Research Article

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Archives in Cancer Research
ISSN 2254-6081

2019
Vol.7 No.1:1

DOI: 10.21767/2254-6081.100190

Persisting Dilemmas in Etiology and Challenges in Screening and Diagnosis of Cervical Pre-cancer and Cancer

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Tel: 91-7152-284342

Citation: **Chhabra S** (2019) Malignant Phyllodes Tumor in Ectopic Breast Tissue: A Case Report with a Literature Review. Arch Cancer Res. Vol.7 No.1:1

Abstract

Introduction: Cervical cancer is probably fifth amongst all cancers, third most common in women after breast, colorectal in some countries. Recent trends reveal resurgence in developed countries too. Dilemmas continue about which cervical dysplasia/ cervical intraepithelial neoplasms are precursors of cancer and after how much interval.

Objectives: The objective is to look at dilemmas in ethology of cervical cancer, challenges in screening and diagnosis of pre-cancer, cancer.

Methodology: Simple review of literature was done by various search engines and personal experience was added.

Results: Geographic variations in cervical cancer rates reflect differences in presence or absence of etiological factors and screening of pre-cancer. Molecular studies revealed human papilloma viruses (HPV)16, 18 as most oncogenic, long-term hormonal contraceptives, high parity, early sexual activity, multiple sex partners, tobacco smoking, co-infection with HIV as identified cofactors, and co-infection with Chlamydia trachomatis, Herpes simplex virus type-2, immunosuppression, low economic status, poor hygiene, low dietary antioxidants probable cofactors. Genetic, immunological factors play some role. However, role of none seems to be clear. Dilemmas continued about many factors.

Discussion: Cervical cytology most commonly used conventional screening has many limitations, danger of cells drying, poor quality, reporting problems. So, liquid based, thin layer cytology is advocated which has limitations. False negative/positive results continue. Histopathology is essential but necrosis in advanced cases creates problems. Visual inspection, visual inspection using acetic acid, lugol's iodine has varying results. Point-of-care, affordable HPV tests are elusive. Standard cytology-based programs in high-resource countries have been colposcopic localization and biopsy in screen-positive. However false positivity and overtreatment continue. Many challenges limit utilily of screening with colposcopy. Research continues to search for useful biochemical, microbiological markers.

Conclusion: Dilemmas in ethology of cervical cancer and challenges in screening, diagnosis still continue. Risk of overtreatment outweigh risk of high-grade lesions, invasive cancers untreated. Research needs to continue.

Keywords: Histopathology; Colposcopy; Immunosuppression; Contraceptives

Received: December 05, 2018; **Accepted:** December 23, 2019; **Published:** January 05, 2019

Introduction

Cervical cancer is reported to be seventh (4%) or even fifth in frequency amongst all the cancers in men and women put together and third (9%) most common cancer in women after breast and colorectal cancers in some countries [1-3]. Earlier Parkin et al. [4] had reported cervical cancer 6% amongst all

cancers in women. Ferlay [5] reported that more than 86% global cases and 88% global deaths due to cervical cancer occurred in developing countries, where cervical cancer has been reported to be the second most frequent cause of cancer deaths in women. Many researchers [5,6] have reported that India contributed to 20-26% of the global burden of cervical cancer and 27% of mortality due to cervical cancer. Parkin [7,8], Kamangar [9,10], Sankaranarayanan [10] and others reported that cervical cancer accounted for 9 to 12% cancers in women and the numbers were expected to increase by 90% in 2020. Trends showed a resurgence (4-6% cancers in women) in developed countries too [11]. Probably 530, 000 new cases of cervical cancer were diagnosed, and 275, 100 deaths occurred in the world in 2008 [5,12]. In a analysis at a rural institute, cervical cancer constituted 29% of all cancers in women [13]. Variations continue, and reasons need to be researched.

Objective

Present article is for sharing information about dilemmas in etiology of cervical cancer and challenges in screening and diagnosis of pre-cancer and cancer.

Literature Review

Simple review of literature was done by available search engines like goggle, up-to-date, ER-MED Consortium, Cochrane Library, Med IND and personal experiences were added.

There were no pre-decided criteria of inclusion of articles. Available relevant articles were looked into. Over the years we have been facing challenges in screening, even community based and diagnosing cases. The information of experiences has been added at appropriate places.

Although the overall incidence has not changed significantly, cervical cancer has become increasingly common between 25-40 years of age and the old peak between 50-60 yrs has been replaced by a plateau between 35 and 55 yrs [14]. Also, aggressive disease is being detected in young women (25- 40 years). Probably there are two peaks, one around 35 years and another at 50-55 years, following which there is a reduced incidence [15]. Why this occurs, needs more studies. Life-style, food or environment may be playing some role. In England, cervical cancer is the second most common cancer in women under 35 years, with increasing incidence in young women. In the study by Foley overall incidence, during 1982-2006, fell significantly from 213 to 112 million per year. However, between 20-29 years, after an initial fall, incidence increased significantly during 1992-2006, with annual percentage change (APC) of 2.16 and between 30-39 years incidence stabilised during the latter part of study [16]. The rise in incidence was unrelated to the change in screening policy. American Cancer Society researchers found that since 2010, diagnosis of early-stage cervical cancer substantially increased in women of 21 to 25 years. They correlated the rise with a provision in the Affordable Care Act (ACA) that allowed young adults to stay on their parents' health insurance until age 26 [17]. However, substantiation was needed.

Ferlay [18] reported that 134, 420 Indian women were diagnosed with cervical cancer yearly and 72, 825 died because most (85%) cases presented in advanced stages. Cervical cytology is less effective in screening adenocarcinoma. So, it seems to have increased over 3 decades. Adenocarcinoma is also believed to be less radiosensitive. But this also needs more research. Severe cervical dysplasia /cervical intraepithelial neoplasm III have been recognised as precursors of cervical carcinoma. While there has been research which revealed that some cases of CIN III became cervical cancer, it was still not clear which ones and also which CIN I and CIN II became CIN III and which regressed [19].

Dilemmas in Etiology

The large geographic variations in cervical cancer rates reflected differences in the presence or absence of etiological factors. One factor does not seem to be responsible for cervical cancer, many are believed to affect the occurrence, as are some human papilloma viruses (HPV). Majority of the women become infected with HPV at some point in their lives, after the beginning of sexual activity. HPV have been detected in healthy women and in women with benign cervical pathology [20]. Singer [21] reported 6 to 18 months median time needed for clearance of HPV infection. Persistent infection with high-grade HPV types may lead to precursor lesions of the cervix with epithelial cellular change with the changed ratio of the cell nucleus size, graded as CIN I (mild dysplasia), CIN II (moderate dysplasia), or CIN III (severe dysplasia) depending on the proportion of the thickness of the epithelium showing mature, differentiated, and undifferentiated cells. Persistent infection with high-risk HPV seems to be necessary but doesnot seem to be sufficient to cause cervical cancer. Other cofactors are necessary. Also, HPV viral load and integration are likely to be important but have not been clearly identified. A lot of research is still needed. Long-term use of hormonal contraceptives, high parity, early initiation of sexual activity, multiple sex partners, tobacco smoking and co-infection with HIV, Chlamydia trachomatis and Herpes simplex Type-2 virus have been identified as established cofactors. Immunosuppression, low socioeconomic status, poor hygiene, diet low in antioxidants seems other probable cofactors with genetic and immunological host factors. Reported prevalence of HPV infection also varies widely, 21% in Africa, 16% in Latin America and the Caribbean, 9% in Asia and 5% in Northern America [22]. HPV has been found to be associated with around 50, 000 new cases of cervical cancer and 250, 000 cervical cancer associated deaths worldwide each year [23]. Villiers [24] reported that of more than 100 HPV types identified, 40 infected the genital tract. Molecular studies showed that HPV16 and 18 were the most common and highly oncogenic types for cervical cancer in around 70% cases. HPV16 has been found more commonly [25]. HPV prevalence among cervical cancer patients in India varied between 87% to 97% [13,26-28]. Prevalence of other high-risk types has been very low.

Results and Discussion

Population-based studies from developed countries have shown marked socioeconomic gradients in the incidence and mortality due to cervical cancer. Women from lower socioeconomic strata have 2-3-fold higher risk of cervical cancer than their affluent counterparts, possibly because of poor personal and sexual hygiene, nutritional deficiencies and lack of healthcare. But all

these still need a lot of research. The possible operating factors may be low standards of cleanliness including penile hygiene, coitus at an early age frequency of sexual intercourse, and promiscuity of both partners. It may be that multiparity is a risk factor, focussing just not on the frequency of coitus but also on the assault on the cervix during birth. Some researchers reported that the failure of recent studies to detect many births as a risk factor, may be due to limitations of pregnancies in modern days but a lot is still not known, may be synergism of some factors plays a role. It could also be diet and other unknown factors. Most of the cases of the cervical cancer are because of infection with the HPV. So, the experts believe that diet high in antioxidants, carotenoids, flavonoids, and folate found in fruits and vegetables can help the body fight HPV and so prevent HPV mediated conversion of cervical cells into cancerous cells. A study revealed that women who had high chemical compounds which indicated diet rich in fruits and vegetables were able to clear HPV faster than their peers. This reduced the risk of cancer [29]. At a referral centre we have seen many cases of advanced cervical cancer in young women. Of all the cases of cervical cancer that came from nearby state Andhra Pradesh of India 47% from were less than 50 years. The food and living habits are different compared to women of Maharashtra where we work. Early marriage does not explain, as sexual activity at young age is common in Maharashtra too. Diet is different and there may be other hidden factors. Sexual activity in young age is common in western world also. So, more research is needed.

Challenges in Screening

Availability of screening for detection of pre-cancerous lesions which can be treated to prevent cancer varies globally and there are many challenges. Bateman et al. did a study and reported that the patients focus group discussions revealed the presence of fear and stigma surrounding cervical cancer as well as a lack of information and access to screening and treatment. The clinician focus groups also identified numerous barriers to screening, diagnosis, and follow-up after treatment in cervical cancer. Participants in both groups agreed that a patient navigation program would be effective way to help women to navigate across the cancer continuum of care including screening, diagnosis, follow- up care and treatment [30]. During the late 20th century, considerable reduction in cervical cancer incidence and mortality were achieved in high-resource countries owing to the systematic implementation of population-based cytology-based cervical cancer screening programs (Papanicolaou smears) [31]. The concept of CIN screening, pre-malignant condition of the cervix, usually asymptomatic, detected during opportunistic or mass cytological screening were introduced first in 1968, when Richart reported that all dysplasia have the potential for progression [32]. The term CIN is equivalent to the term dysplasia, disordered growth and development of the epithelial lining of the cervix. The highest incidence has been observed in Latin America, the Caribbean, sub-Saharan Africa, Southern and Southeast Asia. Because of the low sensitivity of the method, and multiple visits required for confirmation of cancer (colposcopy, histopathology), treatment, and follow-up, low- and middle-income countries (LMICs) have either not been able to implement or sustain. Reasons are believed to be lack of needed infrastructure and resources. However, the problem is not only resources but behaviour of women and families too. Cervical cancer screening at age 21 years is recommended. An abnormal Pap test report leads to additional procedures that can cause harm and unnecessary treatment. Most abnormalities in young women revert back without treatment. So, a lot of understanding and research is needed [33]. Cost effectiveness has also not been studied well. Visual inspection (VI) of cervix has varying results in different places our local experience in a study with planned services 96% cervical smears were abnormal with abnormal looking cervix and 90% cervical smears were abnormal with normal looking cervix too. Around 4% women who had cervical dysplasia had normal looking cervix and around 4% with abnormal looking cervix had dysplasia. Out of 28 cases of dysplasia, cervix looked normal in 20 cases [34]. So, VI does have limitations. VIA, as primary screening test for detecting high grade CIN to perform better when the Pap test is not possible, has also been not feasible [35]. In a study by Nakash et al. [36], the reported sensitivity and specificity for cytology were 46% and 88% respectively, similar to that reported by Cohn et al. [37] and Gaffikin et al. [38] Lancet [39], 44.3% and 90.6% respectively but slightly different from those reported by Samira et al. [40] which were 52.6% and 72.1% respectively. The reported false negative rate for cervical cytology by Nakash et al. [36] was 26.6% which was within the range reported by different studies (6-45%). The limitation for VIA were the high false positive rates, over loading the referral system and unnecessary treatments. So, research continues for this aspect too.

HPV DNA testing has been recommended by WHO as the first choice for primary screening for cervical cancer, because of the objective nature of the test, its high capability, reproducibility, and high negative predictive value, which allows extension of the screening interval to beyond 5 years [40]. However there are many challenges, from nonafforadability to infrastructure and limitation of utility of information as well. Also most infected women clear the infection within 1-2 years and will never develop cervical cancer. A major disadvantage of HPV testing is its low specificity. The pooled estimated specificity of HPV testing from 15 studies involving 45783 participants was 88%, which implied that the test was false positive in 12 of every 100 normal women [41]. Though Sankaranarayanan [42] reported that a clinical trial in rural India found that a single round of HPV testing reduced the number of cervical cancer deaths by about 50% [43], more trials are needed to have mission of translational research. A risk stratification of HPV-positive women is needed for triaging strategies. Cytology is the most widely recommended test to triage HPV-positive women where quality-assured cytology is available. In resource-constrained settings the practicality of recalling the women who are HPV 16/18 negative but positive for other oncogenic types needs to be carefully considered, as these women still have higher risk of having high-grade lesions compared with the HPV-negative women. All said in resource-constrained settings neither cytology nor HPV genotyping may be feasible. In LMICs, the use of HPV testing remains limited to projects. Most hospitals do not provide it because of high costs with lack of even modest laboratory facilities. All these aspects needed a practical look at ground reality of feasibility for women

who needed them the most.

The WHO strongly recommended human papillomavirus HPV testing for primary screening, if affordable if not, then visual inspection with acetic acid VIA, and promotes treatment directly following screening through the screen and treatment approach. While VIA positive women can be offered immediate ablative treatment based on certain eligibility criteria, HPV-positive women need to undergo subsequent VIA to determine their eligibility. Simpler ablative methods of treatment such as cryotherapy and thermal coagulation have been demonstrated to be effective and to have excellent safety profiles, and these have become integral parts of new management algorithms in pre-cancers.

A truly point-of-care and affordable HPV test is still elusive. Values for test sensitivity and lost to follow-up have been the most influential factors when comparing one-visit VI and VIA to two-visits for HPV testing. The most efficient and cost- effective screening techniques in low-resource countries have been believed to be VIA and HPV tests by some [44]. The real program effectiveness of the single-visit screen-and-treat algorithm should be studied further in the countries that have implemented such a strategy. Where single-visit approaches are not feasible, strategies for improving follow-up by mobile phone reminders and outreach treatment services are being evaluated but many challenges persist. The test characteristics of VIA generally improved when performed on a limited number of women with high prevalence of disease. Further one-visit VIA was only attractive when lost to follow-up exceeded 60% and decision of therapy after VIA was likely to lead to over therapy. WHO recommended VIA as the second-best screening test after cervical cytology for low-resource settings, and more than 25 countries have introduced VIA in national screening programs, while others are conducting pilot programs [45]. Muwonge [46] reported that in a community-based multi-center study in India, the colposcopy referral rates for VIA triage and cytology triage were similar, around 41% vs 38%, with comparable sensitivities of CIN II/CIN III, 82% and 84.0%. In a rural community-based setting in India, where trained nurses performed colposcopy and cryotherapy on VIA-positive women, 75% of eligible women accepted treatment at the same visit. Around 56% had CIN on histopathology and 0.5% of women with CIN had subclinical invasive cancer on subsequent histopathology [47]. In a randomized controlled trial in India, the risk of invasive cancer among VIA-positive women with apparently normal colposcopy during 12 years of follow-up was much higher than that of VIA-negative women [43]. The risk was similar to that observed in VIA-positive women with colposcopically detected abnormalities who did not undergo biopsy or treatment. So there is limitation of colposcopy too. Another major limitation of colposcopy, as a triaging technique was its low specificity (50%), for detecting high-grade cervical lesions, even in experienced hands, the specificity was even lower when the specificity of the primary screening test was low, as was the case with the HPV test or VIA. In a large community-based study in India, colposcopy was used to triage VIA and/or HPV positive women. Colposcopy falsely suspected abnormalities in around 69% of women with normal histopathology [48]. A systematic, pooled analysis of the accuracy of colposcopy revealed that for every 1000 screen-positive women referred for colposcopy, 464 were to be falsely diagnosed to have CIN II /CIN III and were going to be unnecessarily treated in a "colposcopy-and-treat" scenario [41]. Based on such evidence, WHO recommended direct referral of screen-positive women for therapy bypassing colposcopy [49]. Also, there is a concern that HPV testing followed by VIA triage can compromise the sensitivity of the original test and offset the benefits of a lower referral rate by missing lesions. Highly-sensitive HPV tests could detect potential CIN II or CIN III at very early stages, when the lesions were too small or subtle to be recognized visually [50]. Sankaranarayanan [47] reported that cervical cancer screening with VIA lead to 25% decrease in cervical cancer incidence and 35% reduction in cancer mortality. There was 10% VIA positive rate and only 65% of positive women underwent further treatment. Also 2% women had invasive cancer at the time of screening but only 30% received adequate follow-up. Among women who delayed care, reasons cited included childcare, cost, and the need of permission from male partner [51]. If the follow up and treatment are delayed obviously, the disease progresses affecting the final outcome. A large prospective cohort study in Greece identified that only 30% of women received regular cervical cancer screening. In women who did not get screening had more chances of preinvasive and invasive cervical lesions [52]. Cohort study of 28, 073 women by Gok [53] revealed that those who did not report for screening had increased relative risk of CIN II. In other large cohort studies, the reported loss to follow-up ranged from 21% to 64% of triaged to repeat testing or follow-up [54,55]. In the triage study, the sensitivity of baseline colposcopy for the subsequent detection of CIN III was only 53%. (Atypical cells of undetermined significance, low-grade squamous intraepithelial lesion ASCUS-LSIL Triage Study Group [56].

The estimated total cost of cervical cancer screening, diagnostic testing, and treatment of pre-cancerous lesions from 2015 to 2024 for 102 LMICs was between US $5.1 billion and US $42.3 billion, depending on the screening scenario, the intensity of screening, and the speed at which the program was rolled out [57]. So opportunistic rather than organized mass screening with VIA or HPV testing and treatment of pre-cancerous lesions have been advocated [58]. In a study of cervical cancer patients in Kenya, the lack of public education about cervical cancer was the barrier to screening. Additionally, fear of alteration in their body image, sexuality, reduction in fertility, and rejection by their spouse led to avoidance of care until they developed advanced cervical cancer [59]. Rojas [60] reported that women in parts of Latin America avoided screening because of fatalistic or religious beliefs.

Challenges of the infrastructure in the system also limit patient access to screening programs. In rural settings, providers are confronted with limited transportation, communication systems, infrastructure, shortages of health professionals, and restricted access to resources for diagnostics, prevention and curative purposes. In a major urban centre of Ethiopia, system delay and practitioner delay were found as the main hurdles within the variable of health care related challenges [61]. Various solutions ranged from improved community health education, patient navigators, and new techniques of self-testing. Community based participatory research can be effective in identifying cultural and

other barriers that limit utilization of screening services. WHO endorsed a three-stage process for strengthening policies and programs in order to establish large scale, sustainable services and effective policies for improved access to and quality of care [62,63]. The patient and the community issues need to be addressed in cervical cancer/pre-cancer screening, techniques and guidelines. Compliance with screening recommendations, the barriers in getting screened, collecting reports and follow up are the challenges and barriers in tracking results and returning for follow-up. Research is going on for future possibilities of biochemical and microbiological markers.

Diagnosis

Over the years various modes have been tried for diagnosis of cervical pre-cancer and cancer, but challenges also continue. Cervical cytology continues to be the most commonly used method. The conventional Pap smear requires special care to avoid air drying of the cells, a leading cause of poor slide quality and so poor reporting. The false negative errors may occur in sampling, preparation and interpretation of the slide because the disease may be in a small area, so exfoliation is less, or the device used for cytology may not pick the cells and transfer to glass slide or preparation errors due to poor fixation on the glass slide, leading to air drying, also create problem. The slide may also be obscured by thick vaginal discharge with mucus or blood, poor fixation. Liquid based thin layer cytology has proven to be more sensitive than conventional glass slide Pap smear because the cells do not clump on top of each other in the liquid based medium and there are less debris on the resulting slide. More intra epithelial lesions were identified [63]. Computer assisted diagnosis has come up with optical scanning by computer used for Pap smear interpretation, but differences in staining and the overlap of cells has made its practical application very difficult. E cardiograph involves photographing the cervix after application of acetic acid and the developed photographs, Cervi grams projected as slides and interpreted by specially trained persons, for accurate diagnosis are helpful as educational tools too, but are relatively expensive and require reliable logistics and infrastructure. Cervical biopsy with histopathology has remained the gold standard of diagnosis of cervical cancer. However, diagnosis is missed in presence of necrosis. Its utility for prognosis is a challenge. High cost imaging investigative modalities cannot be used for those who need the most. Staging continues to be a problem and sometimes unnecessary interventions are done for the disease because of resource crunch in places where the cancer is most common. Also, such techniques do not detect micro metastasis which affect prognosis.

Conclusion

Key goals in cervical cancer are to prevent pre-cancer by removing etiological factors, diagnose when it is pre-cancer with minimum resources to ensure high compliance with treatment specially in low-resource settings. However, in the regions where there is more cervical cancer, there are huge social and economic barriers for screening and treatment. Women sometimes have once-in-a-lifetime opportunity to access services. One of the major barriers to the success of cervical cancer screening programs is the failure of screening and screen-positive women to complete diagnosis, treatment and limitation of all available tests. This problem is more in LMICs, as women cannot afford to travel to health facilities multiple times. There are social and economic constraints. Effective tracking of patients does not take place owing to poor health information systems. Compliance with treatment can be improved by reducing the number of visits but over treatment and delayed treatments are also the issues. All said the risk of overtreatment far outweigh the risk of the women with high-grade lesions remaining untreated and subsequently developing invasive cancer. However, balance is must as every surgery has inherent complications.

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