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EARLY DETECTION OF GYNAECOLOGICAL MALIGNANCIES - REFRESHING AWARENESS FOR MEDICAL FRATERNITY

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Summary

- Regardless of the frequency of cervical screening, an annual gynaecologic examination including pelvic examination is recommended.
- A dedicated team of cytopathologists for the study of PAP smears is essential for the success of any screening program for cancer cervix. However for visual inspection of cervix only the performer of the test should be trained.
- The latest guidelines given by American Cancer Society for screening of cancer cervix seem to be very thought out strategy to curb the tendency to over investigate the population.
- The use of cytobrush along with the conventional Ayre's spatula has reduced drastically the number of unsatisfactory PAP smears.
- Combined use of PAP smear and HPV DNA testing should be offered for suspicious patients with bad cervical erosions.
- Postmenopausal endometrial hyperplasias and endometrial polyps must be followed up with hysteroscopic directed biopsy.
- Lactating breasts, dense breasts and the malignant breasts will greatly benefit from frequent yearly Ultrasonographic evaluation.
- Mammograms must be interpreted by BIRADS classification.
- Ultrasound Breast should be advised more often than Mammography uptill the age of 50 yrs in general population.

Correspondence : Prof (Dr.) Shakti Bhan Khanna, 304, Hauz Khas Apartment. Aurbindo Marg New Delhi-110016. Email:- sbkhanna@yahoo.com. Achanta Lakshmipathi Oration 2005-2006, delivered at Annual Meeting at Hyderabad, 2006.

- Ultrasound Pelvis and CA 125 are two good modalities to diagnose and interpret the morphology of adnexal masses.
- Since majority of ovarian cysts are benign, a mature decision for futher evaluation of cysts by way of specific tumor marker evaluation, excision etc. must be made as per the morphology of the cysts.
- A thorough history taking, examination of breasts, inspection of cervix and biomanual examination of pelvis of all females should be a must in all women irrespective of the systemic disease she is suffering from. This will go a long way off in prevention, early detection and treatment of gynaecological malignancies.

Key Words: Gynaecological malignancy, Screening, PAP smear, Ultrasound pelvis, Mammography, Cancer cervix, Endometrial Cancer, Ovarian tumor, Breast Cancer.

Introduction

Cancer is increasingly recognized as a global problem and not limited to developed world. The incidence of all cancers varies from 90-120/100,000 populations (1). In India gynaecological cancer account for 55 to 60% of all cancers in woman. Cervical and breast cancers together account for 40% of all female cancers. Although ovarian cancer is the third common cancer of women in India, still more women die of it than any other cancers as ovarian malignancies present at advanced stages (2). (Fig 1)

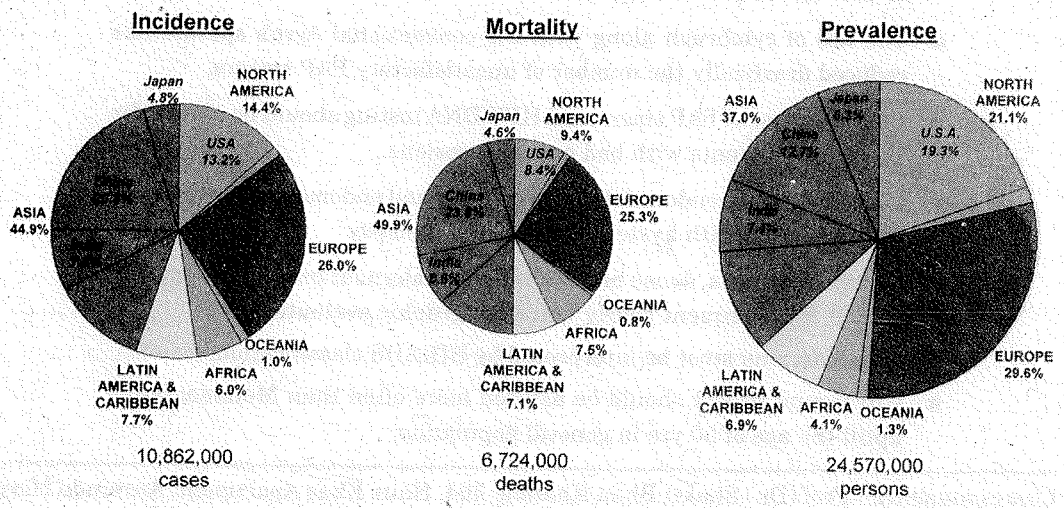

Fig 1. Global Cancer Statistics Incidence, Mortality, and Prevalence by Location (3)

One may think as why to talk about cancer in women in India, where more women die from malnourishment, childbirth trauma, infection, anemia etc than cancer, and very few reach the ages where cancer is prevalent. Very true! But if we aim for positive health in a community, we have to also inculcate amongst medical fraternity the concept of prevention of the disease, and the aim of today's presentation is to sensitize the medical professionals about the concept of preventive gynaecological oncology. The main thrust of the talk will be on cancer cervix which we know is a preventable cancer. One does not need the expensive infrastructure, for its screening. It is only the awareness of the basic facts about the etiology of the disease which all of us irrespective of the speciality to which we may belong, have to keep in mind, while dealing with a woman patient who may not have come for any Gynae complaint. A simple examination of breast and inspection & feel of the cervix is all what is needed to have the suspicion of the cancer of breast and cervix after a few leading questions have been asked from the woman. Prevention and early detection of cancer is also extremely critical in a country like India, where in case of late detection, cost of treatment is very high. Advanced stages of cancer call for expensive modalities of treatment. So cancer prevention and early detection becomes a medico-social responsibility and an economic necessity.

According to WHO "about half to one-third cancers can be prevented (tobacco & alcohol related diet modification and immunization against Hepatitis B & Human Papilloma viruses); about one-third can be prevented by early detection with current knowledge (breast and cervical cancers) and in about one-third cases palliation can improve the quality of life for incurable cancers. The primary prevention is possible if the causative organism is known and Human Papilloma Virus (HPV) is recognized to play a significant role in etiology of cancer cervix (4).

Role of History Taking

Currently, it appears that the best way to detect any early cancer is for both the patient and her clinician to have a high index of suspicion of the diagnosis in the asymptomatic woman. There is a definite role of detailed and appropriate history taking and also making patients aware of the risk of cancer as a strategy for preventing cancer. Advising high risk patients for surveillance and follow up and counseling them to get their peers for preventive health check is one of the important components of advice given to women after undergoing screening programme. Teaching the proper techniques of monthly self examination of breasts and counseling the women about its importance is another important aspect of the preventive gynaecological oncology. Therefore, under this scenario, there is a definite role of a general physician/generalist gynaecologist as a primary health care provider in

implementing the screening programme for cancer detection in the community.

WHO criteria for screening programmes (5) are:

- The condition sought should be an important health problem.
- There should be an accepted treatment for patients with recognized disease.
- Facilities for diagnosis and treatment should be available.
- There should be a recognisable or early symptomatic stage.
- There should be a suitable test for examination with high sensitivity and specificity.

Well Woman check (6)

Keeping the concept of preventive oncology in mind, a health package by the name of "Well Woman Check" is offered in the Indraprastha Apollo Hospital, New Delhi. A prospective study for 9½ years from December 1997 uptill August 2006 was done for all patients who came for this check. During this period, total O.P.D. attendance for the hospital was 1026,143 out of which 1190,76 patients (11.6%) were examined in preventive health checks. 47,630 (40%of all health checks) were females. 4295 women (11.08% of all female patients) had Well Woman Check done. This check is performed by the gynaecologist. It includes a detailed relevant history taking, general physical and systemic examination, and examination of relevant organs i.e., breast, abdomen and female genital organs by way of speculum examination and bimanual examination. The investigations performed under this check include complete blood counts, fasting and post prandial blood sugar, blood grouping and Rh typing, routine and microscopic urine and stool examination, X-ray chest PA view, PAP smear, Ultra sound Pelvis – trans abdominal and trans vaginal , Bilateral Mammogram and Ultra sound Breast.

It will be seen from Table I that 64% of the ladies were above 40 yrs of age. 70% were in the upper middle class and none from the lower socio-economic status.

Cervical Cancer

Cancer cervix is an important public health problem. It is the third cancer in frequency world wide and most or second most common cancer in women in developing countries (Fig 2). PAP smear

Table-1 : Clinical profile of Study Group (Well Woman Check)

Age	Number	(%)	Socio-Economic Class	Number	(%)
18-40yrs	1549	36	Lower Middle and <	0	0
40-60yrs	2199	51	Middle	1288	30
>60yrs.	0547	13	Upper middle and>	3007	70

has been the hallmark for screening of cervical cancer and it has been proved beyond doubt since 1960's that cancer cervix can be prevented by the detection and treatment of precancerous lesions in the Cervix by cytology.

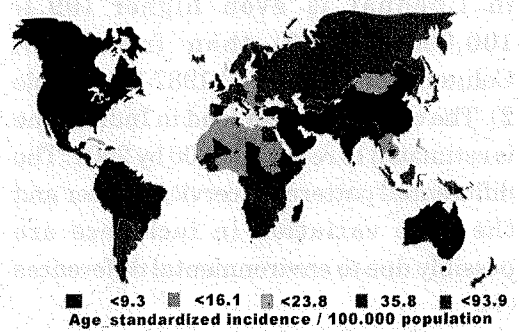

Fig. 2 The global burden of cervical cancer

Some facts about cancer cervix are:

- Cervical cancer is preventable
- Most patients are asymptomatic.
- Patients may present with postcoital bleeding, intermenstrual bleeding and an abnormal vaginal discharge.
- Risk factors for selective and opportunistic screening are:-
  - Multiple partners, S.T.D.s
  - Early onset of sexual activity.
  - HPV infection
  - High parity
  - Immunosuppresion and HIV infection.
  - Oral Contraceptive users have a 4 times increased risk in HPV poitive cases perhaps by decreasing folate levels or by activation of metaplastic cells.
  - Smoking
  - Husband with previous wife having cervical cancer.
  - Low socio-economic status.
  - Poor nutrition and poor hygiene.

During the last 20 years the understanding of the etiological agents for Cancer Cervix has improved a lot. The detection of high risk oncogenic Human Pε pilloma Virus (HPV) type 16 & 18, as the main etiological agent for occurrence of cancer Cervix has been established beyond doubt(4). It seems as if HPV induced Cervical cancer is an anomaly in the otherwise elusive search for the cause of human cancers, as almost no other cancer has a single exposure agent which is a necessary cause of the cancer. The detection of HPV viruses on cervix as a primary screening modality or as an adjunct to cervical cytology is no doubt one of the best screening methods for cancer Cervix, but the availability of the infrastructure and the health care resources is a very important impediment in their usage for mass screening programmes. This cancer being a disease of the poor, and developing nations, the low cost, low technology screening modalities have been evolved lately as an alternative to the cytology.

WHO criteria for screening programme have been fulfilled by cervical screening and the mortality from cervical

cancer is falling in systematically screened population. For cancer Cx, a long latent period of premalignant stage, HPV as a definitive agent, easy and direct access of uterine Cx for examination and sampling and effective treatment for pre malignant changes, make this cancer probably the only gynaecological cancer to satisfy all these criteria.

In India, cervical cancer is the commonest malignancy in the females and accounts for 85% of all gynaecological cancer and 25% of all female cancer. About 18% of all cervical cancer patients are in India (2). Ethnic variations in India reveal varied incidence rate for different communities i.e. 28/100,000 female population for Hindus, 18 for Christians, 15 for Muslims and 4 for Parsis (2). The truncated rate in the age group 35-64 yrs in Chennai is even higher (99.1/100,000;1982-95) than from Cali, Columbia (77.4/100,000;1987-91), (Table 2). The cervical cancer load in India alone is estimated to reach 100,000 by 2001. The differential patterns of cervical cancer and the wide variation in incidence are possibly due to environmental differences (7).

Table-2 : Incidence Rates of Cancer Cervix in India

Registry	Age Adjusted Rate		
	1982	1987	1991
Bombay	17.8	16.1	18.6
Bangalore	34.1	24.2	27.5
Madras	40.6	41.3	38.5

Screening tests for Cervical Carcinoma

1. Conventional cervical PAP smear.
2. Liquid based cervical cytology
3. Visual inspection
   a) Unaided visual inspection (VI)
   b) Visual inspection using Acitic acid (VIA)
   c) Visual inspection using Lugol's iodine (VILI)
4. Colposcopy
5. Cervicography
6. HPV, DNA testing
7. Other emerging techniques
   a) Computer assisted reading of cervical smears.
   b) Use of physical real time devices.
   c) Detection of molecular surrogate markers of cancer progression.

Cervical cytology and visual inspection are the main modalities for early detection of cancer and they will be further discussed here.

Cytology: - Cervical cytology is the gold standard for screening. For the simple and easy test of cytology, one needs a Cuscus speculum, an Ayres spatula and cytobrush. The sensitivity of the conventional Pap test is of only 55-60% with reported false negative rate varying from 25-50% and false positive rates from 15-20%. Sensitivity & specifity of the test is improved by taking smear form ectocervix by Ayres spatula and from endocervix by cytobrush. The fluid sampling techniques have further improved the results of the cytology. It is recommended that Colposcopy and colpomicroscopy directed cervical biopsies should be performed in abnormal PAP smear and appropriate treatment instituted.

VIA & VILI :- These are the low cost techniques for cervical cancer screening which have been extensively investigated in India. Visual inspection is now regarded as the best option for proposed cancer control programme in India. It needs short training course and para medical staff can be trained easily.

In VIA (Fig 3, Fig 4), the cervix is exposed by bivalve speculum and 50% Acetic acid solution is applied on it. After two minutes, the cervix is inspected for the presence of aceto-white areas when test is called positive for VIA. In VILI 50% Lugol's iodine is applied instead of acetic acid. Non uptake of iodine dye by the cervix qualifies for positive test (Fig5, Fig 6). The patients for positive cytology or VIA and VILI are further evaluated by colposcopy and biopsy. The patients with negative tests can be reassured and can have screening done after 5 years (8). The VIA has 90% sensitivity and 92% specificity with 17% the positive predictive value and 97% negative predictive value.

Fig . 3 Normal cervix – VIA negative

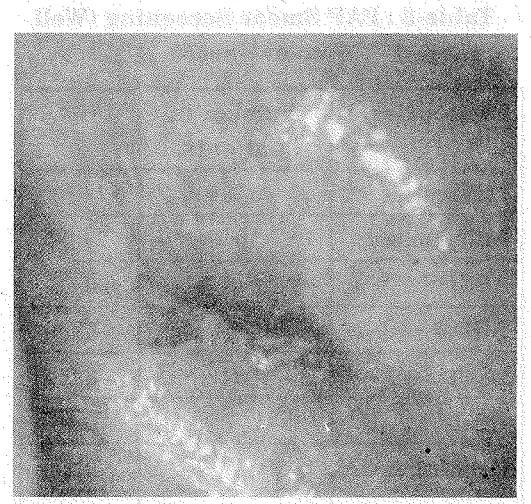

Fig. 4 Ecto Cervix - VIA Positive

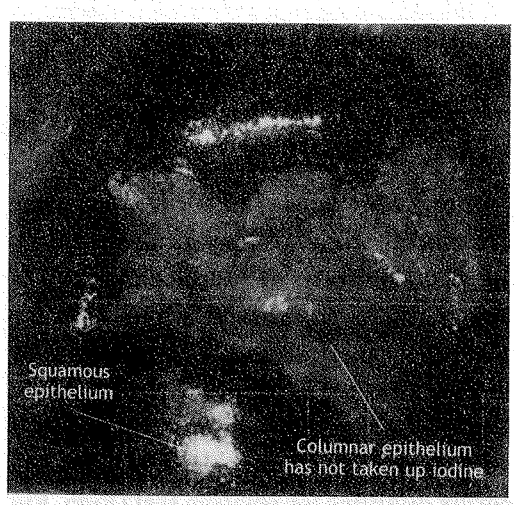

Fig. 5 Ecto Cervix - VILI negative

Fig. 6 Ecto Cervix - VILI positive

Table 3 shows Pap smear screening in well woman check. There were only 30 suspicious PAP smears out of 4295 smears taken. Frank cancer was detected in 5 patients. All the patients in the study group had two smears taken, one from ectocervix by Ayres spatula and the other from endocervix by cytobrush. 74.3% of PAP smears were normal, 24.40% were inflammatory, 0.18% Atypical squamous cells of undetermined significance (ASCUS), 0.09% Atypical Glandular cells of undetermined significance (AGUS), 0.2% low grade squamous intraepithelial lesion (LSIL) and 0.16% were high grade squamous intraepithelial lesions (HSIL). In other words, 30 suspicious smears (0.7%) were positive PAP smears for screening purpose which needed further evaluation. Non inclusion of low socio-economic status women accounted for such low incidence of positive PAP smears.

Table-3 : PAP Smear Screening (Well Woman Check)

Diagnosis	Number of patients	(%)
Normal	3194	74.03
Inflammatory	1049	24.04
ASCUS	8	0.18
AGUS	4	0.09
LSIL	11	0.02
HSIL	7	0.16
Cancer Cervix	5	0.11
Not done	17	0.39

There is no definite protocol for the cervical cancer screening. Where as in U.K.(9), it starts at 25 yrs of age, with 3 yearly interval for the age group 25-49 years, 5 yearly interval from 50-64 years and no screening from the age of 65 years on wards, the American Cancer Society

Guidelines (ASCG) (10) are slightly different.

- All women should begin cervical cancer screening about 3 years after they begin having vaginal intercourse, but no later than when they are 21 years old. Screening should be done every year with the regular Pap test or very 2 years using the newer liquid-based Pap test.
- Beginning at age 30, women who have had 3 normal Pap test results in a row may get screened every 2 to 3 years. Another reasonable option for women over 30 is to get screened every 3 years (but not more frequently) with either the conventional or liquid-based Pap test, plus the HPV DNA test. Women who have certain risk factors such as diethylstilbestrol (DES) exposure before birth, HIV infection, or a weakened immune system due to organ transplant, chemotherapy, or chronic steroid use should continue to be screened annually.
- Women 70 years of age or older who have had 3 or more normal Pap tests in row and no abnormal Pap test results in the last 10 years may choose to stop having cervical cancer screening. Women with a history of cervical cancer, DES exposure before birth, HIV infection or weakened immune system should continue to have screening as long as they are in good health.

Even though, there is no organised screening programme in India, even then 54.4% of women between 21 to 65 years of age have had a smear and 44.30% had it within the proceeding three years. The ACS guidelines cannot be recommended in India due to lack of infrastructure and resource crunch. The WHO recommendation of once a life time PAP smear between the ages of 35-40 years for Indian scenario is a good compromise.

Ovarian Cancer (Fig 7)

Ovarian cancer (204,000 cases and 125,000 deaths) is the sixth most common cancer and the seventh cause of death

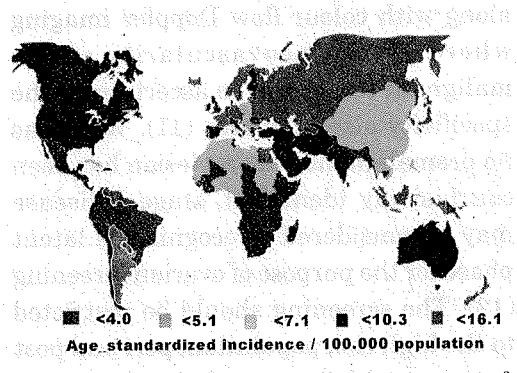

Fig. 7 The global incidence of ovarian cancer[3]

from cancer in women (4.0% of cases and 4.2% deaths). Incidence rates are highest in developed countries with rates in these areas exceeding 9 per 100,000, except for Japan (6.4 per 100,000). Incidence in South America (7.7 per 100,000) is relatively high. Incidence rates have been slowly increasing in many Western countries and Japan. The risk of ovarian cancer is reduced by high parity and use

of oral contraceptives. In India, the incidence is 4.65% of all female cancers (2).

CA 125 and Transvaginal ultrasonography (TVS) are the two extensively investigated diagnostic modalities for detection of ovarian cancer. Although, CA 125 is not a specific tumor marker for diagnosing ovarian malignancy, the rising levels even within the normal range should raise the suspicion of an occult ovarian or primary peritoneal cancer. Since 90% of ovarian tumors are epithelial tumors only, CA 125 is considered a screening marker. TVS has high sensitivity for ovarian cancer, and along with colour flow Doppler imaging where by the neovascularity of the malignant tumor can be ascertained, the specificity also increases (11). Where as no premalignant ovarian lesion has been conclusively identified, stage I disease may be considered a recognisable latent phase for the purpose of ovarian screening (12). The screening should be restricted to the high risk population, peri and post menopausal women with family history of ovarian, breast, endometrial or colon malignancy; late age at first pregnancy, non users of oral contraceptive pills and detection of 5cm or more sized cyst in post menopausal woman. The multilocular ovarian cysts with solid and cystic components are the suspicious cysts for malignancy.

Currently it appears that a high index of suspicion for the disease in the high risk patient, is the best way to detect early ovarian cancer. Routine bimaunal pelvic examination, thorough investigation of adnexal masses and impressing on follow up for patients with positive findings are the methods for early detection.

In the well women check study (Table 4), 8.6% of patient had ovarian cysts detected on TVS. No case of early ovarian cancer was detected in the study. Patients were advised to repeat pelvic ultrasound after 6-12 weeks if the size of the cyst was less than 5 cm with normal Colour Doppler studies. On the other hand, any mass with abnormal vascularity and suspicious of malignancy and all masses >5cm in size need surgical evaluation.

Table-4 : Ultrasound Pelvis - Adenexal lesions (Well Woman Check)

Diagnosis	Number	(%)
Normal	3788	88.01
Ovarian Cysts	371	8.06
Polycystic	119	2.07
Para ovarian cyst	4	0.03
Hydrosalpinx	13	0.03

Endometrial cancer (Fig 8)

Cancer of the endometrium has a rather similar geographic distribution to ovarian cancer. However, it appears more important as a cause of new cases (199,000 or 3.9% of cancers in women) than in terms of mortality (50,000 deaths or 1.7% of cancer deaths in women) because of the much more favorable

prognosis. It is a cancer of postmenopausal women; worldwide, 91% of cases occur in women aged 50 and older. Survival is rather good and similar to that of breast cancer-86% in the US SEER

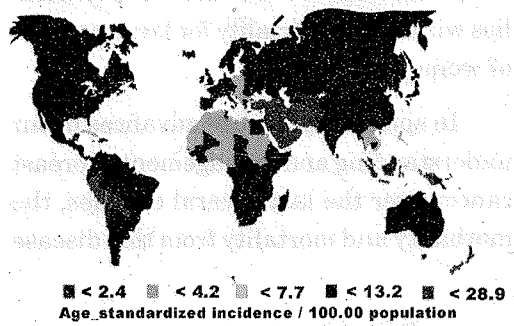

Fig. 8 The global incidence of endometrial cancer[3]

registries and 78% in European registries. The proportion of these cases surviving up to five years in developing countries is greater than the corresponding proportion of breast cancers. The highest incidences are in North America (22.0) and Europe (11.8 to 12.5). Rates are low in southern and eastern Asia (including Japan) and most of Africa (less than 3.5 per 100,000).

The American Cancer Society (10) recommends that at the time of menopause, all women should be informed about the risks and symptoms of endometrial cancer, and strongly encouraged to report any unexpected bleeding or spotting to their doctors. For women with or at high risk for hereditary non-polyposis colon cancer, annual screening should be offered for endometrial cancer beginning at 35 years of age.

U.S.G determined endometrial thickness is used as a screening method for endometrial cancer. A 5 mm thickness of endometrium is generally accepted as normal and anything above it warrants further evaluation of endometrium by aspiration cytology or endometrial biopsy. At an endometrial thickness threshold value of 5mm, TVS has a +ve predictive value of 9% for detecting any abnormality. The sensitivity is 90% and specificity of 48% with negative predictive value of 99%. Diagnosis of endometrial hyperplasia with atypia is considered as a precancerous lesion of endometrium (13). However, the routine screening for endometrial carcinoma is currently not justified.

3.7% of women in well woman check study (Table 5) had Postmenopausal Endometrial Hyperplasia, 1.6% had endometrial polyps and 0.7% had fluid in

Table-5 : Ultrasound Pelvis – Uterine Lesions (Well Woman Check)

Diagnosis	Number	(%)
Normal	2513	58.05
Fibroid Uterus	865	20.01
Adenomyosis	627	14.06
Postmenopausal Endometrial Hyperplasia	159	3.07
Fluid Polyps	30	0.07
Endometrial Polyps	72	1.06
Post Hysterectomy	27	0.06

endometrial cavity detected by TVS. Histopathological evaluation of all the patients was done by hyteroscopic directed biopsies. 4 cases of endometrial cancer from thick endometrial group and two from endometrial polyp group were detected by Histopathology.

Breast cancer (Fig 9)

In India, breast cancer accounts for 22.3 % of all female cancers, second only to the cervical cancer(14). Despite some arguments to the contrary, obstetricians and gynaecologists function as primary care physicians for women upto pre-menopause. Therefore, the diagnosis of breast carcinoma in its most curable form lies within this speciality for large number of women.

In spite of significant advances in our understanding and management of breast cancer over the last several decades, the morbidity and mortality from this disease

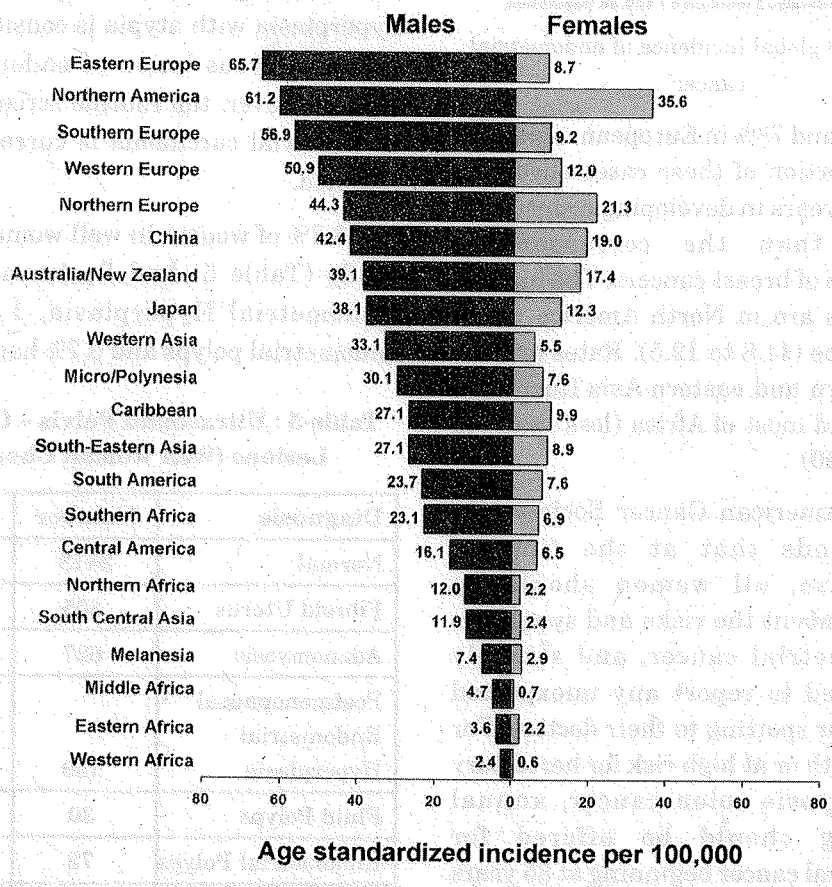

Fig 9. Global incidence of ovarian cancer[3]

remain high. Therefore, prevention of this disease has become one of the most important challenges for the medical community. It is estimated that several billion dollars per year could be saved if its development were prevented.

The ability to identify individuals or populations at risk for breast cancer is an integral part of effective preventive strategies, but until recently we have not been able to accomplish this task with any degree of certainty. Other than gender and age, fewer than 50 % of cases occur in women with other risk factors, and 85% are diagnosed in women without any family history. Recent advances in our understanding of the molecular biology of breast cancer have led to the identification of specific mutations that may help identify women with a hereditary predisposition to developing breast cancer, as well as to predict who will respond to adjuvant therapy (15).

The causes of carcinoma breast seem to be multifactorial and so are the risk factors. These risk factors can be identified and evaluated by good history taking and thorough examination of breasts. Finding a breast lump and evaluation of the nature of the lump is screening for and diagnosis of carcinoma breast. 90 % of breast lumps can be detected by clinical examination alone. Mammography and Ultrasound breast help in detection of rest of the 10 % of the non palpable lumps.

Mammogram and Ultrasound breast is advised to all patients above 40 yrs of age (Table 6, Table 7) Patients who are less than 40 years of age and have low risk for cancer breast are screened for breast lesion by Ultrasound. BIRADS-3 lesions need re-evaluation after about six months where as BIRADS 4 and 5 lesions need FNAC and biopsy from the lesions. In the present study no case of carcinoma breast was detected.

Table-6 : Evaluation of Mammograms (Well Woman Check)

Diagnosis	Number	(%)
BIRADS 0	149	3.04
BIRADS 1	3019	70.02
BIRADS 2	798	18.05
BIRADS 3	243	9.07
BIRADS 4	15	0.03
BIRADS 5	-	-
Not done	71	1.06

Table-7 : Ultrasound Screening for Breast (Well Woman Check)

Diagnosis	Number	(%)
Normal	2882	67.01
Fibroadenosis	827	19.02
Breasts cysts	230	5.03
Fibrocystic disease	226	3.09
Ductal Dilatation	38	0.08
Fibroadenoma	88	2.00
Cancer	4	0.09

Prevention of breast cancer is aimed at detecting pre-invasive lesions, such as ductal carcinoma *in situ* and lobular carcinoma *in situ* or early stage invasive breast cancers that have the potential to be cured with limited treatment. Screening tests aimed at breast cancer prevention include the Breast Self Examination (BSE), clinical breast examination by health care providers, Mammography and Ultrasonography of breast. Monthly self examination of breasts is a recommendation followed for quite some time now, but it has been seen that this has not appreciably decreased the overall mortality rates due mainly to the small number of women who actually perform these examinations. Extensive use of Mammography and Ultrasound screening of breasts have declined the overall mortality rate of breast cancer by 5% in U.S. women

The American Cancer Society guidelines for early detection of cancer breast are as follows:

- Yearly mammograms are recommended starting at age 40 and continuing for as long as woman is in good health.
- Clinical breast exam (CBE) should be part of a periodic health exam, about every 3 years for women in their 20s and 30s and every year for women 40 and over.
- Women should know how their breasts normally feel and report any breast change promptly to their health care providers. Breast self-exam (BSE) is an option for women starting in their 20s.
- Women at increased risk (for example, family history, genetic tendency, past breast cancer) should talk with their doctors about the benefits and limitations of starting mammography screening earlier, having additional tests (for example, breast ultrasound or MRI), or having more frequent examinations.

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