# Oncoprevention in Gynecology

Dhakal S[1]
[1]Maternity Hospital, Thapathali, Kathmandu, Nepal.

## ABSTRACT

Gynaecological Cancers are one of the preventive cancers. There are some preventive factors like change in life style, food habits and some screening tests. Cancer can be prevented and premalignant conditions can be detected before invasion.

Cervical cancer can be detected early by VIA, VILI, Pap smear, colposcopy and HPV testing. Identifying high risk population, transvaginal ultrasound to determine endometrial thickness and endometrial sampling by endocervical curettage, dilation and curettage, fractional curettage and hysteroscopy guided endometrial biopsy are the various modalities for earlier detection of endometrial cancers. For Ovarian cancer, prevention or early diagnosis is done by identifying high risk factors, creating awareness in women, routine pelvic examination, Ultrasonogram, checking tumour marker and prophylactic oophorectomy in indicated cases.

The main screening methods for early detection of breast cancer are clinical breast examination and mammography. Oral contraceptive and HRT are associated with small increase in breast cancer risk. Vulval and vaginal carcinomas are not so common. All molar pregnancies should be followed after evacuation to look for malignant transformation. Hereditary/familial gynaecological cancer like ovarian and breast cancer are manifestation of genetic disorder. Mass screening for gene mutation is very expensive so it is not recommended.

Correspondence:
Dr. Samjhana Dhakal
Department of Obs/Gyn
Maternity Hospital
Thapathali, Kathmandu, Nepal.
E-mail: dhakal_samjhana@hotmail.com
Phone: 9851066093

## INTRODUCTION

Cancer is one of the leading causes of adult death. The incidence of all cancers varies from 90-120/100,000 population. Cancer annually affects 10 million people and causes 6 million deaths all over the world. WHO has predicted that in the next 25 years, there will be 300 million new cases of cancer and 200 million deaths all over the world.[1] It is difficult to say whether there is increased in the incidence of cancer is due to increased awareness or better diagnostic method.

Cancer prevention and early detection becomes medico social responsibility and an economic necessity. The intensive cancer research has identified the causes of some cancers and recognized precancerous stage in some cancers[1]

WHO has stated:

- About ½ to 1/3 cancer cases can be prevented by Diet modification and by immunization against HPV virus.
- About 1/3 of malignancy can be prevented by early diagnosis of pre-malignant condition
- In about 1/3 of the cases palliation care improves the quality of life for incurable cancer.

Cancer control is possible by screening, early detection and treatment and rehabilitation. Primary prevention is possible when the causative agent is definitely known. Human papilloma virus is recognized to play important role in causing cervical cancer. Vaccination against HPV is recognized to play an important role in preventing cervical cancer.[2] Modification of diet may also help in preventing cancer. Fat and body weight has positive correlation with breast and endometrial cancer. Diet which is low in fat, sugar and salt with plenty of green leafy vegetables and fruits help in reducing body weight and therefore preventing breast and endometrial cancer.[3] The oral contraceptive pills is known to give protection against endometrial and ovarian cancer. The SERM (selective oestrogen receptor modulator) are known to give protection against Breast cancer.

Secondary prevention is by early diagnosis and by educating the community and health care providers about early features of cancer. Use of ultrasound and imaging technique, FNAC (Fine needle aspiration cytology), Colposcopy, mammography, tumour markers and biopsy of suspicious lesion helps in early detection. WHO has summarized the screening test should be cheap, comfortable, convenient for patient, easy to perform, noninvasive, cost effective and should have high specificity and sensitivity. Most screening test available does not satisfy all these criteria.

### CERVICAL CANCER

The incidence of cervical cancer in Nepal is 24.2/100,000 women per year and declining trend in developed countries.[4] By simple speculum examination, health care provider can inspect the cervix and can detect cervical cancer. Pre-malignant conditions of cervix can be diagnosed by VIA, VILI, Pap smear and coloposcopy examination,LEEP and HPV testing.[5] In 1980, Mc Dougall demonstrated Herpes simplex virus specific RNA in cervical cancer biopsies.[6] It is suggested that HSV works by hit and run theory, which means HSV may act as an initiator of the transformation process. Walboomers et al were the first to demonstrate the HPV DNA in almost all invasive cervical cancer[7] The association between HPV, Carcinoma in situ and invasive cancer has been confirmed.[8]

#### Prevention of Cervical Cancer

Cervical cancer can be prevented by promoting cervical cancer screening programme and other measures like community awareness programme, PAP smear, VIA( visual inspection with acetic acid) and VILI (Visual inspection with lugol's iodine), colposcopy, HPV testing, early treatment of cervical intraepithelial neoplasia and vaccination against HPV.[9]

#### Community Awareness

The community should be made aware about the risk factors of cervical cancer. The risk factors are multiple sex partners, promiscuous partners, genital hygiene, and smoking and long use of oral contraceptive[9] Monogamous sexual relationship between husband and wife is most ideal. The promiscuous behavior in sex has become common. Smoking is known to modulate immune system reaction. Polycyclic aromatic hydrocarbon present in cigarette smoke are genotoxic.[9,10] Active and passive smoking can be harmful. Early sexual activity is also a risk factor. The Community must be educated to participate in mass screening programme and early treatment. High dose combined oral contraceptive pills (OC) use for more than five years increases the risk of cervical cancer.[11] However, the modern low dose OC pills have very low risk.

#### Mass Screening

Mass PAP smear screening programme does help in early detection of pre-malignant lesion of the cervix. Eddy states that mass screening programme have resulted in 4 to 10 fold reduction in cervical cancer rate.[12] The report can be false negative and false positive. The false positive smear may cause undue tension and anxiety to the women and her family. It may also result in over treatment.

The false negative reports vary from 15 to 20 % and false positive vary from 10 to 20 %.[5] The false negative are mainly due to suboptimal smear and inadequate training.[5] The presence of blood, mucous and inflammation also interfere with interpretation. Screening cytology is less sensitive and less specific for identification of glandular lesion of cervix. The cost of the mass screening is high for most of the developing countries. All women should have PAP smear screening at the onset of sexual activity or 21 years, whichever is earlier. WHO cancer unit suggests that for developing countries, it is most cost effective to recruit high proportion of the population and screen them infrequently than screening the low proportion and quite often. WHO has recommended that the countries with limited resources, women should be screened at least once in her life time in women aged 30 &older.[13] VIA and VILI is also one of the screening programme. It is done in OPD and does not require cytology examination.

Colposcopy should be performed in abnormal PAP smear and treated depending on the extent of the lesion.[14] HPV testing is a new technique and not available in all centers. The present consensus is that cervical screening combined with HPV testing may be more cost effective. Vaccination against HPV is very effective. The most effective Vaccine should be multitrivalent, cheap, easily administered and has both prophylactic and therapeutic potential.[15]

**Speculum Examination**

In some developing countries, early detection of cancer is not possible due to unavailability of equipments. Therefore, WHO has suggested a new strategy in such circumstances. The new approach called down staging.[16] It is defined as detection of invasive cervical cancer at an earlier stage, when it is curable. It involves use of speculum examination for visualization of cervix to note any suspicious lesion. Paramedical workers can do this and can also perform schiller's test. But speculum examination is inferior to cytology. It has a place in areas where facilities are not available or affordable.

**Recent updates**

Some studies have shown that antioxidant helps in preventing cervical cancer, by boosting up the immune system.[17]

**Endometrial Cancer**

No routine screening recommended as in cancer cervix. It is recommended in women with certain high risk factors like obesity, Diabetes mellitus and hypertension, Unopposed oestrogen-HRT, Functioning tumours PCOD, nulliparity, Early age at menarche, Delayed menopause (>50 yrs), personal and family history of breast, colon, ovarian cancer [18]

Ideal screening test should have a high predictive value, easily applied to a large group of women, inexpensive and should diagnose the disease ideally in a pre-malignant condition. There is no satisfactory test to diagnose the pre-malignant condition. In patient on Tamoxifen therapy, presence of endometrial cells in postmenopausal women or atypical glandular cells in pre-menopausal women in pap smear should be screened.[19] Cervical cytology is abnormal only in less than half of endometrial cancer.[18] Transvaginal ultrasound is a single noninvasive technique to determine endometrial thickness with a value of 5mm as a cut off level for normal thickness in post menopausal women.[20] Endometrial sampling is the first definitive step in evaluating a patient with abnormal uterine bleeding, or suspected endometrial pathology.

There are various methods of endometrial sampling endocervical curettage, Dilation and curettage, Fractional curettage, Hysteroscopy guided biopsy.[21]

**Ovarian cancer**

Prevention and control of ovarian cancer is difficult than other cancer, because there is no recognizable pre-malignant condition for ovarian cancer. Unlike breast and cervix, ovaries are located within the abdomen and not possible for inspection. The incidence of epithelial ovarian cancer is 3-5 times more common in industrialized countries to developing countries. Ovarian cancer patients present about 75 % having stage III or IV disease at the time of laparotomy. [22]

Ovarian cancer is responsible for most deaths than deaths due to cervical cancer and endometrial cancer. [23] Prevention or early diagnosis of ovarian cancer is possible by identifying high risk factors, creating awareness in women, routine pelvic examination, through investigations of doubtful cases like tumour markers, and USG prophylactic oophorectomy.[22]

The risk factors for ovarian cancers are vague and not easily identifiable. Incidence of subclinical mumps and persistent mumps antibody titres are seen in ovarian cancer patients. Other risk factors are 40 years age, nulliparous and low parity, elderly age in first pregnancy and those who have not used any oral contraceptive. [23] Creating awareness in women would certainly help in early diagnosis. In spite of advanced diagnostic technology, pelvic examination remains most sensitive means available for early detection of ovarian cancer.[24] Palpable ovarian mass or palpable normal ovaries in menopausal women must be looked upon with suspicion.[25] Oral contraceptive use confers significant decrease in the risk of developing ovarian cancer. The degree of protection is proportional to the duration of use and protection persists even after

OC pill is discontinued.[26] Measuring ovarian volume by ultrasound is also advised for early detection of ovarian cancer.[27] Pap smear shows abnormal report only in 10 -30 %of advanced ovarian cancer.[28] so it is not a suitable screening test .Identifying specific tumour markers may also help in early diagnosis. Tumour markers may be detected biochemically as a protein hormone and enzyme or immunologically as antigen. Unfortunately, none of the presently available tumour markers have high specificity to be useful as screening procedures. RNAase is 95 %sensitive .NB 701K is 85% sensitive, CA 125 is 75 - 80 % sensitive. OCAA is 65 % sensitive. Other tumour markers are CA72-4,CA-19-9,CEA,HCG,AFP, Oestradiol.Inhibin,LDH and PLAP. [29] These tumour markers are very useful in monitoring the progress of the disease but have not much significant role as screening test. In the absence of reliable screening test for ovarian cancer, prophylactic oophorectomy during laparotomy remains a way to prevent ovarian cancer. This is debatable and controversial.[30] Oram suggests following criteria for prophylactic oophorectomy-during pelvic surgery in postmenopausal women and premenopausal women.Grossly abnormal ovaries should be removed irrespective of age or menopausal status. Prophylactic oophorectomy as primary procedure should be considered in women with a strong family history of ovarian cancer ,after she completes her child bearing age.[31] In Summary, prevention and early diagnosis of ovarian cancer remain a distant dream till more specific and sensitive methods are discovered or premalignant condition for ovarian cancer is recognized. Use of OC pills remain only reasonable method for prevention of ovarian cancer. Prophylactic oophorectomy has a limited place. The risk of prophylactic oophorectomy before menopause must be considered.

**Breast cancer**

It is the third most common cancer world wide The incidence of breast cancer is equally common in industrialized countries as well as in developing countries [32]. Breast epithelium appears to be very susceptible to ovarian hormone to cause neoplastic change. More than a year a women is exposed to female hormone during her life time, the reater the risk of breast cancer.[32] Women are 2 times more likely to get breast cancer if they reach menopause after the age of 55 and three times more likely if they have their first child after 32 years.[33]

Mcpherson and Lipworth has suggested that extended breast feeding for a life time total of six years or more, reduces the risk of breast cancer.[34]

These following are risk factors for breast cancer early menarche, late menopause, first pregnancy after 30 years, obesity, OC pills use and HRT(Hormone replacement). Some studies have shown protective effect of late menarche, early menopause, early pregnancy and high parity.[35]

Breast can be easily inspected and early detection of any breast lesion is possible. However breast cancer continues to be a common cancer. Increased life expectancy and changing life styles and food habits are also responsible for rising incidence.[36,37] Age is an important risk factor for breast cancer. Forbes has reported that compared to women in their twenties, women are 10 times as likely to develop breast cancer in thirties ,40 times in forties,60 times in fifties and 90 times after 60 years of age.[32] Women who use Oral contraceptives for 10 years and stops are associated with small increase in breast cancer risk that persists for 10 years after the women stops taking them.[38] However, breast cancer diagnosed among HRT users are likely to be less advanced than in nonusers. HRT is associated with a small increase in risk for each year of use, which continues for 4 years after therapy is stopped.[39]

**Prevention**

Early pregnancy, high parity and breast feeding practice have protective effect on breast cancer whereas high in fat, salt and free sugar and low in whole grain, vegetables and fruits is harmful.[32] Prophylactic Mastectomy is advocating in women with a strong family history.[40] Here is no reliable data to prove the effectiveness of prophylactic mastectomy. Early detection of breast cancer is possible by breast self examination (BSE) and Mammography. [41] It is possible to women to have self breast examination and report to healthcare worker if they find any lump or abnormality. The clinical trials are ongoing all over the world to find out the effectiveness of self breast examination in mass screening programme. Spouse may be educated to detect breast lump or any other abnormality and direct the women to the health worker. This technique may also help in early detection of breast cancer. In clinical breast examination, every women receives annual breast check up by health worker(CBE).CBE has sensitivity of 54% and specificity of 94 %.[39]CBEcan detect some lumps that mammogram can miss, especially in younger women whose dense breast tissue can obscure x-rays.[42]

However effectiveness of CBE in reducing mortality is not clearly established. In a large scale mammography trial in Canada concluded that CBE alone was as effective in reducing mortality as a combination of CBE and mammography. The effectiveness of CBE depends entirely on the skill of the health worker. Therefore, the health worker must be trained in breast examination technique. Mammography can identify cancers and benign breast abnormalities that are too small to palpate. Sensitivity of mammography is higher 83-95 % than that of CBE .[41] Mammography misses 10 % of breast cancer

in women over 50 years of age and even more among younger women.[42] The current opinion is that mammography is not cost effective in women below the age of 40 years. Mammography is the only screening tool available at present. It is used in a great extent in developed countries. It should be repeated in one, two and three year's interval. From 1960 to1980 many randomized clinical trials covering half a million women in USA, Canada and North Europe were concluded to test the impact of mammography and the result showed 15%reduction in mortality due to breast cancer in women aged 50 to 69.[43] This is still controversial. Some workers have pointed to the potential harm caused by screening mammography. 5 % of the screening mammogram that are suspicious, more than 80% are false positive that cause women anxiety and demand expensive follow up procedure, that are complicated and uncomfortable.[43]

Mass screening by mammography may not be possible in many developing countries with limited resources. Mammography requires sophisticated machinery, continuing supply of film and chemicals, skilled technician, experienced radiologists to read film and constant quality control. Significant reduction in mortality can not be achieved unless at least 70% of women are covered by the screening test.[32S]elf examination of breast and clinical examination of breast should be given priority in developing countries. Mammography as a screening procedure must be considered in areas with higher incidence of breast cancer.

**Vulval and Vaginal Cancer**

The incidence of vulval and vaginal carcinoma in Nepal is low. It forms 0.3%of all female cancers.[44] Herpes Virus type 2 is considered as an etiological agent for Vulval intraepithelial neoplasia(VIN). Mass screening programme are not needed for vulval carcinoma, but the clinician must keep in mind the possibility in older women with unexplained pruritus, or suspicious lesion or induration on the vulva.VIN is a well recognized histological entity. Exfoliative cytology has a limited role because surface layers of hyperkerotic cells prevent exfoliation of cells.[44]he lesions are difficult to distinguish from inflammatory process. Double scrapping technique is helpful. The first scrapping remove kerotic cells, the second scrapping would expose dysplastic cells. Colposcopy for VIN has a limited role because thick cornified layer in it does not allow view of underlying terminal vasculature. VIN lesions like CIN are known to undergo spontaneous regression. Since it is not possible to predict which VIN will become invasive. All VIN lesions must be treated. Biopsy of suspected vulval lesion helps in confirming the diagnosis.[32]A primary carcinoma of the vagina is one of the least common of the genital tract malignancies. Cancer from cervix, bladder, urethra, vulva and lower bowel may involve the vagina. Metastasis in the vagina from the tumours arising from the uterus, ovary and distant organ like kidneys are also known. In all suspected cases, cytological examination, schillers test and colposcopic directed biopsies should be done.[45] Clinical examination reveals a papillo-matous or ulcerative growth.

**Gestational Trophoblastic Disease**

The risk of molar pregnancies undergoing malignant transformation varies from 15to20%.[46]This gave rise to the concept of prophylactic chemotherapy in all cases of molar pregnancy. Malignant transformation was reduced. But patient suffered considerable morbidity and there was occasional death. Therefore prophylactic chemotherapy is replaced by close monitoring by HCG radioimmunoassay. Patient is advised not to become pregnant till the HCG level becomes normal. If irregular bleeding persists after evacuation of the mole or the HCG level do not drop by 4 weeks. Chemotherapy should be started.[47]

**Hereditary/Familial Gynecological Cancers**

Recent studies show that some gynecological cancers are likely to have familial/hereditary factor. Familial association between ovarian and breast cancer could be manifestation of a genetic disorder.[48] About 10% of breast cancer and 7% of ovarian cancer have an inherited basis. [49] Cancer usually arises as a result of one or more mutation in gene concerned with regulation of cell growth that is proto-oncogen and tumors suppressor gene .Damage to the cell can be caused by smoking, Viruses, industrial chemicals and sunlight. Inherited mutation such as BRCA1 and BRCA2 are considered to increase the risk of breast and ovarian cancer. [50] Gene testing may be necessary when there is a strong family history of some cancers especially breast, ovary and colon. However laboratory testing for gene mutation is not easy and is also difficult to interpret. Our knowledge and understanding of the role of gene mutation in gynecological cancer is rudimentary .Routine mass screening for gene mutation is not practical. It is expensive and unlikely to help in preventing or for early diagnosis of cancer.

## CONCLUSIONS

The treatment of invasive gynecological cancer is quite long and expensive and is associated with high morbidity and mortality. Therefore, there should be a programme to prevent the cancer and to diagnose at premalignant and noninvasive stage. Limited studies are only done about the treatment of advanced gynecological cancers. Hence, detection of these cancers at an early stage is important. This can be achieved by raising the awareness among the general population to recognize early signs

of disease. Various screening modalities are the only effective way in detecting these cancers.

Routine Pap smear has shown to be very effective in detecting cervical cancer early. Similarly, self breast examination has been found to be better suited to resource poor setups. No best screening methods has been advocated for ovarian, endometrial, vulval and vaginal cancers.

Furthur, research is required about the cost effective, easy, accessible method of screening of gynecological cancers especially ovarian, endometrial, vulval and vaginal cancer.

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