International Journal of Scientific Advances
ISSN: 2708-7972
Volume: 6 | Issue: 4 | Jul – Aug 2025 Available Online: www.ijscia.com
DOI: 10.51542/ijscia.v6i4.1

Aggressive Cervical Cancer in Young Women: Immunobiology Perspectives

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ABSTRACT

Cervical cancer is one of the leading causes of cancer-related deaths in women, mainly caused by human papillomavirus (HPV). Due to HPV's nature and latency, patients are dominated by older women. The existence of aggressive cervical cancer in young women has raised concerns. Immune dysregulation, chronic inflammation, hormonal influences, and persistent HPV infection may contribute to a tumor-promoting microenvironment. Non-squamous histological types are frequently found in younger patients. Additionally, ongoing research regarding cervical cancer stem cells (CCSCSs) may also explain the rapid tumor progression and treatment resistance in this subgroup. This review will discuss how cervical cancer could present aggressive behavior in young women through immunobiological perspectives.

Keywords: cervical cancer; aggressiveness; young women.

INTRODUCTION

Cervical cancer is a major global problem, ranked as the fourth most common cancer in women. In 2022, an estimated 660,000 new cases were reported, with 350,000 deaths [1]. High-risk human papillomavirus (HPV) infection types 16 and 18 contributed to 70% of cervical cancer cases, making them preventable by early screening and vaccines [2]. However, in low- and middle-income countries, prevention protocols remain a challenge; thus, prevalence numbers are still relatively high, accounting for over 80% of cases and 91% of deaths. The natural characteristics of HPV itself, which can remain latent in the host before they progress into cancer, explain why they are commonly observed at a later stage in older populations [3]. In Korea, cervical cancer incidence varies by age. The highest rate is in women aged over 60 years old, comprising about 53% of overall cases. Conversely, the lowest rates are found in women aged 20-29, with those under 30 experiencing increasing trends [4]. There are some concerns that cervical cancer in young women tends to be more aggressive compared to the older population [5,6,7]. The rising concern revolves around the question of how the disease aligns with HPV's nature.

Previous studies in related topics have focused on the characteristics of cervical cancer in young women, examining correlations between age of diagnosis and prognosis. It was later found that age itself is not a related factor, while histological type and risk factors remained significant factors [8,9]. Here, age at diagnosis, which is not directly related to the aggressiveness of the disease, and the contradiction of HPV's nature and the occurrence of aggressive cervical cancer in younger women raise important questions about why this occurs. Despite these findings, there is limited research that studies the mechanisms that contribute to the occurrence of aggressive cervical cancer in young women. By addressing these gaps, we can understand disease progression in this subgroup and develop more clinically targeted interventions.

REVIEW CONTENT

1. HPV Entry, Dynamics, and Natural History

HPV infection causes more than 70% of cervical cancers [2]. HPV infections are transmitted sexually, and nearly all sexually active people will acquire an HPV infection in their lives. For women, several risk factors increase the probability of cervical cancer, such as multiple sex partners and early sexual intercourse. The cervix undergoes histological and anatomical changes as women age. HPV targets the squamocolumnar junction (SCJ), a vulnerable and biologically active zone where two epithelium meet between the endocervix and ectocervix. In young women, the SCJ portion dominates the ectocervix [10]. Microabrasions in the area created during sex will cause inflammation, which will allow easy access for HPV to access immature basal epithelial cells. High-risk HPV types, particularly HPV-16 and HPV-18, interact with cell surface receptors such as integrin α6, which then integrate into host DNA, disrupting cell cycle regulation by inhibiting tumor suppressor proteins such as p53 and Rb [11].

HPV infection is able to clear out on its own before it progresses into cervical cancer. Although this depends on the host immunity and infection severity. In immunocompetent individuals, 90% clearance usually occurs within 1-2 years [12]. Low-grade precancerous lesions in cervical cancer, CIN 1 (cervical intraepithelial neoplasia), involve the lower 1/3 or less of the epithelium and can regress to normal with proper immune performance, while the high-grade precancerous lesions, CIN 2 and CIN 3, have a higher probability of developing cancer. CIN1 lesions that do not regress may advance to CIN 2/3 within 2–3 years after infection, and CIN1 can also transform to invasive cancer at least within 10–12 years [13,14]. Cytological examinations can detect premalignant lesions. Despite histology, until today, knowledge of cellular and molecular mechanisms of CIN has become a challenge, making us unable to differentiate which lesions might possibly progress to invasive cancer and those that will regress spontaneously [15].

2. Immune Response, Inflammation, and Tumor Promoting Environment

A portion of young people have an immature immune system, but they are typically stronger, holding a greater capacity for post-infection immune clearance, as indicated by higher rates of viral clearance compared to older populations [16]. On the other hand, older people face challenges such as immune senescence, a decline in immune function associated with aging [17]. Persistent infection in older women may lead to immune exhaustion or suppression and tissue hormonal milieu alterations, hindering long-term immunity, while approximately 50% of younger individuals who become infected with HPV-16 develop some level of immunity thereafter [18]. Hormonal factors prevalent in young women may also play a role in the heightened immunity, such as higher estrogen levels. Estrogen's immunomodulatory role involves interactions with estrogen receptors (ERα and ERβ), which are expressed on various immune cells, including stromal cells, regulatory T cells (Tregs), and myeloid-derived suppressor cells (MDSCs). Thus, high estrogen levels are often associated with enhanced antibody production, a stronger overall immune defense, and the ability to execute a more vigorous cell-mediated immune response against HPV [19,20]. However, excessive inflammation and immune system dysregulation can create a pro-tumorigenic microenvironment arising from excessive immune attacks and repetitive tissue injury, which can exacerbate the infection. In inflammatory cells, COX-2 is expressed predominantly and upregulated in chronic and acute inflammations. In various types of cervical cancer. Overexpression of COX-2 and PGE2 is seen [21,22]. Indeed, there is a delicate difference between viral clearance and immune-mediated tissue damage that determines disease progression.

The inflammatory response involves the activation of innate immunity and immune cell recruitment to the site of infection or injury and is triggered by the release of chemokines and cytokines such as TNF-α, IL-1β, IL-6, IL-10, IL-12, IL-18, and IL-21, which indicates a flow of protective mechanisms [23]. In this case, a well-regulated system is essential. Studies have indicated that dysregulation in certain key inflammatory mediators can contribute to the oncogenic processes, leading to chronic inflammation that supports tumor growth in both autocrine and paracrine manners [23,24. Dysregulation in pathways such as NF-κB, JAK-STAT, PI3K/AKT, MAPK, and Wnt/β-catenin has vital roles in mediating inflammation-driven tumor progression. Certain cytokines, like TNF-α, are dual-functioning depending on the expression levels and context, able to both promote tumor progression and mediate tumor regression [24]. IL10 can paradoxically induce STAT3, promoting cell proliferation [23]. Tumorigenesis could also be influenced by inflammasome complex sensors like NLRP3 and AIM2, activating caspase processes IL-1β and IL-18, which are then capable of bringing influence in both directions, either by promoting inflammation or immune suppression [24]. Unresolved host immune reactivity produces persistent cytokines and non-healing wounds, which can demand ongoing cell regeneration and lead to a chronic inflammation state, heightening the risk of malignant transformation. Byproducts of phagocytosis, such as reactive oxygen and nitrogen species, also contributed to DNA damage, which has already been damaged by leukotrienes and prostaglandins, affecting inflammation and promoting multiple carcinogenesis pathways [23, 25].

In the tumor microenvironment (TME), cytokines may build a tumor-supporting environment, suppressing antitumor immunity and releasing direct tumor-promoting signals. The process can also occur in further areas through circulations, supporting metastases [23]. Inducement of TME could also be influenced by conditions that exacerbate systemic inflammation, such as obesity, smoking habits, sedentary lifestyle, and chronic infections like persistent HPV [26].

A study in Korea stated that women born after 1973 have an increased ratio of cervical cancer incidence and mortality due to lifestyle changes [27].

3. Tumor Histological Subtypes

There are several histology types of cervical cancer, with two primary histological types: squamous cell carcinoma (SCC) and adenocarcinoma (ADC). Each of them has its own biological behaviors. While SCC is typically linked to transformation at the SCJ, ADC is thought to arise from glandular epithelium. Non-squamous types such as adenocarcinoma and adenosquamous carcinoma are more resistant to treatments, showing worse survival outcomes compared to SCC, with an adjusted hazard ratio of 1.12 for patients with ADC [28,29]. However, other studies described that ADC and SCC displayed equivalent survival outcomes [30,31]. SCC remains predominant, covering 75% to 90% of overall cases; the remainder are distributed as about 10% to 25% adenocarcinoma and less than 1% of rare neuroendocrine variants like small cell cervical cancer (SCCC) and large cell cervical cancer (LCCC) [32]. Despite the small percentage, research has reported that a large portion of rare carcinoma patients are from the young age group, particularly under 30. The rise could possibly be due to the increased lesion detection and improved cytological screenings, because, due to differences in cell origins, Pap smears are more effective at detecting squamous cell carcinoma (SCC) than adenocarcinoma (AC) [33,34,35,36]. The explanation of why adenocarcinoma is found more in young patients is not age-related. It is the behavior of non-squamous types that exhibits more aggressive behavior, hence the rapid growth [35].

4. Cancer Stem Cells

There are current ongoing studies regarding cancer stem cells (CSCs), a subpopulation of cancer cells behaving like normal stem cells, capable of self-renewal, differentiation, and resistance to therapy [37]. Not every cancer necessarily has a stem-like phenotype. Some factors contributing to the formation and maintenance of CSCs are epigenetic alterations (DNA methylation, histone modifications), activation of specific signaling pathways (Wnt, Notch, Hedgehog, PI3K/Akt), and interactions with the tumor microenvironment (e.g., cancer-associated fibroblasts, TAMs). In some cases, where the immune system is still immature in young people, factors like chronic inflammation and the presence of viral infections can increase epigenetic plasticity. When an immature immune system meets with an increase, it may create an environment conducive to the hijacking of normal cellular pathways, allowing for the development of CSCs. At the time of tumor initiation, cancer stem cells (CSCs) can originate either from adult tissue-resident stem cells or from differentiated cells that undergo dedifferentiation, often triggered by epigenetic changes influenced by the tumor microenvironment and persistent infections [38,39]. Due to their importance, several biomarkers to characterize CSCs have been identified and correlated with diagnosis, prognosis, and response to therapy in patients. There is no universal biomarker used to identify CSC, and in cervical cancer, there are markers like CD44, ALDH1, Nanog, and [38,40]. The development of cervical cancer stem cells (CCSC) causes resistance to therapy and aggressive growth, which could explain a portion of aggressive cervical cancer growth in young women, contradicting the nature and latency of HPV.

CONCLUSION

The aggressive behavior of cervical cancer presented in young women has deviated from the nature of the disease, HPV itself, and the common related occurrence. The aggressiveness may not be due to age itself, but may be due to immunobiological factors. Young women generally demonstrate strong immune responses and higher rates of viral clearance; however, paradoxically, some experience rapidly advanced, aggressive cervical cancer. This can be attributed to immune dysregulation, persistent inflammation, and hormonal factors that collectively foster a tumor-promoting microenvironment. Moreover, histological variations, especially the increased incidence of non-squamous subtypes such as adenocarcinoma in younger women, may further exacerbate adverse outcomes. Cervical cancer stem cells (CCSCs), influenced by epigenetic reprogramming and immune interactions, offer an explanation for treatment resistance and rapid tumor progression in this subgroup.

ACKNOWLEDGEMENT

The author would like to thank all supervisors and various parties who have helped carry out this research well.

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