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Challenges in Screening and Early Diagnosis of Female Cancers

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Abstract

Female cancers are considerably increasing the morbidity and mortality among women all over the world. Breast cancer and gynecological cancers are prevalent now days despite having advanced tools and techniques for their management. Recent trends shown by continuously increasing incidence of these cancers are surprising. Breast cancer is the most common type of cancer among women worldwide followed by cervical cancer and ovarian cancer. Detection of these cancers at an earlier stage is highly required to control and limit the rise in new cases data. Use of different strategies in modified manner is being practiced along with some new methods of detection but it is not suitable for majority of cases. Whether using imaging techniques, different biomarkers such as DNA, proteins etc., biosensors or others, there are certain limitations of using these. The matter of sensitivity and specificity remains a major issue; also these cannot be implemented at the level of population at risk. To overcome such drawbacks, conventional methods can be used in combination to improve the efficiency. The concept of personalized screening methods and risk stratification tools are some incredible ideas to combat but it requires more and more precision for individuals.

Keywords: Female cancers; Screening; Early diagnosis; Challenges; Breast cancer; Cervical cancer

Introduction

Burden of cancer is highly increasing in females either it is breast cancer or other gynecological cancers. It is considerably raising the morbidity and mortality among women globally. Most of these cancers are caused due to changes in genetic and epigenetic content. There are specific factors which are offering moderate to high level risk and thus contribute in uncontrolled cell proliferation. Incidence of major female reproductive cancers has been increased rapidly from 2012 to 2018 and further to 2020 [1-3]. In 2018, no. of breast cancer cases reported was 2,088,849 all over the world which accounted for 24.2% of total new cancer cases in females [2]. The no. of new breast cancer cases increased to 2,261,419 in 2020 causing 684,996 deaths worldwide [3]. In India, 205,424 new breast cancer cases were reported in 2018 with a cumulative risk of 1 in every 29 females. In 2020, 178,361 breast cancer cases were reported in India with 90,408 no. of causalities. Trends shown by cervical cancer are also very surprising all over the globe as well as in India [4]. Globally, 569,847 new cancer cases of cervix uteri were reported in 2018 and this no. became 604,127 in 2020. No. of new cases of other gynecological cancers such as ovarian cancer, endometrial cancer etc. are also increasing continuously and can be observed as shown in Figure 1, 2 [1-3].

Breast cancer is the most common type of female cancers in Low and Middle Income Countries (LMICs) as well as in High Income Countries (HICs) [5]. The risk becomes more when there is a strong family history, even if no genetic mutation is known. Further complexity is added by first degree relatives, no. of relatives with breast cancer and age at diagnosis [6]. If diagnosed at an early stage, it can be treated and also has a good survival rate. On the other hand, there is a well-defined risk of developing secondary malignancies even after the treatment of breast cancer [7,8]. Common risk factors, drugs and therapies used in the treatment are found to be responsible for these secondary malignancies [9,10]. Cervical cancer is the most prevalent cancer out of all gynecological cancers with a high incidence rate. In India 75,209 new cases of cervix uteri were reported with cumulative risk of 1 in 75 females in 2020 [4]. Such high no. of cases also imposes relative burden on healthy population. An elevated risk of endometrial and ovarian cancer with a predisposition of Lynch syndrome is observed in many cases. The age of detection of endometrial

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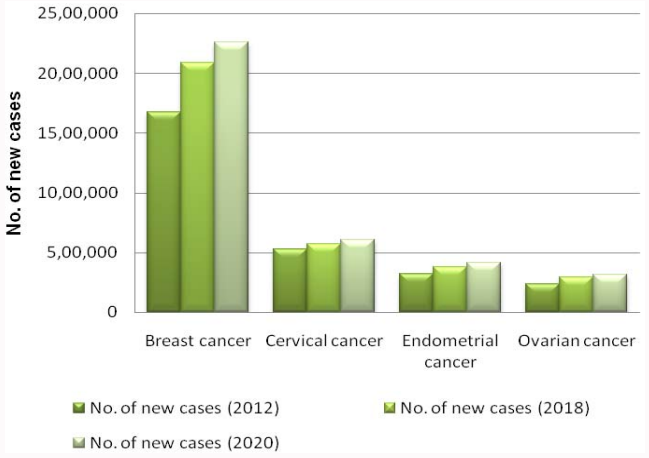


Figure 1: Global increase in incidence of major female cancers from 2012 to 2020.

cancer was also found as early as 47 [11,12]. Prevalence of these cancers varies depending upon the exposure to risk factors and the time of diagnosis. There are certain barriers that limit the chances of early diagnosis of breast cancer and screening of cervical cancer at individual level, provider level and system level [13]. To limit the rise in no. of new cases, screening and early diagnosis of the population at risk is very much required. But there is a lack of definite screening strategies to give precise results about the malignancy. Although different ways are established to confirm the existing malignancy but these are not applicable in case of screening and early diagnosis of population at risk.

Screening of breast cancer

There are certain risk factors that increase chances of breast cancer in women. *BRCA1* and *BRCA2* mutations are counted as known genetic predisposition found in around 5% to 10% of cases. *BRCA1* mutation carriers are at 50% to 85% of lifetime breast cancer risk and *BRCA2* mutations offer approximately 45% risk during life span [6]. Among all the screening methods, gold standard for the screening of breast cancer is referred to mammography. It has been a widely used method in breast cancer screening as proven to reduce the mortality. For the women with risk of breast cancer, it is recommended to undergo mammography every 2 years starting at 50 years age [14]. Sonography is another most commonly available, tolerable and inexpensive method of breast cancer screening with no use of harmful radiations [15]. Cancer detection rate is comparatively high with the use of MRI. It is cost effective and more sensitive than ultrasound and mammography in detecting invasive cancer [16]. Women with breast cancer at or before the age 65 years are better diagnosed with MRI. Also, it can be beneficial in case of dense breast tissue and women with personal history of breast cancer. Selected high risk women can be screened by the combination of MRI and mammography in the form of adjunct [17,18]. Molecular imaging techniques like *BSGI* (Breast Specific Gamma Imaging) and *PEM* (Positron Emission Mammography) are also used commonly because these have high specificity and high positive predictive value [19]. There are some individual risk factors that vary from person to person such as breast density and breast cancer appearance. These variations lead to development of some personalized screening methods. On the other hand, there are risk stratification tools available that help in the evolution of personalized screening techniques by appropriate estimation of individual risk. It can be done by the use of genetic testing, risk assessment tools and understanding of clinical features [14].

Another technology named *MWT* (Microwave Tomography) has the potential to detect early stage tumor and proved to detect tumor with diameter 1 cm [20]. Different types of Radar based microwave imaging are also used to detect small size tumor with high resolution images and are able to generate real-time images at a reduced cost [21]. Detection is also done by using biomarkers (DNA and Protein) as good indicators of breast cancer [22,23]. Heat shock proteins *(HSP60, HSP90), p53, RS/DJ-1, HER2*, Carbohydrate antigen 15-3 *(CA15-3)* and *MUC1* (Mucin 1) are some clinically investigated protein biomarkers. Most commonly used gene biomarkers include *BRCA1*, *BRCA2* and *p53* which are mainly the tumor suppressor genes. Optical biosensor *(Surface Plasmon Resonance)*, piezoelectrical biosensor *(Piezoelectric Microcantilever)*, electrochemical biosensor and nanobiosensors using nonmaterial's (such as *gold, graphene oxide, carbon* etc.) are some trending types of biosensors which are characterized by satisfactory sensitivity, quick analysis and cost effectiveness [24].

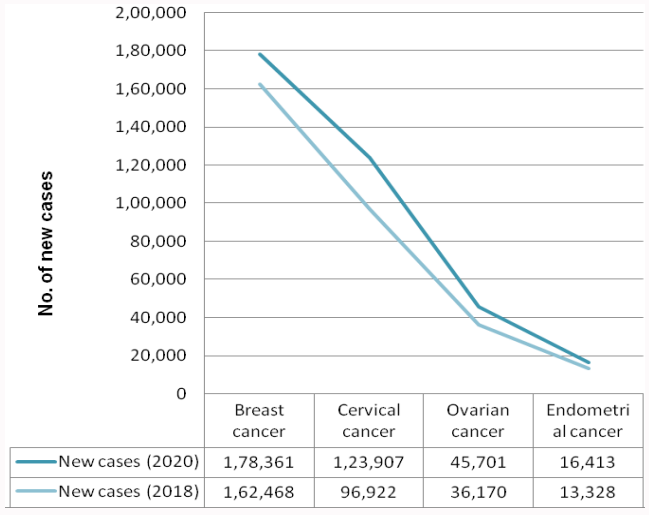
Challenges in breast cancer screening

Breast cancer screening methods involve different effective methods. But these are having some or more limitations. The gold standard method mammography is not considered as perfect screening tool for population based screening and has low sensitivity as the breast density increases [25]. It was reported to be less sensitive in cases already having a personal history of breast cancer [6]. Issue of over diagnosis was found to be related with mammography. It was also reported to show false positive results as well as require more number of biopsies which increase cost of treatment, cause anxiety and discomfort too. Also the concern of effect of radiation dose on breast is raised in mammography [14]. Sonography uses ultrasound waves which are comparatively safe but repeated recalled examinations and biopsies are still required [15]. Use of MRI in screening for the purpose of reduced mortality is not effective. Issues like follow-up imaging, low specificity and prompting biopsy are also involved. Molecular imaging methods are not applicable in current screening due to very high radiation exposure [19]. Also, the concept of complete novelty cannot be applied in personalized screening strategies. But these can be adjusted according to the individual risks and needs due to heterogeneity of human population.

Main limitation of *MWT* methods is the high computational load, low specificity and accuracy [20]. Less ability to differentiate between noise and artifacts is the lacking point of Radar based techniques. Costly electronic equipment for real time imaging, skin-breast artifacts in images, high reflections of skin are some other limitations [21]. Moreover, the use of DNA biomarkers has poor ability for detecting tumor because of having low concentration of markers [22]. Clinically investigated protein biomarkers show poor survival, poor prognosis and limited sensitivity for early stage tumor. There are many challenges in using biosensors such as chances of non-specific binding, small size target and marker levels [24].

Screening of cervical cancer

Cervical cancer is second most common gynecological malignancy and also a key cause of death among women. It is more prevalent in developing and underdeveloped countries as stated by WHO. These countries are facing more challenges in coping with the situation



	Breast cancer	Cervical cancer	Ovarian cancer	Endometrial cancer
New cases (2020)	1,78,361	1,23,907	45,701	16,413
New cases (2018)	1,62,468	96,922	36,170	13,328

Figure 2: Incidence of major female cancers in India in 2018 and 2020.

due to heavy burden of cervical cancer and its highest mortality. Almost all the cervical cancer cases are associated with *HPV* (Human Papillomavirus) and are categorized into high and low risk *HPV*s according to their oncogenic potential [26]. *HPV* type 16 and 18 are responsible for most no. of cervical cancer cases, approximately 70% of all. Majority of *HPV* infections do not develop in cancer rather persistent high risk *HPV* infection (>2 years) is considered as primary causative factor for this malignancy [27]. Pap smear test is the most common test that is used to screen the women for *HPV* and ultimately differentiating those with infection and without infection. Consistent specificity (approx. 98%), relative ease of performance and cost effectiveness are some of the advantages that make this screening method as a gold standard [28]. Liquid based cytology is also being used in conventional Pap smear testing procedures due to better sample collection and preparation, improved results along with filtering of blood and debris. Also, there is not much difference in sensitivity or specificity in detecting abnormality as compared to the conventional Pap smear [29].

In women aged 30 or more, co-testing was introduced which uses *HPV*-DNA testing for cervical cancer screening along with cervical cytology. This combination increases the sensitivity of single Pap smear test from 50% to 85% to around 100%. For women of age group 21 to 29 years, cervical cytology can alone be performed along with screening every 3 years [29]. *HPV* testing can be considered as primary screening modality as it has equivalent or superior effectiveness as compared to cytology alone and can be carried out by self-swabbing rather than pelvic examination by an expert [30,31]. In an FDA (US) modified trial, the specimens with positive results underwent *HPV* genotyping. Colposcopy was done in case when infected with *HPV* 16 or 18, otherwise cytology testing was preferred and only abnormal results underwent colposcopy. It is a diagnostic as well as visual inspection method performed after obtaining abnormal results of the screening test [31]. Another optical technology based digital colposcopy provides ultra-high resolution digital images that can be magnified to higher degrees than the conventional one and allow for superior visualization [32]. *VIA* (Visualization with Acetic Acid) or *VILI* (Visualization with Lugol's Iodine) as primary screening methods are more accurate, safe, feasible and cost effective screening procedures in resource deprived regions. It requires good light source, private screening space, trained professionals for result interpretation etc. [33,34].

Challenges in cervical cancer screening

Cervical cancer is a preventable type of cancer to the most extent. Its prevention depends on the management and strategies that are being practiced in any country. Total eradication of cervical cancer has become a matter of public health emergency as one woman dies of it every 2 min all over the world. To achieve the goal of cervical cancer elimination, it is necessary to use some efficient screening tools and techniques [35]. Although Pap smear is considered as a gold standard for cervical cancer screening and is being used since historical times, it is needed to perform in repeated manner due to low and variable sensitivity (approx. 55% to 80%) and reproducibility [36]. In less developed regions, cytology based screening methods are difficult to be implemented because of dearth of basic facilities like electricity for microscopes, resources for testing and well trained cytopathologists for accurate result interpretation. It becomes difficult for populations where developed infrastructure is not available as it requires continued interval screening time to time and patient follow-up. In such regions, cytology based screening methods are not applicable and demonstrated low range of sensitivity (11%) and specificity (14%) for the detection of high grade lesions [37,38]. Moreover, Co-testing is performed at an interval of 5 years due to its more cost and very high negative predictive value for high grade neoplasia [29]. High cost, laboratory processing requirements and time taken for providing results are some hurdles of using *HPV* testing. Also, the choice to opt self-swabbing method of sample collection makes it to decrease the testing accuracy [39]. Although *VIA* offers a low cost, safe, easy to perform way and provides results immediately without any laboratory processing, limitations arise in population where cervicitis rates are higher. It can give rise to false positive results and lead to overtreatment or other infectious complications. Some degree of training and visual acuity is necessary, lack of which can lead to low quality and improper image collection [40].

Screening of ovarian cancer

Ovarian cancer is considered to be the most fatal of all gynecological cancers as it is generally diagnosed at later stages. Its symptoms are not specific which offer hurdle in early detection and hence majority of cases are reported at advanced stages. Family history of ovarian or breast cancer and specific hereditary cancer syndrome are some high risk predispositions of ovarian cancer [41]. Type I ovarian carcinoma is slow developing but type II carcinoma is highly aggressive and confers induced mortality [42]. Detection of ovarian cancer at earlier stage mainly consists of 2 steps. First step includes cost effective tests, mainly blood test and second, when found abnormal results, it is followed by suitable imaging tests. Trans-Vaginal Ultrasonography (*TVS*) is the most common imaging test adopted for confirming the ovarian abnormality [43]. Recently, *ROCA* (Risk of Ovarian Cancer Algorithm) is also involved in screening methods of ovarian cancer and has been found to detect early cancer stages. This algorithm mainly uses a combination of *CA-125* serial measurements along with the age factor. *ROMA* (Risk of Ovarian Malignancy Algorithm) is another such algorithm that combines *HE-4* (human epididymis protein 4) with menopause status and *CA-125* levels [44].

Use of traditional methods is common for diagnosis of ovarian cancer including serum level of *CA-125*, *TVS*, cytological examination, laparoscopy etc. *CA-125* is the most widely used tumor biomarker in ovarian cancer. Combination of *CA-125* with other proteomic biomarkers (*HE-4, CA19-9, CA72-4, CA-153* etc.)

is recently being used to improve the sensitivity and specificity of diagnostic test [45]. Combination of *CA-125* with *HE-4* proved to be a more precise diagnostic tool and the best predictor of ovarian cancer risk in suspected benign tumors [46]. Serum based scoring strategy *ROMA* is in progress that uses combination of *CA-125* and *HE-4* levels to assess the high or low level risk of developing tumor. Some other biomarkers which are being developed include metabolomic biomarkers, exosomes (*CD63, CD81, MHC1*, lysosomal-associated membrane proteins 1 and 2, tumor susceptibility gene 101 protein etc.), Circulating Tumor Cells (CTCs) and epigenetic biomarkers. Utility of epigenetic biomarkers due to molecular modifications in advance and miRNA as epigenetic modifiers offer great promises for early detection. Promoter hypermethylation of *SFRP*, *SOX1* and *PAX1* genes is reported to be high in malignant cases [47].

Challenges in ovarian cancer screening

Efforts have been made to diagnose ovarian cancer at earlier stages. However, there is no timely screening strategy to detect the population with increased level of risk [48]. There is high value of false positive result in ovarian cancer screening tests leading to unnecessary invasive procedures even when no tumor is developed [41]. Also, different factors act as diagnostic barriers in detection of ovarian tumor such as anatomical location of ovaries, no defined symptoms, rarity of the malignancy etc. [49]. *CA-125* is not much specific and enough sensitive, hence lacking the ability to detect tumor timely. Its level is found to be elevated in some normal physiological conditions and cancers other than ovarian cancer. Only 50% to 60% cases with early stage ovarian cancer are reported to have increased *CA-125* level. In ovarian cancer types, only serous ovarian cancer was found to be strongly associated with elevated *CA-125* levels [50]. The level of serum *HE-4* is affected by smoking and using hormonal contraceptives [46]. Also, *ROCA* is not enough robust in reducing the elevated mortality caused due to ovarian malignancy and is an expensive procedure to be implemented. On the other hand, *ROMA* can predict the risk of tumor to a certain extent but cannot be used as a beneficial screening tool [44].

Combination of Ultrasound and *CA-125* level provides very less or negligible benefit in effective screening as reported by major clinical trials [44]. Use of CTCs for confirming tumor advancement is under validation process, but it cannot be concluded to use in early detection of malignancy. On the other hand, applicability of epigenetic biomarkers is limited by the observations that similar genes are affected in different cancers. Therefore, it cannot be used particularly for a cancer type [47]. Also, it is required to investigate further in this field to validate the findings of various studies [51]. Different protein markers have been identified in blood and urine, but no marker has proved to be enough sensitive and specific to differentiate between cancerous and non-cancerous [52]. Current strategies offer chances of improvement for screening as a single method cannot be remarked as most suitable. Strategies are required for earlier detection of the tumor in both low as well as high risk women to reduce the mortality. Multimodal strategies (like using *CA-125* level and *TVS*) can result in timely diagnosis but no screening strategy is known to definitively decrease the mortality [53].

Screening of endometrial cancer

Endometrial cancer is one of the emerging types of uterine malignancy which is a recent trend in many developing and developed countries. Most common indication of uterine malignancy involves abnormal uterine bleeding. Early detection of this has been focusing on minimum invasion level of sampling procedure. Endometrial samplers are commercially available with simple technique and good results that help in direct endometrial screening during postmenopausal bleeding. Use of *Li brush* as a sampler is efficacious as it allows access to uterine region, has low cost, good flexibility and causes less damage [54]. There are various risk prediction models which indicate the level of risk caused by different epidemiological factors. However, American Cancer Society recommends no routine screening for endometrial cancer in general population when no symptoms are reflected. Intermediate risk population (no *Lynch Syndrome* and any other mutation) including *Tamoxifen* users can be considered for screening of endometrial cancer [55]. Major predispositions to screen the high risk population include strong family history, intake of *Tamoxifen*, genetic disorder *HNPCC* (Hereditary non-polyposis Colorectal Cancer or *Lynch syndrome*) and mismatch repair gene mutations [56]. Annual biopsy is recommended from age of 35 years in such women with very high level of risk [55]. *TVS* is most commonly used technique for the investigation of endometrial cancer in women showing particular symptoms. Endometrial thickness at anterio-posterior diameter is measured by *TVS* to indicate risk of endometrial cancer that leads to further invasive diagnosis such as endometrial biopsy [55]. Risk of endometrial cancer is determined mainly by measuring the thickness of endometrium layer by using ultrasound technique. Normal thickness of endometrial layer is considered to be <4 mm, 4 mm to 5 mm in case of postmenopausal women and up to 16 mm in case of premenopausal women. If abnormal bleeding is present, the cut-off is taken as 4 mm to 5 mm in symptomatic and around 10 mm in asymptomatic patients [56].

The standard diagnostic procedures dilation and curettage and pipelle biopsy are widely used to confirm the malignancy in case of abnormal bleeding [55]. Novel approaches that use digital PCR techniques like interrogation of single mutation, CpG island methylation etc. are also there. Array or sequencing based methods can be used to investigate larger no. of genetic variations but protein biomarkers based tests are much efficient as quantified by standard methods (immunohistochemistry, *ELISA* etc.) and are more cost effective [57].

Challenges in endometrial cancer screening

Despite the global prevalence of endometrial cancer on women's health, there is no standard screening test clinically available for it. Examination done by using ultrasound techniques has a Positive Predictive Value (PPV) of 9% with 48% specificity and the negative predictive value is relatively high i.e. 99%. In dilation and curettage, around 60% procedures evaluate only less than half uterine cavity and show high false negative results even if done by the experienced clinician [58]. Beside this, the pain and discomfort caused is not widely tolerated by the patients [59]. Endometrial sampling becomes difficult in case of cervical stenosis and atrophy in post-menopausal women. Difficulty of access, patient's sufferings; bleeding, infection etc. are some of the highlighted complications [56]. Despite having various benefits of using *Li brush*, there are some limitations too. Major disadvantages of using *Li brush* involve low quantity of sample and inaccurate sampling location [54]. Endometrial thickness measurement can be taken as a screening tool in postmenopausal women. It is a challenge in premenopausal women as the thickness of endometrium layer keeps on changing throughout the menstrual cycle. Moreover, *TVS* is not suitable for annual screening of high risk women as it is not sufficient alone [55].

In *Tamoxifen* user asymptomatic women, thickness of endometrial layer measured by using ultrasound is not highly correlated with pathology. Low positive predictive value and high false positive results even at thickness of 10 mm are major drawbacks of using ultrasound methods in asymptomatic women [60]. Some interference in measuring endometrial thickness is caused by the location of uterus, obesity and co-existing myomas. Moreover, ultrasound procedures are not widely accessible as it is costly and requires well trained clinicians [58]. Low specificity of screening tools and unnecessary investigations leading to additional anxiety in women are some of the limitations of screening in general populations [55].

Conclusion

Continuously growing incidence and disproportionately higher mortality of female cancers is a major health concern. In low resource countries, it is necessary to overcome the challenges of competing healthcare priorities so that female cancer mortality can be effectively reduced. For this, integration of advanced screening and timely detection provides a cost effective modality in the management of female cancers. Organized screening of population at risk is required at different levels as no one strategy fits all solutions. To fulfill this purpose, a robust system of management along with allocation of resources can provide a way to effective treatment strategies. On the other hand, improvement of existing screening and diagnostic methods will help in combating the present scenario. Ability to detect early stage of malignancy, minimally invasive sampling procedures, high throughput capacity and cost effectiveness are some essential conditions that should be reflected by the technique or method used for screening purpose in wide population.

Author's Contribution

SR: Data collection, Manuscript writing, RY: Data analysis, Manuscript editing, MBC: Data analysis, PA: Data collection, Manuscript editing, CY: Manuscript editing.

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