SHORT COMMUNICATION

Editorial Process: Submission:02/27/2018 Acceptance:05/25/2018

Exploring the Causes of the Low Incidence of Cervical Cancer in Western Asia

Ghazi Alsbeih*

Abstract

Anecdotal epidemiologic observations can provide valuable tools to study various biologic elements in complex diseases such as cancer. Although cervical cancer is one of the most frequent malignancy affecting women in the world, it displays wide geographical variations remnant of socioeconomic, ethnic and genetic predisposing factors. The observed low incidence of cervical cancer in western Asia has triggered scientists to try to delineate the causes of this reduced occurrence. Although this region including Saudi Arabia is known for being conservative societies with low incidence of sexually transmitted infections including human papillomavirus (HPV) and associated cervical cancer, scientific research points out multifaceted biological explanations including host genetic variations. Researchers observed that a protective genetic variant TP53 codon 72 proline allele was more commonly found in this population and appear to be over-transmitted compared to others known for their high rate of cervical cancer. Thus, the combination of relative low rate of HPV infection, over-transmission of protective genetic variant along with societal variables are the rationale behind the low incidence of cervical cancer in women in the region of western Asia. The influence of the genetic makeup of the patients has impact on personalized preventive medicine to gauge the risk of developing cervical cancer.

Keywords: Cervical cancer- human papillomavirus (HPV)- TP53 polymorphism- cancer predisposition- Western Asia

Asian Pac J Cancer Prev, **19 (6)**, 1425-1429

Introduction

Cancer of the uterine cervix is mainly a human papillomavirus (HPV) driven disease with an estimated overall involvement rate ranging between 85% and 99% worldwide (zur Hausen, 1991; Walboomers et al., 1999; de Sanjose et al., 2010). HPVs are groups of DNA-viruses that affect skin and moist membranes in the body. The contamination is asymptomatic and the virus is primarily transferred by direct contact between infected skin to skin or to mucous membranes. Currently there are about 120 HPV genotypes that infect human with around 40 types that affect the genital area. High risk HPV genotypes are the primary cause of cervical cancer and the incidence of this tumor is regarded as a surrogate marker for HPV infection particularly in countries lacking epidemiological studies (Alsbeih, 2014). The high risk HPV 16, 18, 31, 52, and 58 are consistently found among the 10 most common genotypes detected in cervical cancer.

Infection with HPV is very common during the active sexual life and it does not elicit any immediate signs until persistent infection develops to pre-cancerous lesions years later (Baseman and Koutsky, 2005; Howell-Jones et al., 2012). Immune system clear the infection in most cases with less than 1% of infected women eventually develop invasive cervical cancer (Wang et al., 2010). The global HPV prevalence in women with normal cervical cytological findings is estimated at 11.7% with marked variability across world regions where Sub-Saharan Africa (24.0%), Eastern Europe (21.4%), and Latin America (16.1%) showed the highest rates (Bruni et al., 2010). Asia is a large continent and shows wide variations in reported HPV prevalence in large community-based studies ranging from as low as 7.2% in multiethnic Malaysia to 20.54% in China (Chen et al., 2017; Khoo et al., 2017). In addition, the prevalence displays age-specific HPV distribution with a first peak at younger ages (≤25 years) and a rebound at older ages (≥45 years). These figures represent the most comprehensive assessment of HPV burden among women with normal cytological findings in the pre-HPV vaccination era worldwide.

The turning points in prevention of HPV-associated cancer risk are cytological screening for precancerous lesions, molecular screening for high-risk HPV infection and the availability of vaccines against the most common HPV genotypes currently in use in many developed countries. In contrast, basic health care is often lacking in disadvantaged populations such as in resource-limited countries, marginalized and immigrants due to shortage of point-of-care access and the complexities of social and

Department of Biomedical Physics, King Faisal Specialist Hospital and Research Centre, Riyadh, Saudi Arabia.
**For Correspondence: galsbeih@kfshrc.edu.sa*

economic situations (Alsbeih, 2015). As a result, there is a tremendous disparity in health consequences for HPV-infected people, as compared to advantaged populations. Thus, healthcare authorities should be more aware of this global cancer disparities.

Geographical variations in cervical cancer

Cervical cancer remains one of the most frequent malignancy affecting women in the world next to breast, colorectal and lung cancers (Ferlay et al., 2015). According to global cancer statistics, there are more than half a million new cases being diagnosed every year and claims the lives of more than a quarter million women (Bray et al., 2013). However, cervical cancer incidence is not uniform in various populations having different socioeconomic and development levels. While cervical swap screening, and HPV vaccinations are helping in reducing precancerous and invasive cases in developed countries, a large majority of the global burden occurs in less-developed regions lacking access to healthcare (Shrestha et al., 2018). About 8 out of 10 cervical cancer deaths occur in low/middle-income countries, particularly in Africa, South America, and parts of Asia, which are the toughest struck by this inequality of mostly a preventable cancer (Bray et al., 2017).

Yet, a few geographical regions in the world, such as western Asia (Figure 1), shows unexplainably low cervical cancer incidence despite the lack of proactive national screening or vaccination programs (Al Moustafa et al., 2014; Al-Hammadi et al., 2017). This area of the world is composed of many countries with no definitive number due to geopolitical and economic considerations. Numerous countries are establishing national cancer registries for providing accurate population-based incidence data in order to efficiently allocate healthcare funds and prioritize screening and prevention (Mohagheghi et al., 2009; Ismail et al., 2013; Ibrahim et al., 2014; Badar et al., 2016; Bazarbashi et al., 2017). However, access to specific data in these registries is not always easy and publically reported cancer incidence rates are extracted from the database of the International Agency for Research on Cancer (IARC; an intergovernmental cancer specialized agency of the World Health Organization). These are based on projections using historic/recent cancer registries data of various quality and population coverage rather than actual number of cases (Bazarbashi et al., 2017). Table 1 lists the most up-to-date estimates of cervical cancer incidence in the western Asian countries including Egypt. The estimated age-standardized rates (ASR) of incidence ranges between 2 and 9.5 with an average of 3, which is below the worldwide mean of 7.9 per 100,000 person-year. Being in the middle of this western Asia region, we have used this paradigm to study the rationale behind this low rate of cervical cancer occurrence in Saudi Arabia. Of course, the conservative society, sexual mores and the widely practiced male circumcision are known to play a role in reducing sexually transmitted diseases (STD) including HPV infections, and lessen the frequency of related diseases and potential long-term consequences such as cervical cancer (Filemban et al., 2015). However, these hard-to-measure factors fall short of providing a definitive answer especially that some other geographical areas with similar societal variables show higher incidence (Al-Harbi et al., 2017).

Causes of low incidence of cervical cancer in Western Asia

To gain insight into the causes of the low incidence of cervical cancer in western Asia, our research team has looked at the rate of HPV infection and the association with potential polymorphic genetic

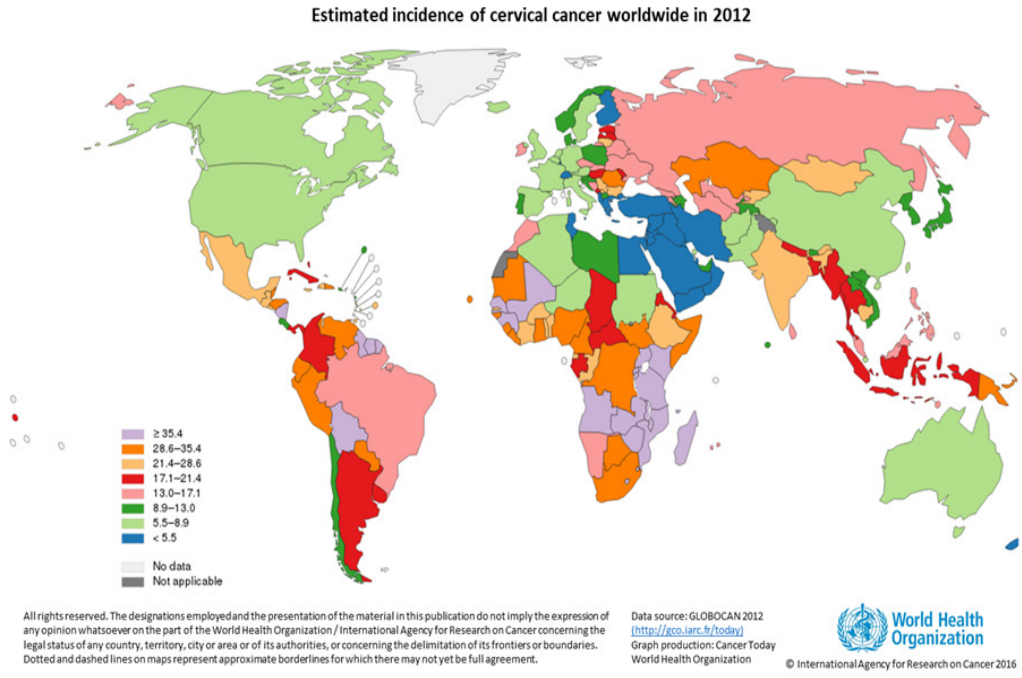

Figure 1. Estimated Age-standardized Rates of Incident Cases of Cervical Cancer in the world according to the most Recent Statistics available to GLOBOCAN 2012. Note that western Asia region displays some of the lowest incidence worldwide. Source: Cancer Today, World Health Organization (http://gco.iarc.fr/today/home).

Table 1. Estimated Number of Cases of Cervical Cancer, Crude and Age-standardized Rates (ASR) in Western Asian Countries Including Egypt in 2012

Country	Number of cases	Crude rate	ASR
Bahrain	22	4.3	5.9
Egypt	866	2.1	2.3
Iran	947	2.5	2.8
Iraq	291	1.7	2.8
Israel	203	5.2	4.6
Jordan	50	1.6	2.4
Kuwait	30	2.6	4
Lebanon	113	5.1	4.6
Oman	38	3.2	5.3
Qatar	15	3.2	5.1
Saudi Arabia	241	1.9	2.7
Syrian Arab Republic	210	2	2.6
Turkey	1686	4.5	4.3
United Arab Emirates	93	3.7	9.5
West Bank and Gaza Strip	22	1	2
Yemen	198	1.6	3.1
Western Asia*	4455		3
Worldwide	527624		7.9

*Western Asian countries as defined by IARC-WHO, Source; IARC Cancer Today, World Health Organization (http://gco.iarc.fr/today/home)

variables in the population that may contribute to the low incidence of this malignancy in Saudi Arabia (Alsbeih et al., 2017). We have collected 232 samples and demographic data from patients treated for invasive cervical cancers. Interestingly, results showed that in dissimilarity with many other cancers in adults that show maximum occurrence at certain age, cervical cancer displayed two peaks of increased incidence at 43 and 61 years of age (Figure 2). This phenomenon was explained by a combination of conjugal behavior and natural progression of HPV infections. As cancer development takes years to decades to take place, the first peak would be consequent to early sexual encounters which often occurs at the end of teenage period to early thirties, while the 2nd relative rebound corresponds to new encounters later in life. The latter is generally occasioned by separation, failure of 1st marriage as portion of households get into divorce, or simply 2nd marriages in polygamous societies, which brings in an added risk of HPV infections as the number of lifetime sexual partners increases.

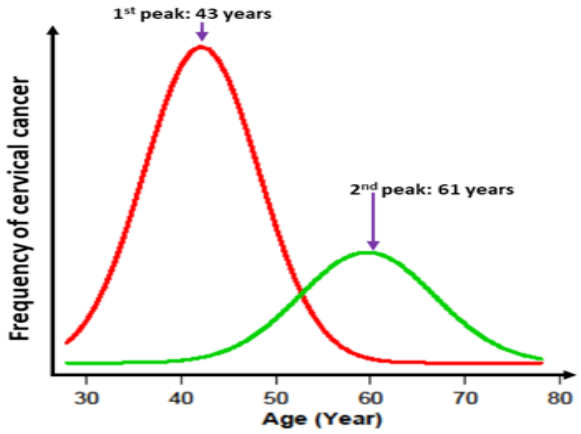

Figure 2. Distribution of Cervical Cancer Frequency Showing the Bimodal Curve of Age-specific Occurrence. A first peak is observed at younger ages (43 years) and a relative rebound at older ages (61 years). These highpoints are shifted 5 to 15 years after primary HPV infection, which may represent the time of cervical malignant transformation to take place with probable variation between populations remnant of possible genetic and socio-cultural differences.

Looking into the rate of HPV infection in cancer samples, we found relatively lower rate (77%) of infection compared to worldwide estimate (85-99%). Similar results were obtained in neighboring country in western Asia with similar socioeconomic composition (Khorasanizadeh et al., 2013). This low incidence of HPV infection rate provided a 1st element of answer, however; it is not enough to explain the very low rate of cervical cancer (2.1 per 100,000 women) in the population (Bazarbashi et al., 2017). In addition, the distribution of various HPV genotypes were comparable to those found in many other populations. Furthermore, these results do not seem to be due to low prevalence of primary HPV infection in cervical swaps of women attending routine gynecologic clinics (Alhamlan et al., 2015).

Therefore, our research team has looked into the pivotal gene encoding the tumor suppressor protein p53 (TP53) which is the most widely evoked candidate gene with potential of modulating cancer predisposition (Lane, 1992). A common genetic variant (G/C, rs1042522) that codes for either arginine (Arg) or proline (Pro) amino-acids in position 72 of p53 protein has longtime suspected to affect the oncogenic potential of the viral HPV-E6 protein (Storey et al., 1998). This single nucleotide polymorphism (SNP) was largely studied in relation to many cancer sites (Stracquadanio et al., 2016),

and in various populations but rarely in cervical cancer in western Asia (Alsbeih et al., 2017). The majority Arg form is supposed to favor HPV infection and predispose to cervical cancer as it is more susceptible than the Pro variant to HPV-E6–mediated degradation. Surprisingly, the study found no difference between cancer patients and a matched control group of 313 women without cancer. In front of this dilemma, the team has reanalyzed the data in cancer patients alone by comparing HPV-positive to HPV-negative cases. Interestingly, we found significant association where cancer patients displayed higher frequency of the Arg risk allele in the HPV-positive patients (Odds Ratio, 0.57; 95% confidence interval, 0.36-0.90; P = 0.016).

Thus, the study suggests that the TP53 genetic variant is only matter when patients are infected with HPV. In the absence of the infection, the TP53 G72C genetic predisposing factor does not play a role in cervical cancer transformation. Thus, the combination of HPV infection and having the TP53 arginine form in the host genetic composition, constitute a risk factor toward developing cervical cancer. Furthermore, the protective variant Pro allele was significantly over-transmitted in the population (P < 0.0003) which lends support to the low incidence of this HPV-related cancer in Saudi Arabia.

In conclusion, anecdotal epidemiologic observations can provide valuable tools to study medical conditions and to better understand the roles of various elements in multifactorial diseases such as cancer. The low incidence of cervical cancer in the specific region of western Asia has triggered researchers to try to understand the causes of this reduced occurrence. Although the laymen would be satisfied with the overall image of conservative society to explain the low incidence of sexually transmitted HPV infection and associated cervical cancer, scientific research points out multifaceted biological explanations including genetic variations. Going back to the initial question on why cervical cancer rate is low in this particular population, the observation that the protective genetic variant TP53 72 proline allele was more commonly found in this population and appear to be over-transmitted compared to others known for their high rate of cervical cancer (Alsbeih et al., 2017). This has further confirmed the results and forward the combination of relative low rate of HPV infection, over-transmission of protective TP53 genetic variant proline along with societal variables as the rationale behind the low incidence of cervical cancer in Saudi women and probably in the region of western Asia.

This conclusion has impact on personalized preventive medicine where genetic makeup of the patients can increase or decrease the risk of developing cervical cancer. This also emphasizes the importance of screening years before cancer development. Thus, to gauge the risk of cervical cancer in women under surveillance for this eventuality, women with abnormal cervical cytology who have the combination of high risk HPV infection and genetic predisposition would require more attention and closer follow up to prevent malignant transformation.

Funding Statement

The study was supported by the National Science, Technology and Innovation Plan (King Abdulaziz City for Science and Technology) grant 12-MED2945-20 (RAC no. 2060 029, 2130 025).

Acknowledgements

I would like to thank the research team at King Faisal Specialist Hospital and Research Centre.

References

Al-Hammadi FA, Al-Tahri F, Al-Ali A, et al (2017). Limited understanding of pap smear testing among women, a barrier to cervical cancer screening in the United Arab Emirates. *Asian Pac J Cancer Prev*, **18**, 3379-87.

Al-Harbi NM, Bin Judia SS, Mishra KN, et al (2017). Genetic predisposition to cervical cancer and the association with XRCC1 and TGFB1 polymorphisms. *Int J Gynecol Cancer*, **27**, 1949-56.

Al Moustafa AE, Al-Awadhi R, Missaoui N, et al (2014). Human papillomaviruses-related cancers. Presence and prevention strategies in the Middle east and north African regions. *Hum Vaccin Immunother*, **10**, 1812-21.

Alhamlan FS, Al-Qahtani AA, Al-Ahdal MN (2015). Current studies on human papillomavirus in Saudi Arabia. *J Infect Dev Ctries*, **9**, 571-6.

Alsbeih G (2014). HPV infection in cervical and other cancers in Saudi Arabia: Implication for prevention and vaccination. *Front Oncol*, **4**, 65.

Alsbeih G (2015). Editorial: HPV-associated cancers, socio-economic disparity, and vaccination. *Front Oncol*, **5**, 223.

Alsbeih GA, Al-Harbi NM, Bin Judia SS, et al (2017). Reduced rate of human papillomavirus infection and genetic overtransmission of TP53 72C polymorphic variant lower cervical cancer incidence. *Cancer*, **123**, 2459-66.

Badar F, Mahmood S, Yusuf MA, et al (2016). Epidemiology of cancers in Lahore, Pakistan, 2010-2012: a cross-sectional study. *BMJ Open*, **6**, e011828.

Baseman JG, Koutsky LA (2005). The epidemiology of human papillomavirus infections. *J Clin Virol*, **32**, 16-24.

Bazarbashi S, Al Eid H, Minguet J (2017). Cancer incidence in Saudi Arabia: 2012 Data from the Saudi cancer registry. *Asian Pac J Cancer Prev*, **18**, 2437-44.

Bray F, Ren J-S, Masuyer E, et al (2013). Global estimates of cancer prevalence for 27 sites in the adult population in 2008. *Int J Cancer*, **132**, 1133-45.

Bruni L, Diaz M, Castellsague X, et al (2010). Cervical human papillomavirus prevalence in 5 continents: meta-analysis of 1 million women with normal cytological findings. *J Infect Dis*, **202**, 1789-99.

Chen X, Xu H, Xu W, et al (2017). Prevalence and genotype distribution of human papillomavirus in 961,029 screening tests in southeastern China (Zhejiang Province) between 2011 and 2015. *Sci Rep*, **7**, 14813.

de Sanjose S, Quint WG, Alemany L, et al (2010). Human papillomavirus genotype attribution in invasive cervical cancer: a retrospective cross-sectional worldwide study. *Lancet Oncol*, **11**, 1048-56.

Ferlay J, Soerjomataram I, Dikshit R, et al (2015). Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer*, **136**, 359-86.

Filemban SM, Yasein YA, Abdalla MH, et al (2015). Prevalence

and behavioral risk factors for STIs/HIV among attendees of the Ministry of Health hospitals in Saudi Arabia. *J Infect Dev Ctries*, **9**, 402-8.

Howell-Jones R, de Silva N, Akpan M, et al (2012). Prevalence of human papillomavirus (HPV) infections in sexually active adolescents and young women in England, prior to widespread HPV immunisation. *Vaccine*, **30**, 3867-75.

Ibrahim AS, Khaled HM, Mikhail NN, et al (2014). Cancer incidence in egypt: results of the national population-based cancer registry program. *J Cancer Epidemiol*, **2014**, 437971.

Ismail SI, Soubani M, Nimri JM, et al (2013). Cancer incidence in Jordan from 1996 to 2009--a comprehensive study. *Asian Pac J Cancer Prev*, **14**, 3527-34.

Khoo SP, Bhoo-Pathy N, Yap SH, et al (2018). Prevalence and sociodemographic correlates of cervicovaginal human papillomavirus (HPV) carriage in a cross-sectional, multiethnic, community-based female Asian population. *Sex Transm Infect*, **94**, 277-83.

Khorasanizadeh F, Hassanloo J, Khaksar N, et al (2013). Epidemiology of cervical cancer and human papilloma virus infection among Iranian women - analyses of national data and systematic review of the literature. *Gynecol Oncol*, **128**, 277-81.

Lane DP (1992). Cancer. p53, guardian of the genome. *Nature*, **358**, 15-6.

Mohagheghi MA, Mosavi-Jarrahi A, Malekzadeh R, et al (2009). Cancer incidence in Tehran metropolis: the first report from the Tehran Population-based Cancer Registry, 1998-2001. *Arch Iran Med*, **12**, 15-23.

Shrestha AD, Neupane D, Vedsted P, et al (2018). Cervical cancer prevalence, incidence and mortality in low and middle income countries: A systematic review. *Asian Pac J Cancer Prev*, **19**, 319-24.

Storey A, Thomas M, Kalita A, et al (1998). Role of a p53 polymorphism in the development of human papillomavirus-associated cancer. *Nature*, **393**, 229-34.

Stracquadanio G, Wang X, Wallace MD, et al (2016). The importance of p53 pathway genetics in inherited and somatic cancer genomes. *Nat Rev Cancer*, **16**, 251-65.

Walboomers JM, Jacobs MV, Manos MM, et al (1999). Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. *J Pathol*, **189**, 12-9.

Wang SS, Gonzalez P, Yu K, et al (2010). Common genetic variants and risk for HPV persistence and progression to cervical cancer. *PLoS One*, **5**, e8667.

Zur Hausen H (1991). Human papillomaviruses in the pathogenesis of anogenital cancer. *Virology*, **184**, 9-13.