Review Article

Modes & Means of Early Diagnosis of Precancerous Lesions of Cervix, Some Glimpses.

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Current Status

In the world as a whole, carcinoma cervix is the second most common cancer among women. Globally, with an estimated 5,24,000 new cases in 1995, developing countries, where it is the most common cancer, account for 80% of cases (Parkin 1984, WHO 1986, 1997). In India, around 90000 cases occur annually (Singh et al 1992), 14000 in USA (Greenberg et al 1995), over 4000 cases of cervical cancer occur annually in the United Kingdom, and 2500 women die of the disease (Fenton et al 1990). Statistics may vary from country to country but cervix is the most common site of genital cancer globally (80 to 85%) (Barlogie 1984). The reported incidence of preclinical invasive carcinoma in India is around 1.5/1000 (Singh et al 1992). In a study by Indian council of Medical Research, when a total of 13540 women wre screened, with 92.8% adequate smears, 73.7% were inflammatory, 0.7% dysplatic and 0.4% malignant in the National Cancer Registry Programme (Annual Report of Director General 1995-96). In the field study done by Chhabra et al in 1987, out of 689 cases screened, there was 1 case of carcinoma cervix and out of 725 cases 1 in 1994; incidence of dysplasia was 3.62% and 8.41% respectively. Differences in risk are seen within a continent or within a given subcontinent. In Europe, the incidence is higher in the German Democratic Republic and Romania than in Spain. In Brazil, rates are two to three times higher in the north than south, In India, there is a higher incidence in Madras as compared to Bombay (WHO 1986).

The accessibility of the uterine cervix, relatively a small organ, the propensity of cells to exfoliate from precancerous lesions, the evidence from pathological studies of the existence of histologic changes from mild atypias through premalignant lesions to frank malignancy, the apparently prolonged natural history, long premalignant phase and ability for detecting cytologically provide perhaps the best potential for the control of a cancer by population screening (Miller 1992). It is therefore, disappointing that cervical screening has not had a greater impact on the incidence of cervical cancer. No wonder an editorial in the Lancet in 1985 is titled, Cancer of the cervix: Death by Incompetence. This perception may not be true globally, though for India's current situation this may still be true. The natural history of carcinoma in situ involves a dynamic process, with most likely regression at younger ages, occuring at a significant rate at older age (Miller 1992). Awareness on the part of health providers and consumers is a must. In a study done recently by the author and colleague (Chhabra et al 1995), it was revealed that before they reached the institution, 21% women had received some medication from quacks or physicians, for weeks together without a gynaecological examination !.

Over the last 2 decades in many countries there is

evidence that indidence of cervical carcinoma is increasing, particularly in young women (Draper & Cook 1983, Hunter 1995, Munoz 1989). In a study of 153 cases, Artman et al (1987), have reported increasing incidence of more aggressive form of cervical carcinoma. In a recent study at Mahatma Gandhi Institute of Medical Sciences, Sevagram, India, the incidence of cervical carcinoma was found to be 3.4% of all gynaecological admissions while 9.5% of patients with invasive disease were less than 35 years, the youngest was 24 years and oldest 78 years, (Chhabra et al 1995). Two decades ago, in the United Kingdom, invasive carcinoma of the cervix was a disease that was uncommon before 40 and had a peak incidence between 50 & 60 years. In the last decade, although the overall incidence has not changed significantly, it has become increasingly common in women between 25 to 40 years of age and the old peak has been replaced by a plateau of incidence between 35 & 55 (Hunter 1995). Kaufman et al (1970) found 23/1000 cases of significant atypia in women under 20.

It has been revealed by studies in North America, particularly in British Columbia, Canada, that majority of cases of cytological dysplasia do not progress to more severe abnormalities & might regress (Miller 1992).

Screening / Early Detection

Much has been written about the accuracy, sensitivity and specificity of the cervical Papanicolaou smear since it's introduction in 1943 (Gay 1985). Actually the cell changes associated with premalignant disease of the cervix were originally described by a Romanian pathologist Aureli Babes at least two years prior to the observations of George Papanicolaou, a Greek working in the USA., in 1928 (Koss 1989), but no notice was taken until 1943, when Papanicolaou published a monograph. The first large scale population screening was done by Boyes et al (1962) in British Columbia in 1947.

A screening programme directed to a precursor lesion such as preinvasive cervical neoplasia can be expected to reduce the incidence of the fully developed clinical lesion and morbidity and mortality from the disease (Miller 1992). In the Nordic countries, Denmark, Iceland, Sweden and Finland, following the introduction of screening in the mid 1960s the incidence did fall (WHO 1986). However systematic application of screening in Iceland and Finland sharply reduced the cervical cancer, in contrast there was slow but steady increase over 20 years, in Norway where screening was not applied systematically until 1980 and a lesser decline in Denmark & Sweden where screening programmes were introduced gradually (WHO 1995). As such due to 4 decades of exfoliative cytology, cancer cervix is in 6th place of cancer morbidity in developed countries (Greenberg et al 1995).

For detection of pre-cancerous lesions among acceptors and nonacceptors of various family welfare methods, a scheme of PAP's Smear test has been approved by the Government of India, in a phased manner, in number of insttitutions, However underutilisation of the facility by health providers and consumers is evident from the fact that the number of instittutions which reported results was 25 in 1988-89, 27 in 1989-90, & 40 in 1990-92 (Family Welfare Program 1989-90, 1991-92). Further facilities for cytology are still mostly restricted to the large urban centres. So only limited information has been generated to assess the impact.

Though cervical screening has evolved into the most cost effective cancer screening allowing millions of women to have potentially precancerous cervical lesions discovered for timely interventions, there have been renewed apprehensions. In addition cytology is intended to have reduction in mortality and morbidity due to cancer cervix, so no mortality and minimum morbidities due to therapies for prevention, is imperative. But whether cytology reduces surgeries performed and so morbidities, needs to be checked.

It is advocated that all women who are or who have been sexually active or have reached 18 years, should have an annual Pap's test and pelvic examination. After a woman has had three or more consecutive satisfactory normal annual examinations, the Pap's test may be done at the discretion of physician (Disaia et al 1989). However one could debate on this statement if we analyse the current

knowledge of status of cervical cancer progression. One must remember there is a considerable risk of overtreating if screening programmes concentrate on younger women, as the incidence of dysplasia is high at 20-29 yrs of age, while the risk of progression to invasive cancer at these ages is very low. To adopt a policy of screening younger women may therefore waste valuable resources on treatment for a condition, that will probably regress. The effect of screening policies is to emphasize the importance of screening at older ages, at a sufficient frequency to ensure that the majority of cases of preinvasive cervical cancer are detected, but infrequently enough to avoid too many nonprogressive cases being detected and therefore treated (Miller 1992).

There is not much of a difference in the reduction in the cummulative cervical cancer between 35-64 years with differnt frequencies of screening within 3 years. Quantitative studies have shown that after one negative cytological smear for cervical cancer, screening once every 3 years accomplished about the same effects among women of 35-64 years of age as screening every year. (Percentage reduction in the cumulative rates in 1 year - 93.3%, 2 years-93.3%, 3 years - 91.4% & 10 years 64.2%) (WHO 1986).

In India, in Kerala, the stage of disease at the time of diagnosis has changed over the past 10 years following the introduction of a down staging programme in which women are informed about the symptoms of the disease and also requested to report to health workers for screening / examination even if asymptomatic. Thus the proportion of cases diagnosed at stages I and II (when treatment is usually successul) has risen from 15 to 45% while the proportion of those diagnosed at stages III & IV (where treatment is usually ineffective) has fallen from 85 to 55% (Miller 1992). Programmes of visual inspection of the cervix by specially trained health workers using a speculum are being evaluated in India and some other parts of Asia & Africa. It is important to recognise that visual inspection has always been a part of cervical cytology screening although it's contribution to early detection of cervical cancer in successful programmes has not been determined (WHO 1995). Suspicion will often be aroused by abnormal symptoms and clinical examination may indicate the presence of a suspicious growth. However this may be too late. Further symptomatology and look of cervix may be deceptive in premalignant conditions. In a community based study of CIN screening no relation was found between clinical abnormalities and Pap's test reports. Women with clinical abnormalities had 96.20% abnormal smears and clinically normal cervix had 90.37% abnormal smears. With clinically normal cervix 3.65% women had dysplasia while with abnormal looking cervix; 4.55% had dysplasia out of 28 women with dysplasia, 79% had normal looking cervix (Chhabra et al 1991 a). A woman who presented with vaginal discharge, had a cervical lesion which clinically looked like cervical erosion, on cytology was CINI, on histopathology was carcinoma in situ, and finally turned out to be invasive carcinoma with secondaries all over the abdomen (Chhabra et al 1991 b). Cytological false negative rates in cervical malignancy vary widely (Morell et al 1982) and a number of studies have shown rates varying from 15% to 55% in the presence of invasive cervical cancer (Berkowitz 1979, Coppleson 1974, Tuncer 1967), and 6% to 45% in the presence of squamous cell carcinoma in situ (Richart 1965, Creasman 1972, Coppleson et al 1974, Sedlis 1974). By removing only sampling errors, false negative rates in cervical malignancy could be reduced from 20% to approximately 12% (Gay 1985). Automation of screening systems for Pap's smear has been attempted (Koss et al 1994). The most reliable sample is a combination of an endocervical aspiration (or cells obtained with a nonabsorbent cotton tipped applicator from the endocervix) and a circumferential scrape of the transformation zone around the squamocolumnar junction. Both samples may be put on a single slide without affecting the sensitivity of the test, (WHO 1986).

Women with significantly abnormal cervical smears should have a colposcopic assessment of the cervix. Colposcopy introduced in 1925 by Hans Hinselmann (Disaia et al 1989) allows full microscopic assessment of both exo and endocervix and directed biopsies can be taken. Naked eye test is being believed to be a promising good screening test for CIN (Londhe et al 1994).

Fawa et al (1988) observed that cervicography is more

sensitive in detecting abnormalities than Pap's smear. Cervicography is being used as an alternative screening method and there have been some promising results. In cervicography, developed by Adolph Staff (Staff 1981), after staining the cervix twice with acetic acid, two photographs (Cervicograms) are taken. Cervicograms are graded into one of four categories, negative, atypical, positive, and technically defective, Cevicography may detect lesions that are not identified by cytology. However cervicography is not designed to be used as an unaccompanied screening test. Cytology and cervicography together detect twice the number of cases as compared to only cytology (Reid 1991). August (1991) reported 586 women, who underwent repeat pap's testing, cervicography and colposcopic examination for prsistent atypia. Of the 43 patients with LSIR both cervicography and colposcopy were equally effective in identifying these lesions. Although the sensitivity of colposcopy and cervicography are similar, the specificity of cervicography is much grater than that for colposcopy (Jones 1987).

Video colpography, has a number of advantages over cervicography. (Etheringtion 1997). It allows inspection of the entire cervix, vaginal fornices and endocervical canal where necessary. Research is presently being carried out using flow cytometry and looks promising. Search is going on for biochemical or microbiological markers in potentially malignant cases.

Even after ten decades, Cervical biopsy continues to be the gold standard. Biopsy is indicated even in a woman with a negative smear where symptoms and / or signs suggestive of cervical cancer or pre cancer are present(Coleman 1989). We found around 21% of cases being diagnosed only ofter biopsy (Chhabra 1995). Elovainio et al (1997) have also reported 20% false negative rate with cytology.

Future Prospectives

It has been estimated that even with a 12 times increase in technicians, Pap's smear screening will be possible only for 25% of the women by the year 2000 A.D. (WHO 1986). Also poor correlation between mild atypia and histology warns against reliability, Presently there are no available methods to differentiate CIN lesions that will progress from those that will not progress though attempts are being made to identify factors which can help in prediction. The progression to CIN III was 42.6%, significantly higher than the 15.8% progression rate noted in controls with similar cytologic abnormalities but unassociated with chlamydia (Harnekar et al 1985). Anderson et al (1991) have also reported that women with CIN have a higher incidence of chlamydia associated changes. But authors themselves feel that the association may be due to nothing more than the fact that both diseases are the consequences of sexual activity. Several case control studies have shown relationship between HPV infection and preinvasive or invasive cervical malignancy. Koutsky et al (1992), studied prospectively a cohort of 241 women who presented for evaluation of sexually transmitted diseases and had either positive or negative cervical cytologic tests. After two years, cervical intraepithelial neoplasia was 28% among women with a positive test for HPV and 3% among those without detectable HPV - DNA. The risk was highest among those with HPV type 16 or 18 viz an 11 fold increased risk of subsequent detection or development of CIN II & III. Ritter et al (1988) observed that women who were either HPV positive or exfoliative cytology positive had 12 times more carcinoma than those neither of the two positive. ICMR'S (1995-96) annual report reveals that more than 98% of cervical cancers have oncogenic HPV DNA, about 50% of which are HPV 16. However, cervical carcinogenesis can not be explained by HPV along and additional molecular events appear to play an important role. Analysis of mutation of Tumor suppressor gene P in a sizeable number of HPV negative & HPV positive cervical carcinomas was carried out by a single strand conformation polymorphism (PCR-SSCP) and cycle sequencing of PCR products. The results revealed rare occurence of P mutation in HPV negative carcinomas. Studies carried out on regulation of HPV oncogenes expression indicate that a specific cellular protein, the product of a cellular gene, fra-1 located on chromosome 11q13 region might be playing an important role in negative growth regulation during cervical carcinogenesis (Annual Report of ICMR 1995 - 96) Integration of HPV DNA may occur near cellular oncogenes, such as c-myc and N-myc, which would result

in activation of these oncogenes and subsequently promote tumor progression. Over expression of the epidermal growth factor receptor and 2/neu gene have been associated with poor survival (Lee 1997). HPV 18 may be more virulent than HPV 16 and may be a prognostic factor. Current evidence suggests that virus is necessary but not sufficient cause of the disease (WHO 1997), blocking the way for prevention strategies.

In view of the developments, National Cancer Institute (NCI) workshop held in Bathesda, Maryland 1989, proposed the Bathesda system for cytologic reporting (National Cancer Institute Workshop 1989). As atypical squamous cells of undetermined significance (ASCUS), low grade squamous intra epithelial lesions (LSIL), within this category are included those with cellular changes associated with HPV and those with mild dysplasia (CINI) and high grade SIL includes those with cellular changes suggestive of moderate or severe dysplasia, as well as carcinoma in situ, (CIN II & III) (Hatch et al 1996).

Major constraints of screening for cancer control include an unfavourable natural hisory of cancer, poor organisation of screening programme, poor compliance of those at risk (Miller 1986). Screening does not mean taking smears from women who walk into the general practitioner's surgery or hospital clinics, it means taking smears from the entire female population at risk. Though here are uncertainties about the natural history of the disease, if the women are told not to disregard relevent symptoms in the screening interval, an interval of 3 years seems appropriate (Forsmo et al 1996). The poor correlation between mildly atypical, cervical cytology and histology suggests that the practice of relying on cytology and histology suggests that the practice of relying on cytology alone for the surveillance of women who have already had a typical smear should be discouraged (Walker et al 1986). Quality control in labs is a must to reduce screening and sampling errors (Graaf et al 1987). There should also be adequate follow up of individuals with positive results, so that diagnosis can be quickly confirmed and appropriate therapy started. Even screening once every 10 years, yields a reduction of almost 2/3 in the incidence of invasive cervical cancer. This evidence led a WHO meeting to conclude that countries with limited resources should aim to screen every woman once in her life time between 35-40 years of age. When more resources are available, the frequency of Screening should be increased to every 10, then every 5 years for women aged 35-55 yrs and ideally once every 3 years for women aged 25-60 yrs. Public awareness of falacies in the system and their reasons is a must (WHO 1995). Increased use of condom and development of vaccine may help, since HPV has been proved to be of central importance (WHO 1997). All the links in the chain must function from sampling, processing, screening, quality control and interpretation, to have triumphs in this tragedy (Koss 1989), for this system must work with the dissemination of information, remembering clinical component and follow up to have satisfied consumer as a Walkie Talkie.

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