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Invited critical review

Cervical cancer: Biomarkers for diagnosis and treatment

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ABSTRACT

Cervical cancer is a major gynecological cancer which involves uncontrolled cell division and tissue invasiveness of the female uterine cervix. With the availability of new technologies researchers have increased their efforts to develop novel biomarkers for early diagnosis, and evaluation and monitoring of therapeutic treatments. This approach will help in the development of early diagnosis and in increasing treatment efficacy with decreased recurrence. The present review explains the currently available biomarkers for cervical cancer diagnosis and prognosis. Apart from the currently available biomarkers the review also explains strategies for the development of biomarkers based on cellular and molecular approaches such as DNA, protein and other metabolic markers with suitable clinical examples. The investigations of specific proteins, enzymes and metabolites will establish more useful biomarkers for accurate detection and management of gynecological cancers especially cervical cancer.

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1. Introduction

Cancer is characterized by abnormal, uncontrolled cell proliferation due to genetic and epigenetic changes that regulate cell growth, differentiation and cell death. Cancer of the uterine cervix is the major cause of death from gynecological cancers in developing countries like India. Cervical cancers (80–90%) are caused by infection with high risk human papilloma virus (HR-HPV). They are mainly involved in the integration of viral DNA into the chromosomal DNA activating the proto-oncogenes to oncogenes, or in deactivation of tumor suppressor genes; this enhances the rate of cell proliferation, leasing to cervical intraepithelial neoplasia (CIN) [1]. The disparities in the evolution of diseases with similar clinical and pathological characteristics are probably related to macromolecular variations which have become the main

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feature in clinical diagnosis. The development of biomarkers by genomic and proteomic means holds the promise of individualized medicine, bringing a new dimension to disease analysis, classification and therapeutics [2].

The most common cancers among females are cancers of the breast, cervix, ovary, esophagus and mouth. Of these, cervical cancer is the second most common cancer among women worldwide, after breast cancer between 15 and 44 years of age [3]. The World Health Organization (WHO) reported that, cervical cancer comprises 12% of all cancers globally and it is the most common gynecological malignancy in the world [4]. The burden of cervical cancer in India is enormous, accounting for about 20% of all cancer-related deaths in women and it is the main cause of death in middle aged Indian women. It is estimated that there will be 16 million new cases by the year of 2020 [5].

2. The importance of biomarkers in cervical cancer

For many decades, the microscopic observation of biopsied samples has been the mainstay of screening/diagnostic processes, even though this technique suffers from intra-observational subjectivity. Therefore, despite numerous technical innovations that have been developed to detect cancer in their earliest stages of formation, unfortunately the detection of many cancers at the microscopic level is often too late for successful intervention [6]. Unlike many genitourinary infections, cervical cancer is not usually associated with immediate symptoms such as itching, burning or vaginal discharge [7]. The initial changes that may occur in some cervical cells are not cancerous. However, these precancerous cells form dysplasia or squamous intraepithelial lesions (SIL) within the epithelial or outer layer of cells.

Fig. 1 shows that the majority of all mild dysplasias regress spontaneously within less than a year. A proportion of the high-risk HPV infections will however become persistent and, if left untreated, proceed to high-grade lesions and invasive cervical cancer. A number of signs and symptoms of cervical cancer are associated mainly with the later stages of the infection (CIN 1, 2 and 3). Cervical cancer seems to be the most appropriate disease for the application of screening principles. The long transit time from early cervical atypia to invasive cancer provides an opportunity to identify pre-cancerous at a stage where safe and affordable treatment is available. In summary, the diagnosis and prognosis of asymptomatic, invasive disease is very poor but treatment of pre-invasive lesions is highly effective [8]. It is well established that no single screening method exists that is highly sensitive, highly specific, affordable and practical [9]. Historically, some screening tools (Pap smears and colonoscopy) have successfully reduced mortality through detection at early stages. Despite these successes, the field of detection has been plagued by problems of over diagnosis, inadequate specificity of individual markers (Cancer antigen-125, Carcino embryonic antigen), low compliance (colonoscopy) and a lack of analytical tools for discovering new detection methods. Hence there is an obvious interest in identifying markers that could complement standard cyto/histopathologic evaluation to determine the presence of cancer cells in tissues [10].

3. Biomarkers

According to the US National Institute of Health's (NIH) working group and the biomarkers consortium, "a biomarker is a characteristic that can objectively be measured as an indicator of normal pathogenic processes or a pharmacological response to a therapeutic intervention" [12]. The primary goal of biomarker development is not only focused on upgraded therapeutics but also focused on improved methods to determine an individual's risk assessment in cancer development, and to detect cancers at early stages, when they can be more effectively treated [11]. Biomarkers are generally found in the blood or tissues or other body fluids providing a sign of normal or abnormal processes or conditions. A biomarker may be measured by genetics, proteomics, cellular or molecular substances found in higher than normal amounts in the body fluids (blood, urine) of cancer patients [13]. An ideal biomarker test would have 100% sensitivity and specificity but none of the currently available biomarkers achieve this [14]. The clinical significance of tumor markers has been demonstrated in several studies which are listed in Table 1 (from the guidelines of the National Academy of Clinical Biochemistry (NACB)).

4. Cervical cancer biomarkers based on biomolecules

4.1. Molecular biomarkers

The major pathological event involved in cervical carcinogenesis is the integration of HR-HPV viral DNA into the host chromosomal DNA which initiates the formation of pre-neoplastic cells by the emergence of cell clones with deregulated expression of viral oncogenes in basal and parabasal cell layers finally leading to invasive carcinoma of the cervix. Hence, DNA based assays can be designed and applied to demonstrate the presence of the DNA responsible for cervical cancer [15].

HPV DNA is the only molecular marker developed for the diagnosis of cervical cancer. Molecular abnormalities such as chromosomal anomalies, DNA mutations, cell cycle check points, expression of oncogenes and tumor suppressor genes, apoptotic markers, epigenetic regulation (hypermethylation) have to be evaluated as markers based on their clinical utility [16].

4.1.1. HPV-DNA

Cervical cancer is a rare complication of a common cervical infection with a HR-HPV type. Persistent HR-HPV infection is necessary for the development, maintenance and progression of CIN 3 [17]. The detection of HPV DNA test alone is employed as a primary screening method to exhibit it as more sensitive than cytology among abundant clinical studies. Since HPV testing is more sensitive than cervical cytology in detecting CIN 2 and CIN 3, women with concurrent negative test results (Pap and HPV test) can be reassured that they have no risk of unidentified CIN 2, CIN 3 or cervical cancer [18,19]. Widschwendter et al. (2003) suggest that the serum HPV DNA might be a useful additional marker for early detection of recurrence in cervical cancer [20]. Recently, Campitelli et al. (2012) reported that mutation in HPV (insertion) constitutes a highly specific molecular marker of circulating DNA (ctDNA) in HPV-associated cervical cancer patients. Using this approach, ctDNA was detected in most of cervical cancer patients over stage I and the ctDNA concentration was found to reveal the tumor burden [21].

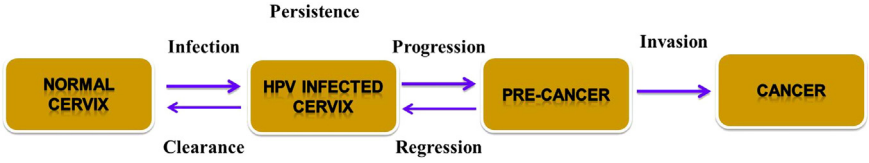

Fig. 1. From HPV infection to cancer: developmental stages of cervical cancer, in which the mild dysplasia regresses spontaneously within less than a year. A proportion of the high-risk HPV infections will however become persistent and may, left untreated, proceed to high-grade lesions and invasive cervical cancer.