ISSN: 0976-3031

Available Online at http://www.recentscientific.com

International Journal of Recent Scientific Research
Vol. 7, Issue, 7, pp. 12487-12491, July, 2016

International Journal of Recent Scientific Research

Research Article

DESIGN AND CHARACTERISTIC STUDY OF NANOWIRE BASED BIOSENSOR FOR CERVICAL CANCER DETECTION

Gopinath P.G[1]*., Anitha V.R[2]., Aruna Mastani S[3]

[1]Department of ECE, JNTUA, Anantapuramu, Andhra Pradesh, India
[2]Department of ECE, Sree Vidyankethan Engineering College, Tirupati, Andhra Pradesh, India
[3]Department of ECE, JNTUA College of Engineering, Anantapuramu, Andhra Pradesh, India

ARTICLE INFO

Article History:

Received 15th April, 2016
Received in revised form 25th May, 2016
Accepted 23rd June, 2016
Published online 28th July, 2016

Key Words:

Cancer, Cervical Cancer detection, Biomarker, Nano biosensor

ABSTRACT

Today, Cancer is a common term in India as the perception of cancer incidence gets increases. The global focus is on cancer awareness, early detection, diagnosis, and availability and affordability of treatment in all cancers. Cancer is a disease caused by the uncontrolled growth and proliferation of cells and it is the second most common disease in India which is responsible for maximum mortality with about 0.3 million deaths per year. Cervical cancer is the most important cancer in women in India over the past two decades. In this paper we reviewed and studied the cancer disease, cervical cancer, biomarker and its equation related to the detection and simulated the nanowire based biosensor model and the proposed model consist array of nanowire based biosensor which detects the cervical cancer concentration in the given sample effectively.

INTRODUCTION

Cancer is a disease in which abnormal cells divide without control and are able to invade other tissues. [1],[2]. Cancer cells can spread to other parts of the body through the blood and lymph systems. Cancer is not just one disease but it is the group of many diseases. There are more than 100 different types of cancer. All cancers begin in cells which is the basic unit of human body. The body is made up of many types of cells. These cells will grow as well as divide in a controlled way to generate more number of cells as they are needed to keep the body healthy. When these cells become old and damaged, they die and are replaced with new cells. However, sometimes this orderly process goes wrong. The DNA of cell can become damaged or changed, producing mutations that affect normal cell growth and division. When this phenomena happens, cells do not die. The extra cells may form like a mass of tissue called as tumor. Possible signs and symptoms includes for a cancer is a prolonged cough, new lump, unexplained weight loss abnormal bleeding, and change in bowel movements. [2] While these symptoms may indicate cancer they may also occur due to other issues, on Indian scene 1.1 million new cancer cases were estimated, indicating that as a single country(out of 184 countries) contributing to 7.8 % of global cancer burden, mortality figures were 6,82,830, contributing 8.33% of global cancer death[4]. All types of cancers have been reported in Indian population including the cancers of breast, rectum, stomach, prostate, liver, cervix, skin, lungs, esophagus, bladder, mouth, blood, etc. The causes of such high incidence rates of these cancers due to both internal (hormonal, poor immune conditions genetic, mutations) and external or environmental factors (over growth of population, food habits, industrialization, social etc.).[5] Employing the life table methodology for estimates, the current probability of developing cancer of all sites from 35-64 years is 4.67% in males and 6.55%in females while life time risk will be found 9.05% and 10.2% respectively.

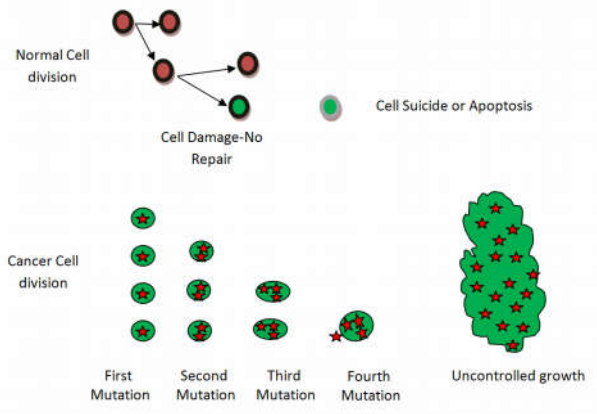

Fig. 1 Normal and Cancer cell division

*Corresponding author: **Gopinath P.G***
Department of ECE, JNTUA, Anantapuramu, Andhra Pradesh, India

The greater risk in females is mainly due to the high risk of development of cancer of the uterine cervix and breast. When the age-period of 35 to 70+ years considered, the probability percentage was found to be 9.94 % in males whereas it was11.6% in females. According to these estimates 1 in 8 women and 1 in 10 men in India can expect develop cancer of any form, in their life span after the age of 35 years.[6]

Cervical Cancer

Cancer is a disease caused by the uncontrolled growth and proliferation of cells. Cancer is a disease which affects the lining of the cervix, the lower part of the uterus, known as cervical cancer. An Inner lining of the cervix consists of two cell types, the squamous and the columnar cells. The region in cervix where there is a transition from one cell type to another is called the squamo-columnar junction. This is the area that is most prominent to develop cancer. Cancer of the cervix develops gradually and becomes fully spread over a period of time. The abnormal changes that the cervical cells develop transform them to a pre-cancerous state which is called as Cervical Intraepithelial Neoplasia (CIN). Based on its intensity, these changes are classified as low grade CIN and high grade CIN. This makes eventually progress to form a localized cancer. The cancer later spreads to adjacent tissues and even distant organs [17].

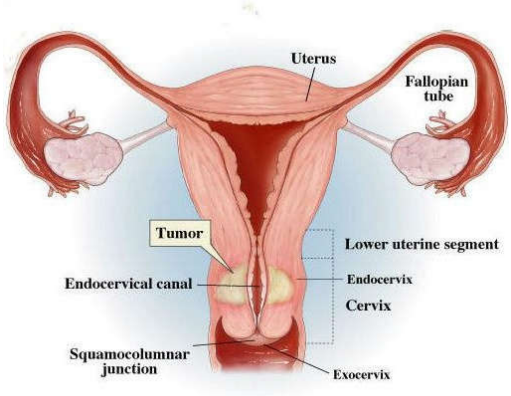

Fig.2 Cancer tumor in the region of cervix
[Image courtesy: http://zampetoglou.com/]

Cervical cancer has been the most important cancer in women in India over the past two decades.[7] Cervical cancer takes either the top or 2nd rank in all developing countries including India, but it does not find a place in the top 5 cancers in any of the rich countries[11]. Cervical cancer has major impact on woman's lives in worldwide and one in every five women suffering from cervical cancer belongs to India.[12]. Over the years, inspite of decreasing the number of cases of cancer, Gynecological cancers have increased in India and are estimated to be around 1,82,602 by the year 2020 constituting about 30% of the total cancers among women in India. Among these cancer of the cervix followed by ovary and corpus uteri is the major contributions. In the year 2010, around 68,903 cases of cervical cancer are estimated to occur which may decrease to 53,654 cases by the year 2020. Poor sexual hygiene, repeated child birth, Early age at first intercourse, multiple sexual partners, etc are some of the reproductive risk factors for cervical cancers. Improvement in living standard of women has resulted in a reduction in the incidence of cervical cancer. Epidemiological studies identified a number of risk factors such as infection with certain oncogenic types of human papillomaviruses, low socioeconomic status, infection with Chlamydia trachamatis, micronutrient deficiency, tobacco smoking, and a diet deficient in vegetables and fruits, that contribute to the development of cervical cancer. Regular cervical cytology examination by all women who have initiated sexual activity can prevent the occurrence of cervical cancer. [8]. Oral cavity, Lip & Pharynx Cancer in Men & Cervical Cancer in woman is the most common cancer responsible for the death in India, based on the study conducted & US National Institute of Health funded by Bill & Melinda Gates foundation. Tobacco-related and cervical cancers at earlier detection are treatable cancers would reduce cancer deaths in India, particularly in the rural regions that are underserved by cancer services. The large variation in cancer rates in India suggests that other risk factors or causative agents that remain to be discovered. The results of nationally representative mortality survey confirms that the cancer is an important cause of adult deaths in India with more than 70% of fatal cancers.[9]. The control of cancer is required with the effective implementation of knowledge derived from more than two decades of successful research. It is now known that over one-third of cancers are preventable, and one-third potentially curable provided they are diagnosed early in their course. The quality of life of patients with incurable disease can be improved with palliative care.[10]. Cervical cancer begins with the development of precancerous benign lesions in the cervical area. According to WHO classification, the first stage of the development of cervical cancer is mild dysplasia, then progress to becoming moderate dysplasia, severe dysplasia, and then invasive cervical cancer or carcinoma in situ(CIS). Mild dysplasia regresses on its own without treatment. A small percentage of women with mild dysplasia, however, sometimes it will progress to more severe forms, although this can take as long as 10 years. Women with moderate to severe dysplasia are at high risk of developing invasive cervical cancer, although the progression from severe pre-cancerous injury to cancer may take several years as well. Cancer of the cervix can develop in women of all ages but it usually develops in women aged 35-55 years. Early detection predicts better prognosis, one of the most effective ways of preventing and controlling cervical cancer is early diagnosis and regular screenin. Despite the fact that more than 80% of cervical cancer cases are in developing countries, only 5% of women there have ever been screened for cervical abnormalities [13]

Biomarkers and Equations for Analyte Concentration

Every human cell type has a unique molecular signature which is called as biomarkers, which are identifiable characteristics such as activities or levels and it is the abilities of genes or proteins to perform their functions of a myriad of genes, proteins or other molecular features. [14].The process of these signature includes all diagnostic tests, imaging technologies, and any other objective measures of a person's health status. Biomarkers are subject to the dynamic modulation, and they are expected to enhance our understanding for the drug metabolism, drug action, effectiveness, and safety. Diagnostic and prognostic biomarkers are quantifiable qualities that help

clinical oncologists at the first interaction with the suspected patients. These particularly assist to identifying who is at risk, diagnose at an early stage and to select the best treatment modality and monitor response to treatment. These biomarkers exist in different forms; traditional biomarkers include those that can be assessed with radiological techniques like mammograms *etc.*, and circulating levels of tumour specific antigens.[15]

The fundamental limits in the concentration of biomolecules can be detected by any sensor under reasonable settling times in a diffusion limited regime and this limit is given by the simple scaling relationship,

$$\rho_0 t_s^{Md} \sim K_d \quad (1)$$

where M_d and k_d are sensor-dimensionality dependent constants, the reaction-diffusion equation that governs the dynamics of analyte capture, then provide a simple derivation of this scaling relationship (1) and it conclude relevance of this trade-off on nanobiosensors.

The surface of the sensor is functionalized with specific receptors for the target molecules. The rate of conjugation between the target and the receptors is given by

$$\frac{dN}{dt} = k_F(N_0 \quad N)\rho_S \quad k_R N \quad (2)$$

where N is the density of conjugated receptors, N_0 is the density of receptors on the sensor surface, k_F and k_R are the capture and dissociation constants, and ρ_S is the concentration of analyte particles at the sensor surface at any given time t. The first term of (2) represents the conjugation between the target and the receptors while the second term denotes the detachment due to thermal fluctuation $\rho_S$is determined by (2) as well as by the diffusion of target molecules set by the concentration gradient at the sensor surface which is given by

$$\frac{d\rho}{dt} = D\nabla^2\rho \quad (3)$$

where D is the diffusion coefficient of biological or chemical target molecules in the solution. The particle flux at the sensor surface is given by

$$I = D\int_{A_d} \nabla_N \rho \, ds \quad (4)$$

where I is the integrated incident flux to the sensor and A_d is the dimension-dependent area of the sensor surface.

The analyte concentration equation is given by[16]

$$N(t) = \rho_0 t\left[\frac{Ad}{C_0} + \frac{1}{K_F N_0}\right]^{-1} \quad (5)$$

ρ_0 is the equilibrium analyte concentration (6)

Where $C_0 = \frac{2\pi D}{\log\left[\sqrt{4Dt} + A_0 / A_0\right]}$

D is the diffusion coefficient of the molecules and A_0 is the radius of nanowires

Nanowire Biosensor

The device structure of nanowire bio sensors is shown in Figure 3 has an active channel made up of nanowires bridges between the source and drain and the silicon substrate (silicon dioxide) is used as gate. Receptors placed on the channel are used to detect the target molecules.

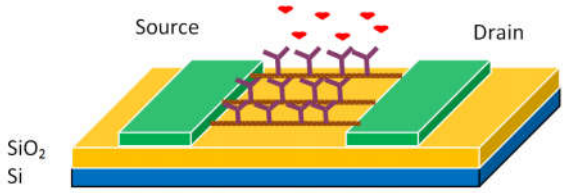

Fig.3 Nanowire biosensor

To predict the performance metrics for various types electronic biosensors and to focuses the sensor that can detect the presence of charged biomolecules near the sensor surface by electrostatic interaction the models are simulated. To avoid parasitic response, the surface of electronic biosensors is first functionalized with receptor molecules of known identity. When unknown target molecules are introduced to the sensor volume, they diffuse throughout the sensor volume and these molecules will be 'captured' by the receptors only if the target is a specific and exclusive complement to the receptor (lock and key principle). Bio-molecules like DNA carry negative charge under normal physiological conditions, while the net charge of a protein molecule depends on the pH of the solution. The excess charge of the receptor-bound target biomolecules modulates the conductivity of FET channel electrons via coulomb interaction. And this change in conductivity signals the presence of complementary target molecules in the solution [18].

Table 1 Nanowire sensor simulation parameters

Nanowire biosensor Simulation parameters	Value
Microfluid channel length	60 cm
Microfluid channel width	6 cm
Microfluid channel height	6 cm
Diameter of nanowire:	10 nm
Length	100 nm
Oxide Thickness	1 nm
Doping Density	$2x10^{20}$/cC
Type of Analyte	DNA
DNA Strand length(basepair)	20
Capture constant K_f	Iteration1 : $1x10^6$ Iteration2 : $3x10^6$ Iteration3 : $5x10^6$ Iteration4 : $7x10^6$
Disassociation constant K_r	1
Diffusion coefficient	10^{-6}
Incubation time	60 minutes
Temperature	300 k
Lower value of analyte concentration	10^{-15} molar units
Upper value of analyte concentration	10^{-6} molar units
No. of intermediate concentration steps	30
Minimum number of molecules	10
Analyte concentration	10^{-9}

The response of a biosensor is characterized in terms of its Settling time, Sensitivity and Selectivity. Settling time is defined as the time taken by the sensor to produce a stable signal change. It is determined by the concentration of the analyte bio-molecules. Sensitivity is a parameter which corresponds to the relative change in sensor characteristics upon attachment of the target molecules on the sensor surface. This is determined mainly by the geometry of the sensor and the characteristics of the fluidic environment. Selectivity denotes the ability of receptors to bind with the desired target in the presence of various other biomolecules and is entirely

determined by the functional schemes. Table 1 shows Nanowire sensor simulation parameter. Figure 4 shows that the settling time taken for the analyte concentration 10^{-9} is 0.01 seconds and settling time decreases with increase in analyte concentration. Figure 5 shows that amount of analyte concentration for time 1 second is 1.5x10-^{11}. Figure 6 shows that for the time 0.01 seconds (for the analyte concentration 10^{-9}) the detectable density of captured target molecule is 10^{7}.

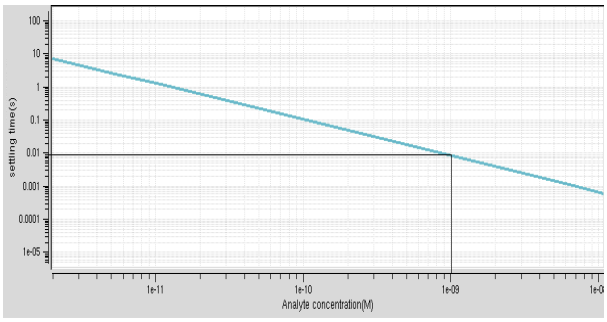

Fig.4 For Analyte concentration 10-9 the settling time is 0.01 seconds

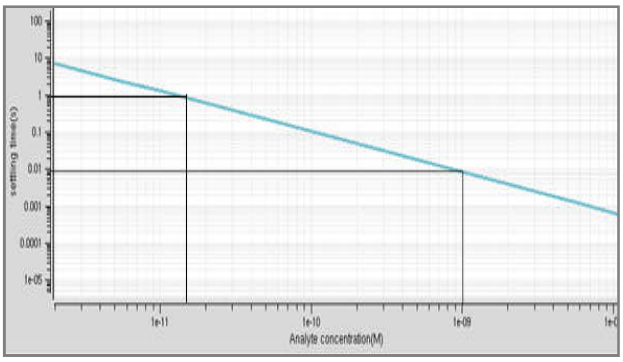

Fig.5 For Analyte concentration of 1e-09 setting time is 0.01 seconds and for 1 second of settling time the required analyte concentration is 1.5e-11

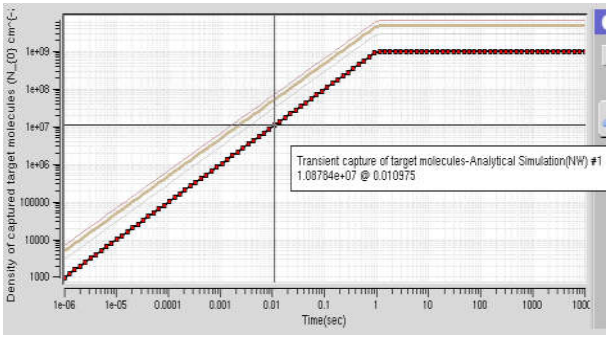

Fig.6 For Time T= 0.01 second the detectable density of captured target molecule is 10^{7}

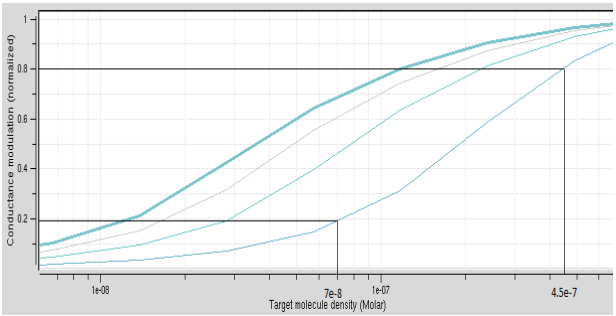

Fig.7 Normalized Conduction modulation value present between 0.2 to 0.8 (60 %) when target molecule density is between 4.5x10^{-7}to 7x10^{-8}

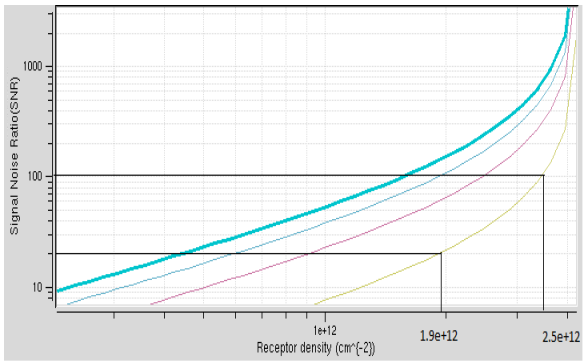

Fig. 8 To achieve Signal to noise ratio between 20 dB to 100 dB the receptor density value must be lies between 1.9x10^{12}to 2.5x10^{12}

Figure 7 shows Normalized Conduction modulation value present between 0.2 to 0.8 (60 %) when target molecule density is between 4.5x10^{-7}to 7x10^{-8}. Fig. 8 To achieve Signal to noise ratio between 20 dB to 100 dB the receptor density value must be lies between 1.9x10^{12}to 2.5x10^{12}. Simulations are performed by varying Capture constant K_f with for Iteration1: 1x10^{6}, Iteration2: 3x10^{6}, Iteration3: 5x10^{6}, Iteration4: 7x10^{6} as shown.

Design of Biosensor Array

The proposed design an array of biosensor since usage of a single sensor for the identification of disease does not give higher sensitivity. Therefore it is essential to use an array of biosensors to identify signatures produced from the array of sensors to detect disease. Figure 10 shows proposed nanowire biosensor array network and control unit for cervical cancer detection. Each of the sensors is made of biomarker and nanowire structure. The control unit consists of a user input or register that is connected to sensor array. The output of sensor array is current that flows from source to drain, at the output node the currents get added and the resulting current is used to detect the presence and concentration of cervical cancer concentration in a given analyte. The output node is connected to current reference circuits, and the node output adds up the current and the current to voltage converter determines the equivalent voltage of the sensor array network. The current flow is controlled by the concentration of target molecules present in the analyte. The input sequence scans the sensor array and thus the current value at every row are identified and are used to detect the presence of cervical cancer concentration in the analyte.

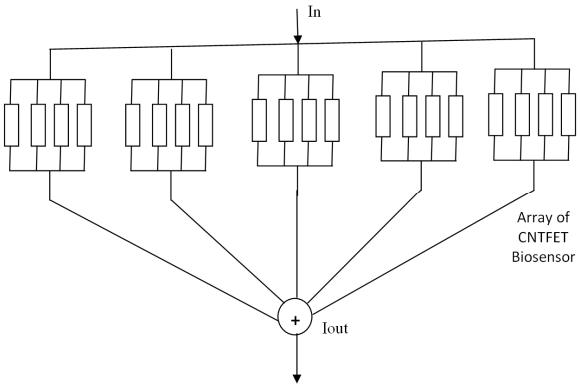

Fig.10 Array of Proposed Nanobiosensor for the detection of cervical cancer

CONCLUSION

In this paper we reviewed about the cancer, projections of cancer and the effect of cervical cancer as it has a major impact on woman's lives in India. In order to detect the cancer concentration in the given sample, study of biomarkers performed. In order to select the model of biosensor for effective performance, nanowire based biosensor model has considered and simulation performed with respect to different diameter. Finally we presented the typical array of biosensor model which will be used for the detection of cervical cancer to improvise the sensitivity and selectivity of the target molecules.

Acknowledgement

The authors would like to acknowledge Nanohub.org for providing permission to access the biosensor labs simulation tools and to carry out the experiments. The authors also acknowledge the support and guidance provided by Cyril Prasanna Raj P., MS Engineering College, Bangalore. His inputs and timely guidance has helped us to study and carry out the experimental analysis

References

1. "Cancer Fact sheet". *World Health Organization*. February 2014. Retrieved 10 June 2014.
2. "Defining Cancer". *National Cancer Institute*. Retrieved 10 June 2014.
3. "Cancer - Signs and symptoms". *NHS Choices*. Retrieved 10 June 2014.
4. Dhanjaya Sarath and Aparna kanna, "Current Status of Cancer burden: Global and Indian Scenario", *Biomedical Research Journal*, 1-5, 2014
5. Imran Ali, Waseem A. Wani and Kishwar Saleem" Cancer Scenario in India with Future Perspectives" Cancer Therapy Vol 8, 56-70, 2011
6. Nandagudi Srinivasa Murthy, Dinesh Rajaram, MS Gautham, NS Shivaraj, BS Nandakumar, Sreekantaiah Pruthvish, "Risk of Cancer Development in India" *Asian Pacific Journal of Cancer Prevention*, Vol 12, 387-391, 2011
7. A. Nandakumar, T. Ramnath & Meesha Chaturvedi," The magnitude of cancer cervix in India", *Indian J Med Res* 130, pp 219-221, September 2009
8. Ramnath Takiar*, Deenu Nadayil, A Nandakumar," Projections of Number of Cancer Cases in India (2010-2020) by Cancer Groups", *Asian Pacific Journal of Cancer Prevention*, Vol 11,1045-1049,2010
9. Rajesh Dikshit, Prakash C Gupta, Chinthanie Ramasundarahettige, Vendhan Gajalakshmi, Lukasz Aleksandrowicz, Rajendra Badwe, Rajesh Kumar, Sandip Roy, Wilson Suraweera, Freddie Bray, Mohandas Mallath, Poonam K Singh, Dhirendra N Sinha, Arun S Shet, Hellen Gelband, Prabhat Jha for the Million Death Study Collaborators," Cancer mortality in India: a nationally representative survey", Article, Published Online March 28, 2012DOI:10.1016/S0140-6736(12)60358-4
10. M. Krishnan Nair, Cherian Varghese, R. Swaminathan, Cancer: Current scenario, intervention strategies and projections for 2015, NCMH Background Papers· Burden of Disease in India, 219-225
11. V.Shanta, Chariman Cancer Institute (WIA) Chennai, Swaminathan, Chief Bio-statistician and Coinvestigator, Article-Population Based Cancer Registry, Cancer Institute (WIA) Chennai, 240-248
12. Aswathy S., Mariya Amin Quereshi, Beteena Kurian & Leelamoni K.," Cervical cancer screening: Current knowledge & practice among women in a rural population of Kerala, India", *Indian J Med Res* 136, August 2012, pp 205-210
13. World Health Organisation. Comprehensive cervical cancer control: a guide to essential practice. Geneva, WHO, 2006 Available at http://www.who.int/ reproductivehealth /publications/cancers/9241547006/en/index.html, 2009
14. Srinivas PR, Kramer BS, Srivastava S. Trends in biomarker research for cancer detection. Lancet Oncol 2001; 2: 698-704.
15. Anant Narayan Bhatt, Rohit Mathur, Abdullah Farooque, Amit Verma & B.S. Dwarakanath, "Cancer biomarkers - Current perspectives", *Indian J Med Res* 132, August 2010, pp 129-149
16. P. R. Nair and M. A. Alam," Performance limits of nanobiosensors", Applied Physics Letters, 88, 233120, 2006.
17. http://www.medindia.net/
18. https://nanohub.org/
19. Chang-Soo Lee *et al*.," Ion-Sensitive Field-Effect Transistor for Biological Sensing", Sensors 2009, 9, page no. 7111-7131; doi:10.3390/s90907111

****

How to cite this article:

Gopinath P.G., Anitha V.R., Aruna Mastani S.2016, Design and Characteristic Study of Nanowire Based Biosensor For Cervical Cancer Detection. *Int J Recent Sci Res.* 7(7), pp. 12487-12491.