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Low Cost Cervical Cancer Screening Methods in Poor Resource Settings

Nandini Manoli[1]*, Sherin S Mathew[1], Devananda Devegowda[2], Ashoka varshini Panga[1] and Nandish Manoli[3]

[1]*Department of Pathology, JSSmedical college, JSS University, India*

[2]*Department of Biochemistry, JSSmedical college , JSS University, India*

[3]*Department of Obstetric and Gynecology, JSS Medical College, JSS University, India*

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***Corresponding author:** Nandini Manoli, Department of Pathology, JSSmedical college, JSS University, Mysore Karnataka, India, Email: nandinimanoli65@gmail.com

Abstract

Cervical cancer (CC) is the fourth most common cancer in women, and the seventh overall, with an estimated 528,000 new cases in 2012 Although the annual number of cases has increased, cancer of the cervix has declined in relative importance: it was the second most common cancer of women in 1975. In addition, the incidence and mortality of CC is variable within low- and middle-income countries (LMIC). In India, there are 20.2 per 100000 new cases of CC diagnosed and 11.1 per 100000 deaths annually, accounting for more than one fifth of the global CC deaths. In sub-Saharan Africa, 34.8 per 100000 women are diagnosed with CC annually and 22.5 per 100000 women die from this disease. Therefore, various cost effective methods are required besides conventional pap smear screening to detect cervical cancer in low resource settings. Various other methods are being introduced in low and middle income countries (LMIC) to improve detection at low cost. The tests discussed are manual liquid based cytology (MLBC), HPV testing, cell block with marker study, and visual inspection by ascetic acid (VIA). The various methods should be implemented by national screening programmes in LMIC countries.

Introduction

Cancer of the cervix uteri. Cervical cancer is the fourth most common cancer in women, and the seventh overall, with an estimated 528,000 new cases in 2012. Although the annual number of cases has increased, cancer of the cervix has declined in relative importance: it was the second most common cancer of women in 1975. As with liver cancer, a large majority (around 85%) of the global burden occurs in the less developed regions, where it accounts for almost 12% of all female cancers High-risk regions, with estimated ASRs over 30 per 100,000, include Eastern Africa (42.7), Mela-nesia (33.3), Southern (31.5) and Middle Africa (30.6). Rates are lowest in Australia/New Zealand (5.5) and Western Asia (4.4). Cervical cancer remains the most common cancer in women in Eastern and Middle Africa. There were an estimated 266,000 deaths from cervical cancer worldwide in 2012, accounting for 7.5% of all female cancer deaths Almost nine in 10 (87%) cervical cancer deaths occur in less developed regions .The average risk of dying from cervical cancer before age 75 is three times higher in the less than in more developed regions Mortality varies 18-fold between the different regions of the world, ranging from less than 2 per 100,000 in Western Asia, Western Europe and Australia/New Zealand to above 20 per 100,000 in Melanesia (20.6), Middle (22.2) and Eastern (27.6) Africa [1,2].

In addition, the incidence and mortality of CC is variable within low- and middle-income countries (LMIC). In India, there are 20.2 per 100000 new cases of CC diagnosed and 11.1 per 100000 deaths annually, accounting for more than one fifth of the global CC deaths. In sub-Saharan Africa, 34.8 per 100000 women are diagnosed with CC annually and 22.5 per 100000 women die from this disease. In contrast, in western Asian countries, only 3.8 per 100000 new cases are diagnosed per year and 1.6 per 100000 die from CC. Therefore, if the chances to survive CC are considered, a woman in Thailand will have an approximately 58% chance of survival, while in India she will only have a 42% chance. This survival is even more critical in Sub-Saharan Africa, where women only have a 21% chance to survive CC. Overall, the mortality to incidence ratio of CC is 52%, 2.

The requisites for cervical screening

It is imperative by looking at the incidence and mortality rates of cervical cancer CC in developing countries (LMIC),. an effective screening procedure is followed. An ideal screening test is one that is minimally invasive, easy to perform, acceptable to the subject, cost-effective and efficacious in diagnosing the disease process in its preinvasive or early invasive state [3].

About conventional pap smear (CPS)

From following its introduction by Papanicolau in 1927 exfoliative cervicovaginal cytology has been extensively investigated and used as a screening test for cervical cancer [4]. The standard technique for Pap smear collection is to sample the portio vaginalis of the cervix and the endo cervical canal using a cervical spatula and endocervical brush. The collected sample is smeared on a slide and then fixed immediately with cytology fixative. Most clinicians are concerned with reducing sampling errors by focusing on the technic of smear acquisition and eliminating drying artifacts through rapid fixation [3].

Its limitations in low resource settings

a) Incorrect and inadequate sampling in 5-10% of cases [5].

b) Only up to 20% of harvested cells are transferred on the slide leading to a reduction in the sensitivity of the test [5].

c) Mean sensitivity of only 55-60% [6].

d) Reported false negative rates varying from 25 to 50% [7].

e) Reported false positive rates varying from 15 to 20 % [8].

f) Inter observer variation in the interpretation of cytological abnormality making reporting subjective and poorly reproducible [9].

Methods to overcome these limitations

Other Screening tests for cervical carcinoma include

a. Fluid sampling techniques with automated thin layer preparation (liquid based cytology)

b. Automated cervical screening techniques

c. Neuro medical systems

d. HPV testing

e. Polar probe

f. Laser induced fluorescence

g. Visual inspection of cervix after applying Lugol's iodine (VILI) or acetic acid (VIA).

h. Speculoscopy

i. Cervicography [10]

Some of the other methods besides CPS are being implemented in various centers especially the higher diagnostic centers reaching out to urban population of women who are economically more independent, educated aware of health issues. Of these fluid cytology has made a beginning.

Liquid based cytology-types

Recently liquid based cytological technologies have been developed and have gained popularity because in preliminary studies the use of such techniques was associated with a reduction in the incidence of inadequate cervical smears [11,12]. Two such technique that have been extensively tested are Thin Prep (Cytyc Corp, Boxborough, MA) and Autocyte (Tri Path Imaging, Burlington, NC). These fluid sampling devices have been approved by the USFDA. Automated liquid based cytology (LBC) have made entry in developing countries like India. Semi automated methods within house methodology are being introduced in various centers.

Manual liquid based cytology

On the other hand, Manual Liquid Based Cytology (MLBC) is a technique that enables cells to be suspended in a monolayer and thus improves detection of precursor lesions and improvement of specimen adequacy. MLBC has been reported to improve the effectiveness of cervical cancer screening in a population by increasing the detection of histologically confirmed neoplastic and preneoplastic disease while simultaneously decreasing over diagnosis of benign processes. Also, in case of MLBC, the residual sample can be used for other tests like detection of HPV DNA, immunocyto chemistry on cell block thereby increasing the utility of MLBC.

HPV methods

Several studies support that HPV testing is feasible in low-resource settings and appears to be the best strategy for CC in this context A large-cluster randomised trial from rural India showed that a single round of HPV screening could reduce the incidence and mortality from CC of approximately 50%, whereas approaches based on VIA and cytology had little effect on these outcomes. Until recently, the greatest limitations of HPV testing were the need for expensive laboratory infrastructure and the 4-7 h time to process the test. The development of rapid molecular methods for detecting HPV DNA screening (eg care HPV, qiagen, genexpert-cepheid) or other POC type of tests is a milestone in CC screening in low-resource settings. This is because these new options may make screening more feasible in the future and reduce the infrastructural requirements of previous screening programmes [13,14]

Human papillomavirus (HPV) detection by PCR in our setup

Polymerase chain reaction (PCR) was used to detect the presence of HPV in the extracted DNA. PCR was done at two levels: First a pair of consensus primers such as MY09/11 and

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GP5+/GP6+ amplifying a 450bp and 150bp length of L1 region respectively was employed in the reaction and then the positive samples were subjected to type specific PCR to detect the most common high risk HPV subtypes like HPV-16 and HPV-18. A brief master mix was prepared containing 2U/µL of Taq ploymerase (Himedia), 2µM of dNTPs, 10x buffer with 25mm MgCl2 (working =1x buffer) and 0.2µM of each of forward and reverse primers. DNA concentration ranging from 50-80ng/reaction was added and the total reaction was made upto 30µL using PCR grade water. Amplification was performed in the Mastercycler gradient (Eppendorf) at 95°C for 5min, followed by 32 cycles of 94°C for 1min, 60°C for 45sec, 72°C for 1min and a final extension of 72°C for 2min. GAPDH gene was used as internal control to check the adequacy of PCR reaction and DNA from HeLa cell line and Siha cell line was used as positive control for HPV-18 and HPV-16 respectively, while water was used as negative control. The amplified PCR products were elecrophoresized on 2% agarose gel with a 100bp ladder (Himedia). Our current PCR set-up gives rapid, type-specific HPV detection with a turnaround time of less than 24hrs and cost-effectiveness compare to commercial avilable alternatives. Nevertheless, type-specific HPV testing is valuable to check the burden of HPV infections epidemiologically. Therefore, it can be considered as an indispensable tool to detect HPV types. It has to be developed further so as to be used as a primary screening method as national programme for HPV detection at low cost in a poor resource country like India.

Cell block and P-16 biomarker

Cell blocks can be prepared from all types of cytological specimens, except preparations with low cellularity such as cerebrospinal fluids. There are several techniques to produce cell blocks, such as cyto centrifugation, either with direct formalin fixation or fixation after addition of plasma-thromboplastin. Cell blocks perform in a highly reproducible way when stained with most antibodies, except for some used in the work- up of lymphoid lesions. One distinct advantage of cell blocks is that many slides can be prepared for extensive panels of immunostains. In addition, the quality control of cell block staining is identical to that of histopathology. The morphology of cell blocks is identical to that seen in histological specimens and therefore familiar to most pathologists. Cell blocks closely resemble Formalin-Fixed Paraffin-Embedded sections and can be stained using methods already established in general immunohistochemical laboratories, which probably explains their providing the best quality of imunocytochemical reactions.

The increased sensitivity of cell blocks in the diagnosis of malignant conditions of cervix may be due to better preservation of cytomorphologic features, better staining characteristics of the nucleus, nucleoli, and cytoplasm, clear recognition of nuclear and cytoplasmic features [15-17].

The oncogenic activity of E7 protein may also be tested indirectly by the host cyclin-dependent kinase inhibitor p16Ink4a. This kinase inhibitor decelerates the cell cycle by inactivating the cyclin-dependent kinases (CDK4/CDK6) involved in retinoblastoma protein phosphorylation. Over expression of p16INK4a in almost all cervical pre cancer (High-grade lesions) and invasive CC has been shown to be directly linked to the transforming activity of E7 oncoprotein, which is produced by HPV. Cellular accumulation of p16INK4a can be measured by cytochemistry on cell blocks. LBC, direct smears and cervical biopsies. other useful marker studied is ki67. As a combination with p16INK4a [18,19].

Visual inspection with acetic acid (VIA)

Visual inspection tests with 3%-5% acetic acid (VIA) and/or Lugol's iodine (VILI) appear to be a satisfactory alternative screening approach to cytology. These tests have been used since the 1990s, mainly in poor resource settings. They are simple, cost-effective with relative ease of use, and may be performed by different healthcare workers (physicians, nurse, midwives and technicians). Moreover, this approach does not require high technology or infrastructure and has been shown to reduce mortality in developing countries. The visible changes that occur in the cervix after application of acetic acid are immediate, and can be categorized as negative or positive for cervical neoplasia. These immediate results facilitate a same-day screen and management strategy. Therefore, this allows most of the eligible women to participate in the programme by minimizing repeat visits. Evidence shows that this single-visit approach leads to the most significant decrease in high-grade cervical intraepithelial neoplasia (CIN) and it is regarded safe, acceptable and fairly effective in India and Sub-Saharan Africa. Despite the limitations of the concept of "screen and treat", it helps to overcome barriers of time, distance and loss to follow-up. [20,21]. In our set up we work with an NGO who regularly check the rural women population of our district by VIA .all VIA cases where the squamocolumnar junction is inadequate are subject to pap smear screening.

The future of cervical cancer detection in low resource settings

The future of cervical cancer detection has many problems to be tackled even though attempts are being made to improve health care in low to middle income countries (LMIC). The factors which require attention are creating more awareness among rural population, national health programmes which include pap smear screening as mandatory in both urban and rural women with each having an health card as it happens in developed countries. Better training of health providers that includes primary health workers and doctors trained for this programmes.

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