Chapter 1

Introduction

Cervical cancer is mostly caused by sexually acquired infection with Human Papilloma Virus (HPV). It contributes to 12% of all cancers and is the second most common cause of death among women worldwide [1]. According to World Health Organisation (WHO) report [2], almost 80% of deaths due to cervical cancer occur in developing countries. Contribution of India to the global burden of cervical cancer is 26.5% [3]. As per the report of Government of India - WHO Collaboration Program 2004-2005 [4], one out of every four women in the world suffering from this disease is an Indian. However, this statistic looks quite different in developed countries where regular screening of cervical cancer is in practice. Considering the case of the UK, cervical cancer is reported as the 14th most common cancer. It is also mentioned that screening saves around 5000 lives each year in the UK [5]. It takes several years for the epithelial changes to progress from pre-cancerous stages to invasive cancer. Hence, it is amenable for screening and early detection. There is adequate time for screening, detection and management of the pre-cancerous stages. Section 1.1 provides details of various screening methods for cervical cancer and their suitability as a screening tool in resource poor settings. Section 1.2 describes the importance of Visual Inspection with Acetic acid (VIA) screening test in resource poor settings. Need for automation is explained in section 1.3. Different image analysis approaches are explained in section 1.4.
1.1 Cervical cancer screening methods

Screening methods namely visual examination, cytology, HPV-DNA and screening based on physical properties are used for early detection of cervical cancer. Section 1.1.1 describes the visual screening methods. Section 1.1.2 describes cytology based screening methods. A screening method based on HPV-DNA is described in section 1.1.3. Screening methods based on physical properties are explained in section 1.1.4.

1.1.1 Visual screening

Visual screening approach involves naked eye examination of cervix to observe changes in its appearance. Solution of either dilute acetic acid or Lugol’s iodine is applied on the cervix which enhances the appearance of abnormal lesions. These lesions are analysed by a trained personnel. Through visual examination, normal landmarks of the cervix namely os, Columnar Epithelium (CE), Squamous Epithelium (SE), Squamocolumnar Junction (SCJ) and Transformation Zone (TZ) are observed. A schematic showing all these regions is shown in Figure 1.1.

![Figure 1.1: Schematic of cervix [6].](image)

Os is the opening at the centre of the cervix which leads to uterus. CE is the tissue surrounding the os which has uneven texture and is bright red...
in color. It is surrounded by squamous epithelium, which is homogenous and pink in color. Columnar epithelium and squamous epithelium meet at squamocolumnar junction, which appears as a contour. Region where columnar epithelium has matured into squamous epithelium is called transformation zone. Most of the cellular abnormalities associated with the cervix arise in the transformation zone. So, transformation zone is usually examined for the presence of abnormality. Visual screening methods enable on-the-spot evaluation of the cervix. Various visual examination methods are explained below.

**Unaided visual inspection**

Cervix is visually examined during a speculum examination to detect the abnormalities such as surface ulcers, raised lesions, erosions, polyps, growth and friable lesions that bleed on touch. Adequate visualization requires good lighting facility, an examination table, swabs and speculum. According to the studies reported in [7,8], performance of this method is poor in detection of cervical cancer.

**Visual Inspection with Acetic acid**

VIA test involves visual examination of cervix one minute after application of 5% acetic acid. Both pre-cancerous and cancerous lesions turn white on reacting with acetic acid. These white regions are called acetowhite (AW) regions. Acetowhite regions appearing due to cervical cancer persist even after one minute. Acetowhite regions disappearing within one minute are not due to cervical cancer. Figure 1.2a shows cervix image before application of acetic acid.
Figure 1.2: Typical cervix images a. Before application of acetic acid, b. After application of acetic acid.

Figure 1.2b shows the acetowhite region representing the pre-cancerous region which has turned white. VIA performed using low magnification devices is called as VIA with magnification (VIAM) or gynoscopy.

**Visual Inspection with Lugol’s Iodine (VILI)**

Cervix is visually examined after application of Lugol’s iodine. Figure 1.3a shows pre-cancerous lesions appearing as white regions during VIA examination. Figure 1.3b shows pre-cancerous lesions as distinct, thick, mustard or saffron yellow areas during VILI examination.

Figure 1.3: Cervix images a. VIA positive, b. VILI positive.

**Cervicography**

Cervicography [9] comprises of obtaining and assessing an image of cervix called ‘Cervicogram’. Since images acquired can be stored and sent over
the internet, it enables remote diagnosis. Cervicograms are interpreted by experts who have undergone specialized training. Results of the test are usually available after obtaining the expert opinion.

**Colposcopy**

Cervix is observed using a colposcope [10], after the application of different solutions such as normal saline, 3-5% dilute acetic acid and Lugol’s iodine with variable magnifications of 10X, 20X, 30X and 40X. A closer, magnified and illuminated view of the cervix during VIA examination is achieved with a colposcope. Abnormal regions appear white after the application of acetic acid. Abnormal vascular patterns such as mosaics and punctations which are difficult to be observed through naked eye within the AW region can also be viewed under a colposcope. Punctations are characterized by a series of reddish dots scattered throughout the AW lesions. Mosaics appear as irregular polygonal structures in the region of AW. Typical colposcopic views of cervix containing mosaics and punctations are shown in Figure 1.4.

![Figure 1.4: Colposcopic views of cervix showing a. punctations, b. mosaics.](image)

**Gynocular**

Cervix is observed with a gynocular, a pocket-sized battery driven colposcope with 5X to 12X magnification, after the application of acetic acid. Gynocular offers an accurate, cost effective and practical approach to combat cervical cancer in resource poor settings [11].
1.1.2 Cytology screening

In the case of cytology screening, cell samples are collected from the cervix, processed and subsequently analysed. A few cytology based screening methods are explained below.

**Papanicolaou smear**

Papanicolaou smear test also called as Pap test has been considered as the gold standard for cervical cancer screening. Cell samples are collected by scraping the cervix surface, spread onto a slide, fixed with preservatives and stained. These slides are evaluated by a trained personnel. Pap smear test has effectively reduced the incidence and mortality of cervical cancer in countries having well established screening programs [12]. It has moderate sensitivity of 52% [13,14]. Results of the test are usually available after 1 to 2 weeks.

**Liquid Based Cytology (LBC)**

Cell samples are collected from the cervix and transferred into a liquid solution for preserving cells. Subsequently, the liquid is treated in laboratory to remove blood, mucus, inflammatory cells and to produce a thin layer of cells on a glass slide. Cells are stained and examined under a microscope. LBC is an expensive test and requires laboratory infrastructure. It has a sensitivity of 85.7% and specificity of 87.8% [15]. Test results are usually available after 1 to 2 weeks.

**Automated Cytological Screening**

AutoPap and AutoCyte Screen tests are the commonly used automated cytological screening tests [16]. In these tests, pap smears are analysed using computers. AutoPap uses an algorithm for studying and scoring the sample slides. The algorithm incorporates features such as shape and optical density of cells. In the case of AutoCyte Screen, a human reviewer determines whether a given slide requires manual review. Slides are reviewed manually only if there is a mismatch in opinion of the reviewer and the algorithm.
1.1.3 HPV-DNA test

Infections caused by some of the high-risk human papilloma viruses are commonly associated with cervical cancer. The HPV-DNA test can detect infections before cell abnormalities become evident. This test detects different high-risk HPV types. Its sensitivity varies in the range 45-80% and specificity varies in the range 91-94% [17, 18]. This test requires sophisticated infrastructure. Test results are usually available after 6 to 7 hours.

1.1.4 Screening based on physical properties

Screening devices under this category evaluate the physical properties of human tissue. Human tissues can be examined using radiation, magnetic and electric fields, sound waves and light. Normal tissues have a different structure compared to HPV infected tissue and hence there is a difference in optical and electrical properties between the tissues. Screening devices based on physical properties enable on-the-spot evaluation of the cervix. A few such screening devices are discussed below.

TruScreen

TruScreen is an optoelectronic device. Currents of different frequencies are injected into the tissue and the voltage response is measured to compute the impedance. Impedance is different for normal tissues and abnormal tissues. A study on TruScreen assessment for cervical cancer screening reported in [19] achieved false positive and false negative rates of 10%.

Spectroscopy

Spectroscopy is a technique based on an optical device. It has a probe that emits light onto the cervix. Abnormal tissues have different optical properties than normal tissues. These differences are used to classify them as normal or abnormal [20].

Hyperspectral Diagnostic Imaging (HSDI)

Ultraviolet and white light are used to scan cervix surface. The pattern of
light reflected by cervix tissues is analysed by a spectrometer to determine the features which discriminate among the various stages of cancer. A study of cervix imaging using HSDI is reported in [21]. Summary of different methods for cervical cancer screening is provided in Table 1.1.

Table 1.1: Cervical cancer screening methods

<table>
<thead>
<tr>
<th>Visual</th>
<th>Cytology</th>
<th>HPV-DNA</th>
<th>Screening based on physical properties</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Unaided visual inspection</td>
<td>• Pap smear</td>
<td>• TruScreen</td>
<td></td>
</tr>
<tr>
<td>• VIA</td>
<td>• LBC</td>
<td>• Spectroscopy</td>
<td></td>
</tr>
<tr>
<td>• VILI</td>
<td>• Automated cytology screening</td>
<td>• HSDI</td>
<td></td>
</tr>
<tr>
<td>• Cervicography</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Gynocular</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Colposcopy</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

A comparison of cytology, HPV-DNA and visual screening methods is provided in Table 1.2.

1.2 Importance of VIA in resource poor settings

Cervical cancer can be prevented through primary and secondary approaches. Primary prevention includes safe sexual practices and HPV vaccination [24]. Cervical cancer is noted to be higher among women with multiple sexual partners [5]. Hence, creating awareness in adolescence regarding the disease and its risk factors [25,26] can play a major role in prevention. HPV vaccine is a major addition to the preventive programs and recommended for girls of age 9 to 13. This vaccine protects against 70% of cervical cancers [27]. Since
Table 1.2: Summary of cervical cancer screening methods

<table>
<thead>
<tr>
<th></th>
<th>VIA</th>
<th>Cervicography</th>
<th>Colposcopy</th>
<th>Pap test</th>
<th>LBC</th>
<th>HPV-DNA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cost</td>
<td>Low</td>
<td>Medium</td>
<td>High</td>
<td>High</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>Requires power supply?</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Special equipments needed?</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Sample size</td>
<td>58000</td>
<td>12000</td>
<td>12000</td>
<td>58000</td>
<td>10049</td>
<td>18085</td>
</tr>
<tr>
<td>Laboratory facility needed?</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Availability of test results</td>
<td>On the spot</td>
<td>After expert opinion</td>
<td>On the spot</td>
<td>After 1-2 weeks</td>
<td>After 1-2 weeks</td>
<td>After 6-7 hours</td>
</tr>
<tr>
<td>Level of expertise needed to perform the test</td>
<td>Low</td>
<td>Low</td>
<td>High</td>
<td>High</td>
<td>High</td>
<td>High</td>
</tr>
</tbody>
</table>

* Not Available

Vaccination does not protect against all types of HPV, secondary prevention through screening is still important. In developed countries such as the UK, vaccination is an established practice. It has been demonstrated that regular screening would reduce mortality due to cervical cancer [27]. Cytology tests are used for screening. There is a well established mechanism for call/recall.

People in developing countries are unable to afford vaccination due to its high cost. Regular screening is not feasible due to the cost involved in conducting screening programs and due to lack of resources. Health services are not easily accessible for people due to less number of healthcare personnel in proportion to population. In developing countries, health facilities provided by hospitals lack resources and are overburdened [28]. Uniform implementation of screening programs in developing countries faces challenges such as
lack of skilled manpower, inadequate infrastructure, poor awareness about the disease, poverty, shyness and limited accessibility to the healthcare delivery system [29]. Consequently, more than three-fourth of the cases are detected at an advanced stage [30].

Pap smear is the most commonly used method for cervical cancer screening. But it requires efficient networking between smear collection and cytology laboratories [13]. Also, it suffers from low sensitivity of 52% [14]. HPV-DNA testing is more sensitive compared to cytology. However, all these methods are expensive and require well established laboratory infrastructure. Also, results are not immediately available. In developing countries, cytology based screening programs are not feasible due to lack of sophisticated laboratory, trained personnel and financial resources [31,32]. This problem is addressed by cost effective non-cytological cervical cancer screening methods [33]. For resource poor settings, there is a need for a screening method which is simple, sensitive, cost effective, convenient and provides instant results to facilitate referral to tertiary hospitals. VIA is found to be the promising test in resource poor settings as observed from Table 1.2. It is recommended as the low cost alternative to Pap test in developing countries [34,35]. It is beneficial due to its attractive feature of screen-and-treat which can be performed in a single visit. Hence, VIA is the most suitable screening test in resource poor settings.

1.3 Need for automation

VIA is a simple and cost effective test which is the most suited for resource poor settings. Diverse health workers such as physicians, nurses, midwives and local health workers can perform VIA. Considerable training is required to discriminate between cancerous lesions and benign lesions. Accuracy of this test depends on the skill level of the person who performs the test [36]. Blumenthal et al. [37] reported that health workers need to be trained well for successful implementation of VIA. Digital images of cervix during VIA procedure can be acquired as in cervicography and sent over the internet
to a remote expert for a second opinion. But this is not a practical solution in screening camps, where many people need to be examined. Further, evaluation of VIA images suffers from interobserver variability [38]. Limited number of experts and a large number of patients result in a long queue for the screening process. A method for detection and instant decision making to facilitate referral to hospitals for further investigations is lacking. Hence, it is desirable to develop a decision support system which when combined with existing screening methods, makes the screening effective and objective.

1.4 Approaches for cervix image analysis

Images can be classified into VIA positive and VIA negative categories using traditional image processing approach and deep learning approach. Block diagram of traditional image processing approach for image analysis is shown in Figure 1.5.

![Figure 1.5: Traditional image processing approach.](image)

Block diagram of deep learning approach for classification is shown in Figure 1.6.

![Figure 1.6: Deep learning approach.](image)

We use pre-processing and segmentation of cervix region for both approaches to improve the performance. Traditional image processing approach involves a sequence of steps such as feature extraction, feature selection and
classification. The feature extraction step aims to extract the distinguishing characteristics of images of different classes. Feature selection step identifies the most relevant features for classification. Based on the selected features, a classifier detects the VIA positive cases. In deep learning approach, Convolutional Neural Networks (CNNs) are used for image analysis. CNNs can be employed for image classification in two ways. The first approach is to train the CNN from scratch which is called full training. Depending on the number of layers, CNNs can be classified as deep layer CNN and shallow layer CNN. Full training of CNNs with deep architecture requires large amount of annotated data which is usually not available in the medical domain. Hence, the most popular deep CNNs [39], [40], [41] are trained with ImageNet data [42, 43]. Deep CNNs are capable of obtaining full representation of the training data. Image analysis in medical domain usually uses shallow layer CNNs for full training. However, images in the medical domain have high feature variability. To exploit the advantages of deep architecture on limited dataset, another approach known as transfer learning is utilized. This approach facilitates the use of the knowledge acquired by pre-trained CNNs which are trained using large amount of ImageNet data. Transfer learning can be performed either by extracting the features from different layers of CNN or by fine-tuning the layers.

1.5 Objectives and scope

The goal of this research is to develop a decision support system for a care giver in rural setup for cervical cancer screening. The objectives of this work are given below.

1. To implement an efficient algorithm for segmentation of cervix region
2. To identify suitable features for classification of acetic acid test based cervix images
3. To use machine learning approaches to classify the acetic acid test based cervix images
1.6 Organization of the thesis

This thesis includes a total of seven chapters. This chapter provides the introduction of the thesis.

Chapter 2 provides a review of state-of-the-art methods used for analysis of cervix images. We provide a comprehensive summary of traditional machine learning approaches for cervix image analysis. We have also considered bodies of literature reporting application of deep learning for medical image analysis.

Chapter 3 describes data collection. It also describes the study on interobserver variability among gynecologists in the case of manual cervix image analysis for detection of VIA positive cases.

Chapter 4 describes image pre-processing method used for detection of specular reflection and cervix region segmentation for improving the efficiency of image analysis algorithm.

Chapter 5 describes traditional image processing approach for the analysis of cervix images. This chapter describes the various features extracted and classification into VIA positive and negative classes.

Chapter 6 provides introduction to deep learning and various deep learning approaches available for image analysis. Also, a novel hybrid transfer learning technique, in which a CNN is built and trained from scratch, with initial weights of filters in the convolutional layers adapted from pre-trained VGG-16 net and VGG-19 is described.

Chapter 7 concludes the thesis, highlights the contributions of this research and lists the visible research outputs.