Current Problems in Cancer 44 (2020) 100605

Contents lists available at ScienceDirect

Current Problems in Cancer

journal homepage: www.elsevier.com/locate/cpcancer

Commentary

HPV, vaccines, and cervical cancer in a low- and middle-income country

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ARTICLE INFO

Keywords: Cervical cancer; Human papilloma virus; HPV; Global health; Low and middle income countries

Real-world conditions test effectiveness, the next step after establishing efficacy in controlled settings. From the annual flu shot to HPV vaccination, effectiveness measures what happens when best efforts for vaccine development meet the realities of challenging viruses and changing subtypes in regions around the world. After testing 2,645 women from multiple locations in Honduras for types of high-risk HPV (hrHPV) and finding the prevalence of virus types to be quite different from those in the US, we asked what vaccine would be the most efficacious for the local situation, and which hrHPV types are most commonly found in cervical cancer tissues from Honduran women.

Human Papilloma virus (HPV)-related cervical cancer is among the most prevalent forms of cancer in women around the world.[1] With screening and early detection, cervical cancer is preventable. Inadequate screening in low- and middle-income countries (LMICs) results in high rates of late-stage disease upon clinical presentation. The burden of cervical cancer in LMICs is increasing; options for prevention and therapy are insufficient in quantity and quality to have

☆ Declaration of Competing Interest: The authors have no conflict of interest to declare.

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https://doi.org/10.1016/j.currproblcancer.2020.100605

a major impact on this trend. In contrast, over more than 5 decades, countries with high resources have reduced deaths from cervical cancer by widespread adoption of screening by Pap test. LMICs struggle with implementation of Pap testing due to inadequate infrastructure for this cytology-based method requiring well-trained cytotechnologists and cytopathologists.

In 2013, as part of our institution's global oncology initiative, we implemented brigade-style cancer screening health fairs in Honduras (pop. 8M). In that context, we introduced hrHPV DNA testing to provide local oncologists information about cervical cancer risk from hrHPV and address our research questions about location-specific prevalence of hrHPV by type. We recruited 2645 women from urban and rural settings to explore distribution of hrHPV types in the northern region of Honduras.[2-4] Participants were from remote, rural regions (in the states of Yoro and La Mosquitia) or from factories in urban San Pedro Sula in the state of Cortes.

We established the landscape for hrHPV prevalence in those regions of Honduras by using a multiplexed real-time polymerase chain reaction (PCR) assay to detect hrHPV types by melt curve analysis (QuanDx/Zeesan Biotech, San Jose, CA). DNA was isolated from cervical brush specimens using a heat initiated crude lysis procedure in a boiling pot of water or a rice steamer. An aliquot of cell lysate was added directly to the lyophilized PCR reagents for real time PCR and melt curve analysis. This extraction method allowed us to minimize costs and obtain the throughput to process large numbers of samples. The lyophilized MeltPro high-risk genotyping reagents were stable and robust under environmental conditions not typically seen in laboratories.

In the US, hrHPV types 16 and 18 are the most common; worldwide, they are thought to account for almost 70% of all cervical cancers. Our screening studies indicated distribution of hrHPV, by type, differed among the regions of Honduras where we conducted cancer screening health fairs (Fig). Tracking 16 and 18 among our study locations suggests a more complex story. In rural Yoro, 12 of 14 known hrHPV types were identified and HPV18 comprised just 1% of the total while HPV59 was most common (15%). HPV52 (29%) followed by HPV16 (25%) were the most frequent types of hrHPV in women from La Mosquitia, the largest wilderness tract in Central America. In urban San Pedro Sula, testing results from 2 factories just a few miles apart were different from each other with HPV16 most prevalent (18%) at Factory #1 and ranking third (13%) at Factory #2 where HPV58 (19%) was most prevalent. Overall, prevalence of HPV18 ranged from 1% to 6%.

Given the different distribution of these hrHPV types in Honduras versus the US, we were concerned about the relative utility of HPV vaccines for Honduran women and asked questions about effectiveness of HPV vaccines locally. The HPV bivalent vaccine (Cervarix) only protects against HPV16 and 18. The quadrivalent vaccine (Gardasil) protects against HPV16 and 18, plus low-risk HPV6 and 11. The new 9-valent vaccine (Gardasil 9), protects against hrHPV types 16, 18, 31, 33, 45, 52, and 58 as well as low-risk HPV types 6 and 11. Eighteen low-income countries utilize GAVI funding to vaccinate young girls with the less expensive and narrowly protective quadrivalent vaccine rather than the relatively more expensive (non-GAVI covered), broader coverage 9-valent vaccine. Atkinson et al showed most women in our screening studies would not be protected by either the bivalent or quadrivalent vaccines that are commonly used in LMIC vaccination programs. According to the types of hrHPV found in these study groups, only 14%-26% of the women would have been protected from their hrHPV types by the bi- or quadrivalent vaccines; the 9-valent vaccine would have protected 40%-70% of our study participants.

HPV is considered the most common sexually transmitted virus in the world and in approximately 80%-90% of infections, the virus is cleared with no further clinical consequences. Knowing only a small percentage of HPV infections progress to cervical cancer, we wanted to interrogate actual cervical cancer tissue from Honduras for the prevalence of hrHPV, by type. Our research partners at the Hospital of la Liga Contra el Cáncer in San Pedro Sula Honduras provided 100 formalin-fixed, paraffin embedded tissue blocks from cervical cancers diagnosed at their cancer center. Though the tumors may not represent precisely the individual geographic distribution of our screening studies, they represent true disease caused by hrHPV in Honduras. DNA was

extracted from 100 tumor tissues and tested for hrHPV using our real-time PCR assay followed by melt curve analysis. Thirteen samples did not give any results for hrHPV genotyping. At 57%, HPV16 was most prevalent, followed by HPV33 in 16% (14/87) tumors. Other hrHPV types were found at these rates: HPV45 in 8% (7/87), HPV18 in 7% (7/87), HPV59 in 7% (6/87), and HPV52 in 6% (5/87). The most common coinfection was HPV16 and HPV45 in 7% (6/87) of tumors. hrHPV types 35, 39, 58, and 56 were also detected, though in 3 or fewer tumors each. Overall, even the 9-valent vaccine would not have been protective against 13% (11/87) of the hrHPV that caused

High-Risk HPV Types and Protection by Vaccines	Rural Yoro (n=401)[2]	Rural La Mosquitia (n=111)[3]	San Pedro Sula Factory #1 (n=401)[2]	San Pedro Sula Factory #2 (n=1,732)[4]	Cervical Tumor Tissue (n=87)
HPV16 Bivalent Quadrivalent 9-valent	13%	23%	18%	13%	57%
HPV18 Bivalent, Quadrivalent 9-valent	1%	3%	4%	6%	7%
HPV31 9-valent	13%	3%	4%	6%	0%
HPV33 9-valent	0%	0%	4%	5%	16%
HPV35	6%	3%	9%	13%	2%
HPV39	4%	10%	12%	12%	2%
HPV45 9-valent	7%	6%	4%	9%	8%
HPV51	4%	3%	7%	5%	0%
HPV52 9-valent	0%	29%	2%	9%	6%
HPV56	6%	0%	0%	5%	2%
HPV58 9-valent	6%	6%	13%	19%	2%
HPV59	15%	3%	9%	11%	7%
HPV66	10%	3%	4%	3%	0%
HPV68	13%	6%	9%	7%	0%

Fig.. (A) Comparison of hrHPV types from screening studies performed in rural and urban regions of Honduras. HPV type with vaccine coverage and percent prevalence. (B) Graphic representation of high-risk HPV distributions by site tested.

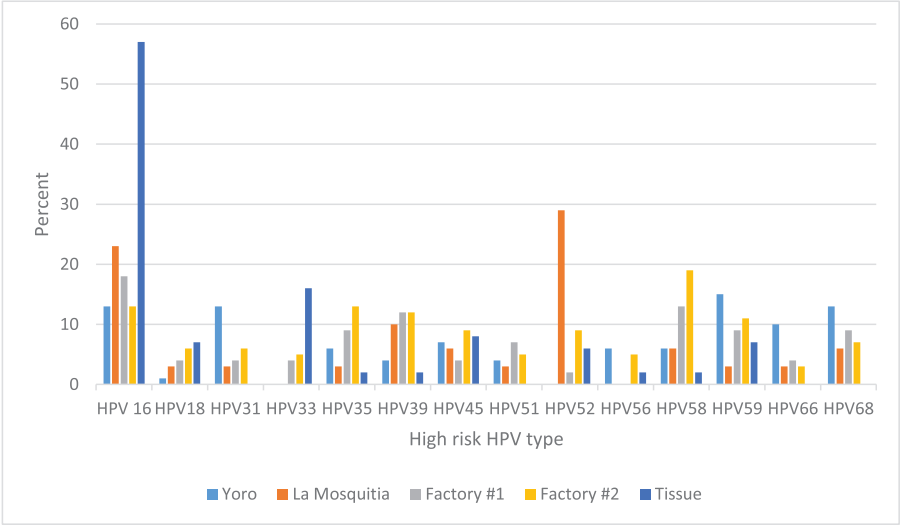

Fig.. Continued

the tumors in our study. In contrast to the potential of 40%-70% for protection by vaccine in the 2645 women who were screened, if the 9-valent vaccine had been actually used to protect the women who developed the cervical tumors we tested, more than 80% of their tumors may have been prevented.

Our hrHPV studies on cervical cancer tissue provide a better understanding of the viral types associated with causation of cervical cancer in this population. With respect to vaccination, bivalent and quadrivalent vaccines against HPV16 and 18 would protect half of hrHPV-infected women while the 9-valent vaccine would protect the majority of women from developing cervical cancer. This data further supports the use of the 9-valent vaccine for optimal coverage and protection. As a leading cause of cancer-related mortality, improved prevention of cervical cancer is possible through implementation of robust 9-valent vaccination programs.

Author statement

Lauren M. Petersen: Methodology, Investigation, Data curation; Jamie M. Fenton: Investigation, Data curation; Linda S. Kennedy: Conceptualization, Writing- Review and editing, Funding acquisition; Ethan P.M. LaRochelle: Formal analysis, Writing-reviewing and editing; Suyapa Bejarano: Resources, Writing-reviewing and editing; Gregory J. Tsongalis: Conceptualization, Supervision, Writing-original draft, Project administration.

Acknowledgments

The authors acknowledge the support of the Pathology Shared Resource, a section of the Laboratory for Clinical Genomics and Advanced Technology, in the Department of Pathology and Laboratory Medicine of the Dartmouth Hitchcock Health System and the Norris Cotton Cancer Center at Dartmouth with NCI Cancer Center Support Grant 5P30 CA023108-37.

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