Human Vaccines & Immunotherapeutics 8:12, 1867–1868; December 2012; © 2012 Landes Bioscience

Does the Syrian population have to wait for the new generation of human papillomaviruses vaccine?

Ala-Eddin Al Moustafa,[1,2,3,*] Amber Yasmeen,[1] Lina Ghabreau[4] and Nizar Akil[4]

[1]Syrian Research Cancer Centre of the Syrian Society against Cancer; Aleppo, Syria; [2]Segal Cancer Centre & Department of Oncology; McGill University; Montreal, QC Canada; [3]Department of Mechanical Engineering; Concordia University; Montréal, QC Canada; [4]Department of Pathology; Faculty of Medicine/University of Aleppo; Aleppo, Syria

Keywords: high-risk HPV, colorectal cancer, vaccine, Syrian population

We recently conducted several studies regarding the presence of high-risk HPVs in human cervical, colorectal and breast cancers in the Syrian population. Herein, we report that high-risk HPVs type 16, 18, 33, 45, 51, 52 and 58 are frequently present in colorectal cancer in this population. Therefore and based on previous studies and present data, we conclude that the most frequent high-risk HPV types, in the Syrian population, are 16, 18, 33, 35, 45, 51, 52 and 58. Thus, our data suggest that it will be useful to use the new generation of HPV vaccine to protect the Syrian population from high-risk HPVs and their associated cancers.

Human papillomaviruses (HPVs) have been established as etiological agents of invasive cervical cancer, as roughly 96% of these cancers are positive for high-risk HPVs, specifically types 16, 18, 31, 33, 35, 45 and 52, which are the most common viral sexually transmitted infection worldwide.[1] Persistent infection with high-risk HPVs is necessary for the development of premalignant lesions and/or progression of the disease.[1] Furthermore, high-risk HPVs have carcinogenic effects at several other anatomical sites in women and men such as colorectal, head and neck (HN) as well as breast,[2-4] studies showed that high-risk HPVs are present in roughly 91%, 30% and 50% of these cancers, respectively.[3,4] Therefore, 9%, 70% and 50% of these cancer are negative for high-risk HPVs; however, we believe that some of these high-risk HPVs-negative cases could be infected by low-risk HPVs. High-risk HPV E6 and E7 onco-proteins, which are consistently expressed in these cancers, play a major role in high-risk HPV-related cancer development and progression.[5]

We recently conducted several studies regarding the presence of high-risk HPVs in human cervical, colorectal and breast cancers in the Syrian population,[6-8] we found that high-risk HPV types, 16, 18, 31, 33 and 35 are present in these cancers, and the majority of high-risk HPV positive cancers are invasive carcinomas; this phenotype is accompanied by overexpression of numerous genes such as Id-1, Fascin and P-cadherin, which are important regulators of cell invasion and metastasis.[6-8]

In this current study, we used the same samples and protocol as our recent investigation of colorectal cancers and HPVs. The samples were analyzed for HPVs by multiplex PCR using PGMY09/11 L1 primer pools and specific primers for E7 gene of HPV types 45, 51, 52 and 58, as previously described by our group.[6] Herein, we report that high-risk HPVs type 45, 51, 52 and 58 are frequently present in colorectal cancer in this population ($p < 0.001$, $p < 0.001$, $p < 0.001$ and $p < 0.0001$, respectively) (**Table 1**), in some cases multiple types of HPV infections were detected. Therefore and based on previous studies,[6-8] and our present data on colorectal cancer, we conclude that the most frequent high-risk HPV types, in the Syrian population, are 16, 33, 35, 45, 52 and 58 (**Table 1**). In parallel, it is important to mention that our preliminary data of HN cancers in the Syrian population show that 43% of these cancers are positives for high-risk HPVs; while, genotyping of high-risk HPVs is presently under investigation by our group, we believe that data of this analysis will be similar to our data of cervical and colorectal cancers (Ghabreau et al., in preparation).

On the other hand, recent availability of two HPV vaccines: HPV 6/11/16/18 L1 VLP (Gardasil®) and HPV 16/18 (Cervarix®),[9,10] has offered protection against the two most prevalent high-risk HPV types (16 and 18) in cervical cancer worldwide. This will lead to a decrease in the incidence of cervical cancer as well as other HPV 16 and 18-related cancers in the near future. To date, modeling studies assumed that the vaccine is effective against high-risk HPV types 16 and 18 only. Meanwhile, there is accumulating evidence suggesting that HPV vaccination also confers some degree of cross-protection against a few other oncogenic HPV types, including HPV31 and HPV45.[9,10] Increased protection against high-risk HPV is expected to lead to a further decrease in cervical cancer and other high-risk HPV-related cancers. However, a new generation of broad spectrum HPV vaccines, protecting against multiple high-risk HPV types is emerging. At present, a phase III trial is running to assess the

*Correspondence to: Ala-Eddin Al Moustafa; Email: ala-eddin.almoustafa@mcgill.ca
Submitted: 07/05/12; Revised: 08/18/12; Accepted: 08/26/12
http://dx.doi.org/10.4161/hv.21973

Table 1. Incidence of high-risk HPV types 16, 18, 31, 33, 35, 45, 51, 52 and 58 in human cervical, colorectal and breast cancers in the Syrian population

Anatomic location of cancer (number of cases)	High-risk HPV type positive cases								
	16	18	31	33	35	45	51	52	58
Cervical (44)	21	18	5	24	9	17	7	17	13
Colorectal (78)	36	30	6	36	15	45*	21*	24*	25*
Breast (113)	10	11	8	63	42	ND	ND	ND	ND

*Data reported in this study; ND, not determined.

efficacy of a 9-valent vaccine including 7 high-risk HPV types (16, 18, 31, 33, 45, 52 and 58) and 2 low-risk HPVs (6 and 11) (Merck and Co. Inc., NCT00543543). Filing with the FDA is anticipated in 2012 (www.merck.com). A main goal behind the development of the 9-valent vaccine is to reduce high-risk HPV-related cancers especially cervical and colorectal.

Therefore, based on the cost of the existing vaccine and its limited protection against two high-risk HPVs (types 16 and 18) as well as our data on the presence of high-risk HPVs in human carcinomas in the Syrian population,[6-8] we firmly believe that the new generation of high-risk HPVs vaccine will present the best protection for the Syrian people against HPV viruses. This great advancement could reduce the development of cervical, colorectal, breast and HN cancers by more than 50%, as well as decrease their progression to a metastatic form which is responsible for the majority of cancer-related deaths.

Disclosure of Potential Conflicts of Interest

The authors declare the absence of any conflicting or dual interests.

Acknowledgments

We are grateful to Mrs. A. Kassab for her reading of the manuscript.

Funding

This work was supported by the Canadian Institutes for Health Research (HPV team grant), the Fonds de la Recherche en Santé du Québec (FRSQ- Réseau du Cancer) and the High Commission for Scientific Research in Syria.

References

1. Smith JS, Lindsay L, Hoots B, Keys J, Franceschi S, Winer R, et al. Human papillomavirus type distribution in invasive cervical cancer and high-grade cervical lesions: a meta-analysis update. Int J Cancer 2007; 121:621-32; PMID:17405118; http://dx.doi.org/10.1002/ijc.22527.
2. Abramowitz L, Jacquard AC, Jaroud F, Haesebaert J, Siproudhis L, Pradat P, et al. Human papillomavirus genotype distribution in anal cancer in France: the EDiTH V study. Int J Cancer 2011; 129:433-9; PMID:20839262; http://dx.doi.org/10.1002/ijc.25671.
3. Umudum H, Rezanko T, Dag F, Dogruluk T. Human papillomavirus genome detection by in situ hybridization in fine-needle aspirates of metastatic lesions from head and neck squamous cell carcinomas. Cancer 2005; 105:171-7; PMID:15822131; http://dx.doi.org/10.1002/cncr.21027.
4. Antonsson A, Spurr TP, Chen AC, Francis GD, McMillan NA, Saunders NA, et al. High prevalence of human papillomaviruses in fresh frozen breast cancer samples. J Med Virol 2011; 83:2157-63; PMID:22012724; http://dx.doi.org/10.1002/jmv.22223.
5. Vousden KH. Regulation of the cell cycle by viral oncoproteins. Semin Cancer Biol 1995; 6:109-16; PMID:7647307; http://dx.doi.org/10.1006/scbi.1995.0014.
6. Darnel AD, Wang D, Ghabreau L, Yasmeen A, Sami S, Akil N, et al. Correlation between the presence of high-risk human papillomaviruses and Id gene expression in Syrian women with cervical cancer. Clin Microbiol Infect 2010; 16:262-6; PMID:19438642; http://dx.doi.org/10.1111/j.1469-0691.2009.02774.x.
7. Ghabreau L, Segal E, Yasmeen A, Kassab A, Akil N, Al Moustafa AE. High-risk human papillomavirus infections in colorectal cancer in the Syrian population and their association with Fascin, P-cadherin and Id-1 expressions: a tissue microarray study. Clin Cancer Investig J 2012; 1:26-30; PMID: 22999294; http://dx.doi.org/10.1186/1687-9856-2012-26
8. Akil N, Yasmeen A, Kassab A, Ghabreau L, Darnel AD, Al Moustafa AE. High-risk human papillomavirus infections in breast cancer in Syrian women and their association with Id-1 expression: a tissue microarray study. Br J Cancer 2008; 99:404-7; PMID:18648363; http://dx.doi.org/10.1038/sj.bjc.6604503.
9. Brown DR, Kjaer SK, Sigurdsson K, Iversen OE, Hernandez-Avila M, Wheeler CM, et al. The impact of quadrivalent human papillomavirus (HPV; types 6, 11, 16, and 18) L1 virus-like particle vaccine on infection and disease due to oncogenic nonvaccine HPV types in generally HPV-naive women aged 16-26 years. J Infect Dis 2009; 199:926-35; PMID:19236279; http://dx.doi.org/10.1086/597307.
10. Paavonen J, Naud P, Salmerón J, Wheeler CM, Chow SN, Apter D, et al.; HPV PATRICIA Study Group. Efficacy of human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine against cervical infection and precancer caused by oncogenic HPV types (PATRICIA): final analysis of a double-blind, randomised study in young women. Lancet 2009; 374:301-14; PMID:19586656; http://dx.doi.org/10.1016/S0140-6736(09)61248-4.