

REVIEW ARTICLE**Female Lower Genital Tract Cancer Prevention: A Review****Author**

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Abstract

Female lower genital tract cancers ranks fourth common among all female cancers. They comprises cervical, vaginal, and vulvar cancers. They also share common carcinogenic causes which are oncogenic human papillomaviruses (HPV) infections. Therefore, similar ways of prevention could be applied to these cancers. Those are primary, secondary, and tertiary preventions. Primary prevention comprises preventing HPV transmission and preventive immunization against HPV. Secondary prevention comprises early detection of precancerous lesions by screening means in combination with treatment of the precancerous lesions detected. Vulvar lesion might be seen by a woman herself, however, health personnel are definitely better in doing that during a routine check-up visit for cervical cancer. Tertiary prevention comprises early diagnosis, staging, and effective treatment to these cancers. Although cervical and vaginal cancers still use clinical staging, radiologic and pathologic data has been integrated since 2018. Vulvar cancer has been surgically staged since 1988, and its staging also has been updated in 2018. By using effective primary and secondary prevention, the incidences of these cancers would be decreased. By using effective tertiary prevention, the persistent (resistant/ refractory) or recurrent rates would be decreased.

Keywords: Female lower genital tract, cervix, vagina, vulva, cancer prevention

Introduction

In all over the world, most common female cancer is breast (ASR = 46.3).¹ Fourth most common is cervical cancer (ASR = 13.1).¹ It is one of the three female lower genital tract cancers which are cervical, vaginal (ASR = 0.4), and vulvar cancers (ASR = 0.9).¹ The incidences of these cancers vary worldwide. Less of them are found in developed countries, and more are found in developing countries. The problem of these variations is, in most cases, due to different strategies, coverage, and effectiveness in prevention.

Moreover, these three cancers share common carcinogenic causes, which are oncogenic human papillomaviruses (HPV) infections. These causes are found in 100%,² 80%,³ and 50%,⁴ of cervical, vaginal, and vulvar cancers, respectively. Therefore, similar ways of prevention could be applied to these cancers. Those are primary, secondary, and tertiary preventions.

Primary prevention comprises preventing HPV transmission and preventive immunization against oncogenic HPV by HPV vaccinations. Secondary prevention comprises early detection of precancerous lesions by screening means in combination with treatment of the precancerous lesions detected. Tertiary prevention comprises early diagnosis, staging, and effective treatment to these cancers.

Aim of this article is to present the integrative ways of different strategies to prevent female lower genital tract cancers in any parts of the world. While these cancers have common causes, they should have common ways in coping with them too. Taken from working in this field for two

decades, author will point out some concepts of female lower genital tract cancer prevention in this article.

Primary prevention

In general, primary prevention means avoiding of risk factors (HPV infections). Any of primary prevention is a stand-alone strategy, not needed to be combined with another primary prevention method. These comprise preventing HPV transmission and preventive HPV immunization. However, if avoiding sexual intercourse is not used, any of them must be combined with a secondary prevention method to be effective.

Preventing HPV transmission

Avoiding sexual intercourse is the perfect way to prevent HPV transmission. However, this is not usually possible. Barrier methods like condoms (male and female) could prevent some but not all of these sexually transmitted infections. HPV can hide in wide area of tissues around penis and vagina. Delaying first sexual activity until after 20 year-old in a girl, when the transformation zone (T-zone) on her cervix maturely developed, seems to be the most plausible way in preventing cervical cancer.⁵ HPV infections tend to cause cancer most when first infection occurred while squamous metaplasia on a cervix was still immature (young).

Preventive HPV immunization

Some interventions such as cryotherapy⁶ and Papanicolaou smears⁷ might act like therapeutic immunization. Their uses should be limited to only some high risk groups of women to weigh justified

between risks and benefits. As therapeutic immunization vaccines are still not available, only preventive immunization such as bivalent, quadrivalent, or nonavalent vaccines are only options.⁸⁻¹⁰ World Health Organization (WHO) has recommended the cheaper and simpler but equally effective 0,6 regimen (comparable with 0,2,6 regimen) for girls aged 9-15 year-old in 2014.¹¹ Thailand has also adopted this regimen for grade 5 (or 11 year-old) girls since 2018.

Secondary prevention

In general, secondary prevention means early detection of abnormalities after HPV infections and getting rid of those abnormalities (preinvasives) before their progression to cancers (invasives). Screening tests must be used in combination with diagnosis and/or treatment of any abnormalities detected. Therefore, any of secondary prevention is not a stand-alone strategy. It must be combined with another strategy like diagnosis, follow-up, or treatment, to be effective. In some circumstances, diagnosis may be omitted. Coverage rate of the population at risks (such as women aged 30-60 year-old) must be more than 80% to have enough effect of reaching the high-risk group of women. Vulvar lesion might be seen by a woman herself, however, health personnel are definitely better in doing that during a routine check-up visit for cervical cancer.

Screening tests

All screening tests can be done by trained health personnel. There are three common options of screening test available in many countries. They are; 1) Papanicolaou

smears (conventional cytology) or liquid-based-cytologic examination (LBC), 2) visual inspection with acetic acid (VIA) and, 3) HPV testings.

Visual inspection (VI) alone or visual inspection with Lugol's iodide (VILI) seem to be improper for screening. VI could not help in detection of preinvasive lesions. VILI has high false positive rate and low positive predictive value (PPV), in addition, it can stain dark to women's clothes. Cytologies or HPV testings could not identify where the lesion is.

Cytologic examinations have low sensitivity but high specificity for high grade lesions or more.¹² HPV tests have high sensitivity but low specificity for high grade lesions or more.¹² VIA has both moderate sensitivity and specificity compared to the two aforementioned methods but with highest cost-effectiveness.¹³ Moreover, VIA is the only method that can identify where the lesion is, either on vulva, vagina, or cervix.

Diagnostic tests

When a screening test is positive, a woman should be referred to a colposcopist. A colposcopist might be a trained nurse or a trained physician. They are the one who would do magnifying examination of vulva, vagina, or cervix, to identify where the lesion is and take biopsy of the assumed severest lesions. Like colposcopy, 3-5% acetic acid is used to wash where to be examined by VIA, 1 minute before. The only difference between colposcopy and VIA is naked-eyed versus magnified examination.

Diagnosis must be made upon the severest result of pathological examination

of sampled tissue(s) from colposcopic-directed biopsy (CDB). This result will lead to proper treatment of the lesion(s). For example; low grade lesions (LSILs) may need only follow-up method, high grade lesions (HSILs) may need ablative (cryotherapy, thermal coagulation, electrocautery) or excision methods (loop electrosurgical excision procedure [LEEP], cold-knife conization [CKC]), but invasive lesions may need hysterectomy or radiotherapy.

Diagnosis may be omitted in low-resource settings as a second visit might be difficult or impossible there, if the proposed intervention is easy to be used by trained personnel, has high effectiveness with minimal adverse effects but low cost, such as cryotherapy. Any of screening tests (cytologies, VIA, HPV tests) might be used in the community or any centers nearby her places by an in-advance-group appointment, when positive, a woman would have cryotherapy in a single visit approach (SVA).¹¹

If cytologies or HPV tests are used first, after then VIA must be used (instead of colposcopy) to identify where the lesion is, and to evaluate if the lesion could be treated by cryotherapy in SVA. Not only cervical, vaginal or vulvar lesions could also be treated by cryotherapy. If her lesion seems to be ineligible (too large or too severe) for cryotherapy, woman should be referred to colposcopist for diagnosis or treatment by other methods such as thermal coagulation, electrocautery, or LEEP.

Treatments for preinvasives

Cryotherapy could be used by trained health personnel for both LSILs and HSILs. Its effectiveness is as high as 80-100% cure¹⁴ depending on size of the lesion. Not recommended for treating cancer but some positive results were reported. Size of the lesion should not be larger than 2 mm from cryotip, as the iceball usually expand to 5 mm and recovery (refractory) zone is 3 mm. No electricity or anesthesia but CO2 tank is needed during the procedure. Adverse effects are very minimal, which are light cramping and watery leucorrhea for 2-3 weeks. Infections were found in less than 1%.

Thermal coagulation, electrocautery, or LEEP should be used by trained physicians, as electricity and anesthesia are needed. The effectiveness of these methods is also as high as 80-100%.¹⁴ Although some mobile unit with electricity could be applied, local anesthesia is compulsorily having physician operating it and monitoring its adverse effects. When adverse effects occur, timely complex medical managements must be in place.

The advantage of LEEP is not only curing the large lesion, more accurate diagnosis of the lesion could also be achieved. When larger and deeper excision of tissue was done, thorough examination of its margins or depths of invasion might be documented. When margins are not free or invasions are found, further treatment such as second LEEP, CKC, hysterectomy, or radiotherapy might be recommended.

Tertiary prevention

In general, tertiary prevention means early diagnosis and treatment of cancers (or

invasives). In details, diagnosis of invasives must come first from punch biopsy, CDB, or LEEP, then, staging process is followed. After proper staging is documented, then proper treatment is followed. Staging process of these three cancers (cervical, vaginal, vulvar) has been recently revised in 2018.

Staging process of cervical cancers¹⁵

After a biopsy or LEEP reveals microinvasive cancer (depth of less than 5 mm), a thoroughly pathological examination must be done to identify margins and depths of all invasions. If it is less than 3mm, the case should be allotted to stage IA1. If it is 3 mm or more but less than 5 mm, the case should be allotted to stage IA2. Pelvic and/or radiologic (if available) examinations must also be done to support clinical data for staging process.

If depth of invasion is 5 mm or more, or a biopsy or LEEP reveals frankly invasive cancer, but greatest dimension is less than 2 cm, the case should be allotted to stage IB1. If the greatest dimension is 2 cm or more but less than 4 cm, the case should be allotted to stage IB2. If the greatest dimension is 4 cm or more, the case should be allotted to stage IB3.

When there is upper 2/3 vaginal involvement but the greatest dimension is less than 4 cm, the case should be allotted to stage IIA1. However, if the greatest dimension is 4 cm or more, the case should be allotted to stage IIA2. If there is also parametrial involvement, the case should be allotted to stage IIB.

If there is upper 2/3 vaginal involvement, the case should be allotted to stage IIIA. If there is parametrial

involvement up to the pelvic wall or ureteric obstruction, the case should be allotted to stage IIIB. If there is pelvic node metastasis, the case should be allotted to stage IIIC1, but if there is para-aortic node metastasis the case should be allotted to stage IIIC2. Addition of r (radiologic) or p (pathologic) must be done according to the source of supporting data. When spreading to pelvic organ(s) is (are) found, the case should be allotted to stage IVA, but when there is (are) spreading(s) to distant organ(s), the case should be allotted to stage IVB.

Treatments of cervical cancers¹⁵

For stage IA1, conization with free margins may be adequate, if further pregnancy is still the case. If there is no further pregnancy desire and no lymphovascular space invasion (LVSI), extrafascial hysterectomy is recommended. For stage IA1 with LVSI, IA2, IB1, IB2 and IIA1, radical hysterectomy with pelvic node dissection is recommended. After this kind of surgery, patient and physician might have more new data to allot the new stage from pathological examination of the surgical specimens. For stage IB3, IIA2, and IIB-IVB, concurrent chemoradiation therapy has been standard treatment since 1999.

Staging process of vaginal cancers¹⁶

After a biopsy reveals invasive cancer of vagina, pelvic and/or radiologic (if available) examinations must be done to support clinical data for staging process. If it is in the vaginal wall only without paracolpial involvement, the case should be allotted to stage I. If there is paracolpial involvement, the case should be allotted to

stage II. However, when there is lower third vaginal involvement, pelvic or groin node spreading, ureteric obstruction, or pelvic wall extension, the case should be allotted to stage III. If it is growing into bladder, rectum, or out of pelvis, the case should be allotted to stage IVA. However, when it has spread to distant organ(s), the case should be allotted to stage IVB.

Treatments of vaginal cancers¹⁶

Only two sites of vaginal cancers are found to have possibility for therapeutic surgery. They are 1) posterior upper and 2) lower third. For 1), radical hysterectomy with pelvic node dissection should be done. For 2), radical local excision with groin node dissection should be done. Both surgical procedures aim to have at least 1 cm margin free from tumor. For other sites, radiation therapy remains the cornerstone of treatment while CCRT seems to be better, if plausible. Ovarian transposition may have some benefits in young women. Debulking of the large metastatic pelvic or groin node(s) may also be done in selected cases.

Staging process of vulvar cancers¹⁷

Vulvar cancer has been surgically staged since 1988. If the tumor is potentially beyond IA (larger than 2 cm or suspicious node metastasis), only incisional biopsy should be performed for diagnosis. However, potentially stage IA lesion (smaller than 2 cm without suspicious node metastasis) should be referred to a gynecologic oncologist to have radical local wide excision (RLWE) of more than 1 cm free margin. If the pathologic examination turn out to have tumor size of 2 cm or less,

invasion depth of 1 mm or less, and margin of 8 mm or more (after shrinkage), groin node dissection is not necessary and that surgery is adequate. This tumor is still staged as IA.

If the pathologic examination reveals tumor size of larger than 2 cm, or invasion depth of more than 1 mm, groin node dissection is recommended. If only margin is not free (less than 8 mm), re-excision for adequate margin may be performed. Unilateral or bilateral groin node dissection might be selected depending on location (less than 2 cm from midline or more), size (up to 4 cm or more), and ipsilateral node positivity. The pathological examination of the second surgery will be performed later and the results must be integrated with the first one. If nodes are negative, the case should be allotted to stage IB.

When there is extension to adjacent perineal structures (lower third urethra, lower third vagina, anus), without nodal metastasis, the case should be allotted to stage II. If there is nodal metastases, very detailed of those must be considered as follows. One node of 5 mm or larger, or 1-2 nodes of smaller than 5 mm, are stage IIIA. Two nodes or more of 5 mm or larger, or 3 nodes or more of smaller than 5 mm, are stage IIIB. If the positive nodes have extracapsular spread, the case should be allotted to stage IIIC.

If the tumor invades upper urethral, upper vaginal, bladder, rectal mucosa, fixed to the pelvic bone/ groin node, or ulcerated groin node, the case should be allotted to stage IVC. If there is any distant metastasis including pelvic nodes, the case should be allotted to stage IVB.

Treatments of vulvar cancers¹⁷

Except for stage IA which only RLWE is adequate, unilateral or bilateral groin node dissection should be done together in all cases. However, these procedures might not be possible or adequate in all cases, neo-adjuvant or adjuvant therapies may be needed. For positive nodes, close (less than 5-8 mm) or positive margin, if re-excision is not possible, adjuvant RT or CCRT should be delivered to groin node or primary site, respectively. Pelvic radiation may be needed in some cases according to radiologic or pathologic evaluation. For unresectable tumor, primary CCRT may be delivered. Sometimes, pelvic exenteration is needed for central pelvic disease or central pelvic recurrence.

Summary

Although cervical cancers are common but vaginal/vulvar cancers are rare, they shares common causes. Therefore, primary prevention could also be shared for these three cancers. Secondary prevention by screening/treatment for cervical cancer

should be integrated with vaginal/vulvar cancer screening/treatment. Visual inspection is crucial and may be used with acetic acid to identify where the lesion is, when cytologies or HPV tests are positive. Vulvar lesion might be seen by a woman herself, however, health personnel are definitely better in doing that during a routine check-up visit for cervical cancer. During each routine check-up visit for cervical cancer, the health personnel should examine thoroughly from vulvar, vagina, to cervix. Any suspicious lesions must be further investigated by screening or diagnosing method. After then, palpation for uterine/ ovarian lump or mass must also be done. Primary HPV testing followed by VIA should also be evaluated in future research. Early diagnosis, staging, and effective treatment for these cancers are still classified as tertiary prevention, as they could decrease recurrence and morbidity for women.

Conflicts of interest

None declared.

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