CHAPTER 1

INTRODUCTION
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Cancer of the cervix uteri is the second most common cancer among women worldwide with an estimated 493,000 new cases and 274,000 deaths in 2002. Some 83% of the cases occur in developing countries, where cervical cancer accounts for 15% of female cancers, while developed countries it accounts for only 3.6% of the new cancers. The incidence is generally higher in the developing countries of South East Asia, age standardized incidence rates 18.3 per 100,000 (Parklin et al., 2005).

On a worldwide basis cervical cancer is the second most prevalent cancer of women. Over 99% of cervical cancers are positive for high-risk HPV (Urogenital Human Papillomavirus) (Alvarez-Sales et al., 2003).

The most important risk factor for cervical cancer is human papilloma virus (HPV) infection; HPV DNA can be found in 95-100% of cervical cancers. HPV has multiple types, both oncogenic and non-oncogenic, and many cervical cancers reveal multiple HPV types. (Bosch et al., 2003). Recent vaccines have been developed for types 16 and 18, which account for approximately 70% of HPV cases associated with cervical cancer (Schiffman et al., 2005; Munoz et al., 2004).

Poverty, poor socio-economic status, widespread ignorance, poor personal hygiene, early marriage and childbirth and high parity status continue to prevail in our country, are the some factors which make carcinoma of cervix continues to lead the list of cancers afflicting the female genital tract in India.

An excellent overview on the epidemiology of cervical cancer is reported by Brinton (Brinton et al., 1992) and Franco (Franco et al., 2003).
Numerous studies of the epidemiology of cervical cancer have shown strong associations with religious, martial and sexual patterns. Although it is well established that women with multiple partners and early ages at first intercourse are at high risk, less is known about how these factors interact or how risk is affected by specific sexual characteristics. Recent studies indicate that number of steady partners and frequent intercourse at early ages may further enhance risk.

In India among all types of genital cancer carcinoma of cervix accounts for 80%, ovary 10% and uterine body 4-5%. In India 16% of the World’s cases occur only 5% are reported in early stages. Survival rates for women which carcinoma cervix are 90% for local, 51% for regional, 12% for distant metastasis even in the best centres.

Early detection and prevention of cancer is the slogan of the day. World Health Organization, ICMR and Govt. of India has given more emphasis in this aspect. The carcinoma of the cervix uteri does not arise de-novo, but follows a spectrum of epithelial cell abnormalities of squamous cells.

Atpical squamous cells. Of undetermined significance (ASC-US):
Can not exclude HSIL (ASC-US).

Low grade squamous intraepithelial lesion (LSIL). Encompassing:
HPV/mild dysplasia/CIN-1.

High grade squamous intraepithelial lesion/HSIL. Encompassing:
Moderate & severe dysplasia, CIS/ CIN-2 and CIN-3.

With features suspicious for invasion (if invasion is suspected).

Squamous cell carcinoma (BETHESDA TERMINOLOGY 2001).

Though cervical cancer is the second leading cancer in the female in worldwide basis but interesting fact is that stomach cancer is the leading female cancer in our neighbouring state Mizoram (ICMR 2009,
Silchar Medical College). Though traditionally accepted high risk epidemiologically factors which were included earlier like low socio-economic status, early age of coitus, multiple childbirth, smoking, plays a significant role in development of cervical carcinoma but it is now almost hundred percent proved that human papilloma virus (HPV) is the main aetiological culprit in the formation of cervical carcinoma. HPV types 16, 18, 31, 33 and 45 are those most associated with invasive cervical cancers; these strains take longer time to clear than other nonpathogenic strains (Eifel et al., 2005; IARC Working Group on the Evaluation of carcinogenic Risks to Humans, (Giuliano et al., 2002).
Fig 1.1: Electron Microscopic picture of HPV virus
Table 1.1: The clinical association of HPV with Cervical Cancer is presented below:

<table>
<thead>
<tr>
<th>Cervical Cancer:</th>
<th>HPVs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strong association</td>
<td>HPV 16, 18, 31, 45</td>
</tr>
<tr>
<td>Moderate association</td>
<td>HPV 33, 35, 39, 51, 52, 56, 58, 59, 68</td>
</tr>
<tr>
<td>Weak association</td>
<td>HPV 6, 11, 26, 42, 43, 44, 53, 54, 55, 62</td>
</tr>
</tbody>
</table>
Fig. 1.2: Gross specimen of carcinoma cervix

Fig. 1.3: Microscopic picture of squamous cell carcinoma of cervix
It has been found that two types of genes in HPV, so called E6 and E7 genes produce proteins that can attach themselves to Rb and p53 and block their effect on regulating cell division leading to uncontrolled proliferation of infected cell leading to cancer (Coman et al., 1999; Chou et al., 1996).

**Fig 1.4**: Schematic presentation of pathogenesis of cancer cervix

**Fig 1.5**: Integration of HPV DNA to host cell of cervix in the genesis of carcinoma cervix.
The importance of sex steroids hormones like estrogen and androgen is well studied as a co-factor in the development of the disease (Brabin, 2002). Different enzymes like: LDH, MDH, ascorbic acid, (Vit C), has been studied as tumour metabolism and expression.

WHO classification of cervical carcinoma (Histological types) are presented below: (http://pathologyoutlines.com/cervix.html#WHO)

1. Squamous cell carcinoma:
   - Keratinizing
   - Non keratinizing
     (a) Large cell
     (b) Small cell

2. Adeno carcinoma:
   - Endocervical cell carcinoma
   - Endometroid carcinoma
   - Clear cell carcinoma

3. Mixed Carcinoma:
   - Adenosquamous cell carcinoma
   - Mucoepidermoid carcinoma
   - Glassy cell carcinoma
   - Adenoid cystic carcinoma

4. Undifferentiated carcinoma:

5. Carcinoid tumour:

6. Malignant melanoma:

7. Malignant non epithelium carcinoma:
   - Sarcoma
   - Lymphoma
Most of our cases were squamous cell carcinoma (90%).

In our present study, the main contributing factors or association is with HPV 16 and 18. HPV infection and associated co-factor like smoking, multiple childbirth, low socio-economic factors.

Prevention of cervical cancer can be accomplished by implementing well organized population based screening program. The screening programme is necessary and to trace cervical precursor lesions by cytologically analyzing cervical smears.

Table 1.2: A compact classification system:

Description, various classification systems and translation of codes for normal squamous epithelial cells and (pre) neoplastic changes are described as follows:

<table>
<thead>
<tr>
<th>Description</th>
<th>Papanicolaou</th>
<th>Bethesda</th>
<th>Kopac P-code</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>Pap I</td>
<td>Normal</td>
<td>P 1</td>
</tr>
<tr>
<td>Borderline changes</td>
<td>Pap II</td>
<td>ASCUS</td>
<td>P 2-3</td>
</tr>
<tr>
<td>Mild dysplasia</td>
<td>Pap III A</td>
<td>(L) SIL</td>
<td>P 4</td>
</tr>
<tr>
<td>Moderate dysplasia</td>
<td>Pap III A</td>
<td>(H) SIL</td>
<td>P 5</td>
</tr>
<tr>
<td>Severe dysplasia</td>
<td>Pap III B</td>
<td>(H) SIL</td>
<td>P 6</td>
</tr>
<tr>
<td>Carcinoma in -situ</td>
<td>Pap IV</td>
<td>(H) SIL</td>
<td>P 7</td>
</tr>
<tr>
<td>Micro invasive carcinoma</td>
<td>Pap V</td>
<td>Carcinoma</td>
<td>P 8</td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>Pap V</td>
<td>Carcinoma</td>
<td>P 9</td>
</tr>
</tbody>
</table>
Table 1.3: Another system of classification of epithelial changes is as follows:

<table>
<thead>
<tr>
<th>Classification</th>
<th>Synonyms or similar entities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low grade squamous intraepithelial lesion (LSIL)</td>
<td>Candyloma acuminate</td>
</tr>
<tr>
<td></td>
<td>Flat Candyloma (CIN-1)</td>
</tr>
<tr>
<td></td>
<td>Immature candyloma (Papillary immature metaplasia)</td>
</tr>
<tr>
<td>High grade squamous intraepithelial lesion (HSIL)</td>
<td>Flat metaplasia with mild atypia</td>
</tr>
<tr>
<td></td>
<td>CIN 2</td>
</tr>
<tr>
<td></td>
<td>CIN 3</td>
</tr>
<tr>
<td></td>
<td>Keratinising dysplasia</td>
</tr>
<tr>
<td></td>
<td>Moderate dysplasia</td>
</tr>
<tr>
<td></td>
<td>Severe dysplasia</td>
</tr>
<tr>
<td></td>
<td>Carcinoma in-situ</td>
</tr>
<tr>
<td></td>
<td>HSIL with metaplastic differentiation</td>
</tr>
<tr>
<td>Other forms of squamous intraepithelial lesion</td>
<td>Eosinophilic dysplasia</td>
</tr>
<tr>
<td></td>
<td>(CIN 1-2)</td>
</tr>
<tr>
<td></td>
<td>CIN in microglandular change (CIN 1-2)</td>
</tr>
<tr>
<td></td>
<td>SMILE (Stratified ACIS/CIN3)</td>
</tr>
</tbody>
</table>

- ACIS : Adenocarcinoma-in-situ
- CIN : Cervical intraepithelial neoplasia
- HSIL : High grade squamous intraepithelial lesion
- SMILE : Stratified mucin producing intraepithelial lesion
Cancer, in general, is a dreadful disease which usually terrorizes the mind of common people. It accounts for 9% of deaths worldwide. Out of the total 50 million deaths annually, more than 5 million are attributed to cancer. According to WHO estimate, by the year 2002, the numbers of deaths were 8 million annually. In the developed countries, cancer is the leading cause of death next only to cardiovascular diseases. But the scene in developing countries are different, as here it ranks fourth as a cause of death. (WHO 1983, 1984).

Picture of the cancer is changing in India since the control of communicable diseases. Incidence of cancer is rising here. Jussawala (1973) observed that cancer is one of the 10th leading causes of death in India and is advancing in rank year by year. The incidence of cancer is about 70 per, 1,00,000 population in India. (Times of India, New Delhi 1st April & 25th April) as against 289 per, 1,00,000 population in developed countries (WHO, 1981).

![Incidence (Women of all ages) – Cervical Cancer vs other Cancers](image)

Fig. 1.6 : Cervical cancer vs. other cancers :

Cervical cancer globally is the fifth common cancer and an estimated 4,600,000 new cases occur each year (three quarters occurring in developing countries). In fact carcinoma of cervix is the second most common site of malignancy in the female body, next to breast. It continues 31.20% of all malignant tumours in women and 86.80% of all malignant diseases of the female genital tract. In fact developing nations account for 86% of cases with 14% occurring in developed countries. (Miller, 1986).

Screening will probably decrease the incidence of cervical cancer by 60% or more. There is a direct relationship between the number of women screened by Pap smears and the decreased incidence of cervical cancer. In Iceland, where more than 90% of women were screened in that time, the incidence decreased by 80%. In Norway, where only 5% of the women were screened, the incidence decreased only by 10% Bosch, et al., (2003). In South Africa, it is estimated that Pap smear were taken in 18.8% of white women and only 2.6% of black women in 2002.

Real world obstacles to successful cervical cancer prevention in developing countries involve people more than technologies. This can be manages by focusing on system quality management. The root causes of poor quality must be examined. Suba et al., (2006) found causes such as obsolete supplies, poorly maintained microscopes, insufficient training and suboptimal working conditions. Successful follow-up for screen-positive women has been achieved through the allocation of budgets for dedicated personnel to recontact women with positive test results.

Human Papillomavirus (HPV) infection is known to cause cervical cancer. Human Papillomavirus (HPV) infection is also regarded as the
common sexually transmitted infection worldwide, with an estimated life time risk of 79% for women to contract at least one infection between the ages of 20 and 79 years. Although some men have anal or genital lesions associated with HPV16 and 18, most men serve as vectors of oncogenic HPV. Male partners may be important contributors to their female partners’ risk of cervical cancer.

**Age-Specific Rates of HPV Infection & Cancer**

![Image of graph showing age-specific rates of HPV infection and cancer](image)

**Fig. 1.7: Age-specific rates of HPV infection and cancer**

*Bosch et al., 2002*
Squamous cell cervical cancer constitutes approximately 80% of cervical cancer. Adenocarcinoma is the most common histological type and shows a rising incidence, even in developed countries.

There is geographical variation in type-specific HPV prevalence. HPV 16 is the most common type associated with adenocarcinomas, except in Southeast-Asia, where the prevalence of HPV 18 exceeds that of HPV 16. HPV 16, 18, 35, 45 and 59 are present in 96% of adenocarcinomas of cervix (Castellsague et al., 2006).

A pooled analysis by Clifford et al., (2005) showed that prevalence of high risk HPV types is around 18% in sub-Saharan Africa, with HPV 16 and HPV 35 present in 8% of women. HPV 31 and HPV 33 were present in 7% of women and HPV 18 was present in 4% of women. Sub-Saharan Africa had the highest prevalence of all HPV types and Europe the lowest. The variation in prevalence of HPV 16 across regions was smaller for HPV 16 than for the other high-risk types. The next common high-risk types were HPV 33 and HPV 56 in Asia, HPV 58 in South America and HPV 31 in Europe.

This study can also act as a pilot study for future studies to test the effectiveness of using high risk HPV types as a primary screening method, instead of Pap smears, to identify patients who are at a higher risk to develop cervical cancer and who need further investigations such as colposcopically directed biopsies.

The incidence of HPV virus infections vary according to age, sexual activity, the number of times tested and the laboratory technique used.

Acquisition of high risk HPV genotype (HR HPV) is age dependant, with the highest frequency being amongst the youngest women.
Persistent of HPV Infections:

An incident of HPV infection may regress spontaneously. A persistent HR HPV of infection is one of the causative factors of cervical intraepithelial neoplasia. Brabin, L. (2002).

Franco et al., (1998) calculated a monthly incidence rate of 1.3% for new infection resulting in 38% cumulative positivity after 18 month.

Syrrjänen et al., (2004) found a monthly rate of acquisition of incident HR HPV infections of 1.0% in women who were HR HPV DNA negative and Pap smear negative at baseline. In these women, time of acquisition of a HR HPV infection preceded an abnormal Pap smear by approximately 3 months (16.6 and 19.4 months, respectively).

The time to acquisition of an incident abnormal Pap smear was significantly longer in women who were HR HPV DNA negative at baseline (19.4 months v 9.2 months in women who were HR HPV DNA positive at baseline). The rate of acquisition of an abnormal Pap smear was significantly higher in the women who were HR HPV DNA positive at baseline (3.1% v 1.5% in women who were HR HPV DNA negative at baseline).

Schlecht et al., (2003) found an incidence rate of SIL by Pap smear of 8.68 per 1000 women-months among women with HPV type 16 or 18 infections that persisted over 2 visits.

Sherman et al., (2002) reported that the prevalence of HR HPV infections declines with age: only 31.2% among women with ASCUS who were 29 years or older, compared with 65% in those ages 28 and younger.
The majorities of HPV infections are transient and are not clinically evident with 70-90% of infected women spontaneously clearing their infections within 12-30 months.

Women with persistent HR HPV infection have the greatest risk of developing cervical precancer and cancer. The longer an HPV infection persists, the less likely a patient is to clear her infection. In a population based study, women with type-specific persistence for more than 2 years were 800 times more likely to develop a high-grade cervical lesion. The progression from HPV infection to HPV persistence to the development of high-grade CIN and ultimately invasive cervical cancer appears to take, on average up to 15 years, although cases of rapid-onset cancers do occur.

In light of the high prevalence of HPV in young women, screening strategies have focused on women 30 years of age or older in an attempt to minimize the identification of transient HPV infection. Schlecht et al., (2003).

Infections with Multiple HPV Genotypes:

Levi et al., (2002) found that of 208 HIV positive women, 79% had multiple HPV genotypes. Trottier et al., (2006) found that at individual visits, 1.9-3.2% of women had multiple HPV infections. Cumulatively during the first year and the first 4 years of follow up, 12.3% and 22.3% were infected by multiple types, respectively. HSIL risk markedly increased with the number of types. Co-infections with HPV 16 and 58 seemed especially prone to increase risk.

Wheeler et al., (2006) found a non-significant greater risk for > CIN III in women with multiple HP HPV types without HPV 16 than
women with single HR HPV types without HPV 16 (10.9% v 7.9%). They found that the HR HPV types other than HPV 16, had a collective risk of > CIN III of 7.9%. Multiple infections with HPV types of different risk classes resulted in a risk similar to, and not significantly different from, the risk observed for the highest class.

**Pathophysiology:**

The HPV gets access through scratches, scars or at the transformation zone of the cervix, infecting the basal and parabasal cellular layers, where latent infection ensues. Integration of highly oncogenic HPV DNA into host- cell chromosomes of the basal cells of cervical squamous epithelium is followed by the binding of HPV E6 and E7 oncoproteins to tumour suppressor genes p 53 and Rb, respectively. This HPV DNA integration precedes the transformation from low grade to high grade cervical lesion.

In non-infected cells: the p53 tumour suppressor gene levels increase in response to cellular or DNA damage or aberrant cell proliferation signals. High levels of p53 cause the cell to stop growing in the G1 phase of the cell cycle and allow it to either repair damaged DNA before the next round of DNA synthesis or be eliminated through apoptosis.

The E6 and E7 gene of the high risk HPV genotypes encode main transforming proteins. The E6 gene protein binds to the p53 levels diminishes the cell’s ability to control the cell cycle and repair DNA damage and ultimately leads to uncontrolled cell growth.

The E7 gene protein forms a complex with the retinoblastoma protein (pRb) and disrupts the complex between the cellular transcription
factor E2F-1 and pRb. This results in the release of E2F-1, stimulating cellular DNA synthesis and uncontrolled cell growth.

In summary: the above processes result in impaired tumour-suppressor-gene function, involving DNA repair, decreased apoptosis and eventual cell immortalization.

HPV 16 E7 protein also induces centrosome-related mitotic disturbances that are potentiated by HPV 16 E6 protein. The above results in the desegregation of the chromosome during mitosis leading to numerical and structural chromosomal aberrations.

Mutations causing chromosomal alterations, loss of heterozygosity, genetic instability & proto-oncogene and telomerase activation in immune permissive individuals have important roles in virus-induced carcinogenesis.

Co-factors such as genetic or environment factors, such as smoking, may also be necessary for progression to the invasive stage. The so-called non-European variants of HPV 16 and 18 may increase the degradation potential of p53. HPV 16 is polymorphic and the Arg/Arg genotype of p53 could have greater susceptibility to HPV-E6 degradation than the other genotypes. The coincident interplay between the non-European genomic variants of HPV 16/18 and p53 Arg/Arg may explain, at least in part, the persistence of HPV infection and tumour progression in women with cervical neoplasia.

HPV persistence in HIV positive patients has been linked to a reduction in HLA class II molecules and a greater number of immature Langerhans cells within the cervix.

Evidence-based epidemiological and molecular data suggest that persistent infections with HR HPV types are the intermediate endpoints, leading to both intraepithelial and invasive cervical neoplasia.
The multihit, multistage model of carcinogenesis is a physiologically based quantitative model uniting the processor of mutation, cell growth and turnover. It also accounts for human heterogeneity for inherited traits and environment experience. It is an attempt to explain the relationship between the molecular mechanisms of mutagenesis and the actual processes by which most people get cancer.

Age-incidence relationship and experimental evidence suggest that cancer is a multi-stage disease. Tumours are monoclonal implying that multiple hits need to affect a single clone of cells. Genes may interact in an unordered or ordered fashion along a polygenic pathway. Cancers almost always are heterogenous.

Hanhan and Weinberg (2000) argued that most cancers have to achieve six essential alterations on the way to malignancy: self-sufficiency in growth signals, insensitivity to growth-inhibitory signals, evasion of programmed cell death, limitless replicative potential, sustained angiogenesis, tissue invasion and metastasis. However, the number of stages cannot be deduced this way, because some of the acquired capabilities probably interact.

Herrero-Jimenez et al., (2000) developed a model to compute the essential parameters of the two-stage initiation promotion model, using colon cancer as an example. Their work was based on the work of Nordling, armitage, Doll, Moolgavkar and Knudson. When Hemminki et al., (2001) tested the model on cervical cancer; they found that the number of initiation mutations required for cervical cancer are stages.

In cervical cancer, immune surveillance plays an important role. Immunosuppressed patients are at a marked risk for many types of
squamous cell carcinomas. Suppressed immune function is also likely to modulate host response to virus, such as HPV.

Hemminki et al., (2001) found the effect of nonshared environmental factors (sporadic causes of cancer) to be 80% for cervical cancer. Shared environmental effects between twins were shows to be 20%. This suggests that the genetic effects are masked by strong environmental influence such as HPV.

The Pap smear as primary screening for cervical cancer & its precursors:

The goal of cervical screening is the detection of cervical cancer and precursor lesion.

Papanicolaou showed that exfoliated cervical cells could be reliable harvested and spread, screened and stained on a glass plate. With the Papsmear, he laid the foundations of cervical screening.

Organized screening versus opportunistic screening programmes:

During the 1960s, it became apparent that a population screening programme could reduce both the incidence and death rate from cervical cancer, as first demonstrated in British Columbia. Until the 1980s, cervical screening was not applied in a systematic fashion in UK, with the result that many women at greatest risk were not screened. The death rate from cervical cancer was essentially unchanged until the national call and recall program was instituted in 1988 in the UK.

The program originally involved every woman between the ages of 20-64 years (20-60 years in Scotland) being called and recalled for a Pap smear every 3-5 years. The death rate from cervical cancer is now 50% of what it was in 1988 with 2700 cases of invasive cancer, 19000
cases of carcinoma in situ and approximately 1200 deaths each year. Similar falls in death rates have been seen in Finland, Iceland and the USA.

In 1990, target payments were introduced for GPs in the UK to do Pap smear of 80% or more of their female patients. The national coverage has risen to 85.3% in the UK, because of the call and recall system and the target payment to GPs.

The national Cervical Screening Policy (SA Department of Health, 2000) in South Africa allows for female public health care patients to have 3 Pap smear at ten year intervals from age 30 years. The aim is to reduce cervical cancer incidence rates by 60% (Department of Health, 2000). It is an opportunistic screening programme.

*Miles et al., (2004)* compared organized screening programs with opportunistic screening programs & identified seven lessons learnt:

1. Organized screening has greater potential ability to reduce cancer incidence and mortality due to higher achievable levels of population coverage, follow up and quality compared with opportunistic screening.
2. Organized screening programs aim to achieve a population-level benefit and a balance of benefits and harms; as a result, organized programs may not provide screening that offers maximum protection to each individual but offer them greater protection from harms.
3. Equality of access if often a key principle of health care provision in countries with organized screening.
4. In organized programs, the opportunity to be screened is determined by health policy and by the adequacy of the call-recall system; in opportunistic screening, the opportunity is determined to a
greater extent by individual factors, such as the knowledge and behaviour of patient and provider, insurance coverage, and the patient's pattern of encounters with health services.

5. Cost of screening as barrier is largely remedied by organized programs, but limitations in terms of access remain.

6. Organized programs do not eliminate socioeconomic and ethnic disparities in the uptake of cancer screening, and each model faces challenges related to informed consent.

7. Introducing an organized system of screening presents many challenges related to existing and required infrastructure, resources, vested interest, public and provider acceptance of centralized health care.

To achieve the goal of reducing South African cervical cancer incidence by 60%, our national screening policy will have to be changed to an organized screening policy. To introduce a call and recall system, a reliable centralized data base must be used. The National Electoral Rolls are the biggest South African centralized population data base, but presently are not up to date. In 2008, however, it was made up to date, because, a national election was due to be held.

Pilot programs can be initiated in the Primary Health Clinics of larger metropolitan areas, using the local electoral rolls for a call programs. This can be done by the Municipal Health Departments. Primary Health Care Physicians and sisters can be paid a target payment to motivate the taking of Pap Smears.

If the pilot programs are proven to be cost-effective, the program can be extended to smaller towns and ultimately to rural areas. In the rural areas, the tradition leader can be asked to facilitate the call and
recall program amongst their people. Mobile clinics can be used to reach areas where there are no permanent Primary Health Care Clinics.

The cost of the target payment, diverse costs of the program and the cost of the cytology screening can be offset against the cost of treating patients with cervical cancer and its precursor lesions.

In South Africa, 5203 cervical cancer cases were reported in 1999. This amounts to an estimated average of 26, 1 per 1000 000 women (National Cancer Registry). If a Call and recall program is started in South Africa, the cervical cancer incidence can be reduced by 50% as per the UK example.

A South African example of a successful Public Health National Programme is the National Immunization Programme where 84% of all infants were fully immunized during 2006 (Every Death Counts Report). The immunization programme is hybrid call and recall programme, where the infants are immunized at birth and the mothers are then given a return date for the next appointment. At each immunization, a return date for the next appointment is given.

A possible Call and recall program for cervical screening in South Africa can be started at the 6 weeks post partum appointment at the Post natal clinics, where a Pap smear or a liquid-based cytological screening could be done on every women of 30 years and above, who haven’t had a Pap smear in the past. Their results could be given to the patients on the date of the next appointment for immunization for their infant. A card could be given to the patients, similar to the immunization cards, with a perforated section for notification of change of address. They could be informed that, should they move in the next ten years, they should send the perforated section with correct contact details to the
Health Department of municipality where they move to. In this way, a national data base could be started, supplementing the Electoral voters rolls.

**Current challengers in cervical screening:**

**Sensitivity:**

The Pap smear has a low sensitivity of 58% to detect CIN3 lesions. The Pap smear has a high false-negative rate. The specificity of the Pap smears is 94.2%. The majority of missed lesions are due to failure to sample the lesion. In order to achieve maximum sensitivity, it is necessary to act on the most minor abnormalities.

This creates one of the major difficulties in cervical screening—the management of low grade abnormalities, which carry a very low positive predictive value for the presence of CIN, yet are associates with a significant number of underlying high-grade CIN lesions.

Where the cytology is reported as unsatisfactory, the Pap smear needs to be repeated, Liquid based cytology involves a fluid suspension of exfoliated cells being placed in liquid medium. The cell suspension is aspirated through a filter and the resulting thin layer of cell is deposited on a glass slide. This provides cleaner preparations, which are easier to read.

Despite a half century of intensive research effect through-out the world, cancer still remains an enigma. A malignant feature of this malignant disease is the tenacity with which it retains the secret of its initiation and maintenance.

As the intensity of cancer research multiplies there is crescendo of accomplishment that is truly mind boggling. Fifty years ago, the epoch making discovery of the role of DNA as the master template of
organized life processes made it possible to envision the ultimate understanding and conquest of disease. Slow and painfully but with increasing certainty DNA has come sharply into focus as the target for the initiation of the neoplastic transformation, whether caused by viruses, chemicals or radiation.

An epochal leap forward in cancer research has been the actual identification of some 25 or 50 genes, the so called oncogenes, which appear to play a casual role in cancer.

The picture that is now emerging is that these oncogenes and the protein products for which these genes code, are crucial elements in the growth and tissue differentiation that accompany normal embryonic development, then are turned off or kept in check. Cancer occurs when one or more of these normally silent oncogenes are triggered to activity by carcinogenic stimuli. In one of the most intensive efforts of cancer history, the nature of the activation processes, and the identification of the products for which these genes are coded, are being pursued with the expectation that such new information will uncover those critical but still obscure intermediate steps that define the neoplastic process. The oncogene story is only one of many developments that are creating a feeling of cautious but justified optimism towards understanding and ultimate conquest of cancer.

Simultaneously, other areas of epidemiology and experimental study are making their impact in pointing to diet and nutrition as risk factors and in revealing ways in which we ourselves, as individuals can do much to lower our risk of cancer. The changing patterns of cancer incidence with time and with geographic location throughout the world provide further evidence for dietary components in cancer risk.
Epidemiologic studies suggest that dietary practices are a promising area to explore in the search for preventive measures against cancer. If definitive links can be established to certain foods and/or specific nutrients, they will have enormous implication for public health and public policy.

Carcinoma of uterine cervix is the most important cancer to affect the female genital tract. A variety of factors nutritional, demographic and biochemical appear to be associated with this disease. If these factors could be combined and their inter-relationship taken into account, it may be possible to estimate more preciously the risk of future cancer. As there is little data available in India, on the biochemical profile of women suffering from cancer of the uterine cervix, this study will provide the much needed baseline data encompassing nutritional, immunological and epidemiological status.
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