REVIEW

Editorial Process: Submission:10/20/2017 Acceptance:04/03/2018

Epidemiology of HPV Infection and HPV-Related Cancers in Kazakhstan: a Review

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Abstract

Background: Cancer is one of the most prevalent causes of mortality worldwide. In the cervix it is considered to be caused by different high-risk human papillomavirus (HPV) types. Although many studies have already been conducted worldwide on the epidemiology of HPV infection and their oncogenic properties, limited data are available on HPV prevalence, incidence and genotype specific dissemination in Kazakhstan. **Methods:** To review the distribution of HPV infection, electronic databases (e.g. PubMed, Web of Science and Google Scholar) were searched for peer reviewed articles in English. The study was performed during June-July 2017 with a review of 39 relevant articles, published up to July 31, 2017. The following inclusion criteria were applied: general population data, cytology results available, and use of polymerase chain reaction (PCR) and/or Hybrid Capture® 2, Digene Corp., USA for HPV detection. **Results:** As reported in limited studies, the prevalence of HPV infection in Kazakhstan ranges from 43.8% to 55.8%. However, the scenario with regard to epidemiology of HPV related cancers in Kazakhstan is not very clear. One study reported a decline of laryngeal cancer observed during the recent years, whereas cervical cancer incidence has increased to about 3000 new cervical cancer cases, and about 1,000 cervical cancer deaths each year. **Conclusion:** The high incidence of cervical cancer with a significant mortality rate in Kazakhstan is evidence of HPV infection abundance despite an absence of HPV screening and low public awareness of the problem. Having a well-informed understanding of the role of HPV infection could enhance the public's acceptance of screening and intervention programs to reduce morbidity and mortality in the country due to HPV infection. Thus, the purpose of this review article is to summarize the existing data, identifying directions for future research on HPV epidemiology and HPV-related diseases in Kazakhstan.

Keywords: Human papillomavirus- cervical cancer- HPV epidemiology- HPV-related cancers-HPV vaccination

Asian Pac J Cancer Prev, **19 (5)**, 1175-1180

Introduction

According to World Health Organization's (WHO) statistics, common cancers are one of the most prevalent causes of mortality worldwide with 8.2 million deaths in 2012, and this trend has not changed in recent years. Viral infections contribute to 15-20% of all human cancers, whereby several viruses play significant roles in the multistage development of malignant cancers. The correlation between a given virus and its associated cancer ranges from 15-100% (McLaughlin-Drubin et al., 2008). Cancer became a priority public health challenge in Kazakhstan as a Member State of the WHO. Cervical cancer is the second most common cancer among women all over the world, with more than 85% of the cases occurring in developing countries (Senapathy et al., 2011). Almost 90% of cervical cancer cases are caused by HPV infection (Schiffman et al., 2009). HPVs are a large group of viruses, which consists of more than 180 different types, among which 15 have high oncogenic properties (Bernard et al., 2010). HPV infection can lead to various types of diseases from benign lesions to cancer. In 2007, an International Agency for Research on Cancer (IARC) working group classified 21 HPV types (HPV 6, 11, 16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 68, 70, 73 and 82) as the most prevalent for their association with cervical cancer (IARC, Monographs on the Evaluation of Carcinogenic Risks to Humans, Volume 90, 2007).

However, very scarce and scattered information are available about HPV infection epidemiology in Kazakhstan. Therefore, the purpose of this review article is to summarize the existing data, identify the direction for the future research, and enhance public awareness about HPV infection and HPV-related diseases in Kazakhstan and the Central Asian region.

Materials and Methods

Systematic literature search was performed by a detailed survey of issued peer reviewed articles on HPV infection and cervical cancer in Kazakhstan up to July 31, 2017 from the following databases: PubMed, Web of

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Science and Google Scholar. The search was done without language limitation, during June-July 2017. The key words "HPV", "Kazakhstan", "genotype", "vaccination", "screening" and "cervical cancer" were used for the search. This resulted in 229 relevant articles. Abstracts of all the 229 articles were read to determine relevance to this review. Inclusion criteria; articles that were included in this review mentioned at least one specific HPV-related test that was being evaluated. Since we have included the epidemiologic data from international journals and local non-indexed medical journals, the following inclusion criteria were applied: general population data, cytology results available, and use of polymerase chain reaction and/or Hybrid Capture® 2, Digene Corp., USA for HPV detection. Exclusion criteria; articles that were published before 1990, and articles describing contribution of other infections sexual transmitted infections to cervical cancer morbidity were not included. Application of inclusion/exclusion criteria resulted in 36 relevant articles on the topic of the review. Of the articles reviewed, 3 were additionally included in this report from the local non-indexed journals, published in Russian and translated into English with the links provided in the list of references. This search strategy resulted in 39 total articles that are included in this analysis. Since published data in international indexed medical journals are very limited and scarce, additional data have been obtained from the Catalan Institute of Oncology (ICO) HPV Information Centre report – 2017 and International Agency for Research on Cancer Monographs on the Evaluation of Carcinogenic Risks to Humans.

In general, the information available on HPV prevalence in Kazakhstan is very tenuous and it became obvious that further research studies need to be done within this scientific field.

Results

Epidemiology of HPV infection in Kazakhstan - prevalence and type distribution

There have been many studies worldwide on the epidemiology of HPV infection, and oncogenic properties due to different HPV genotypes (Munoz et al., 2004; Clifford et al., 2003; Smith et al., 2007). However limited data are available on HPV prevalence, incidence and genotype specific dissemination in Central Asia, Africa and Eastern Europe. According to the report of HPV Information Centre (2017), no data on the epidemiology of HPV infection are available in Kazakhstan. There are only a few articles on the epidemiology of HPV infection in Kazakhstan published in international peer reviewed journals and several articles in local medical journals.

The search in the international journals on HPV epidemiology has allowed us to find the largest study of HPV prevalence (1,661 samples), which was done in the Western part of Kazakhstan (Bekmukhambetov et al., 2016). The study on HPV prevalence and distribution was performed by analyzing retrospective data, obtained from Russian-Kazakh joint venture "Olympus" laboratories network" accredited by International Organization for Standardization (ISO 15189). The laboratory network used AmpliSens® Real-Time PCR kits and the PCR analyzer Rotor-Gene 6000 (Germany) for HPV testing, which detected 12 different HPV genotypes (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59) (Bekmukhambetov et al., 2016).

This study identified the five most common HPV types, which were 16 (10.7%), 39 (5.83%), 51 (5.27%), 31 (4.85%) and 56 (4.58%) (Bekmukhambetov et al., 2016). Type 16 was found as dominating and widely spread in the Western region of the country. The study did not assess the different type of the cervical lesion using the Papanicolaou test (Pap test).

Another article, published in the local non-reviewed journal presented the results of 595 patients' HPV PCR genotyping in the Western region (Junerbayeva et al., 2015). PCR genotyping was done in the "Olympus" laboratories network" using AmpliSens® Real-Time PCR proceeded with the use of analyzer Rotor-Gene 6000 (Germany) to determine 12 most oncogenic types. This study demonstrated that 55.8% of the surveyed women were infected with HPV. The most prevalent types detected were HPV 16 (27.7%), HPV 31 (13.6%), HPV 52 (9.9%), HPV 18 (9.6%) and HPV 33 (3.6 %) (Junerbayeva et al., 2015).

Yet another study on HPV prevalence was performed by us in the Central part of Kazakhstan and included 140 samples (Niyazmetova et al., 2017). HPV genotyping of 12 different types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58 and 59) was done in the Republican Diagnostic Center (RDC), University Medical Center (UMC) with real time multiplex PCR methodology, using the specific PCR kit. The laboratory method used was based on simultaneous real-time multiplex PCR of HPV-specific DNA fragments and a noncompetitive internal control. The real time PCR instrumentation used for the assay was the CFX 96 Real -Time PCR (BIO-RAD). The findings demonstrated that 43.6% of the patients were HPV positive. The most prevalent types detected were HPV 16 (18.4%) and HPV 18 (9.22%), followed by HPV types 33, 51 and 52 (nearly 5% each) (Niyazmetova et al., 2017). HPV types 59, 39, 31, 45, and 58 were found in at least 2% of the total amount of samples, while only about 1% or less of positive samples had HPV types 35 and 56. The study, along with PCR HPV genotyping, performed the microscopic examination of Pap smear samples using standard UMC hospital protocols to evaluate the grade of HPV caused cervical lesions.

From the research data summarized above, we know that HPV testing is available on a self-payment basis in large cities of Kazakhstan. However there is no published statistical information on HPV epidemiology from the rural areas of the state. The reason may be due to absence of the specialized equipment for testing HPV and/or low awareness of the population and medical staff about the importance of HPV detection and Pap smear screening in cervical cancer prevention.

Epidemiology of HPV-related cancers in Kazakhstan
Head and neck cancers

Human papillomaviruses infect basal skin and mucosal cells. There is an international consensus that "high-risk"

genotypes can lead to cervical cancer and are associated with other mucosal anogenital and head and neck cancers (IARC, Monographs on the Evaluation of Carcinogenic Risks to Humans, Volume 90, 2007). Three cancer groups have been linked to HPV infection: the cervix, other anogenital tract (vulvar, vaginal, anal, and penile), and head and neck (oropharynx, oral cavity, and larynx). Most HPV infections are asymptomatic whereby more than 90% of detected infections are cleared within 12-24 month without causing any lesions (Moscicki et al., 2006). Progression to cancer depends on the degree of immune protection of each particular person. Current evidence suggests that HPV16 is associated with tonsil cancer (including Waldeyer ring cancer), base of tongue cancer and other oropharyngeal cancer sites (IARC, Monographs on the Evaluation of Carcinogenic Risks to Humans, Volume 100 (B), 2012).

Very limited data are available on the epidemiology of HPV-related cancers in Kazakhstan (Igissinov et al., 2011; Igissinov et al., 2012; Igissinov et al., 2013; Zatonskikh et al., 2016). For example, cancer of the oral cavity and oropharynx is the most common form of head and neck tumors (Adilbayev et al., 2016). However, in Kazakhstan, only one study on the general prevalence of HPV-associated head and neck cancer has been conducted and published by Adilbayev (2016) in the international peer-reviewed journal. Some studies were done on HPV related diseases in Kazakh ethnic group among China population (Lu et al., 2008; Cui et al., 2014), but these did not contribute to the Kazakhstani statistical database.

When discussing particular HPV-related head and neck cancers, according to available research data, the most studied in Kazakhstan is laryngeal cancer (Igissinov et al., 2013; Zatonskikh et al., 2016). Epidemiological study of laryngeal cancer in Kazakhstan shows that the dynamics of incidence are decreasing. The actual decline of the laryngeal cancer cases is significant and is equal to 36.9% for the entire population (Zatonskikh et al., 2016). However, the worldwide epidemiological observations define that with the population growth and changing in its age structure, the number of patients with malignant tumors of the larynx should increase. As the author Zatonskikh (2016) explained these controversial data with the demographic and socioeconomic changes in the recent 15 years, as one of the most important epidemiological factors that influenced the occurrence of cancers in the Kazakhstani population (Igissinov et al., 2013; Zatonskikh et al., 2016). Crude incidence rate of oral cavity and pharynx malignant neoplasms tended to increase from 1999 to 2011 among the total population (Igissinov et al., 2011). According to the International HPV Centre report, crude incidence rate of pharyngeal cancer in 2017 (excluding nasopharynx) was 4.4 for male and 1.5 for female, with crude mortality rate of 3.0 and 1.0 relatively (Bruni et al., 2017).

Anogenital cancers other than the cervix

According to the recent HPV center report, no data were available on the epidemiology of anogenital cancers other than the cervix (anal, vulvar, vaginal and penile cancers) in Kazakhstan (Bruni et al., 2017). Anal cancer is rare in the general population with an average worldwide incidence of 1 per 100,000. Globally, there is an estimated 27,000 new cases of anal cancer every year (de Martel et al., 2012). Women have higher incidences of anal cancer than men. Incidence is particularly high among populations of women with history of cervical or vulvar cancer, people practicing anal sexual intercourse, and in immunosuppressed populations. The type of anal cancer is mostly squamous cell carcinoma, adenocarcinomas, or basaloid and cloacogenic carcinomas.

The annual burden of penile cancer has been estimated to be 22,000 cases worldwide with incidence rates strongly correlating with those of cervical cancer (de Martel et al., 2012). Incidence rates are higher in less developed countries than in more developed countries, accounting for up to 10% of male cancers in some parts of Africa, South America and Asia. Cancers of the penis are primarily of squamous cell carcinomas type (95%) (Bruni et al., 2017). Approximately 60-100% of precancerous penile lesions are HPV DNA positive.

Cancer of the vagina and vulva are rare cancers, representing 2-4% of all gynecologic cancers (de Martel et al., 2012). Similar to cervical cancer, the majority of vulvar and vaginal cancer cases (68%) occur in less developed countries and present slightly higher incidence in urban compared to rural regions (Makimbetov and Shalbaeva, 2014). Most vaginal cancers are squamous cell carcinoma (90%) generally attributable to HPV. Vulvar cancer has two different histological types: the warty and keratinizing types (IARC, Monographs on the Evaluation of Carcinogenic Risks to Humans, Volume 100(B), 2012).

Cervical cancer

Cancer of the cervix uteri is the fourth most common cancer among women worldwide, with an estimated 527,624 new cases and 265,672 deaths in 2012 (Globocan). The majority of cases are squamous cell carcinoma followed by adenocarcinomas. (Wright et al., 2006; IARC, Monographs on the Evaluation of Carcinogenic Risks to Humans, Volume 90, 2007; Giuliano et al., 2008; Bruni et al., 2017). In spite of effective screening methods, cervical cancer continues to be a major public health problem (Arbyn et al., 2008; Ferlay et al., 2015). Statistical data in Central Asia are limited (Bruni et al., 2017), although a slight increase has been noted over the last ten years in Kazakhstan, especially among the middle-aged groups (Igissinov et al., 2011). The incidence rates of cervical cancer in many countries of Central Asia are quit high (ranging from 9.9 per 100,000 women in Tajikistan to 29.4 per 100,000 in Kazakhstan) (Bray et al., 2013), compared to Europe (ranging from 4.0 per 100,000 in Finland and 7.0 per 100,000 in Germany) (Curado et al., 2007). Approximately 25,700 women are diagnosed with cervical cancer and 12,700 die from this disease annually in Central Asian countries (Bray et al., 2013). The mortality rates - range from 4.9 per 100,000 women in Tajikistan to 11.2 per 100,000 in Kyrgyzstan (Bray et al., 2013; Bruni et al., 2017). The indicators are higher than in Western European countries (incidence rates ranging from 2.1 per 100,000 women in Malta to 12.2 per 100,000 in Portugal; mortality rates ranging from 0.8 per

100,000 women in Iceland to 3.6 per 100,000 in Portugal) (Ferlay et al., 2010).

In Kazakhstan, at least one woman in 50 develops cervical cancer before the age of 75 (Bray et al., 2013). Cervical cancer is the 1st most common female cancer in women aged 15 to 44 years in Kazakhstan, and ranks as the 2nd leading cause of female cancer with the incidence about 2,789 new cervical cancer cases diagnosed annually (estimations for 2012) (Bruni et al., 2017). Cervical cancer is the 4th leading cause of female cancer deaths in Kazakhstan with of about 982 cervical cancer deaths annually (Bruni et al., 2017).

Epidemiologic investigation on cervical cancer by Igissinov (2012) shows that the average age of cervical cancer patients in Kazakhstan is 53.5±0.7 years, with the average incidence rate of 14.5 per 100,000 women and mortality rate of 8.0. The incidence among women of reproductive age is 2.2 times lower than those figures for postmenopausal age (Igissinov et al., 2012). There is significant geographical difference in cervical cancer incidence and mortality in Kazakhstan. The incidence among women of reproductive age was found to be the highest in Northern part of the country at 16.3 per 100.000 and the lowest on the West of the country with 12.7 per 100.000 populations. The incidence among women of postmenopausal age is 1.7 times higher than in reproductive age (27.9 and 34.4 respectively). The mortality rate ranges from 7.1 to 12.6 per 100.000 in the same parts of the country respectively (Igissinov et al., 2012).

Having the significant high incidence and mortality from cervical cancer makes the screening program very important. Enhancing public awareness of underlying causal factors is a high priority for developing an appropriate cancer control and prevention program.

Cervical cancer screening in Kazakhstan

Cervical cancer screening strategies are different between countries. Some countries have population-based programs, whereby women in the target population are individually identified and invited to attend screening. In opportunistic screening, invitations depend on the individual's decision or on encounters with health-care providers. The most frequent method for cervical cancer screening is cytology (Bruni et al., 2017). There is also discrepancy in the frequency of the screening tests. In developed countries like England and the USA, screening is scheduled for every 3 years for women in their reproductive age (Chorley et al., 2017; Smith et al., 2017), while in developing countries (India, Peru, Kenia) the screening is scheduled every 5 years or even rarer (Gupta et al., 2017).

Results of the population-based survey of adults aged 50–70 in England suggest that although awareness of the purpose of early detection screening is high, awareness that screening can prevent cancer is low across all demographic groups.

Cervical cancer screening in Kazakhstan was mainly opportunistic till 2005 and was characterized by cytology testing, using Romanowsky staining. Starting from 2005 cytological screening of cervical cancer has been conducted, and the government covers expenses on cytology screening, biopsy and treatment (Nikulshina et al., 2016).

Screening program covered different age groups in different years; in 2005 it covered the age group 30 to 34 years, whereas in 2006 and 2007 the program covered the 18 to 49 years age group. Since 2008, the State Cancer Screening Program has been adopted, and target groups of women aged 30 to 60 years have been identified. Screening for the program is conducted for women every 5 years.

The cervical sample material for the study should be obtained from the cervix using Cervix-Brush. The method of staining preparation in 2006, 2007 was performed according to the Romanowsky method. Starting from 2008, 60% of all studies were prepared using the Papanicolaou method and 40% according to Romanowsky. Since 2009, 100% of all screening studies are stained by Papanicolaou. According to the HPV Information Center database, cervical cancer screening program covered 80% women aged 25-64 (Bruni et al., 2017). The Pap test combined with a regular screening program, has been shown to reduce mortality from cervical cancer by more than 70% (Arbyn et al., 2010).

Starting from September 2013 liquid based cytology screening was implemented and applied into the daily screening practice (Kairbayev et al., 2009). The method of liquid based cytology (LC) was first developed to improve the effectiveness of the traditional Pap test, as well as to improve the quality of specimens from the cervix. A special feature of the LC method is the presence of a liquid medium, which is designed to preserve the cellular material obtained from the cervix. Subsequently, the cell suspension is processed to obtain a more uniform, thin layer of cervical cells with less cell debris on the slide. The goal of this process is to potentially reduce the incidence of two major deficiencies that occur in the traditional cytological study; (1) obtaining a relatively small and potentially unrepresentative cell sample (in fact, only about 20% of the cells obtained are transferred to glass), and (2) the effects of other types of material, including mucus, blood and other cells (not from the cervix) (Abulafia et al., 2003).

In general, the screening program in Kazakhstan is improving. Advantages of the liquid based cytology in terms of detection of the early stages lesion are confirmed. Accurate cervical screening practice will result in significantly reducing cervical cancer mortality.

HPV vaccination in Kazakhstan

HPV vaccines are very effective at preventing infection and disease related to the vaccine-specific genotypes in women with no evidence of past or current HPV infection (Cutts et al., 2007). Vaccination program have been very successfully implemented in many countries all over the world [Mesher et al., 2013; Osborne et al., 2015; Tanaka et al., 2017). For example, the most recent study from Japan demonstrated results from women aged 20-24 years who received HPV vaccination, and had significantly lower rates of abnormal cervical cytology results when compared to those who did not receive the

vaccine (Tanaka et al., 2017).

In Kazakhstan, a vaccination program supported by the government was started as a pilot project in the years 2011-2013. During this time, the prophylactic vaccination of adolescent girls ages 10-13 years was performed, but later found to be improperly implemented, and now almost fully discontinued. Currently there is no the state program for HPV vaccination in Kazakhstan. However, adult women have the opportunity to be vaccinated in private hospitals or vaccination outpatient departments.

Cost-effectiveness study, which was done in Kazakhstan by Nurgozhin (2013) shows benefits from HPV vaccination (Nurgozhin et al., 2013); however in spite of this knowledge, the HPV immunization program has not yet been implemented at the national level that would cover the entire population of Kazakhstan.

Discussion

As reported in different studies, the prevalence of HPV infection in Kazakhstan ranges from 43.8% to 55.8%, with the most prevalent types of HPV being 16 (10.7-27.7%), 18 (9.2-9.6%), 51 (5%), and 33 (3.6-5%). However the scenario with epidemiology of HPV related cancers in Kazakhstan is not very clear. Accordingly, one study reported a decline of laryngeal cancer observed during the recent years, cited to be equal to 36.9% of the whole population. Crude incidence rate of oral cavity and pharynx malignant neoplasms tended to increase from 1999 to 2011 within the total population. Statistical data on anogenital cancers in Kazakhstan however are not available.

Cervical cancer is the 2nd leading cause of female cancer and the 4th leading cause of female cancer deaths in Kazakhstan. The incidence of cervical cancer is about 3000 new cervical cancer cases, with about 1,000 cervical cancer deaths each year. There is an inequality of cervical cancer incidence and mortality in the different regions of the country. The incidence was found to be the highest in Northern part of the country at 16.3 % and the lowest on the Western part of the country at 12.7% with mortality rate that ranges from 7.1 to 12.6 % respectively. In comparison with the developed countries of Europe and North America, where the age-standardized incidence of cervical cancer is less than 9 % (Curado et al., 2007), Kazakhstani statistical data reveals depressing indicators. This imbalance is attributed mainly to the effective and successful implementation of organized cervical cancer screening programs in developed countries leading to early detection and appropriate management of precancerous lesions (Peto et al., 2004).

High incidence of cervical cancer with significant mortality is an evidence of HPV infection abundance with absence of the HPV screening and low public awareness of the problem. The educational health promotion projects for the population should be provided to enhance the knowledge and conversance of this public health problem. From the review given here, it is clear that the HPV screening along with the vaccination program should be implemented at the governmental level in Kazakhstan.

Competing interests

The authors declare that they have no competing interests.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Author's contributions

GA compiled, analyzed and reviewed data and prepared the manuscript. AA provided intellectual input to contribute towards manuscript preparation and edited the manuscript. All authors reviewed and approved the final manuscript.

Acknowledgments

The authors would like to acknowledge the Nazarbayev University School of Medicine for the support that enabled completion on this review article.

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