Review on the Statistics of Cervical Cancer and its Biomarkers

Aditi Prasad¹, Sruthi SS Kumar² and Vaishnavi A.³
¹Student, Department of Biotechnology, BMS College of Engineering, INDIA.
²Student, Department of Biotechnology, BMS College of Engineering, INDIA.
³Student, Department of Biotechnology, BMS College of Engineering, INDIA.

¹Corresponding Author: aditip.bt18@bmsce.ac.in

ABSTRACT

The study's goal is to examine DNA-based nanobiosensors for cervical cancer detection, with an emphasis on statistical data on cervical cancer, which characterizes the problem of this illness impacting society and aids in better understanding the disease and its functioning in society affecting patients. From the point of diagnosis, numerous biomarkers for the detection of cervical cancer are also investigated.

Keywords- Human Papillomavirus, Mortality, Nanobiosensor.

I. INTRODUCTION

The human papillomavirus is a double-stranded DNA virus with approximately 100 genotypes. In women, HPV is the most common cause of cervical neoplasia and cancer, as well as the most common risk factor. The virus infects epithelial cells and is divided into two groups based on how it contributes to cervical cancer development: high risk and low risk. HPV possesses 14 high-risk genotypes, two of which, subtypes 16 and 18, are the most prevalent high-risk genotypes and are found in the majority of cervical cancers. Early diagnosis through screening techniques is crucial since this form of cancer is avoidable ¹.

Biomarkers for the onset of transformation processes in cervical cancer epithelial cells infected with the human papillomavirus (HPV). Some biomarkers, such as HPV E6, HPV E7, MCM, CDC-6, and p16ink4a, have demonstrated good diagnostic potential and have increased feasibility of application as alternative triage tests for visual inspection, thanks to improved understanding of biomarkers and cancer epigenetics. Because these indicators are involved in the cell cycle, they may be useful in the detection of cervical cancer.

II. DNA BASED NANOBIOSENSORS

There is a definite need for early diagnosis to prevent diseases from progressing to advanced stages, which may be supplied by these nanobiosensors, which enable easy, quick, cost-effective, and ultrasensitive detection for a variety of diseases. Based on DNA Nanobiosensors are biosensors that have the following components:

a. A biological recognition element, such as DNA.
b. Transducers that use nanostructured materials to translate molecular biological signals to digital or electric signals.
c. A signal processor capable of amplifying, quantifying, displaying, and analysing the signal transmitted by the transducer.
d. Last but not least, the analyte or target biological molecule for which the entire nanobiosensor is designed.

Immobilizing single stranded probes on different electrodes of the transducer, which is made up of nanomaterials such as semiconductor nanoparticles known as quantum dots (QD), nanotubes, nanorods, nanofibres, and so on, creates these Nanobiosensors. This improves the surface area of the transducers, resulting in improved electrical communication, increased catalytic activity, and high sensitivity when evaluating illness indicators ². Because of its excellent features such as molecular recognition, self-assembly, programmability, and implementation is relatively simple as its assembly can be controlled by base pairing, predictable nanoscale structure, easily synthesised, and of comparatively low cost, DNA is used as the molecule of choice for the biological recognition element or analyte ³.

There are various methods for producing nanoscale designs, but the top-down and bottom-up approaches are the most frequent. The biological recognition element (ssDNA) on the transducer can be immobilised through covalent contact, cross-linking, adsorption, or electrostatic interaction between DNA and a substrate, among other methods. In addition, the function of the transducer is dictated by the parameter to be monitored, resulting in electrochemical, optical, potentiometric, amperometric, piezoelectric, and acoustic waves, as well as calorimetric nanobiosensors ⁴.

III. CERVICAL CANCER STATISTICS

Cervical cancer is the most common cause of death among women in developing countries. Because 86 percent of all cervical cancer deaths occur in developing, low-, and middle-income countries, cervical cancer mortality is a metric of health inequity. India has had a national cancer programme since 1975, with an initial concentration on equipping premier cancer...
institutes, before changing to primary prevention and early identification of cancer cases in 1984–1985, and then to the district cancer control programme in 1990–1991. New regional cancer centres were being formed or recognised in 2008, existing regional cancer centres were being strengthened, and medical cooperatives’ oncology wings were being strengthened. New regional cancer centres were being formed or recognised in 2008, and existing regional cancer centres were being strengthened, as well as oncology wings at medical colleges.

Cancer control became a component of the National Programme for the Prevention and Control of Cancer, Diabetes, Cardiovascular Disease, and Stroke (NPCDCS) in 2010, a bigger, more comprehensive non-communicable disease programme that addresses shared risk factors in a coordinated manner.

The current study shows a retrospective examination of histologically established cervical cancer detected in TMH (Tata Memorial Hospital, Mumbai) between 2006 and 2008, of which roughly 75% received full therapy at TMH. This study was conducted in TMH by Ganesh Balasubramaniam, Rajshree H. Gaidhani, Arshi Khan, Sushama Saoba, Umesh Mahantshetty, Amita Maheshwari.

- Data: A total of 2428 patients were identified and treated, with 1678 cases diagnosed between 2006 and 2008 being treatment naïve prior to registration at TMH (Tata Memorial Hospital, Mumbai) and so “Eligible” for this study. Survival rates and log-rank tests were calculated using an actuarial approach.

- Parameters: demographics, co-morbidities, tumor features, and treatment specifics such as surgery, radiation, and chemotherapy were all taken into account.

Stage II and Stage III jointly accounted for over 80 percent.

5. Treatment type:
Approximately 93.1 percent of patients completed the initial cancer-directed therapy in its entirety. Only 6.9% of patients were unable to finish the therapy.

Radiotherapy, either alone or in conjunction with chemotherapy, accounted for a significant share of the treatment offered to patients. Radiation was used alone in 37.0 percent of the cases, whereas radiotherapy in conjunction chemotherapy was used in 50.7 percent of the cases.

6. Type of Surgery:
Approximately 13.8 percent (231 patients) were surgically treated, with 10.7 percent (179 cases) undergoing “Radical abdominal hysterectomy.” Of those who received radiation, 1441 received “Tele-therapy” while 1051 received “Brachytherapy.”

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Figure 1: Distribution of patient’s general and clinical characteristics

1. Residence and marital status:
Outside of Mumbai, 76.2 percent were non-residents, 74.6 percent were married, 49 percent were literate, and 86.1 percent were Hindus, with 7.9 percent Muslims.

2. Co-morbidities:
Hypertension, diabetes, and acquired immunodeficiency syndrome/human immunodeficiency virus (AIDS/HIV) were all present in 12.9 percent, 6.7 percent, and 3.3 percent of the participants, respectively.

3. Histology:
Squamous cell carcinoma accounted for 89.5 percent of the patients, with adenocarcinoma accounting for 5.8%.

4. Disease stages:
In Stage I, Stage II, Stage III, and Stage IV, the distribution was 12.9 percent, 33.8 percent, 45.7 percent, and 6.8 percent, respectively.

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Figure 1: Distribution of cervical cancer from a study conducted in India Ganesh Balasubramaniam, Rajshree H. Gaidhani, Arshi Khan, Sushama Saoba, Umesh Mahantshetty, Amita Maheshwari
The survival rates were calculated in percentages over a period of five years.  

1. **Age:**
   Those under the age of 50 had a greater chance of surviving than those beyond the age of 50.

2. **Residence and Education:**
   Patients who lived outside of Mumbai had a somewhat better survival rate than those who lived in Mumbai. Between illiterates and literates, there were fewer variations in survival rates.

3. **Religion and Marital Status:**
   There were variations in survival rates across religious groups, although they were statistically inconsequential.

4. **Co-morbidities:**
   There were no variations in survival rates between those with and without co-morbidities (hypertension, diabetes, and AIDS/HIV).

5. **Histology:**
   There were no statistically significant variations in survival rates depending on histological categories.

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Figure 2: Survival rates (%) by patients characteristics and stage of the disease respectively (Survival rate of cervical cancer from a study conducted in India Ganesh Balasubramaniam, Rajshree H. Gaidhani, Arshi Khan, Sushama Saoba, Umesh Mahantshetty, Amita Maheshwari)
6. Illness Stages:
The stages of the illness were a significant element in determining survival rates. The 5-year survival rates for Stage I, Stage II, Stage III, and Stage IV were 84.4 percent, 80.3 percent, 65.9%, and 37.1 percent, respectively. As the severity of the condition worsened, the survival rate declined, as seen in the graph above. The lowest rates were found in Stage IV. As a result, changes in survival rates across illness stages were statistically significant.

7. Types of Treatment method:
Only patients that completed therapy, 1562 (93.1%) were included for analysis. Graph 2 shows that individuals who were treated with surgery alone (95.6%) or in conjunction with radiation (90.6%) had the best results. Those treated with chemotherapy alone had the poorest prognosis (15.9 percent). The most favored treatment, either alone or in combination with other treatment modalities, was radiotherapy, and the differences in survival rates across treatments were extremely significant (P 0.001).

8. Treatment based on stage:
In each of the phases, there was statistically significant difference in survival rates between treatments.
In Stage I, individuals who were treated with surgery alone (95.6 percent) had the greatest results, followed by those who were treated with surgery and radiation (95.6 percent) (92.3 percent).

Stage II: rates were greatest for those treated with surgery and chemotherapy (88.9%), followed by irradiation and chemotherapy (85%); the majority of patients in this stage were treated with radiation.

Stage III: The majority of patients treated with either radiation alone or radiotherapy plus chemotherapy had survival rates of 61.7 percent and 71.1 percent, respectively, in Stage III

Stage IV: patients who received radiation in addition to chemotherapy had the greatest survival rates (49.3 percent).

Finally, it was determined that younger patients, early stage illness, non-involvement of any sites/nodes, and radiation, either alone or in conjunction with other types of treatment, resulted in improved results. Early detection and prevention strategies are keys to obtain better outcomes.

IV. BIOMARKERS OF CERVICAL CANCER

Biomarkers are chemicals, genes, or proteins found in a certain organism that are linked to a disease. Enzymes, carbohydrates, proteins, DNA, RNA, or any other type of molecule could be included. HPV E6, E7, MCM, CDC6, and p16ink4a are some of the biomarkers used to determine the existence of cervical cancer. These biomarkers aid in the detection of commencement of transformation, cell cycle regulation, biomarker transformation, established cell lines, immortalization of primary cell lines, and chromosomal stability regulation in human papillomavirus infected cells.

The carcinogenic potential of these human papillomaviruses (HPV) has been detected in HPV types 16, 18, and 45, but the oncogenicity of other viruses is less than that of these strains. HPV is made up of an 8-kilobyte double-stranded DNA molecule. E6 and E7 proteins are biomarkers with carcinogenic characteristics.

4.1 Cervical Cancer Molecular Biomarkers
4.1.1 HPV E6

E6 is a larger protein with 150–160 amino acids and an 18 kDa protein coding for it. It is divided into two zinc finger binding domains by four Cys-X-X-Cys motifs, which are assumed to be responsible for the protein's oncogenicity. The carboxy terminal domain's PDZ-binding motif is responsible for interacting with many biological proteins.

By boosting proteasome-dependent degradation, the E6 oncoproteins of the high-risk human papillomavirus (HR-HPV) affect the function of the p53 protein. In cells, p53 acts as a tumour suppressor protein. E6-AP, a cellular E3 ubiquitin ligase complex, links HPV E6 to protein p53. The p53 protein is now marked for degradation by the 26S proteasome. By transferring ubiquitin peptide from the complex to the p53 protein, it marks it for degradation by the 26S proteasome.

The proteasome pathway is unable to degrade the cellular p53 protein in low-risk HPV E6 proteins. E6-induced cellular transformation includes the loss of p53 as a crucial component.

4.2.2 HPV E7

E7 is the most recent HPV oncogene to be discovered. It's a small, 100-amino-acid phosphoprotein with three conserved regions 1/2/3 (CR1/2/3). A small portion of CR1 and nearly the whole amino terminus of CR2 have sequence similarities to adenovirus (Ad) E1A proteins and the large T antigen of SV40. The CR2 domain begins with a sequence that is poorly conserved and then moves on to the CR3 region. The CR3 region of the carboxy terminus encodes a zinc finger domain with two CXXC motifs separated by 29 amino acid residues. It is responsible for zinc-dependent dimerization as well as E7 interaction with cellular proteins.
4.2.3 Mini chromosomal maintenance (MCM) and Cell division cycle protein 6 (CDC6)

MCM and CDC-6 work together to form a complex that keeps cells licenced. Because of a mechanism called licencing, DNA replication occurs just once each normal cell cycle. The development of a protein complex involving the MCM proteins and the cell division cycle protein 6 is required for this process. 5 (CDC) Eukaryotic DNA replication is regulated by both MCM5 and CDC6. CDC6 is a polyclonal antibody used to detect cervical dysplastic cells in biopsies and smears. CDC6 protein expression is seen in proliferating cells, but not in differentiated or quiescent cells, in the same way that MCM is. CDC6 staining is often absent or restricted to the basal proliferative layer in normal cervical epithelium. In squamous and glandular cervical carcinomas, however, CDC6 protein expression is significantly higher.

4.2.4 p16INK4A

p16INK4A, a tumour suppressor gene, also regulates cell cycle. Using tissue sections and cervical smears, researchers looked into the expression pattern of p16INK4A in dysplastic squamous and glandular cervical cells. Gene products that are overexpressed in HPV-transformed cells as a result of the production of the transforming viral oncoproteins E6 and E7 could be used to replace proliferation-associated proteins. In normal cells, the p16INK4A protein is a cyclin-dependent kinase inhibitor that regulates cell cycle progression (Figure A). p16INK4A inhibits phosphorylation of the cyclin D-dependent kinase 4 and 6 complex, causing hyperplasia. 6

Increased free E2F then activates S-phase progression genes, causing the cell to enter the S-phase of the cell cycle and bypassing the G1/S-phase restriction. Increased p16INK4A levels result in less active phosphorylation of CDK4/cyclin D, which prevents the latter complex from phosphorylating pRB. As a result, less free E2F accumulates in the nuclei of the relevant cells. The biological ramifications are cell cycle arrest and senescence. In cells expressing high levels of p16INK4A, cell cycle arrest seems to be irreversible. As a result, genomic damage induced by genomic stress, such as oncogene activation, ageing, or other conditions that can cause the p16INK4A locus to activate, is effectively protected. 6th. Cells that have experienced genotoxic damage as they age, cells that have difficulty with cellular maturation and differentiation, and cells with activating oncogene mutations all have greater levels of p16INK4A expression.

The processes that cause the expression of p16INK4A to be triggered are currently unknown. A variety of cellular stress inducers cause demethylation of the histone K27 marks, which may affect the histone architecture of the p16INK4A locus. Increased E2F activity in cycling cells may trigger an autoregulatory mechanism, leading to overexpression of the p16INK4A gene product 6.

4.2.5 Why are E6 and E7 oncoproteins chosen?

The E6 and E7 genes, which were found to be the most essential determinants in cellular transformation induced by high-risk HPV, were discovered to be the most important determinants in cellular transformation caused by high-risk HPV. A section of the HPV genome's E6 region has been

Figure 7: Viral and Cellular Biomarkers in the Diagnosis of Cervical Intraepithelial Neoplasia and Cancer (Magnus von Knebel Doeberitz, Miriam Reuschenbach, Dietmar Schmidt & Christine Bergeron (2012) Biomarkers for cervical cancer screening: the role of p16INK4a to highlight transforming HPV infections, Expert Review of Proteomics, 9:2, 149-163)
identified as a biomarker due to its unique region characteristic. The E6 region is used to code for an oncoprotein with strong transforming activity. Following infection, it can also sustain HPV carcinogenic regions, whereas E2 and L1 can be removed. Significant sequence conservation can also be found in the E6 region, which distinguishes between high-risk and low-risk HPV strains. During double-strand denaturation cell repair procedures, HPV DNA gets unintentionally incorporated.

Even in advanced stages of cervical cancer, inhibiting E6 and E7 can help prevent it from developing. Cancer cells senesce or die in the absence of E6 and E7 activity, according to several in vitro and xenograft studies, demonstrating that E6 and E7 are definitely essential for the persistence of HPV-mediated malignancy. E6 and E7 contribute to the six key hallmarks of cancer by contributing to several metabolic pathways that urge a cell toward malignancy. Both E6 and E7 are polycistronically transcribed from a single promoter at the upstream regulatory region's 3' end (URR). Several transcription factors, such as AP1 and SP1, which function by binding to the URR region, regulate E6/E7 transcription.

4.2.6 Manipulation of Cancer Markers:

E6 and E7 contribute to the six basic cancer hallmarks through a variety of molecular pathways, which can lead to malignancy in a cell. The processes by which the oncogenes E6 and E7 produce each of the phenotypic hallmarks of cancer are listed below:

1. Resistance to Growth Suppressors
2. Cell Death Resistance
3. Sustained Proliferative Signaling
4. Enabling Replicative Immortality
5. Angiogenesis Induction
6. Activation of Invasion and Metastasis

E6 and E7, popularly known as "HPV oncoplayers," are the key drivers of cervical carcinogenesis as an outcome. They are in responsible of everything from angiogenesis and invasion to metastatic phases, as well as the maintenance of continuous proliferative signals, tumour suppressor escape, and telomerase activation. E6 and E7 cooperate together to establish all six hallmarks of cervical cancer and contribute in its successful progression.

V. CONCLUSION

To summarize, cervical cancer is one of the most common cancers, accounting for a large number of deaths worldwide. We may deduce from the data that those under the age of 50 have a better chance of surviving, that the presence or absence of co-morbidities (hypertension, diabetes, and AIDS/HIV) had no effect on survival, and that the stage of the disease was an important determinant. The importance of early detection and preventative methods in achieving improved outcomes cannot be overstated. Biomarkers that indicate the start of transformation processes in HPV-infected epithelial cells are becoming a focus of cancer prevention research in areas like cervical cancer. P16INK4A plays a role in cancer prevention and detection. Cervical cancer is detected using DNA nanobiosensors which have the advantages of low cost, simplicity, and ease of downsizing. These nanobiosensors are the multidisciplinary technology which creates a room for integrated innovative solutions for the health care problems and also can potentially help in increasing the health care system mainly with respect to diagnosis. However few challenges are also faced while designing and functioning, especially in case real-time detection/diagnosis. But with the help of rapidly growing nanotechnology and biotechnology, it is possible to overcome certain challenges leading to the efficient diagnosis in the future.

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