

**REVIEW ARTICLE:****Intrauterine device and cervical cancer****Brahmana Askandar Tjokroprawiro\***

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**ABSTRACT**

From normal epithelial cells to invasive cervical cancer take a long time. It needs a step-by-step process. Normal cervical cells may be infected with the high-risk human papillomavirus (HPV). The infection may persist or be cleared. The HPV persistence may change normal cells to invasive cancer. Recent findings showed that the intrauterine device (IUD) might have a protective effect on cervical cancer. Inflammation in the cervix induces the immune response that may alter normal cells' progression to cervical cancer. This article will explain the change from normal cells to invasive cervical cancer, the role of the IUD in cervical cancer prevention.

**Keywords:** IUD; cervical cancer; HPV; immune response; cervical cancer prevention

**ABSTRAK**

Perkembangan dari sel epitel normal hingga menjadi kanker serviks invasif membutuhkan waktu lama yang memerlukan proses langkah demi langkah. Sel-sel serviks normal dapat terinfeksi human papillomavirus (HPV) risiko tinggi. Infeksi bisa berlanjut atau hilang. Persistensi HPV ini dapat mengubah sel normal menjadi kanker invasif. Temuan terbaru menunjukkan bahwa alat kontrasepsi dalam rahim (IUD) dapat memiliki efek perlindungan terhadap kanker serviks. Inflamasi pada serviks menyebabkan respons imun yang dapat mengubah perkembangan sel normal menjadi kanker serviks. Artikel ini menjelaskan perubahan dari sel normal menjadi kanker serviks invasif, dan peran IUD dalam pencegahan kanker serviks.

**Kata kunci:** IUD; kanker serviks; HPV; respon imun; pencegahan kanker serviks

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## INTRODUCTION

The Intrauterine device was considered a risk factor for cervical cancer because IUD may cause long-term irritation and promote cancer. The natural history of cervical cancer is well established, especially after the discovery of HPV as the cause of cervical cancer.<sup>1</sup> Recent studies showed surprising findings; IUD may prevent cervical cancer.<sup>2,3</sup> The development of cervical cancer started with the high-risk HPV infection that progresses slowly to invasive cancer. The intrauterine device may play a role in the natural history of cervical cancer.

## NATURAL HISTORY OF CERVICAL CANCER

One of the cancers that have a clear natural history is cervical cancer. Harald Zur Hausen studied HPV in cervical cancer in the 1970s and awarded The Nobel prize in medicine in 2008. He discovered that HPV causes cervical cancer. Cervical cancer may be considered as the result of viral infection.<sup>1</sup> There are more than 100 types of HPV, and 15 classes are categorized as a high-risk HPV that can change a normal cervix to cervical cancer if the infection is persistent. High-risk HPV types are HPV : 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, and 824. The most two most common type of HPV in cervical cancer is HPV 16 (57%), and HPV 18 (16%).<sup>5</sup> Not all HPV infected women will get cervical cancer. Most of them will be cleared. HPV persistency will change the cervical epithelial cells. Slowly the normal cells will turn into a precancerous lesion of the cervix if the HPV infection is persistent. It takes years for normal cells to change to malignant cells. The prevalence of HPV infection was studied in A meta-analysis by Bruni et al. involving 1.016.719. The global estimated HPV infection prevalence was 11.7%, and most of them were women less than 25 years old.<sup>6</sup> A Study by Munoz et al. showed that from 1793 patients, HPV was detected in 90.7% of patients. Among the HPV positive group, some patients were infected with a single HPV type (91.9%) and multiple types (8.1%).<sup>4</sup>

Human papillomavirus infects the basal cells of the stratified epithelium through a micro abrasion of the cervix. The viruses stay in the cell as an extra-chromosomal episome. In the early phase, the viral genome remains in low copy numbers. The virus' early genes E1, E2, E3, E5, E6, and E7 then help the viral replication. Protein E6 inactivates p53, and protein E7 inactivates pRb. These inactivations make the infected cells escape from cell cycle checkpoints and apoptosis. In the later phase, the viral genomes turn into high copy numbers and integrate with the host chromosome.

Infected basal cells differentiate into upper superficial cells, and in the superficial layer of the cervix epithelial, the viruses are shed and infect other cells. The most important step in cervical cancer carcinogenesis is the integration of the viral genome with the host chromosome. After integration, the cell loss its ability to control proliferation. Amplification of oncogenes and disruption of tumor suppressor genes occurs and makes the cells lose the control mechanism.

After infected with high-risk HPV, clearance or persistency will occur. If it is persistent, it changes to cervical cancer through some steps that are recognized as a precancerous lesion of the cervix. Based on the latest Bethesda system in 2014, the squamous lesion is divided into atypical cells of undetermined significance (ASCUS), a low-grade squamous intraepithelial lesion (LSIL), a high-grade squamous intraepithelial lesion (HSIL), and cancer. The ASCUS may back to normal as well as LSIL and HSIL. Once the cervix's epithelial cells turned into cancer, it could not back to the previous step. Sixty-one percent of women with LSIL returned to normal within 12 months, and 91% returned to normal within 36 months.<sup>8</sup> A High-grade squamous intraepithelial lesion consists of cervical intraepithelial neoplasia 1 (CIN-1) and cervical intraepithelial neoplasia 2 (CIN-2). Most of CIN-2 (74.7%) and CIN-3 (21.6%) will regress.<sup>9</sup> Systematic review by Tainio et al. showed that most CIN-2 patients would regress, and just less than one-fifth will progress. The regression rate is influenced by age, younger than 30 years old has a higher regression rate.<sup>10</sup>

The cervical cancer screening program aims are to detect a woman before she has invasive cervical cancer. Cervical cancer is one of the most preventable cancer. The natural history from a normal cell to cancer is clear and takes years. Cervical cancer also has a simple and practical screening modality, by performing cervical smear (pap smear) routinely. Human papillomavirus vaccine also decrease the risk of cervical cancer

## IMMUNE RESPONSE IN THE CERVIX

The infected epithelial cells may fight against HPV through an innate and adaptive immune response. An Innate immune response is the first-line defense mechanism against HPV infection. It induces natural killer-cells (NK-cells) activation and cytokines release. Some cytokines as tumor necrosis factor- $\alpha$  (TNF), interferon  $\alpha/\beta$  (IFN $\alpha/\beta$ ), and interleukin-1 (IL-1) play a role in inhibiting the virus growth.<sup>11</sup> Women with the elevation of interferon- $\alpha 2$  (IFN- $\alpha 2$ ), Interferon- $\gamma$ , interleukin-12 (IL-12), interleukin 10 (IL-10), interleukin 1 $\alpha$  (IL-1 $\alpha$ ), interleukin-6 (IL-6), interleukin-8

(IL-8) and tumor necrosis factor (TNF) has a higher clearance rate of HPV infection.<sup>12</sup> The Cellular innate immune response also has a role in HPV clearance. Reduced NK-cells cytotoxicity caused chronic HPV infection.<sup>13</sup> One of the mechanisms of HPV immune evasion is making NK cells less potent to the HPV.<sup>14</sup> Evasion of the immune response may cause carcinogenesis to occurs. It is challenging to study a cell-mediated immune response in HPV infection as HPV infection is a localized infection, not a systemic infection. Human papillomavirus is an epitheliotrophic virus, living in the epithelial cells, and there is no viremia.

A cellular-mediated immunity is also activated by HPV infection. There are 2 phases of cell-mediated immunity against HPV infection, the recognition phase, and the effector phase. In the recognition phase, The dendritic cells (DCs) recognize the virus and, via the major histocompatibility complex (MHC) molecules, present the virus antigen to the T cells. One of the factors that may induce carcinogenesis is the low distribution of DCs or the immature DCs. Low levels of DCs in the epithelial cells facilitate lesion progression. T helper cells (Th cells) and T cytotoxic (Tc cells) play a significant role in the effector phase. T helper cells help other immune cells by releasing cytokines, and T cytotoxic cells kill the HPV infected cells. A cell mediated-immunity is very important in HPV clearance. Evasion immune response by the HPV is the pivotal step of HPV infection persistence. The Protein of the virus is expressed inside the epithelial cells, and the cell does not lyse, so it is hard for APC to recognize the viral antigen. However, the precise mechanism of HPV clearance is still not completely established. The immune response to the HPV is a crucial factor for the progression to invasive cancer

## **INTRAUTERINE DEVICE AND CERVICAL CANCER**

The history of an intrauterine device (IUD) started in 1909 when Richard Richter, a German doctor, inserted a ring made from silkworm into the uterus. In 1967, Howard Tatum and Jamie Zipper introduced a T-shaped IUD covered by copper.<sup>15</sup> The copper IUD induces local intrauterine inflammation that kills sperms and changes the uterus' lining to prevent implantation. The copper added in the IUD works at the uterus's opening as spermicidal and destroys the eggs.<sup>16</sup> The other IUD is the levonorgestrel intrauterine system (LNG-IUS) that releases levonorgestrel (progesterone) intrauterine. It is

marketed in Europe and The United States of America (USA) since 1990-2000. The action mechanism includes thickening the cervical mucous to inhibit sperms' motility and thinning the endometrium to prevent implantation.

The cervix's transformation zone, ectocervix, and endocervix contained T-lymphocytes, natural killer cells, and antigen-presenting cells such as dendritic cells. Cervicitis increased the number of T-helper cells and T-cytotoxic cells. This study showed that in inflammatory conditions, immune cells are activated. The transformation zone of the cervix is the location where cellular-mediated immunity significantly increased if there is inflammation.<sup>17</sup> Trauma in the cervix, such as cervical biopsy, may increase the chance of regressing cervical intraepithelial neoplasia (CIN). The inflammation in the cervix may induce HPV clearance.<sup>18</sup> Insertion of the IUD may activate a cellular immune response that plays a significant role in HPV clearance. The Intrauterine device creates chronic sterile inflammation in the uterus and a long-lasting immune response and may reduce cervical cancer risk.<sup>2</sup>

LNG-IUS users had a higher concentration of inflammatory chemokines such as TNF- $\alpha$ , IL-1 $\beta$ , IFN- $\gamma$ , IL-12, IFN- $\gamma$  and IL-8 than non-user in the endocervical fluids. Human leukocyte antigen-DR (HLA-DR) is a marker for activated T-cells. The proportion of cytotoxic T-cells expressing HLA-DR in endocervix is higher in the LNG-IUS users than in non-users.<sup>19</sup> The importance of immune response in the progression of cervical lesions is shown in the study by Petry et al. Progressions of cervical lesions occurred in all patients with a low cytotoxic cell level.<sup>20</sup>

Several studies have been conducted to analyze the relationship between an intrauterine device and cervical cancer. The pooled analysis of 26 published articles and a meta-analysis of 16 published articles evaluated the odds ratio association between IUD and cervical cancer. Both studies support the benefit of an intrauterine device in reducing cervical cancer risk.<sup>2,3</sup>

Castellsaque et al analyzed 26 six studies in 2011, and the result of a meta-analysis by Cortessis et al. supports the finding of Castellsaque study. These studies are showing a lower risk of cervical cancer among IUD users. IUD's mechanism in lowering the risk is by preventing HPV infection progression to cervical cancer, not by avoiding women from HPV infection.

Table 1. Studies on association between IUD and cervical cancer

First Author	No of Studies Analyzed	Number of Case Participant (Cervical Cancer)	Number of Control Participant (No Cervical Cancer)	Odds Ratio for Association Between IUD and Cervical Cancer
Castellsaque et al <sup>2</sup>	26	2205	2214	0,55 (95% CI 0,42-0,70), p<0,00001
Cortessis et al <sup>3</sup>	16	4945	7537	0,64 (95% CI 0,53-0,77), p=0,037

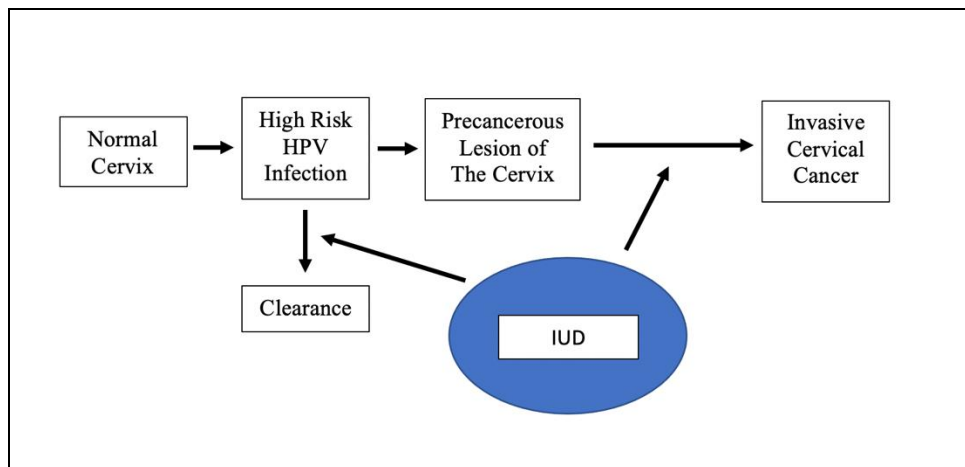


Figure 1. The postulated role of IUD in cervical cancer prevention. The Intrauterine device may induce an HPV clearance and also prevent the progression of precancerous lesion of the cervix

Intrauterine device users have the same risk as to the non-users in HPV acquisition. The HPV clearance rate is also the same in both groups.<sup>21</sup> Three HPV types that are most likely to persist are HPV 16, 58, and 31. Another study showed that IUD users were more likely to clear HPV than non-users.<sup>22</sup> Women with one high-risk HPV type had more benefit in HPV clearance by using IUD.<sup>23</sup> This finding is important as most women with cervical cancer were infected with only one HPV type.<sup>4</sup>

The precise mechanism of IUD in cervical cancer prevention is not well understood. IUD may induce chronic inflammation in the endocervix and ectocervix. This inflammation will modify the immune response in the cervix. A study conducted by Castellsaque et al. showed that the duration of IUD use does not affect the protective effect. Women who have used IUD for more than ten years have the same protective effect as the women who use IUD just less than a year.<sup>2</sup> He proposed a theory that trauma in the cervix caused by the IUD insertion induces chronic inflammation and long-lasting immune response. A study that supports this theory was done By Petry et al. Women who underwent a cervical punch biopsy has a faster and higher proportion of HPV clearance than women who did not experience a cervical punch biopsy.<sup>24</sup> The study conducted by Castellague et

al. and Petry et al. showed that local and short-term manipulation in the cervix might induce a long-lasting immune response.

The benefit of the intrauterine device in cervical cancer prevention is not justifying IUD as preventive modalities for all women to reduce cervical cancer risk. Pap tests and HPV vaccine are still the primary modalities in cervical cancer prevention. The findings that IUD may have a protective factor of cervical cancer are milestones for further randomized cohort and molecular study. The precise mechanism of IUD in cervical cancer prevention should be established. Explanation to the patient that the IUD as a protective effect of cervical cancer should be based on the evidence and without tendency. The Intrauterine device may be useful in cervical cancer prevention in the area where cervical screening is not always accessible. Pap smear and HPV vaccine are still highly recommended for cervical cancer prevention.

**CONCLUSION**

The natural history of cervical cancer is well established. Human papillomavirus is the cause of cervical cancer. HPV infected women may undergo

clearance or persistence. Recent findings showed that IUD might be a protective factor in cervical cancer. The intrauterine device may play a role in HPV clearance and inhibit the progression of the cervix's precancerous lesions. Further study is necessary to establish the precise mechanism of IUD in cervical cancer prevention.

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