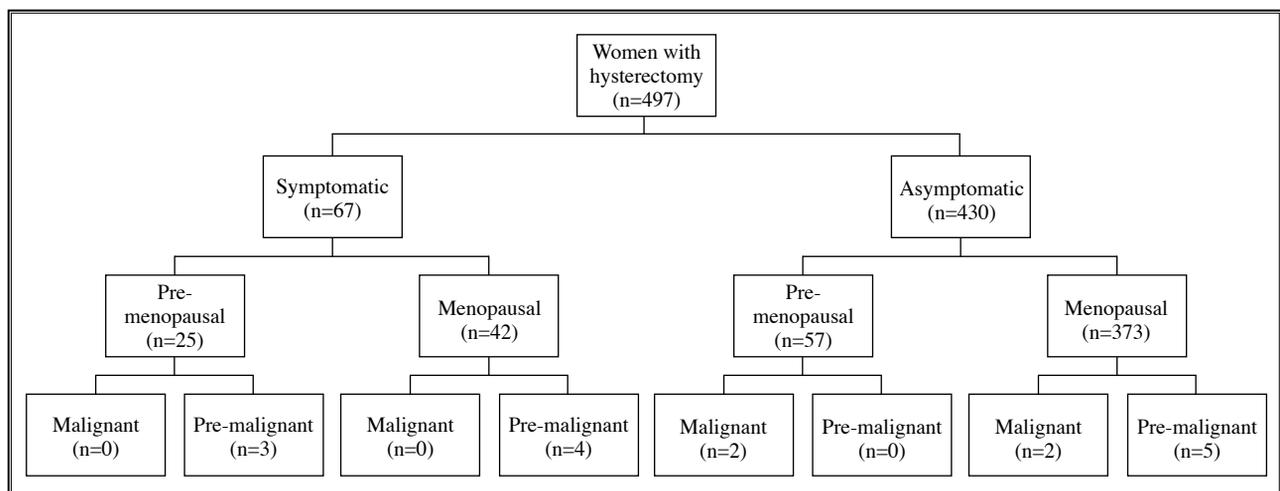


Figure. Flowchart showing outcomes of subjects

Table 1. Clinical characteristics of all subjects

Variable	Value*
Age (years)	64.98 ± 11.21
No. of vaginal births	3.38 ± 1.75
Body mass index (kg/m ²)	25.15 ± 3.56
Stage of pelvic organ prolapse	
Stage I/II	366 (73.6)
Stage III/V	131 (26.4)
Operative procedure	
Vaginal hysterectomy	439 (88.3)
Laparoscopic-assisted vaginal hysterectomy	58 (11.7)
Concomitant bilateral salpingo-oophorectomy	47 (9.5)

* Data are presented as mean ± standard deviation or No. (%) of patients

Preoperative ultrasonography showed an 8-cm ovarian cyst, and concomitant BSO was performed. The cyst was ruptured during surgery. Pathology of the right ovary showed borderline serous cystadenoma. The patient was followed up by the gynae-oncology team for a stage Ic borderline tumour of the ovary.

Of the two menopausal women with malignancy, one was 76 years old with an incidental finding of stage 1A endometrioid adenocarcinoma grade 1 of the uterine corpus. Subsequent laparoscopic BSO was performed for staging and showed no residual malignancy. The other patient was 71 years old with an incidental finding of smooth muscle cell tumour of uncertain malignant potential (STUMP). She presented with uterine prolapse with increasing urinary symptoms but no post-menopausal bleeding or abdominal mass. The uterine size was small and compatible with her menopausal status. Baseline computed tomography was normal. She was followed up yearly by the gynae-oncology team for surveillance of recurrence.

Twelve patients had pre-malignant conditions. In asymptomatic women, five (1.2%) pre-malignant conditions were detected including two cases of cervical intraepithelial neoplasia (CIN) in those aged >65 years with no prior cervical smear screening, two cases of endometrial hyperplasia, and one case of vaginal intraepithelial neoplasm. In symptomatic women, seven (10.4%) pre-malignant conditions were detected including three cases of CIN (two patients were aged >65 years; two patients had abnormal cervical smear and colposcopy but no malignant or pre-malignant conditions), and four cases

of endometrial hyperplasia.

In asymptomatic women, the risks of malignancy and pre-malignancy were 0.9% and 1.2%, respectively. The risk of pre-malignancy in symptomatic women was significantly higher than that in asymptomatic women ($p=0.037$, Table 2).

Three (3.7%) cases of endometrial hyperplasia were detected in pre-menopausal women. Nine (2.2%) cases of pre-malignancy were detected in menopausal women, including three cases of endometrial hyperplasia, five cases of CIN, and one case of vaginal intraepithelial neoplasm (Table 2).

The overall risk of missed malignancy and pre-malignancy was 0.8% and 2.4%, respectively, in women who underwent hysterectomy for POP.

Discussion

In our study, the risk of missed pre-malignant and malignant gynaecological pathology was 3.2%, which is slightly higher than that reported in other studies⁸⁻¹¹. The prevalence of unexpected pathology in menopausal women was 2.6%, which is comparable with a previous study¹⁰.

Some argue that it is unnecessary to routinely perform microscopic assessment of macroscopically normal hysterectomy specimens after vaginal hysterectomy because the incidence of significant pathology is very low and does not alter subsequent patient management⁸. Nonetheless, given the risk of unanticipated abnormal pathology, we recommend routine histopathological examination of hysterectomy specimens.

In symptomatic women, seven (10.4%) had an undetected pre-malignant condition including four cases of endometrial hyperplasia and three cases of CIN. The prevalence of pre-malignancy was significantly higher in symptomatic women. This may reflect the long waiting time for elective surgery for genital prolapse, typically between 6 months and 1 year (the longest waiting time in this series was 18 months). Unexpected pathology can develop over such a long period. Furthermore, preoperative investigations may not be able to detect pre-malignancy. An endometrial biopsy may not be able to thoroughly sample the uterine cavity to detect pre-existing, pre-malignant endometrial pathology. Patients should be reviewed regularly for their presenting symptoms, and investigations repeated if necessary, before surgery.

Table 2. Prevalence of malignant and pre-malignant pathology in surgical specimens

Pathology	Symptomatic women (n=67)*	Asymptomatic women (n=430)*	p Value	Pre-menopausal women (n = 82)*	Menopausal women (n = 415)*	p Value
Total uterine malignancy + pre-malignancy	4 (6.0)	4 (0.9)	0.0139	3 (3.7)	5 (1.2)	0.1301
Uterine malignancy	0	2 (0.5)	1.00	0	2 (0.5)	1.00
Uterine pre-malignancy	4 (6.0)	2 (0.5)	0.0037	3 (3.7)	3 (0.7)	0.059
Complex hyperplasia with atypia	0	1 (0.2)	-	0	1 (0.2)	-
Complex hyperplasia without atypia	3 (4.5)	1 (0.2)	-	2 (2.4)	2 (0.5)	-
Focal hyperplasia without atypia	1 (1.5)	0	-	1 (1.2)	0	-
Total cervical malignancy + pre-malignancy	3 (4.5)	3 (0.7)	0.0347	1 (1.2)	5 (1.2)	1.00
Cervical malignancy	0	1 (0.2)	1.00	1 (1.2)	0	0.165
Cervical pre-malignancy	3 (4.5)	2 (0.5)	0.0192	0	5 (1.2)	1.00
Cervical intraepithelial neoplasia 2	3 (4.5)	1 (0.2)	-	0	4 (1.0)	-
Cervical intraepithelial neoplasia 3	0	1 (0.2)	-	0	1 (0.2)	-
Vaginal pre-malignancy	0	1 (0.2)	1.00	0	1 (0.2)	1.00
Vaginal intraepithelial neoplasm 2	0	1 (0.2)	-	0	1 (0.2)	-
Ovarian malignancy	0	1 (0.2)	1.00	1 (1.2)	0	0.165
All malignancy + pre-malignancy	7 (10.4)	9 (2.1)	0.0025	5 (6.1)	11 (2.7)	0.1593
All malignancy	0	4 (0.9)	1.00	2 (2.4)	2 (0.5)	0.1289
All pre-malignancy	7 (10.4)	5 (1.2)	0.0003	3 (3.7)	9 (2.2)	0.4278

* Data are presented as No. (%) of patients

Uterine Pathology

The prevalence of unexpected endometrial carcinoma and STUMP was 0.2% and 0.2%, respectively. Both uterine pathologies occurred in menopausal, asymptomatic women. The prevalence of endometrial carcinoma (0.2%) was in line with a local study¹¹ and was lower than that in other studies^{9,10}. There was no uterine malignancy identified in symptomatic women. This may reflect an effective preoperative screening policy of detailed history taking, physical and pelvic examination, and review of previous endometrial investigation results. Those who were symptomatic of endometrial cancer had already been investigated and referred to the gynaecology team. In the case of STUMP, currently there is no effective screening method to detect this rare entity.

In a study assessing the role of routine transvaginal ultrasonography prior to vaginal hysterectomy in 103 patients with uterine prolapse, six patients were identified to have endometrial abnormalities (four with endometrial hyperplasia and two with endometrial polyp)¹². A thin and regular endometrial line has been shown to reliably exclude endometrial carcinoma in menopausal women¹³. Transvaginal ultrasonography is not sufficiently sensitive

or cost-effective to screen for endometrial cancer¹⁴. We suggest evaluation of endometrial pathology with transvaginal ultrasonography and biopsy only in women who present with symptoms suggestive of malignancy.

Cervical Pathology

Patients with an abnormal cervical smear were referred to the gynae-oncology team to exclude pre-malignant or malignant lesions prior to hysterectomy. The sensitivity of a cervical smear to detect a high-grade lesion has been improved with the advent of human papillomavirus co-testing, especially in symptomatic women¹⁵. The sensitivity of a cervical smear to detect adenocarcinoma in situ has been reported to be 40% to 68%¹⁶. This may be due to the irregular distribution of the lesions within the glands (compared with the surface distribution of CIN lesions) and the smaller size of glandular abnormalities.

With the implementation of effective cervical cytology screening, the incidental finding of CIN lesions in hysterectomy specimens is 1% and of adenocarcinoma in situ is 0.2%. There were five cases of CIN in menopausal women and none in pre-menopausal women. Four of them were older than 65 years, and three of them had not

undergone any cervical smear screening. One of them had a cervical smear that showed a low-grade squamous intraepithelial lesion with a colposcopy finding of condyloma 3 months prior to hysterectomy. The other patient with colposcopy 1 month prior to surgery for persistent atypical squamous cell of uncertain significance showed cervicitis only. In the routine cervical screening programme, screening stops after the age of 65 years in those with previously normal smears. Most of our patients were older than 65 years and thus may not have had a recent cervical smear test. Many elderly patients had undergone no previous cervical screening. This might partly explain the higher prevalence of CIN in menopausal patients. It is advised to perform a cervical smear before surgery, even in those aged >65 years, to reduce the chance of missing a pre-malignant condition of the cervix.

Ovarian Pathology

Of 47 (9.5%) women who underwent concomitant BSO, one (2.1%) was found to have malignancy. She was a 49-year-old pre-menopausal woman with prolapse symptoms and fibroid. An ovarian cyst was detected preoperatively by ultrasonography, with no evidence of malignancy. This highlights the importance of preoperative assessment including pelvic examination and ultrasonography. The true incidence of ovarian malignancy was difficult to estimate as not all women underwent concomitant BSO. For women with ovarian preservation after hysterectomy for benign pathology, the absolute risk of ovarian cancer is 0.1%-0.75%¹⁷ and of ovarian cancer mortality is 0.3%¹⁸. To reduce the future risk of ovarian cancer, prophylactic bilateral salpingectomy at the time of hysterectomy should be discussed with patients. The benefits of ovarian preservation decrease with advancing age; concomitant BSO should be discussed with patients who are menopausal¹⁹.

Vaginal Pathology

One asymptomatic menopausal woman had an

incidental finding of vaginal intraepithelial neoplasm II. This raises concern about the risk of vaginal intraepithelial neoplasm or vaginal cancer in patients who undergo hysterectomy for benign pathologies. The incidence of pre-cancerous or invasive vaginal lesion was comparable between patients who underwent hysterectomy for benign pathology and those for malignant pathology^{20,21}. Therefore, follow-up with a vault smear should be reserved for those with evidence of pre-cancerous disease or when hysterectomy is performed for a malignant condition²¹.

Limitations

This study had limitations. It was a retrospective study of one urogynaecology team in Hong Kong over 9 years. A multicentre, long-term study with a larger sample size may be required to draw any conclusion about the prevalence of incidental malignant and pre-malignant lesions.

Conclusion

Routine histological examination of hysterectomy specimens is recommended to avoid missing any previously undetected malignancy or pre-malignancy. Symptomatic patients are at higher risk of developing pre-malignant lesions despite preoperative investigations to exclude malignancy. A comprehensive preoperative examination and close follow-up are recommended for symptomatic patients, even if initial findings are normal. A cervical smear test is recommended for all patients before surgery, especially for menopausal women who do not have recent cervical cytology screening. In Hong Kong, the mainstay surgical treatment for uterine prolapse is hysterectomy. The findings of this study can be used to counsel patients about their choice of uterine-preserving surgery for uterine prolapse. The life-time risk of uterine malignancy and the risk of missing an existing pathology should be stressed if women opt to conserve their uterus.

Declaration

All authors have disclosed no conflicts of interest.

References

1. Bump RC, Norton PA. Epidemiology and natural history of pelvic floor dysfunction. *Obstet Gynecol Clin North Am* 1998; 25:723-46.
2. Territory-wide obstetrics and gynaecology audit report 2004. *Hong Kong College of Obstetricians and Gynaecologists*; 2004.
3. Rortveit G, Brown JS, Thom DH, Van Den Eeden SK, Creasman JM, Subak LL. Symptomatic pelvic organ prolapse: prevalence and risk factors in a population-based, racially diverse cohort. *Obstet Gynecol* 2007; 109:1396-403.
4. Chan SS, Cheung RY, Yiu KW, Lee LL, Pang AW, Chung TK. Symptoms, quality of life, and factors affecting women's treatment decisions regarding pelvic organ prolapse. *Int Urogynecol J* 2012; 23:1027-33.

5. Oliphant SS, Jones KA, Wang L, Bunker CH, Lowder JL. Trends over time with commonly performed obstetric and gynecologic inpatient procedures. *Obstet Gynecol* 2010; 116:926-31.
6. Iliev VN, Andonova IT. Uterus preserving vaginal surgery versus vaginal hysterectomy for correction of female pelvic organ prolapse. *Pril (Makedon Akad Nauk Umet Odd Med Nauki)* 2014; 35:243-7.
7. Elkattah R, Brooks A, Huffaker RK. Gynecologic malignancies post-LeFort colpocleisis. *Case Rep Obstet Gynecol* 2014; 2014:846745.
8. Salmon HA, Smith JH, Balsitis M. Is microscopic assessment of macroscopically normal hysterectomy specimens necessary? *J Clin Pathol* 2002; 55:67-8.
9. Mahajan G, Kotru M, Batra M, Gupta A, Sharma S. Usefulness of histopathological examination in uterine prolapse specimens. *Aust N Z J Obstet Gynaecol* 2011; 51:403-5.
10. Frick AC, Walters MD, Larkin KS, Barber MD. Risk of unanticipated abnormal gynecological pathology at the time of hysterectomy for uterovaginal prolapse. *Am J Obstet Gynecol* 2010; 202:507.
11. Wan OY, Cheung RY, Chan SS, Chung TK. Risk of malignancy in women who underwent hysterectomy for uterine prolapse. *Aust N Z J Obstet Gynecol* 2013; 53:190-6.
12. Srikrishna S, Robinson D, Cardozo L, Yazbek J, Jurkovic D. Is transvaginal ultrasound a worthwhile investigation for women undergoing vaginal hysterectomy? *J Obstet Gynecol* 2008; 28:418-20.
13. Van den Bosch T, Van Schoubroeck D, Domali E, et al. A thin and regular endometrium on ultrasound is very unlikely in patients with endometrial malignancy. *Ultrasound Obstet Gynecol* 2007; 29:674-9.
14. Havrilesky LJ, Maxwell GL, Myers ER. Cost-effectiveness analysis of annual screening strategies for endometrial cancer. *Am J Obstet Gynecol* 2009; 200:640.
15. Guideline for cervical cancer screening and prevention. *Hong Kong College of Obstetricians and Gynaecologists Guideline*; 2016.
16. Schoolland M, Segal A, Allpress S, Miranda A, Frost FA, Sterrett GF. Adenocarcinoma in situ of the cervix. *Cancer* 2002; 96:330-7.
17. Parker WH. Bilateral oophorectomy versus ovarian conservation: effects on long-term women's health. *J Minim Invasive Gynecol* 2010; 17:161-6.
18. Parker WH, Broder MS, Chang E, et al. Ovarian conservation at the time of hysterectomy and long-term health outcomes in the nurses' health study. *Obstet Gynecol* 2009; 113:1027-37.
19. Committee on Gynecologic Practice. Committee opinion no. 620: Salpingectomy for ovarian cancer prevention. *Obstet Gynecol* 2015; 125:279-81.
20. Mouithys P, Papadopoulos C, Allier G, et al. Is it necessary to make screening pap smears after hysterectomy? [in French]. *Gynecol Obstet Fertil* 2003; 31:620-3.
21. Frega A, French D, Piazze J, Cerekja A, Vetrano G, Moscarini M. Prediction of persistent vaginal intraepithelial neoplasia in previously hysterectomized women by high-risk HPV DNA detection. *Cancer Lett* 2007; 249:235-41.