

Rising Trend of Adenocarcinoma of Cervix: A Global Perspective

*Akhter S,¹ Khatun S²

Worldwide incidence of invasive cervical cancer including squamous cell carcinoma has been decreasing for the last 40 years, but incidence of adenocarcinoma of cervix shows a steady increase. This increase is mostly reported from the developed countries with organised cancer screening system and cancer registries. Human papillomavirus (HPV) has been established as the most important etiological factor for cervical cancers including adenocarcinoma. This review article discussed the epidemiological data from several articles including meta-analyses and international projects to give an overview of the increasing incidence of cervical adenocarcinoma throughout the world. The article then delved into the epidemiological studies that provided data regarding association of HPV with adenocarcinoma of cervix. It is evident from these studies that HPV types 16, 18 and 45 are responsible for more than 90% of adenocarcinoma of cervix. Differences in type specific HPV prevalence among countries might be the reason for the variation in the incidences of adenocarcinoma of cervix from region to region. The rising trend in the incidence of cervical adenocarcinoma can be explained as a cohort effect related to increased exposure to prevalent HPV infection in younger women, and also to less effective performance of cytology screening methods in detecting glandular lesions of cervix. In this context, the currently available prophylactic vaccines against HPV should come in the frontier to prevent occurrences of invasive cervical cancer including adenocarcinoma worldwide.

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Introduction

Worldwide incidence of invasive cervical cancer has been decreasing over the last 40 years owing to organised as well as opportunistic practices of cytology screening mostly in the developed countries. Majority of cervical cancers are squamous cell carcinomas (SCC), while adenocarcinomas (ADC) are small in number. There is no doubt that cytology screening programs have lead to increased detection and early management of precursor lesions of cervical carcinoma. However, despite the decline in overall incidence of cervical

cancer, several studies have reported increasing incidence of cervical ADC in comparison to SCC, particularly among younger women and mostly in the developed countries since the 1970's.¹⁻⁶

When German virologist Harold zur Hausen and his team, after their extensive works from 1972 to 1984, revealed their revolutionary discovery that human papillomavirus (HPV), notably HPV 16 and HPV 18, are causative agents of cervical cancer, subsequent researches related to cervical cancer were

1. *Dr. Shabnam Akhter, Associate Professor of Pathology, Bangabandhu Sheikh Mujib Medical University, Dhaka. akhtershabnam66@gmail.com
2. Dr. Shahana Khatun, Assistant Professor of Pathology, MH Samorita Hospital and Medical College, Dhaka

*For correspondence

directed towards HPV. Several years later, Bosch et al. (1995)⁷ reported from their international survey that 93% of cervical cancers contained HPV DNA. They also found that the prevalence of HPV did not show variation between histologic subtypes of cervical cancer (SCC, ADC and adenosquamous carcinomas). By 1999, Walboomers et al.⁸ published their seminal study findings that the prevalence of HPV in cervical cancers was 99.7% worldwide, thus proclaiming that infection with high-risk HPV was central to the pathogenesis of almost all cervical cancers.

With this background this review article will give an overview of the changing trend of cervical ADC from the data provided by epidemiological studies. The studies are mostly from the developed countries of North America and Europe, while few international works have also included data from underdeveloped countries of Asia, Africa and South America.^{3,9} In the latter half of the article, the etiological aspect of cervical ADC will be discussed, that will include the role of HPV and other risk factors identified so far.

Rising trend of adenocarcinoma of cervix

Peters et al.¹ reported in 1986 about increase in the proportional incidence of ADC of the cervix during 1972-1982 among white women aged less than 35 years in Los Angeles County, California. The authors' thought that this was due to use of oral contraceptives before the age of 20 years. Being intrigued by such observation, Schwartz and Weiss² followed the rates of invasive cervical cancer by age, time period and histologic types between 1973 and 1982 among 8,647 women identified by the SEER (The Surveillance, Epidemiology, and End Results) program registries. They found that the incidence of ADC of the cervix in women under the age of 35 years had increased more than twofold between 1973 and 1982. They speculated that

other potential risk factors related to sexual behaviour were also to be considered, as for example, in young women early age at first intercourse or increased number of sexual partners concurred with the early use of oral contraceptives.

Vizcaino et al. (1998)³ conducted a study with International Agency for Research on Cancer (IARC) to find out the time trends in the incidence of cervical ADC, particularly in young women. They collected incidence data on ADC and adenosquamous cell carcinoma during the period 1973-1991 from 60 population-based cancer registries of 32 defined populations in 25 countries. Their analyses focused three aspects of the incidence trend: age, calendar period of diagnosis and birth cohort. The final results reported a significant increase in incidence among women born after 1930 in the United States (white and Hispanic women), Canada, Australia, United Kingdom, Denmark, Sweden, Slovakia and Slovenia. Increasing trend was also observed in Bombay (Mumbai, India), in Japan (Osaka) and among Chinese women in Singapore. The analyses also showed that besides age, the increasing incidence was found related to year of birth, with each successive cohort showing higher risk at a given age compared with their precedent cohorts. However, a decreasing trend was also observed in Finland, France and Italy, and no significant changes in incidence were found in several other countries. The authors concluded that part of the increase might be due to an increasing prevalence of HPV infection and partly to increased detection of atypical glandular lesions by cytology screening.³

Later, Smith et al. (2000)⁴ used the SEER (The Surveillance, Epidemiology, and End Results) database to identify all cases of cervical cancer registered from 1973 to 1996 with the objective to find out the trends in the

age-adjusted incidence of ADC of the uterine cervix relative to SCC in the United States. Their results showed that over 24 years the age-adjusted incidence rates decreased for all invasive cervical cancers by 36.9% and for SCC by 41.9%, but increased for ADC by 29.1%. The percentage of SCC relative to all cervical cancer had decreased from 76.21% (between 1973 and 1977) to 70.17% (between 1993 and 1996). On the other hand, percentage of ADC had increased from 12.4% (1973-1977) to 24.2% (1993-1996). The findings were all in favour of the fact that the absolute frequency as well as the relative frequency of ADC showing a rising trend.⁴

Subsequently Bray et al. (2005)⁵ carried out a study to examine the secular trends in the incidence of ADC of cervix in women ages <75 in 13 European countries using an age-period-cohort- model. The study reported that age-adjusted ADC incidence rates had increased throughout Europe, the rate of increase ranging from around 0.5% per year in Denmark, Sweden, and Switzerland to $\leq 3\%$ in Finland, Slovakia and Slovenia. The increases were calculated first to affect generations born in the early 1930s through the mid-1940s, with risk rising in women born in the mid-1960s relative to those born 20 years earlier.⁵

Bulk et al. (2005)⁶ of Netherlands did a population-based study on the incidence of invasive cervical cancer to evaluate trends in relation to age at time of diagnosis. The cases were collected from the Netherlands Cancer Registry for all women with invasive cervical cancer between 1989 and 1998. The results depicted that in this 10-year period, the incidence of SCC had decreased substantially from 7.1/100,000 to 6.1/100,000, and the incidence of ADC overall remained static, but it had increased in women aged 15-29 and in women aged 30-44.⁶

Etiological factors related to adenocarcinoma of cervix

ADC of cervix, like SCC, has been reported to be associated with high-risk HPV infection, which is considered to play the central role in cervical carcinogenesis.⁷⁻⁹ So, the etiological factors will be discussed in two parts, the first will be about the association of HPV in ADC of cervix, and the second part will encounter the postulated risk factors other than HPV infection.

HPV and adenocarcinoma of cervix

With regard to increasing incidence of cervical ADC, Andersson et al. (2000)¹⁰ tried to find out the presence of HPV in diagnosed cases of ADC of cervix during 1986-1996, the cases identified through Swedish Cancer Registry. HPV was identified in 71% cases of ADC; in the HPV-positive cases, HPV18 was present in 52% and HPV16 in 33%. They also reported that the prevalence of HPV in ADC differed with age; women <40 years were HPV-positive in 89% of cases, while women ≥ 60 years were HPV-positive in 43% cases.

Clifford et al. (2003)¹¹ carried out a meta-analysis and reported HPV18 to be the most frequent type (37.7%) in ADC followed by HPV 16 (31.3%) and HPV 45 (5-7%), whereas HPV 16 was the dominant type in SCC of cervix. On the other hand, the population-based study by An et al. (2005)¹² in Korea revealed that HPV16 was the most frequent type followed by HPV 18, while overall HPV prevalence in the cervical ADC among Korean women was 90%.

To find out the extent to which HPV and cofactors may be responsible for the increasing trend of cervical ADC, Castellsague et al. (2006)¹³ examined eight case-control studies during 1985-1997 from eight different countries with differences in the incidence of cervical cancer. Countries were from North Africa, South America and

Southeast Asia. They found HPV to be the main risk factor, prevalence ranging from 86% in Paraguay to 100% in Algeria. HPV16 and HPV18 were the most dominant HPV types, together being present in 82% of the cases.

International Collaboration of Epidemiological Studies of Cervical Cancer (2006)¹⁴ conducted a collaborative reanalysis from 12 epidemiological studies. Their analyses revealed that HPV16 was the commonest type in both SCC and ADC of cervix. However, HPV16 was more common in SCC (56% versus 40%) whereas HPV18 was more common in ADC (35% versus 16%). Similarly, Smith et al. (2007)¹⁵ published their meta-analysis update on HPV type distribution covering six continents where they reported that HPV positivity overall was a little more in SCC (90%) than in ADC (85%), HPV16 was less frequent in ADC (33%) and more frequent in SCC (55%), and HPV18 was the dominant type in ADC (37%) compared with SCC (13%). They also found that HPV 16/18 proportion was higher in Europe, North America and Oceania (74-77%) than in Africa, Asia and South/Central America (65-70%).

On behalf of the Retrospective International Survey and HPV Time Trends Study Group, Silvia de Sanjose (2010)¹⁶ completed an international project with the aim to provide distribution pattern of HPV genotypes in samples of invasive cervical cancer. Samples were collected covering 38 countries from Europe (10), North America (USA), central South America (10), Africa, Australia and Asia (12 including Bangladesh). From the analyses of data, they found that HPV types 16, 18 and 45 were the three most common types in each histological type of SCC, ADC and adenosquamous cell carcinoma of cervix. Both HPV18 and HPV45 were more common in ADC than in SCC. The other intriguing

finding was that cancers related to HPV18 and HPV45 occurred at a much younger age (<50 years). The early presentation of invasive cancers in these cases indicates that these virus types possibly require a short time of progression to invasive cancer with a high integration rate into the host genome.

Afterwards, Pirog et al. (2014)¹⁷ did a worldwide analysis of HPV prevalence and genotypes in different histological subtypes of cervical ADC. They found that relatively narrow spectrum of high-risk HPV types, HPVs 16, 18 and 45 were present in the vast majority of ADC, together constituting 94.1% of HPV-positive cases. In contrast to the earlier meta-analyses by Clifford et al. (2003)¹¹ and Smith et al. (2007)¹⁵, they found HPV16 to be the most frequent type (50.9%) followed by HPV18 (31.6%) and HPV 45 (11.6%) in HPV-positive ADC cases. Though the ratio of HPV16 to HPV18 in ADC varied from study to study, the percentage of combined HPV16 and HPV18-positive cases were found much uniform among studies (75.7-94.8% of cases) with an average of 89.8%.

To find out the HPV subtypes in cervical ADC in women of Bangladesh, Akhter et al. (unpublished data, presented as poster at the Annual meeting of USCAP 2017)¹⁸ studied 71 cases of cervical ADC. The results showed that, in contrast to western countries, HPV16 was the most frequent type (63.4%) followed by HPV18 in 16.9%. HPV DNA was detected in 100% cases. These data indicate a significant epidemiological difference in the type-specific prevalence of HPV between the developed and underdeveloped countries.

Risk factors other than HPV infection

The other risk factors for ADC are more or less similar to those for cervical cancer in general, being related to factors that promote spread of HPV infection from person to

person as any other sexually transmitted disease.

Several studies^{12,14,19-21} have worked with risk factors associated with cervical ADC in comparison to SCC. The notable risk factors other than HPV are described in the following sections.

1. Lifetime number of sexual partners was reported to show strong association with both SCC and ADC, risk of cancer increasing with the increasing number of partners.^{12,14,19-21}
2. Earlier age at first intercourse was found to be associated with increased risk of both SCC and ADC of cervix, the association being stronger for SCC.^{12,14,19-21}
3. Longer duration of use of oral contraceptives was reported to be strongly related to risk for both SCC and ADC.^{12,14,19-22}
4. Smoking was considered a risk factor for SCC compared to never smokers whereas it was found not to be a risk for adenocarcinoma.^{12,14,19-21}
5. High parity showed significant association with both SCC and ADC (three or more live births or full-time pregnancies versus none), the association being stronger for SCC.^{12,14,19-21}
6. Herpes simplex virus type 2 (HSV-2) seropositivity was reported to be associated with a more than twofold increase in the risk of cervical ADC.¹²

Conclusions

The review discussions have highlighted infection with high-risk HPV as the most important etiological factor for cervical ADC. In terms of type specific prevalence, HPVs 16, 18 and 45 are reported to be responsible for more than 90% of ADC of cervix. Differences in type specific HPV prevalence among countries may be responsible for the variation in the incidences of ADC of cervix

from region to region. The rising trend in the incidence of cervical ADC can be explained as a cohort effect related to increased exposure to prevalent HPV infection in younger women, and also to less effective performance of cytology screening methods in detecting glandular lesions of cervix. In this context, the currently available prophylactic vaccines against HPV should come in the frontier to prevent occurrences of invasive cervical cancer including adenocarcinoma of cervix worldwide.

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