

A Review on Preventive Measures for Cervical Cancer

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ABSTRACT

The present review is an attempt to compile information related to role of HPV and other causes along with their different stages for cervical cancer. The large number of deaths occurring globally due to cervical cancer gives researchers opportunities to explore more on this health issue. Many studies have confirmed that persistent infection with human papillomavirus (HPV) is the one of key component and drugs targeting and other available treatments for cervical cancer in women are also discussed here. The present study also focused on to incorporate the available diagnostics and therapeutics against the cervical cancer. This paper helps the readers to develop the new lab tests as well as drug molecules to tackle this worst health condition.

Keywords: Cervical cancer, Human papillomavirus, Pap test

INTRODUCTION

Cervical cancer is considered to be the most common cancer worldwide, specifically found in the female population, marked by uncontrolled cell growth in the cervix. [1] Women in developing countries are at higher risk due to lack of screening techniques. The statistical data from the survey depicts that in India, there were around 60,070 deaths estimated in a single year i.e. 2018 and the incidence of cervical cancer seems to take a hike every year. [2] In many studies, it was observed that the cause behind the infection is a virus known as the HPV (human papillomavirus) genotypes. Many studies have proved that the infection

caused by HPV is non-curable at the later stages, out of which majorly it leads to the risk of cervical cancer. [3] The early diagnosis and treatment (like vaccination) to be an effective preventive measure for reducing the peril of cervical cancer. Therefore, it is an important to analyze the causes and find out the ways to prevent from it. In the present study, the review of will have focus on various available preventive measures against cervical cancer in effective way. [4]

Preventive measures for cervical cancer: The infection by the HPV (mainly HPV 16 and HPV 18) is the main cause that leads to the development of cervical cancer which becomes more prominent if this virus persist for a long time in the body. The recent development of the vaccines against these HPVs is an emerging trend to prevent the risk of cervical cancer in women. The risk of cervical cancer increases with the lack of screening techniques predominantly in the developing countries. [5] As a result there were less than 50 percent of women who survived for more than 5 years in the developing countries and 66 percent of the 5 year survival rate was seen in the developed countries. The prevention of cervical cancer gives rise to many new opportunities since HPV is said to be the cause and preventing the infection by this virus can lead to decrease in the rate of cervical cancer. [6] Furthermore after the infection with the HPV development of the cervical cancer takes up to 10 to 20 years which helps to interfere before the development of cancer.

Vaccination as the primary prevention of cervical cancer The primary prevention can be attained by avoiding the infection of the HPV in the genital tract and also to prevent the persistent infection by the virus in cervix. By giving education about the infection of the HPV we can decrease risk of cervical cancer and also by the means of use of protective measures during sexual intercourse like condoms or mutual monogamy. [7] Even though these protectives are used to prevent the HPV infection but it cannot promise the prevention of the transmission of the virus. Hence, it cannot be relied upon. There are two main vaccines being developed for HPV which are prophylactic vaccines that used for the prevention of HPV infection and other related diseases. The other one is the therapeutic vaccine which cause deterioration of precancerous lesions or that cause the diminution of the progressive cervical cancer. [8] The therapeutic vaccine cannot be considered as a primary prevention since there is already existence of the disease. It has been found that the Virus like proteins (VLP) cause hormonal response with the antibodies which can be helpful in the development of the HPV vaccines and to check the immune response to HPV by the host. There were two controlled trials published by the pharmaceutical companies Merck and Co. Inc. [9] and GlaxoSmithKline which showed the proof for HPV vaccination. [10] In both the studies done it was seen that the vaccine showed 100 percent efficacy in preventing the persistence of HPV infection. It has been put forward that vaccination for the HPV types 16 and 18 alone has the capability to decrease the incidence of cervical cancer by 70 percent while if vaccination is done for the eight most commonest HPV types then the incidence of cervical cancer can be decreased to 95 percent. [6] The three prophylactic vaccines which are approved by the Food and Drug Administration (FDA) are Gardasil (Merck and Co, Bluebel 1, PA, USA), Gardasil 9 and Cervarix (GlaxoSmithKline, Rixensart, Belgium) LI

are known to exist and they have proved to be efficacious and safe to prevent the cervical neoplastic lesions but not the infection which are already established. [11] All the three vaccines are given in the series of three injections into the muscles for a period of 6 months. In 2016 FDA approved two doses for both girls and boys. [12] The protection from HPV by Gardasil was found to be 8 years and by Cervarix was 9 years. [13]

Secondary preventive measures for cervical cancer: The screening test can be considered as the secondary prevention for cervical cancer. The screening test involves visual test, cytological test and the test for HPV infection. The visual test was first introduced by Schiller in 1930s. [14] Even though they had limitations, they were inexpensive and delivered quick results. The visual testing can be done by the use of acetic acid (VIA) or Lugol's iodine solution (VILI) and the test is very helpful for the prevention of cervical cancer in the places where there is absence of the cytological test or HPV testing. This visual inspection is done by observing the cervix with a torch light after the interval of few minutes following the application of acetic acid to the cervix. The solutions can be conveyed to the cervix by a spray or a cotton swab. [15] It has been seen that any white color growth or area present in most part of the cervix or the squamocolumnar junction is the evidence of a positive visual test and in absence of these results it is considered as a negative test. [16] The color of the area remains dull white in cervical intraepithelial neoplasia while it turns dense in precancerous growth. Since the visual method had less specificity so it was soon replaced by the cytological methods. In one of the studies conducted by the International Agency for Research on Cancer showed that the presence of a definite screening procedure is helpful to decrease the risk of cervical cancer. [17] The study that was done on the specific age range in the Nordic countries in 1960s provided an idea that the important element to reduce the risk was the target age range

rather than the screening frequency of the specific age range. The results were in correlation with the estimation of the IARC that the screening interval up to 5 years can serve as protection if the screening procedures were well defined in the specific age group almost 80 percent. [18] The advancement and application of the cytology based screening systems like Papanicolaou (PAP) test which have been used to detect the precancerous lesions have shown to be very effective in the reduction of the death caused by cervical cancer. [19] The cytological screening can be difficult to accomplish even though if the liquid cytology can prove to be useful. The evidence that the liquid cytology will be more precise than the conventional Papanicolaou tests is still doubtful usually when HPV testing is done as adjunct. [20] On the other hand the liquid based cytology has decreased the amount of poor smear samples. HPV testing has also been recognized to one of the important screening technique in cervical cancer. [13] The test has been seen to maximize the sensitivity in detection of precancerous lesions in women with uncertain cytology. [17] It is also considered to be more sensitive but less specific compared to the cytological method of testing. [21] It was seen that when the HPV test was done as a follow up in the screening after the colposcopy it was able to detect the precancerous cells which could not be found. The IARC has authorized the use of the HPV testing as the primary screening in cervical cancer. [22] In 2011 FDA approved the use of HPV test along with Pap test. The American Cancer Society states that the HPV test and Pap test should be done together for every five years and this process is known as Co-Testing. A Pap test can also be done alone for women of age 30-65 for every 3 years. The guidelines also suggest that only a HPV test can be done for women of 21-29 years if the Pap test is found to be abnormal. The guidelines also state that screening is not compulsory for women below 21 years. The other screening test can be colposcopy and

biopsy. In colposcopy the physician can view the cervix by using a special magnifying device known as colposcope. Mostly colposcopy is followed by biopsy if any abnormal cells are found. The technique involved in biopsy is the removal of a tissue sample from the cervix which is checked under the microscope. [23]

Approaches for the management of cervical cancer The treatment of cervical cancer solely depends on the stage it belongs to, as shown in the clinical staging and surgical staging process. The clinical staging by the FIGO is the accepted one and it should not be reformed because of the surgical outcomes. [24]

Treatment for Stage 1A This stage is also referred to as the micro-invasive cervical carcinoma. It is named so because it has the minimum potential of metastasis and most probably can be cured by non-radical treatment. In this stage histological factors are used to regulate extend of operation and to determine whether the treatment of the lymph node is important. Usually in micro-invasive carcinoma the involvement of the nodal is less and the risk of nodal metastasis is seen mostly in the patients who have tumor emboli in spaces of the lymph. [25] If the tumor spread is found to be simple than the complete removal of the lesions can be done but if the tumor is found to spread than a prolonged operation should be performed.

Treatment for Stage 1A₁ This stage of cancer can be treated by conservative measures. There are two methods to treat the women in this stage which involves conization (taking a cone shaped tissue from the cervix) if women want to retain their fertility potential. This process of Conization can be used as a diagnostic tool and also helpful in removing the precancerous cells. The other treatment can be the method of hysterectomy for the women who do not desire to maintain their fertility. The involvement of the lymph node is very less in this stage but in cases of the lymphovascular invasion than radical surgery or radiation can be done. [26]

Treatment for Stage 1A2 In this stage the depth of the invasion of the cancer increases and because of the increase in depth there is high risk present in the involvement of the lymph vascular space and the metastasis of the pelvic node. It has been seen that the patients in this stage have 7 percent risk of acquiring nodal disease. [27] If the women want to retain their fertility than the treatment involved could be pelvic lymphadenectomy and radical trachelectomy or the other primary option would be radical hysterectomy. Radical trachelectomy is preferred in young women who are in the early stage of cervical cancer so as to maintain their fertility. It has been seen that 50 percent of the women suffering from cervical cancer are of age 40 or below and this treatment can be suitable for this category of women. [24]

Treatment for stage 1B and 2A The standard treatment of these stages is still not established. Most of the women of this stage are treated by radical radiotherapy or radical surgery. It was seen that both the treatment was found to be equally effective but differed in the morbidity rates. [28]

Treatment for stage 1B1 and early stage 2A: The primary treatment of this stage is pelvic lymphadenectomy and radical hysterectomy. When the pelvic lymph nodes are removed largely it is known as lymphadenectomy. The number of lymph-nodes to be removed by this process is 23-28. The advantage of the surgery is that it removes primary disease and also permits correct surgical staging. This allows adjuvant treatment to treat more accurately. [29] In a recent study it was revealed that the treatment of cervical cancer by laparoscopic supported by radical vaginal hysterectomy (LARVH) was seen to have the same efficacy as the radical hysterectomy. [24] Different findings have also shown the involvement of the para-aortic lymph nodes (PALN) which creates doubt in the treatment processes. The treatment of the patients who have shown to have positive PALN is extended radiotherapy and this has shown to achieve 30 to 40 percent survival

rate among the patients. It was also seen that the use of chemotherapy radiation along with cisplatin chemotherapy had been beneficial in women having PALN. [30]

Treatment stage 1B2 cervical cancer This stage is also considered as the bulky stage cervical cancer. Since the relapse rate of this stage is high related to stage 1B1 so, it becomes very difficult to choose any primary treatment for this stage. The patients in this stage are considered to be poor responder to radical surgery because eventually they require radiotherapy. Studies have shown that when the radical surgery is done after neoadjuvant chemotherapy to the patients in this stage there was improved survival rate. [31]

Treatment for stage 2B, stage 3 and stage 4A: These stages are also known as the advanced cervical cancer. The treatment of this advanced cervical cancer has been done majorly by radiotherapy but recent evidences suggest that chemotherapy should be included along with radiotherapy. The choice of treatment for the advanced and relapse cervical cancer is cisplatin based chemo-radiation. [32] The results of three RCTs showed that the survival rates are more by the use of chemo-radiotherapy rather than radiation alone in the patients with advanced stage of cervical cancer. [33]

Treatment for stage 4B The treatment for the patients suffering from this stage is palliative so it is very important to consider the toxicity profile and the quality of life of patients before the selection of treatment. There was a study done in a RTC for cisplatin and cisplatin plus topotecan which showed advantage in overall survival and measured quality of life. [34] It also discovered that the combined chemotherapy was more beneficial in survival rate even though it had higher risk of toxicity but it did not decline the quality of life.

CONCLUSION

In present study we have discussed about global prevalence of cervical cancer. The role of HPV in the pathogenesis of cervical cancer has been discussed. Apart

from this various methods which can be used for diagnosis and treatment of cervical cancer in stage wise manner has been also discussed.

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