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Evolution of cervical cancer screening and prevention in United States and Canada: Implications for public health practitioners and clinicians☆,☆☆

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ABSTRACT

Objective. Declines in cervical cancer incidence and mortality in the US and Canada have been widely attributed to the introduction of the Papanicolaou (Pap) test. This article reviews evolution of screening towards HPV testing and primary prevention through HPV vaccination.

Method. Sentinel events in the evolution of cervical cancer screening and primary prevention through HPV vaccination in the US and Canada are described.

Results. Despite commonalities, cervical cancer screening and prevention differ between the two countries. Canada has a combination of opportunistic and organized programs at the provincial and territorial level, while the US has opportunistic screening and vaccination systems. In the US, the HPV test along with the Pap test (co-testing) is part of national recommendations for routine cervical cancer screening for women age 30 and older. Co-testing is not being considered anywhere in Canada, but primary HPV testing is currently recommended (but not implemented) in one province in Canada.

Conclusion. Many prevention strategies are available for cervical cancer. Continued public health efforts should work to increase vaccine coverage in the target age groups and cervical cancer screening for women at risk, at appropriate intervals. Ongoing evaluation will be needed to ensure appropriate use of health resources, as vaccinated women become eligible for screening.

Background

In the United States and Canada, cervical cancer screening is a public health success (Centers for Disease Control and Prevention, 2011b; Public Health Agency of Canada, 2012). Declines in cervical cancer incidence and mortality in both countries have been attributed to the introduction of the Papanicolaou (Pap) cytology test, but declines have recently leveled off and disparities continue (Freeman and Wingrove, 2005). Today, the United States(U.S. Cancer Statistics Working Group, 2010) and Canada(Canadian cancer society's steering committee on cancer statistics, 2012) have respectively approximately 12,400 and 1350 cases of cervical cancers diagnosed and 4000 and 390 deaths annually.

While screening with a Pap test remains an important prevention tool, several key developments in cervical cancer prevention have slowly shifted focus from cytology-based screening alone to incorporate human papillomavirus (HPV)-based screening with Pap testing and HPV vaccination. A sentinel event in 1975, was Dr. zur Hausen's hypothesis that HPV was the primary cause of cervical cancer (Fig. 1) (zur Hausen et al., 1975). This laid the groundwork for development of HPV-based diagnostics and HPV vaccines in following decades. Better understanding of the natural history of cervical cancer led to more refined screening parameters and options for prevention. While considerable progress has been made in the discovery of new technologies related to cervical cancer screening and HPV vaccination, challenges remain in making public health prevention of cervical cancer more efficient.

Natural history

HPV infection is common, but cervical cancer is comparatively rare and usually slow to develop. Almost all sexually active persons will be infected with HPV at least once in their lifetime (Weinstock et al., 2004). Most HPV infections clear within a few years (Rodriguez et al.,

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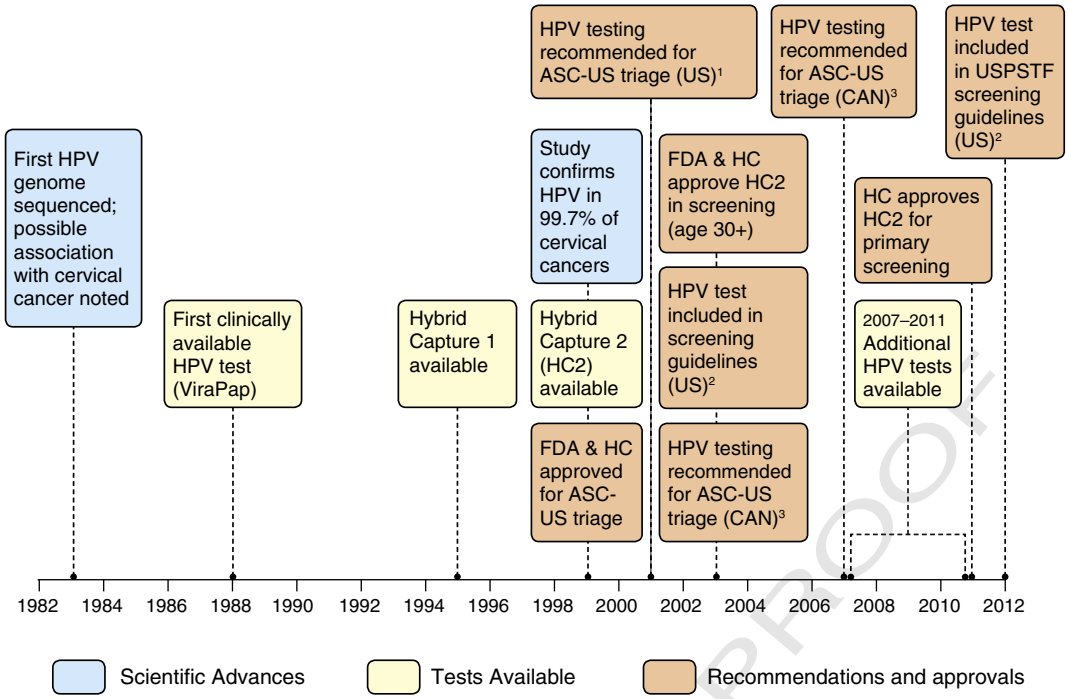

Fig. 1. Evolution of HPV testing in Canada and the United States. Footnotes: US = United States. CAN = Canada. FDA = US Food and Drug administration. HC = Health Canada. USPSTF = US Preventive Services Task Force. ASC-US = Atypical squamous cells of undetermined significance. HPV = Human Papillomavirus. HPV testing was first recommended for triage of ASC-US lesions by the American Society for Colposcopy and Cervical Pathology in 2001. The American Cancer Society and American College of Obstetrics and Gynecology recommended HPV tests as an option for screening women 30 years and older starting in 2003. The US Preventive service Task Force made a similar recommendation in 2012. The Pan-Canadian Forum on Cervical Cancer Prevention and Control first recommended HPV testing for triage of ASCUS lesions in Canada in 2003. The Society of Obstetricians and Gynecologists of Canada made a similar recommendation in 2007. SOURCES: Cox, JT. History of the use of HPV testing in cervical screening and in the management of abnormal cervical screening results. Journal of Clinical Virology 2009;45:S3-S12. Centers for Disease Control and Prevention. Cervical Cancer Screening Guidelines for Average-Risk Women. Available at http://www.cdc.gov/cancer/cervical/pdf/guidelines.pdf.Accessed November 6, 2012. FDA. U.S. Food and Drug Administration website. Available at www.fda.gov. Accessed November 6, 2012.

2008). Screening detects many lesions, but most regress, especially low grade squamous intraepithelial lesions (LSIL) and atypical cells of undetermined significance (ASC-US), confirming that not all lesions need to be treated (Ostor, 1993). Integration of HPV and persistence over time, not merely infection, leads to development of high-grade precancers and sometimes invasive cervical cancer (Schiffman et al., 2011). Of the 14 oncogenic HPV types, HPV 16 and to a lesser degree, HPV 18 are considered the HPV types that progress most rapidly and most often from infection to significant lesions (Schiffman et al., 2011).

HPV-based screening

HPV testing identifies individuals at increased risk of developing high-grade cervical precancer or cancer, and has been evaluated as a screening test with cytology (co-testing), as a stand-alone screening test (primary HPV screening), and as part of management and surveillance strategies. Although invasive cervical cancer is rare in screened populations, false-negative screening cytology results may be responsible for up to 30% of invasive cervical cancers (Spence et al., 2007). HPV testing has a higher sensitivity but lower specificity (i.e. more false-positive test results) than cytology in the detection of high-grade lesions (Moyer and Force, 2012).

Available HPV tests

The most commonly used HPV test in the United States and Canada has been the Digene (i.e. Qiagen Inc., Valencia CA) Hybrid Capture 2 (HC2) test (Hogarth et al., 2012). In the last 5 years, additional tests have been approved by the US Food and Drug Administration (FDA) and Health Canada (HC) for detecting clinically significant levels of 13–14 high-risk HPV types (see Table 2).

HPV test use in the United States

Although the first HPV test was FDA-approved in 1988, the HC2 test was only FDA-approved in 1999 for follow-up of ASC-US cytology to identify women who may benefit from immediate colposcopy (Fig. 1). Shortly thereafter, the ASC-US, LSIL (ALTS) trial confirmed the efficacy of HPV testing as a triage method for women with ASC-US Pap test results, increasing the use of HPV testing (Solomon et al., 2001). Guidelines from the American Society for Colposcopy and Cervical Pathology and the American College of Obstetrics and Gynecology (ACOG) recommended using the HPV test for ASC-US management and in other less common scenarios (2003; Wright et al., 2002). In 2003, the HC2 High-Risk test was FDA-approved for screening women ≥ 30 years as a co-test. ACOG and American Cancer Society (ACS) recommended either co-testing or cytology alone, both at a 3-year interval. In 2009, ACOG recommended starting screening at age 21, since lesions among younger women are likelier to regress and treatment may cause adverse pregnancy outcomes. In 2012, because of the high negative predictive value of an HPV test, ACS and ACOG recommended co-testing as the preferred option for screening at a 5-year interval (American College of Obstetricians and Gynecologists, 2009; Saslow et al., 2012) The USPSTF released new recommendations in 2012 and for the first time, also included the option of co-testing as a screening strategy with similar intervals (i.e. 5-year interval for co-testing or 3-year interval with cytology alone) (Moyer and Force, 2012). Despite several randomized clinical trials evaluating the efficacy of primary HPV testing, current U.S. guidelines do not support primary HPV testing alone, because of limited evidence and concerns about the high number of referrals for colposcopy. Both USPSTF and ACS guidelines mention a potential role for primary HPV testing, most likely in the context of an organized screening system. Guidelines also agree that adequately screened

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