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ORIGINAL ARTICLE

Early Detection of Breast, Cervical, Ovarian and Endometrial Cancers in Low Resource Countries: An Integrated Approach

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Abstract The incidence of breast and gynecological cancers continues to increase in low and middle resource countries [LRC'S and MRC's] with a disproportionately higher mortality rate compared to that in high resource countries. This has been attributed to factors such as an increased life span due to better control of communicable diseases and improved nutrition, as well as lifestyle and reproductive changes. A lack of public awareness and understanding of these cancers, absence of an organized screening program and a lack of accessible and effective treatment options, is responsible for the higher mortality rate. A practical approach of a combined program of integrating a well woman examination with screening for breast and cervical cancer and diagnostic evaluation for Ovarian and Endometrial cancer in symptomatic women is proposed in this article which can serve as a model to be studied for efficacy in low resource countries.

Keywords Screening · Diagnosis · Breast cancer · Cervical Cancer · Ovarian cancer · Endometrial cancer

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Introduction

In a low resource country, health care manpower and infrastructure available for prevention, early detection or treatment of cancer, is limited or nonexistent. Low income countries are those countries where the per capita gross national income is $995 or less [1]. In such a setting due to a combination of lack of health care infrastructure, limited access to health care, as well as economic, social and cultural barriers that prevent women from seeking timely care, the cancer mortality is high [2, 3]. Competing healthcare needs in these countries with limited resource means lower priority for cancer control interventions. The background data on common cancers afflicting women are presented below.

Background – Breast Cancer

Breast cancer is now the most frequently diagnosed cancer as well as the leading cause of mortality from cancer in women worldwide. It accounts for 23% of the total cancer cases and 14% of deaths resulting from cancer in females [4]. About 1 million new cases of breast cancer are reported annually with 375,000 deaths. It has been estimated that of more than 1 million new cases of breast cancer that will be diagnosed worldwide in 2009, low- and middle-resource countries will be burdened with 50% of breast cancer cases and 60% of breast cancer related deaths [4]. In 2010 the annual incidence of new cases is expected to be 1.5 million, and it is estimated that by 2020 70% of all breast cancer cases will be in low and middle resource countries [5].

Background – Cervical Cancer

Low resource countries account for 80% of the half a million cases of cervical cancer occurring annually. About 233,000 deaths result from cervical cancers [5]. Population based screening programs in place in the developed nations have successfully controlled mortality from cervical cancer. Eighty-five percent of the deaths from cervical cancer occur in low resource countries where screening programs are not in place [5]. Current estimates of cervical cancer in these countries may be an underestimate due to lack of reliable cancer registries.

Background – Ovarian Cancer

The worldwide incidence of ovarian cancer according to the GLOBOCAN database was 204,499 cases in 2002. Ovarian cancer has a very high case fatality rate that results from it being often diagnosed at late stages of disease [5].

Ovarian cancer (204,000 cases and 125,000 deaths) is the sixth most common cancer and the seventh cause of death from cancer in women (4.0% of cases and 4.2% deaths [5]. Ovarian cancer occurs almost equally in the developing and developed regions of the world. The case fatality ratio is generally greater than 50% and over 70% in East Africa. The prognosis has remained poor with no change in the overall mortality rate. Women are often diagnosed in Stage III and IV which carry a five year survival rate of 27 and 16% respectively [5].

Background – Endometrial Cancer

There are about 200,000 new cases of endometrial cancers diagnosed each year with about 50,000 fatalities. The incidence is comparable to ovarian cancer with a much better survival rate due to diagnosis at an earlier stage [5]. The relationship between obesity, anovulation and endometrial cancer make prevention and early diagnosis reasonable goals even in low resource settings

Integrated Screening Strategy

The nucleus of this strategy would be a community based, combined program for early detection of breast, cervical, ovarian and endometrial cancer in low resource countries delivered through a free standing or a mobile Well Woman Clinic. The goal of such a program would be to downstage cancers and improve mortality rates. The core strategy would include combining a well woman examination with Screening of asymptomatic women for breast and cervical cancer and diagnostic assessment of symptomatic women for Ovarian and Endometrial cancer. The methodology of such a program is outlined in greater detail below.

Screening – Breast and Cervical Cancer

Breast cancer: In low resource countries the age distribution of breast cancer is generally lower than in high resource countries, although this has been attributed to the average lower age of women in the population rather than due to a higher age specific incidence, it is still advisable to start screening at an earlier age. The target population should include women in the age group of 30–59 years. The proposed methodology would include an annual clinical breast examination [CBE] followed by diagnostic breast sonographic evaluation in screen positive women. Those women in whom a palpable solid mass is seen and determined to be suspicious based on ultrasound morphologic features, Fine needle aspiration biopsy (FNAB) is performed under ultrasound guidance for optimal sampling. The rationale of this suggested methodology is explained below.

Clinical Breast Examination [CBE] has been studied as a low cost alternative to mammographic surveillance to reduce mortality by early detection of breast cancer. CBE identifies about 60% of cancers that are detected by mammography and a few that are not seen at mammography. There has been no randomized clinical trial undertaken to evaluate the efficacy of CBE in the early diagnosis of breast cancer by comparing women who received CBE and those who did not. An estimate based on all randomized clinical trials reported sensitivity of CBE for detection of breast cancer at 54% and specificity at 94%. Indirect evidence of its value comes from the Canadian National Breast Screening study, where women were divided into two groups one that received screening with physician performed CBE alone , and a second group that received both CBE and screening mammography . There were 39,405 women enrolled in this clinical trial. These investigators found that in the two groups, breast cancer mortality and nodal involvement was similar [6–9]. A cost effectiveness analysis of screening mammography and clinical breast examination in India reported that a single CBE at age 50 lead to a 2% decrease in breast cancer mortality rate and had an estimated cost effectiveness ratio of Int.$793 per life year gained, a 16.3% mortality rate reduction was possible with biennial CBE at a cost effectiveness ratio of Int.$1341, CBE performed annually from ages of 40–60 years was estimated to be as effective as Screening mammography for reducing breast cancer mortality at a fraction of the cost [10]. It is

therefore a very cost effective way of a first step in screening for breast cancer.

Following a screening clinical breast examination further assessment of screen positive cases is most optimally carried out by diagnostic sonography rather than by diagnostic mammography for many reasons. Mammography has limitations in the evaluation of the symptomatic woman, particularly in those with dense breasts. A false negative rate as high as 16.5% has been reported for mammography in patients with a palpable breast abnormality [11]. Mammographic abnormalities identified in a symptomatic woman usually require additional diagnostic ultrasound work up and those with a suspicious palpable solid mass seen on a mammogram and a sonogram, the latter is a better modality for tissue sampling (Fig. 1a–c). Overall, diagnostic Ultrasound is superior and a cost effective alternative to diagnostic mammography for the assessment of the symptomatic patient in a LRC. Ultrasound is safe, well tolerated by women, relatively inexpensive modality that can be readily used in the evaluation of a palpable lump in a woman where a positive physical finding was detected during the course of a screening CBE. Ultrasound has also the added potential of being used to stage breast cancer. Furthermore this modality can be used for diagnosis of ovarian and endometrial cancers making it a very cost effective investment in a well woman clinic that is envisaged in this discussion (Tables 1 and 2).

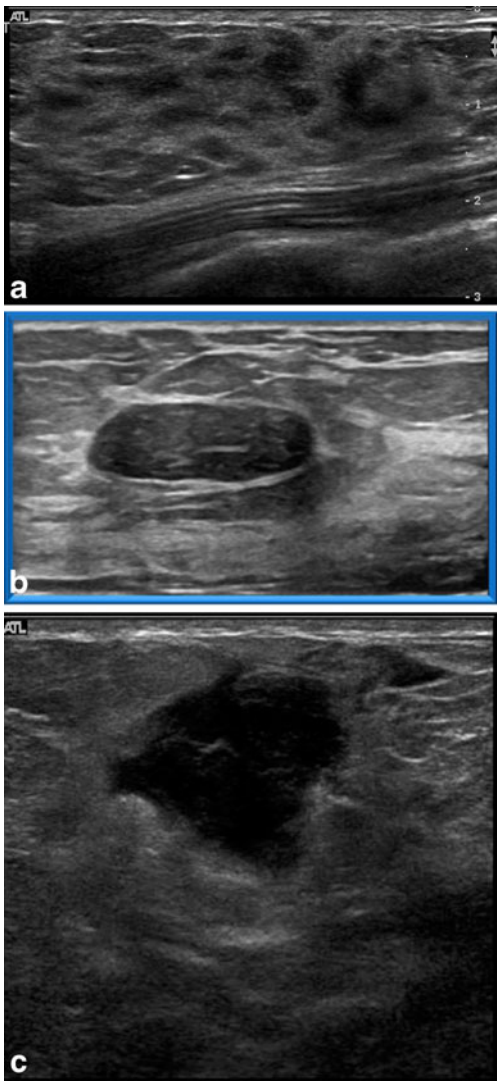

Fig. 1 Series of ultrasound images in women with positive findings on clinical breast examination. **a** 49 Year old female with a palpable abnormality at the 9'o clock position of the right breast, sonography reveals normal breast tissue. **b** 37 year old female with a palpable abnormality at the 2 0' clock position of the left breast , sonography reveals a solid mass with benign morphologic features, proven to be a Fibroadenoma at biopsy. **c** 43 year old with a palpable abnormality at the 3' o clock position of the left breast, sonography reveals a solid mass with malignant morphologic features, proven to be an invasive ductal cancer at biopsy

The recommendations for triple assessment of symptomatic women at a breast clinic traditionally consisted of physical assessment, diagnostic mammography and fine needle aspiration cytology [FNAB] [12]. As stated above, substituting diagnostic mammography with diagnostic ultrasound is particularly suitable in low resource settings. There is data to support the fact that findings of cytology have to be considered in combination with imaging morphology and characterization of solid masses to improve the PPV thereby allowing for optimal management of symptomatic women with suspicious findings at imaging and cytology. In a consecutive series of 2334 women PPV cytology findings of atypical, suspicious and malignant was 55, 95.9 and 99.4%. However when a atypical finding at cytology is seen in combination with a suspicious finding on imaging the PPV improved to 83.3% and PPV for suspicious lesions increased to 98.5–98.7% potentially allowing for management decisions of open biopsy and or planning surgery. Although Core needle biopsies have been reported to be more accurate than FNAB, in a LRC the latter is a more

Table 1 Advantages of breast ultrasound over mammography in the early detection of breast cancer

1. Cost effective modality: Initial capital expenditure and operational expenses are considerably lower than for mammography
2. Sonographic examination of the breast is better tolerated by women due to lack of breast compression unlike in mammography
3. Optimal modality for imaging guidance to improve accuracy of FNAB
4. Ultrasound can be used to stage breast cancers thus aiding in treatment planning and management
5. Ultrasound can be used for diagnosis of other cancers in Women such as ovarian and endometrial cancer
6. Telemedicine feasible
7. Portable equipment easy to transport and for use in mobile clinics

Table 2 Limitations of mammography as a screening modality in LRC'S

1. Expensive to set up, resource intensive modality
2. Poor sensitivity in women with dense breasts
3. Cannot be used to guide FNAB
4. Mammographic findings of breast masses and focal asymmetry need additional sonographic evaluation
5. 10% or higher recall rate is to be expected for women undergoing screening mammography requiring an additional clinic visit
6. Not suited for telemedicine reads
7. Minimally invasive biopsy procedures for mammographic findings requires stereotactic biopsy equipment which are expensive and time consuming

cost effective and feasible alternative. FNAB has the advantages of being a minimally invasive procedure well tolerated with minimal complications and patient discomfort with rapid results. FNAB'S are usually performed using a 21–25-gauge needle and a 10-mL syringe mounted on an aspiration device [13–17].

Cervical Cancer

In developing economies screening for cervical cancer is generally recommended to commence at the age of 30 years of age, the maximum impact of screening has been shown when women are screened in their thirties [18–20]. Commencing screening of women in their 30's allows for identifying cancers in the preclinical phase thereby maximizing the benefits of screening [20]. The optimal age group to be targeted for cervical cancer screening is 30–59 years. Data published recently from a cluster randomized trial of 137,461 women studied in India demonstrated that even a single round of testing with HPV [Human Papilloma Virus] DNA testing demonstrated significant reductions in the number of cases of advanced cancer and mortality from cervical cancer [18]. This clinical trial examined the efficacy of a single round of screening using Visual Inspection with acetic acid [VIA], cytology testing [PAP smear] and HPV DNA testing on the incidence of cervical cancer and associated death rates [18]. Based on this large clinical trial and other previous studies HPV DNA testing has been recommended for implementation as a method for cervical cancer screening in low resource countries [19]. The cost effectiveness of such a strategy has also been previously published. The most effective strategy — in terms of lives saved — was use of a single lifetime HPV test, followed by Cryotherapy for women who tested positive. Such an approach demonstrated that the cost per year of life saved was $14 and the reduction of cervical cancer incidence was 32% [20]. Although a single life time testing shows significant reduction in mortality, more frequent testing adds to the benefit of screening. Testing for HPV every three years has been shown to be very cost effective in saving lives [21].

HPV DNA testing can be undertaken in a two step processes where during the initial clinic visit the test is administered and test positive women are recalled for Colposcopy. At Colposcopy women with abnormal findings undergo biopsy followed by treatment by means of Cryotherapy or LEEP [Loop electrosurgical Excisional procedure] depending on the size of the abnormality. Alternatively, use of single visit strategy may be adopted which may be more beneficial in terms of cost savings and ensuring better patient compliance and minimizing the risk of loss to follow up. Single visit strategies is made possible by using HPV testing of self collected samples or using rapid processing of clinician collected sample. A simple, affordable, and accurate HPV test [CareHPV test, Qiagen] provides results within 3 h and was recently evaluated in China; in this study the accuracy was found to be similar to that of the Hybrid capture 11 test, with a higher sensitivity than VIA. In the near future this test kit should be available to be used in low resource countries. These two studies clearly demonstrate the appropriateness of using HPV testing as a primary screening method in low resource countries [22].

Diagnostic Assessment – Ovarian and Endometrial Cancer

Unlike Breast and Cervical cancer screening, benefits of screening for ovarian and endometrial cancers have not been shown, and is not appropriate in countries with limited resources. However there may be a potential to detect these cancers at an earlier stage by selectively examining post menopausal women with symptoms suggestive of ovarian and or endometrial cancer as part of a well woman examination. We recognize that the yield may still be low given the relatively low prevalence of these cancers; however one has to keep in mind that performing these additional evaluations suggested below, adds very little cost to the envisaged program and may have the potential to reduce the high mortality from being diagnosed at advanced stages of ovarian and endometrial cancers.

Ovarian Cancer

It has been shown in several retrospective studies that majority of women with ovarian cancer are symptomatic even though some of these may be non gynecologic in nature [23]. Goff and others have studied the value of using a symptom index to help in the early diagnosis of ovarian cancer. Women with ovarian cancer experienced symptoms

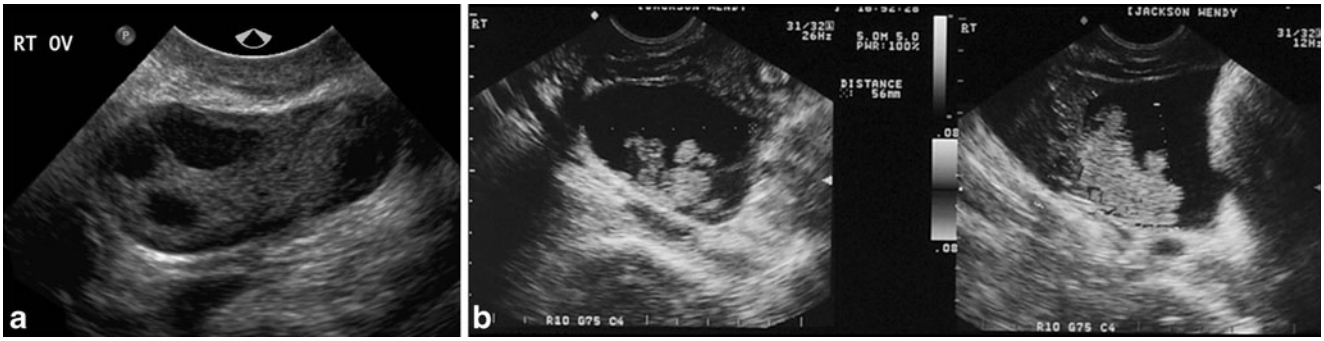

Fig. 2 Endovaginal ultrasound images of the ovaries in post menopausal women. **a** 50 year old woman with normal appearing ovary. **b** 56 year old symptomatic woman, sonographic images demonstrate morphologic features that are suggestive of a malignancy, surgery confirmed Ovarian cystadenocarcinoma

more frequently, of higher severity and of more recent onset than women with benign masses or in the control population. A combination of bloating increased abdominal size and urinary symptoms was found in 43% of those with cancer compared to 8% of those presenting to primary care clinics. The authors of this study concluded that women with more frequent, more severe and recent onset symptoms warrant further diagnostic investigation because they are more likely to be associated with both benign and malignant ovarian masses [23]. Goff and others in another study reported that symptoms that were associated with ovarian cancer were pelvic abdominal pain, urinary frequency/urgency, increased abdominal size and bloating and difficulty eating/feeling full. These symptoms are particularly significant if present for less than year and present >12 days per month. A symptom index was considered positive if any of the following symptoms occurred >12 times per month and present for <1 year: Pelvic/abdominal pain, increased abdominal size/bloating, difficulty eating/feeling full. In the confirmatory sample the index had a sensitivity of 56.7% sensitivity for early disease. Specificity was 90% for women >50 years [24]. Based on these studies we propose using the Goff symptom index to identify women who need additional diagnostic evaluation. Women in the age group of 50 to 69 with symptoms indicating increased risk for ovarian cancer are subjected to a pelvic examination and Endovaginal sonography. The value of sonography in the diagnosis of ovarian cancer has also been extensively studied. These studies evaluated the role of sonography in screening for ovarian cancer in combination with CA-125 testing. Data from The United Kingdom Collaborative Trial of Ovarian Cancer Screening (UKCTOCS), a randomized controlled trial designed to assess the effect of screening on mortality, reported that screening strategies for ovarian cancer are feasible. Data from the initial screen demonstrated that sensitivities for both multimodality screening and Ultrasound screening strategies are encouraging [24]. In another large study, TVS screening, when it was performed annually, was associated with a decrease in disease stage at detection and with case-specific ovarian cancer mortality [25].

Despite these encouraging results, sonographic ovarian cancer screening of asymptomatic post menopausal women has its limitations. High prevalence of benign adnexal abnormalities detected on ultrasound means increased surgical interventions which can lead to increased morbidity and additional cost to the cancer control program. We therefore recommend the selective use of Endovaginal ultrasound in symptomatic women rather than as a screening modality (Fig. 2a, b) .This is particularly relevant in a low

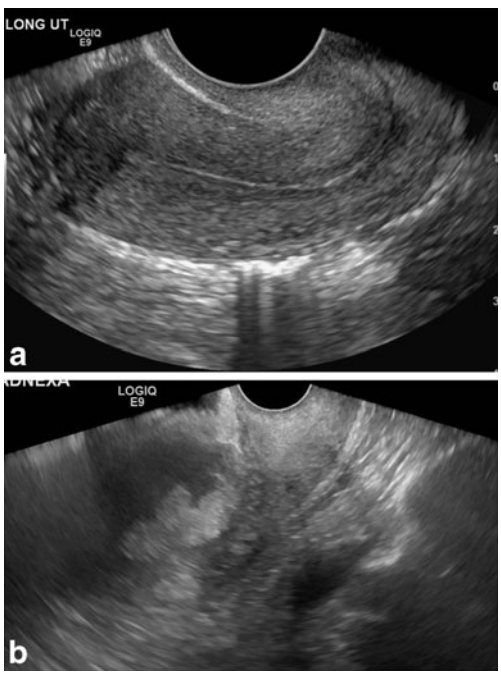

Fig. 3 Endovaginal ultrasound images of the uterus in women with post menopausal bleeding. **a** 56 year old woman, sonography demonstrates a normal appearing endometrium of 3 mm thickness. **b** 51 year old woman, sonography demonstrates an abnormally thickened endometrium, at biopsy endometrial cancer was confirmed

resource setting cost effectiveness and minimizing false positive cases is critical.

Endometrial Cancer

Ultrasound evaluation of the endometrial thickness is the accepted method to assess endometrial abnormalities in post menopausal women. About 10% of post menopausal women with abnormal bleeding are diagnosed with endometrial carcinoma. About 75–80% of women with endometrial carcinoma will present with abnormal post menopausal bleeding. In these patients performance of transvaginal ultrasound for assessment of the endometrium identifies an abnormality in most women with endometrial cancer. A large clinical study reported that 96% of endometrial carcinomas will be detected in symptomatic post menopausal women if additional procedures are performed only in those with an endometrial thickness of >4 mm [26–29]. A thin and regular endometrial lining is very reliable for the exclusion of endometrial carcinoma in a post menopausal patient with abnormal bleeding [30]. We recommend use transvaginal sonography on post menopausal women with abnormal bleeding to identify those women who will need endometrial biopsy (Fig. 3a, b). An abnormal endometrium detected on sonography would trigger endometrial sampling following sonographic assessment. Like with screening methods for Breast and cervical cancer, diagnostic assessment for early detection of Endometrial and ovarian cancer can be accomplished during a single visit.

Conclusion

There has been a dramatic increase in the incidence of breast and cervical cancer associated with a high mortality rate due to late presentation and lack of effective treatment options in low resource countries. There is an urgent need to implement a cost effective early detection healthcare intervention strategy combined with making available accessible and affordable treatment options. A cost effective approach of combining strategies to detect multiple cancers during a single clinic visit as a part of a well woman examination is recommended.

Such a strategy would involve screening for breast cancer using Clinical breast examination, diagnostic breast ultrasound of screen positive cases and fine needle biopsy of all solid masses that are deemed to be suspicious on sonographic evaluation. For Cervical cancer screening, HPV DNA testing followed by Colposcopic diagnosis and treatment of precancerous lesions using a screen and treat approach is recommended. Endovaginal sonographic assessment of the ovaries in symptomatic post menopausal women is recommended to aid in the early detection of ovarian cancer. Sonographic assessment of the endometrium in symptomatic post menopausal women followed by endometrial sampling in those with an abnormal endometrium would aim to detect endometrial cancer at an early stage. Screening for cervical and breast cancer and diagnostic evaluation for early detection of ovarian and endometrial cancers during a single clinic visit serves to optimize patient compliance. We recognize that unlike breast and cervical cancer, screening benefits have not been proven for endometrial and ovarian cancer. Proposed addition of testing of symptomatic post menopausal women is still worthwhile despite the relatively lower prevalence of these cancers considering that these tests add little to the overall cost of the program when performed in conjunction with a well woman examination.

We hope that the strategy outlined here can serve as a starting point in implementing an intervention aimed at controlling the increasing mortality from Breast and Gynecological cancers in low resource countries. The efficacy of such a combined screening and diagnostic approach will have to be prospectively studied in a large population of women so as to demonstrate its feasibility and cost effectiveness.

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