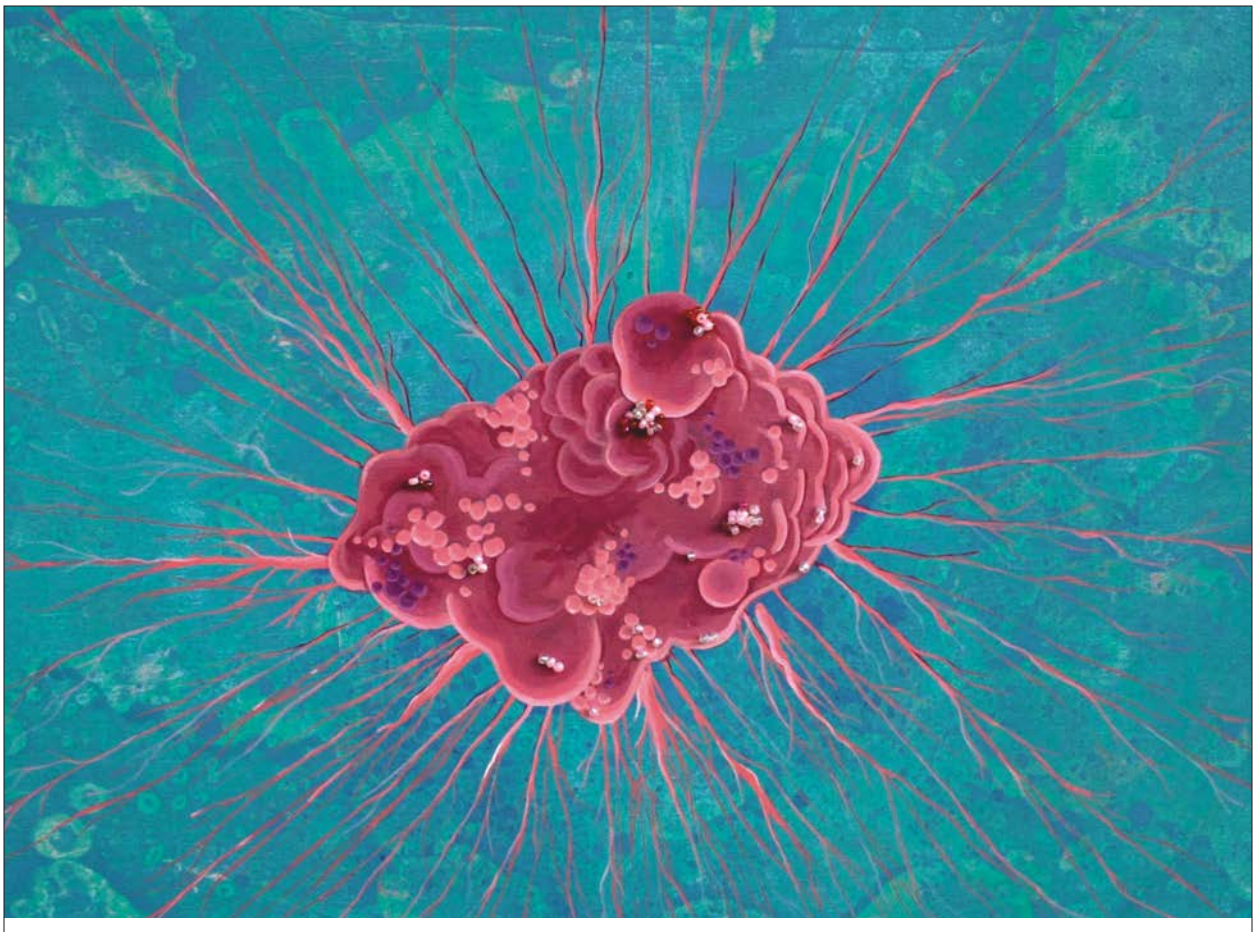

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Cervical Cancer: A Perspective on Recent Patents

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ABSTRACT

The multi-factorial events and complex molecular pathways that are involved in the pathogenesis of cervical cancer have made treatment difficult in the past. Fortunately, recent advances both in understanding the disease and in treatment strategies have led to the development of drugs, which target signaling molecules i.e., the root causes of the disease. Multiple patents granted in the field of cervical cancer include novel detection methods and therapeutic agents, but it remains to be seen how useful these advances are to the common man with respect to availability and cost. This review aims to highlight the recent patents granted in the field of cervical cancer treatment and detection.

Key words: Human papilloma virus, hypermethylation, biomarkers, histone methyltransferase

INTRODUCTION

Cervical cancer is defined as a cancer occurring in the cell lining of the cervix (Dunne *et al*., 2007). It is considered as, the fourth most frequent form of cancer among women worldwide (Cancer Research UK, 2014) and killed 265,000 women in 2012 (Cancer Research UK, 2014). The pathological stress is more towards Human Papilloma Virus (HPV) due to its early association with cervical cancer. There are 118 types of HPV that are described with possible risk. A few are given in Table 1 (De Villiers *et al*., 2004; Munoz *et al*., 2003; Berry *et al*., 1993).

HPV causes cancer only if it persists for a longer duration along with immune response failure and hence mere HPV exposure is not sufficient for a diagnosis of cervical cancer. Cervical cancer being a multifactorial event, various other cofactors such as age, persistent infections, smoking or multiple pregnancies show their contribution and motivate the high risk form, whereas low risk types are at low susceptibility to develop cancer (Adam *et al*., 2000; Magnusson *et al*., 2000; Wright *et al*., 2007). This review aims to highlight the recent patents granted in the field of cervical cancer treatment and detection.

STAGING OF CERVICAL CANCER

The International Federation of Gynaecology and Obstetrics (FIGO) have issued guidelines on the staging of cervical cancer. These stages are (Duenas-Gonzalez *et al*., 2003):

Table 1: Classification of types of HPV and their associated risk

Class	Type
Low risk	6, 11, 42, 43 and 44
High risk	16, 18, 31, 33, 34, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68 and 70
Cervical carcinoma caused	16, 18, 31 and 45

- Stage 0: The pre invasive stage that is restricted to cervical lining
- Stage I: Invasive form but confined to cervix and categorized into two stages
  - IA: It can be seen with a microscope
  - IB: It can be seen without a microscope
- Stage II: Invasive form that spreads out of the cervix. Again categorized into two stages-
  - IIA: Spreads within the vagina but not to the uterus
  - IIB: Spreads beyond the vagina
- Stage III: The cancer spreads to lower third portion of vagina
- Stage IV: The advanced form that spreads to other organs of body
  - Stage IVA: Cancer spreads to other organs close to the cervix
  - Stage IVB: Cancer spreads beyond the pelvic region to organs, such as; liver, lungs etc

TREATMENT

While surgery was the initial treatment mode for cancer (still utilized for early stages), it was realized that the disease complexity called for something more. Hence, chemotherapy with radiation therapy came to be utilized. Unfortunately, even these did not prove very useful in the treatment of metastatic cancers. Therefore, now a days we are looking to target the molecular basis of cancer by utilizing anti-angiogenetic agents or tyrosine kinase receptor antagonists.

Vascular Endothelial Growth Factor (VEGF) and basic Fibroblast Growth Factor (bFGF) are the two principal molecules released by tumour cells into the local tissue area that are implicated in angiogenetic stimulation. The endothelial cell surface contains receptors to which signalling pathway activating factors bind, resulting in new endothelial cell propagation. Now, degradative Matrix Metallo Proteinases (MMP's) are released into the surrounding tissue by the activated endothelial cells. The MMP's degrade the extracellular matrix causing endothelial cell migration, division and organization to form a new blood vessel network (Chawapun, 2006).

Promoting and inhibiting factors regulate normal cell growth but malignant tumours wreak havoc with the growth regulation cycle, causing unmitigated proliferation. Epidermal Growth Factor (EGF) and its receptor (EGFR) are involved in growth regulation. The EGFR belongs to a family of four receptors-EGFR (HER1/ErbB1), ErbB2 (HER2/neu), ErbB3 (HER3) and ErbB4 (HER4) (Chawapun, 2006). These cell membrane located receptors contain external binding domains which facilitate factor binding. This process results in receptor dimerization and activation of the Ras-Raf-mitogen activated protein kinase (MAPK) or phosphatidylinositol-3-kinase (PI3K) pathway causing angiogenesis, cell proliferation and cell migration (Baumann and Krause, 2004; Chawapun, 2006; Santarpia *et al*., 2012).

PATENT REVIEW COVERAGE

Recent years have witnessed a lot of growth and development in the field of cervical cancer especially with biomarkers or mechanical approaches being utilized to enhance cervical cancer detection. Epigenetic biomarkers have been identified for diagnosis of premalignant cervical cancer lesions. The genes GGTLA4 and ZNF516 were found to be hypermethylated in tumours (100% and 96%, respectively) compared to normal samples (Guerrero-Preston *et al*., 2014). This was accomplished using methylation specific PCR markers and subsequently quantifying the relevant protein expression. Detection systems utilizing HPV biomarker antibodies (Gombrich and Vichi, 2013) or specific probes capable of hybridization with a HPV polynucleotide target (Quint *et al*., 2014) have been developed too. Additionally, kits have been designed to measure a decrease or loss

of gene expression situated at the loci 3p1 1.2-p14.2 (Lyng and Lando, 2014) using specific gene binding nucleotide probes or antibodies binding to the gene encoded polypeptide. Advancements in detection using Sentinel Lymph Node (SLN) biopsy have also been made. The SLN is a diagnostic technique, wherein a lymph node is biopsied and examined for the presence of cancer. Depending on the proliferation of cancer in the sample, an idea about its metastasis in the lymphatic system is made. The technique thus prevents removal of all the lymph nodes (De Greve and Snyman, 2014). However, there is a risk of the biopsied sample not containing cancer cells, which could lead to an incorrect diagnosis (Nakabayashi and Hiyama, 2012). Specific molecular markers are being utilized to distinguish between lymph nodes negative for metastasis and positive for metastasis. This is accomplished by measuring the mRNA expression levels of the markers Serpin peptidase inhibitor, clade B member 5 (SERPINB5), Cytokeratin 15 (CK15), Cytokeratin 4 (CK4), Peptidase inhibitor 3 (PI3) and Annexin 8(ANXA8). The basic principle of this method states that atleast one of these markers will be expressed in samples that are positive for lymph node metastasis. Hence, if expression is observed, a correct diagnosis for lymph node metastasis can be made (Nakabayashi and Hiyama, 2012).

While the above mentioned tests are exceptional tools in detection of cervical cancer, immediate availability of the required equipment and other resources throughout the globe might prove to be a hindrance in their successful implementation. Since HPV presents in multiple forms, with some even resolving spontaneously, an initial, easy method to decide whether expensive confirmatory testing is required would be a blessing. Patterson recently elucidated a method which combines data garnered by measuring Mean Corpuscular Volume (MCV), nuclear to cytoplasmic ratio (NC ratio) and post Gi percentage data i.e., cells that have undergone the Gi phase of the cell cycle to decide, whether the tested sample has to be sent ahead for more time consuming and expensive tests (Patterson, 2014).

A few therapeutic options have also been developed specifically for cervical cancer. One of them involves administering Interleukin-20 alone or with other chemotherapeutic agents like bleomycin, methotrexate, cisplatin etc. or with surgery to remove cancerous lesions or with radiation. While, the dose of IL-20 is calculated by taking into consideration other factors like concomitant drugs, patient health etc, a range of 1-1000 μg kg^{-1} b.wt. is established (Chandrasekher and McKeman, 2014). A novel pessary has also been designed for cervical cancer treatment. This pessary makes use of 16-dehydropregnenolone (16-DHP) as the active ingredient (Lixin *et al*., 2013). 16-DHP causes tumour suppression by inducing G1 arrest through activation of the Ataxia Telangiectasia Mutated (ATM)-Checkpoint Kinase 2(CHK2)-Tumor protein p53 (p53) pathway (Ma *et al*., 2012). ATM is a serine/threonine protein kinase, which is activated by DNA strand breaks. ATM is responsible for phosphorylation and recruitment of several adaptor proteins including the effector kinase CHK2. CHK2 and ATM also phosphorylate p53, which gets activated and brings about a halt in the cell cycle and also mediates apoptosis. 16-DHP was formulated as a pessary because of its low bioavailability, short half life and rapid metabolism.

While the above patents relate to novel combinations or formulations, the next one relates to a new pharmacological agent. Suppressor of variegation 3-9 homolog 2 (SUV39H2) is a histone methyltransferase that methylates the H3K9 lysine residue located at the N-terminal of the core histone protein H3. Upregulation of SUV39H2 mediated methylation has been implicated in carcinogenesis and hence agents that could target this process were required. Hamamoto *et al*. (2014) synthesized double-stranded molecules (a sense and an antisense strand) that were able to penetrate cells and inhibit SUV39H2 gene expression as well as the downstream processes.

These agents have the general formula 5'-[A]-[B]-[A']-3' or 5'-[A']-[B]-[A]-3', wherein [A] acts as the sense strand marked for the target sequence and [A'] acts as its complementary antisense strand, while [B] is a spacer consisting of 3-23 nucleotides. Additionally, they also describe methods to evaluate the carcinogenic status of a patient. These methods utilize marker kits to measure the transcripted SUV39H2 mRNA, translated protein or biological activity of said protein.

CURRENT AND FUTURE DEVELOPMENTS

Cervical cancer is a disease which affects a majority of women globally and hence adequate treatment is necessary. The number of studies conducted bear testimony to the fact that the disease is one of the top priorities of the industry and the government. However, cervical cancer's different stages and conditions make therapy an onerous task. The future might yield better detection systems, which make use of more and more molecular markers to identify potential diseased candidates. These systems could also utilize refined techniques, so as to perform detection using minimum sample amounts. On the clinical trial front, there could be more utilization of existing drugs based on rationales which are yet unknown. These ideas could be based on physiological tumour mechanisms that are still unascertained. Chemotherapeutic agent development based on similar lines is also on the horizon. New drugs isolated from nature could begin a new era of treatments. With advancements in detection, treatment regimens and chemotherapeutic agents occurring every year, we can hope that the future holds promise of a cancer free world.

CONCLUSION

Cervical cancer is widespread among women worldwide, but even today, many do not know about the importance of diagnosing early and obtaining treatment. Although therapeutic options have come a long way from radiation and chemotherapy to utilization of specific molecular targets, a complete cure is still a distant dream. Developments in the field including; faster detection and better pharmacotherapeutic options will definitely help women throughout the globe.

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