Primary Cervical Cancer Screening Using HPV Testing

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Introduction and Natural History

Cervical cancer affected roughly 1450 women in 2021 and approximately 380 women died from this disease (CCS, 2021). The overall incidence of cervical cancer has been decreasing since screening began in the 1950's; immediate and uniform uptake in screening at that time. The steady decrease in incidence has been more notable since the 1970's with widespread uptake of cervical cancer screening in Canada (Canadian Task Force, 2012). The last environmental scan of cervical screening in Canada indicates that there are still provinces in our country that do not have an organized screening program, including the Yukon, Northwest Territories, Nunavut and Quebec (Canadian Partnership Against Cancer, 2018). Since screening began, the standard of care has been using cervical cytology to detect precancerous changes to the cervix. In 1983 HPV (human papillomavirus) 16 was detected in a biopsy of invasive cervical cancer and since that time HPV has been investigated as the causative agent behind cervical cancer and precancerous lesions (Viruses 2018). These precancerous changes are largely due to infection from an HPV strain; there are more than 100 different types of HPV and some have been identified to be specifically oncogenic. These high risk HPV strains consist of 16/18/31/35/39/45/51/52/56/58/66/68 and are connected to about 97% of cervical cancers (Viruses, 2018). The low risk types consist of 6/11/40/42/43/44/54/61/72 and are linked to anogenital warts and laryngeal papillomas (Viruses 2018). Cervical cancer results from a proliferation of malignant cells that arise in the cervical tissues and represent a variety of changes from noninvasive to an invasive carcinoma (Canadian Task Force, 2012). Research shows that roughly 30-35% of HSIL (high grade squamous intraepithelial lesion) or CIN3 (cervical intraepithelial neoplasia) actually progress to an invasive cancer (Cox & Sneyd, 2018) (Canadian Task Force, 2012). However, finding these changes early and treating them appropriately leads to less morbidity and mortality of a preventable disease. The precancerous lesions are proliferations of atypical cells that form due to an infection of the human papillomavirus (Canadian Task Force, 2012); these changes typically start in the transformation zone of the cervix, which is an area of high cellular turnover due to hormonal changes throughout the lifetime (Canadian Task Force, 2012). With the transformation zone being comprised of mainly squamous cells, it supports the statistics of squamous cell carcinoma being the most prevalent form of cervical cancer at 80% (Canadian Task Force, 2012), followed by adenocarcinoma (15%) and other more rare cell types such as small cell neuroendocrine, melanoma, sarcoma, lymphoma and clear cell adenocarcinoma (Tjalma, 2018). With the discovery and strong supporting evidence of the HPV being the causative agent behind the vast majority of invasive cervical cancers, our screening methodologies need to change. There has been a paradigm shift in the method for which screening is done for people with cervixes, which has been adopted by many other countries internationally. Primary HPV testing has been proven to be more sensitive and accurate than cytology alone with a high negative predictive value (Viruses, 2018) and for this reason, Canada is preparing to update its recommendations for screening going forward.

Risk Factors for Developing Cervical Cancer

The most important risk factor for developing cervical cancer is an infection with a high risk strain of HPV. The second known risk factor for developing cervical cancer is being an active cigarette smoker. This risk is mitigated with the cessation of smoking and can also facilitate regression of precancerous lesions (Kjellberg et al., 2000). The American Cancer Society reveals that women who smoke are twice as likely to develop cervical cancer than those who are non-smokers (2020). Substances in the cigarette damage the DNA of cervical cells and that may be the contributing factor that allows cancer to develop in these tissues. Smoking cigarettes also decreases the effectiveness of one's immune system thereby decreasing a person's ability to clear an HPV infection.

There is an association between an early initiation of sexual activity as well as multiple sexual partners with developing cervical changes (American Cancer Society, 2020). There is also an association between a woman being younger than 20 years old at the time of their first term pregnancy and the likelihood of that woman developing cervical cancer in their lifetime (American Cancer Society, 2020). Being immunocompromised is another risk factor that increases the chance of precancerous changes progressing to cervical cancer such as having an infection with the human immunodeficiency virus (CCS 2020). A history of sexually transmitted infections; especially chlamydia trachomatis, increases risk as well. The correlation is believed to be linked to prolonged cervical inflammation by the chlamydia infection making it more difficult for the body to clear an HPV infection. This risk increases as well with repeated chlamydia infections (CCS 2020). There is an unclear association between taking the oral contraceptive pill over long periods of time, such as longer than 5 years, and developing precancerous changes of the cervix. This risk goes down over time after stopping the oral contraceptive pill and after 10 years off of the pill, the risk has returned to normal (CCS, 2020). Another known risk factor is in utero exposure to diethylstilbestrol (DES), a drug used between 1940 and 1971 to treat problems of pregnancy. Daughters of the mothers who were treated with this medication have been suggested to have higher risk of developing cervical changes and carcinoma of the cervix (CCS, 2020).

HPV Testing Stats and Proposed Algorithm

The current Canadian guidelines for screening of cervical cancer are to begin at age 21 if sexually active and be screened every 3 years thereafter if they have a normal cytology report. Screening ends at age 70 as long as the person has had 3 normal cytology reports in the last 10 years. The new proposed screening guidelines recommend participants begin screening at 21 with cytology as is current practice; then begin screening with HPV testing alone at age 30. With a negative HPV result, screening

intervals vary amongst countries between 3 and 5 years. The age to complete surveillance would remain the same at 70 years old as long as the last 3 tests were negative. The evidence to support this change has been accumulating over the past 15 to 20 years and many countries have already adopted the above algorithm with slight variations. Australia, Europe and certain states in the United States have all adopted primary HPV testing for population screening. Evidence has been supportive that if a woman has a negative HPV test on primary screening then their risk for CIN3+ or HSIL is very low for the following 5 years or more (Whitlock et al., 2011). The sensitivity of HPV testing for CIN 2+ and CIN 3+ (HSIL) was between 95.4-96.1% (Cuzick et al., 2006; Naucler et al., 2009). This is in contrast to cytology where sensitivity was considerably less at 53-71% for CIN 2+ and 74% for CIN 3+. The specificity for HPV testing did not, however, outperform cytology with only 94.2% for CIN 2+ and 93.6% for CIN 3+ versus 98.6 % for CIN 2+ and 98.2% for CIN 3+ (Naucler 2009). The principle approach when there are 2 tests available to screen for the same outcome suggests using the more sensitive test first and then follow up positive results with the more specific test (Cuzick et al., 2006). The way that countries are managing the new colposcopy screening protocol is to follow up positive HPV results with reflux cytology testing. The results of the cytology determine those who go to colposcopy and those that get rescreened with cytology. People who are identified with high grade dysplasia (HSIL) are sent straight to colposcopy, while those with low grade changes (ASCUS/LSIL) will undergo repeat HPV testing in 12 months (Naucler et al., 2009) (Whitlock et al., 2011). The European Union has endorsed primary cervical cancer screening with HPV testing on a population level since December 2015 (Anttila, 2015).

Post Implementation Data

There is limited large scale post-implementation data on a population basis at this time regarding cancer incidence and detection rates. However, Australia has published an article with data modeling incorporating HPV vaccination and (high risk) hrHPV screening on a population level. The modeling shows reassuring data about the significant reduction in both the incidence of cervical cancer and the overall mortality of the disease. Australia is predicting a decrease in CIN2/3 histology by about 40% by 2035 (Hall et al., 2018), a decrease in the overall cervical cancer incidence by 50% and a reduction of the mortality of this disease by 44% by 2035 (Hall et al., 2018). Their model does predict an initial increase in cervical cancer detection and CIN2/3 lesions due to the increased sensitivity of HPV testing and with a plateau in the second and third round of screening (Hall et al., 2018). A Dutch study found similar results and it was reflected in their colposcopy referral rates (Aitken et al., 2019). Their data showed lower HPV positivity in self collected samples than those collected by a clinician (Aitken et al., 2019) which was a surprise and the group is advocating for more investigation for non-inferiority studies.

Harms of Screening

With increased detection of HPV, more women will be referred to have colposcopy for potentially regressive infections. Along with these unnecessary colposcopy exams, there are related diagnostics and treatments in the form of biopsies and repeated pelvic examinations (Whitlock et al., 2011). There is also the work-up associated with false positive tests that would result in overtreatment and futile diagnostic procedures for unaffected women (Whitlock et al., 2011). This predicament can be avoided by ensuring

- 1 in 168 women is expected to develop cervical cancer during her lifetime, and 1 in 478 will die of it.
- An estimated 1,450 women will develop cervical cancer in 2022 and 380 will die from it.

Source: cancer.ca/statistics

that positive HPV testing is automatically triaged with reflex cytology to avoid colposcopy on a normal cervix. An Australian study looked at obstetrical outcomes of women who undergo excisional treatments for precancerous lesions and those who are vaccinated and therefore would be at less of a risk for such procedures. They found that women are more likely to have a preterm baby and/or low birth weight baby when they have undergone an excisional procedure such as a LEEP (Loop Electrosurgical Excision Procedure) (Velentzis et al., 2017). The women who are vaccinated have a significantly decreased risk of an excisional-based obstetrical outcome and this would support the population-based vaccine program for protecting babies as well as mothers.

Limitations

Rare, or less common types of cervical cancer are not shown to be positive for HPV DNA and therefore would not be found with the new proposed screening method. However, it is not known if traditional cytology would actually be accurate at detecting these lesions either (Tjalma, 2018). There are known histologies of cervical cancer that have very low/rare HPV positivity that would not be captured; these include serous, clear cell, gastric types and mesonephric (Tjalma, 2018). Another limitation of HPV testing would be failure of the test itself, giving a false negative. A false negative can be obtained by inadequate sampling of the cervix or inadequate cellularity, such as when there is necrosis of the cervix or inflammation and if the cervix is coated with excess blood or lubricants it can also obscure HPV sampling (Tjalma, 2018). There was also data presented from multiple studies that cited the importance of HPV testing being done under standardized operating procedures and through an accredited laboratory (Tjalma, 2018). (Chrysostomou et al., 2018) (Ogilvie et al., 2018) (von Karsa et al., 2015). With the widespread implementation of HPV vaccination of the population at large, this will likely impact the numbers of HPV positive cancers in the future. The long-term effect of vaccination will in theory reduce demand for invasive colposcopy services and hopefully less demand for treatments related to cervical cancers from a gyneocologic oncology service.

Closing

There is a sizable body of evidence that supports a national primary HPV screening program in Canada. However, in Canada each province and territory is responsible for deciding on its own health policies, therefore a uniform uptake across the country is unlikely at this time. Providers should be comfortable educating our patients about the efficacy and protective properties of HPV primary screening going forward. Many long-term studies performed to date have shown protection to people tested for HPV for 5 years and beyond. Future areas of research include ongoing evaluation of people who have received the HPV immunization to assess the lasting effect of the vaccine. Another area of potential research should be the most effective screening test for women vaccinated against the oncogenic forms of HPV, as it is unknown at this juncture if cytology or HPV testing is optimal for these people.

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