The Use of Self-sampling for HPV Testing to Improve Cervical Cancer Screening Participation among Under-screened Women Living in Rural Ontario

by

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A thesis submitted in conformity with the requirements for the degree of Doctorate of Philosophy

Graduate Department of Public Health Sciences
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Abstract

Papanicolaou (Pap) testing has greatly reduced the incidence of and mortality due to cervical cancer. However, human papillomavirus (HPV) testing is being increasingly recommended for primary cervical cancer screening. One benefit of HPV testing is the opportunity for self-sampled specimen collection. The purpose of this dissertation was to determine if HPV self-sampling can improve participation in cervical cancer screening in under-screened rural communities. A systematic literature review and mixed methods study design addressed three objectives. A systematic literature review and meta-analysis calculated a pooled estimate of HPV self-sampling uptake in under-screened women (objective 1). Qualitative thematic analysis of community focus groups explored barriers to cervical cancer screening in an under-screened rural population and described women’s initial attitude towards HPV self-sampling (objective 2). These findings supported the design and implementation of a pragmatic randomized HPV self-sampling pilot study that determined the feasibility and acceptability of at-home HPV self-sampling to increase uptake of cervical cancer screening in an under-screened rural community (objective 3). Meta-analysis of the literature found under-screened
women were 2.1 (95%CI 1.3 – 3.5) times more likely to participate in screening when HPV self-sampling was offered compared to re-call letters for Pap testing. Thematic analysis found logistical, procedural, and knowledge barriers to cervical cancer screening. HPV self-sampling addressed logistical barriers, such as inconvenient clinic hours, and procedural barriers, such as embarrassment and lack of privacy. However, self-sampling does not address knowledge barriers, specifically a women’s fear of cancer or lack of awareness of the benefits of screening. The HPV self-sampling pilot study included 818 eligible women. Women who received a HPV self-sampling kit were RR=3.7 (95%CI 2.2 – 6.4) times more likely to be screened (HPV self-sampling or Pap testing) compared to women with no intervention, and RR=2.1 (95%CI 1.5 – 2.8) times more likely to be screened compared to women who received a Pap test reminder letter. The absolute participation with HPV self-sampling was moderate at 20.9% (95% CI 16.7–25.7%), indicating that barriers to screening remain. Together these results contribute further evidence for the use of HPV self-sampling to increase uptake of cervical cancer screening in under-screened rural women.
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List of Abbreviations

95%CI - 95% Confidence Interval
AB - Alberta
ASC-US - Atypical squamous cells of undetermined significance
BC - British Columbia
CBPR - Community-based participatory research
CCCaST - The Canadian cervical cancer screening trial
CIN - Cervical intraepithelial neoplasia
DNA - Deoxyribonucleic acid
EMR - Electronic medical record
HBM - Health belief model
HCII - Hybrid capture 2 assay
HIV - Human immunodeficiency virus
HPV - human papilloma virus
HR-HPV - High risk human papillomavirus
HSIL - High-grade squamous intraepithelial neoplasia
IARC - International Agency for Research on Cancer
ICC - Invasive cervical cancer
ITT - Intention-to-treat analysis
LBC - Liquid-based cytology
LHIN - Local health integration network
LR-HPV - Low risk human papillomavirus
LSIL - Low-grade squamous intraepithelial neoplasia
MB - Manitoba
MFFHT - Mount Forest family health team
NFL - Newfoundland and Labrador
NML - National microbiology laboratory
NS - Nova Scotia
OCR - Ontario Cancer Registry
OHIP - Ontario health insurance plan
ON - Ontario
OR - Odds ratio
PAF - Population attributable fraction
Pap - Papanicolaou
PCCF+version6a – Postal Code Database
PCR - Polymerase chain reaction
PEI - Prince Edward Island
PPA - Per-protocol analysis
RCT - Randomized control trial
RPDB - Registered Person Database
RR - Risk ratio
SIL - squamous intraepithelial neoplasia
SK - Saskatchewan
STI - Sexually transmitted infection
Chapter 1: Introduction and Objectives

1.1 Introduction

Papanicolaou (Pap) testing has been used with great success to reduce the incidence of and mortality due to cervical cancer. However, human papillomavirus (HPV) testing is being increasingly recommended for primary cervical cancer screening given prophylactic HPV vaccination, improved HPV testing technology, and below-acceptable levels of participation in cervical cancer screening programs (8-10). One benefit of HPV testing is the opportunity for self-sampled specimen collection. HPV self-sampling is an acceptable specimen-collection technique for cervical cancer screening in women reluctant to undergo Pap testing (11). Self-sampling has the potential to improve uptake of screening, as it could address many of the current clinic barriers (inconvenient hours or transportation) and procedural barriers (embarrassment or physical discomfort) women experience with Pap testing. Internationally, the use of self-sampled HPV testing has, in fact, been shown to have great promise at improving the uptake of cervical cancer screening in women who do not regularly attend cervical cancer screening programs (12-20).

Rural communities continue to face unique challenges within the health-care system, including the need to improve rates of cervical cancer screening (21). Currently, there is limited evidence regarding the impact of HPV self-sampling to improve uptake of screening amongst under-screened women in rural Canadian populations. Under-screened women are defined as sexually active women who have not received a Pap test in the last two to three years, or who have never received a Pap test.

1.2 Study Objectives

The purpose of this dissertation is to determine if HPV self-sampling can improve participation in cervical cancer screening in rural communities, with a specific focus on under-screened women. Under-screened women are those who are not up to date on their cervical cancer screening based on current cervical cancer screening guidelines. The under-screened include a subset of women who are eligible, but have never received screening (never-screened). This was accomplished through three objectives using a mixed methods design. The first objective was to review the published literature to determine if cervical cancer screening rates were higher when HPV self-sampling was offered compared to Pap testing in under-screened women. This was accomplished through a systematic review of the literature and meta-analysis. The second objective of this dissertation was to explore barriers to
cervical cancer screening, describe women’s attitudes towards HPV self-sampling as an option for cervical cancer screening in rural communities, and identify knowledge gaps and educational initiatives that could improve acceptance and uptake of HPV self-sampling and cervical cancer screening, in under-screened rural communities. In addition, factors for improving participation in the randomized control trial (RCT) were explored to help strengthen the design and implementation of the HPV self-sampling pilot study. This objective was accomplished using a qualitative thematic analysis of community focus groups (qualitative strand). The third objective was to determine the feasibility and acceptability of mail-out, at-home HPV self-sampling to increase uptake of cervical cancer screening in a rural community. The rural community of Mount Forest, Ontario, was selected as the study setting because it had a large population of under-screened women residing in the area and there was strong interest from the local Family Health Team to improve cervical cancer screening and participate in rural community based research. The third objective was accomplished using a pragmatic RCT pilot study of HPV self-sampling (quantitative strand).

This dissertation demonstrates that HPV self-sampling has a significant potential to improve uptake of cervical cancer screening among under-screened women; however, further work is needed to address the question of uptake among never-screened women, and what barriers to self-sampling and cervical cancer screening remain for under-screened women. This work also supports the need for the development and implementation of a robust tracking system to ensure appropriate lifelong screening with increased screening intervals, and to be able to target self-sampling to under-screened women. In addition, the work identified a number of logistical considerations that will need to be addressed prior to the implementation of HPV self-sampling into an organized screening program.

1.3 Readers Note

The second chapter provides an overview of the literature on cervical cancer epidemiology, etiology, and screening. The third chapter describes all methods used, which includes, and expands upon when necessary, the method sections of the respective manuscripts. The results chapter comprises three published manuscripts answering the three objectives, with additional results that were not presented in any published manuscripts, but are relevant to answering the objectives. The last chapter provides an overview of the key findings, the limitations and strengths of the dissertation as a whole, and the future direction of research and implementation of HPV self-sampling in cervical cancer screening in Canada. A list of references appears at the end of the dissertation, with the exception of those references embedded in inserted manuscripts, which will appear directly after their respective manuscript.
Chapter 2: Background and Literature Review

The natural history of HPV infection, and an up-to 80% lifetime risk of cervical HPV infection (22), puts all sexually active women at risk for cervical cancer. The catastrophic consequences of cervical cancer can be prevented with early detection through screening, and more recently through vaccination as primary prevention. Routine cervical cancer screening is recommended for all women, including those vaccinated against high-risk HPV types, as current HPV vaccines only prevent an estimated 70-80% of HPV related cervical cancers (23). The epidemiology, etiology, and development of cervical cancer will be reviewed before exploring screening as a secondary prevention of cervical cancer. This review of the literature will provide the foundation for discussing cervical cancer screening, and the importance of this dissertation research and findings.

2.1 Epidemiology and Etiology of Cervical Cancer

The cervix is a part of the female reproductive tract that is located at the inferior aspect of the uterus. It is cylindrical and narrow, and surrounds the external opening of the uterus at the end of the vaginal canal. The cervix regulates mucus secretions to prevent bacterial infections of the uterus (especially during pregnancy), aids in the transportation of sperm into the uterus, and regulates flow of the sloughed endometrial lining into the vagina during menstruation.

Cancer of the cervix is defined as cancer that originates in the cells of the cervix. Cervical cancer is the fourth-most common cancer in women worldwide, with an estimated 528,000 new cases diagnosed in 2012 alone (24). Cervical cancer deaths account for 7.5% of all female cancer deaths, with over 87% of deaths due to cervical cancer occurring in less developed regions (24). Infection with oncogenic HPV is a necessary, but not sufficient cause, for the development of cervical cancer (25).

In Canada, invasive cervical cancer incidence and mortality has been greatly reduced by the introduction of Papanicolaou (Pap) testing (see Section 2.2.1). Incidence of cervical cancer declined 58%, from 22.3 per 100,000 women to 9.4 per 100,000 women, between 1972 and 2006. Similarly, the mortality from cervical cancer also declined, with a 71% reduction from 7.7 to 2.2 per 100,000 women (26). The greatest gains made in cervical cancer prevention were among women over 45 years of age, as cervical cancer is a rare event in very young women (26).
Incidence of cervical cancer begins to increase in women after the age of 30, with the highest peak incidence being among women 40-44 years of age (15.9 cases per 100,000 women in Canada), which is considerably younger than most other cancers (27). Cervical cancer is still rare in young women <25 years (<1 case per 100,000 women) (27). Likewise, death from cervical cancer is a rare event in young women. After the age of 40, mortality rates steadily increase with age (with 16 deaths per 100,000 women in women 80 years of age or older in Ontario) (28). For 2016 it was estimated there would be 1,500 new cases (8.0 per 100,000 women) of cervical cancer in Canada, with 630 cases in Ontario (8.8 per 100,000 women), and 1.1% of all female cancer deaths in Canada would be attributed to cervical cancer (29).

In Canada, all-cause cancer mortality is higher in urban compared to rural areas, with the exception of cervical cancer (21). Rural women 20–44 years of age are up to two times more likely to die from cervical cancer compared to their urban counterparts, which is likely due to later stage diagnosis due to lower rates of cervical cancer screening (21). In the most rural regions of Canada the incidence of cervical cancer is up to 13.1 cases per 100,000 women, which exceeds that of urban areas at 9.6 cases per 100,000 women (21).

2.1.1 Human papillomavirus (HPV)

In the early 1990s, human papillomavirus was shown to be a necessary, though not a sufficient cause, of cervical cancer(25). Human papillomaviruses (HPV) are members of the \textit{Papovaviridae} family, and are small double-stranded circular DNA viruses that infect the basal cells of the epithelium. There are over 150 different types of HPV identified, with approximately 40 infecting the mucosal epithelial cells of the cervix (30). A phylogeny of HPV and related disease states is depicted in Figure 2.1 of the International Agency for Research on Cancer’s (IARC) Monograph Series on the Evaluation of Carcinogenic Risk to Humans: Biological Agents Part B (31). The International Agency for Research on Cancer (IARC) classification of HPV carcinogenicity varies by type, from highly to weakly carcinogenic. Carcinogenic HPV involved in cervical malignancy are derived from the alpha species, of which there are currently 13–15 alpha HPV types considered high-risk (HR) and involved in cervical cancer development (32-34). IARC classification of Group 1, carcinogenic to humans, includes HPV 52, 33, 58, 16, 31, 35, 59, 18, 45, 39, 51, 56 and 66. HPV 6 and 11 are classified as Group 2B, possibly carcinogenic (35). Not all HR-HPV are equivalent in their role in cancer development, with an estimated 70% of cervical cancers caused by HPV 16 and 18 in the pre-vaccine era (36)
2.1.2 Cervical Cancer Development

Cervical HPV infections are sexually transmitted through skin-to-skin or skin-to-mucous contact, and not exclusively through vaginal intercourse. HPV is highly transmissible between sexual partners. Transmission of HPV from an infected partner occurs when a break in the skin or mucosal lining (epithelial layer) enables the virus to infect the basal cell layer of the cervix in the uninfected partner.

The probability of HPV transmission between partners has been estimated to be 0.20 over 6-months (or 3.7 transmissions per 100-person months), with persistent infections having a slightly higher probability (37, 38). HPV transmission rates are comparable to bacterial sexually transmitted infections (STIs) (38, 39). However, unlike many bacterial STIs, condoms only offer moderate protection against HPV transmission (40, 41).

The transformation zone of the cervix is particularly susceptible to carcinogenic changes caused by HPV infection, as demonstrated by a 20- to 40-fold increase in cancer at this site compared to other anogenital tract sites (with the exception of the transformation zone of the anus) (42). The cervical transformation zone is a natural break in the epithelia layer where columnar and stratified cells meet each other, which facilitates access to the basal cell layer. HPV can also infect basal epithelial cells in other anogenital tract sites causing warts or other genital cancers.

As the infected cells mature, they move to the surface of the epithelium and begin viral replication, which takes place over approximately six weeks (43) (Figure 2.1.3.1). The viral replication, cellular growth, and immune response can result in a variety of cellular lesions including warts or cervical dysplasia (42). Most infections are asymptomatic with a period of active infection, followed by regression of lesions, and then clearance of the infection. Upwards of 90% of infections resolve spontaneously within the first 24 months (44), with the mean length of time of infection with an oncogenic HPV type being just over a year (45). However, the rates of clearance vary depending on HPV type, with lower clearance rates observed in HPV 16, 18, 31, and 33 (46). Clearance of infection is thought to be a host cell mediated immune response, with approximately 10–15% of women failing to mount an immune response and developing persistent infection (43). Women who develop persistent infections are most at risk for the development of cervical cancer (47).

Persistent infections are regulated by the integration of the HPV genomes into the host cells (43). In particular, the viral-replicating genes E6 and E7 are important carcinogenic markers as they produce proteins that interfere with tumour-suppressing proteins, p53 and pRh, which are important cellular regulators (42, 48). In addition to the presence of HPV integration, cervical cancer development requires an accumulation of mutations, which can
arise from active, persistent HPV infections, and usually develop over an extended period of time (42).

2.1.3 Cervical Cancer Progression

Understanding the different pre-cancerous disease states, and their related risks for development of invasive cancer, compared to self-resolution, is important to screening strategies so that the medical community can balance the benefits of disease avoidance with the harms of invasive treatments and psychological distress.

Cytological changes associated with cervical dysplasia are currently described using the Bethesda System of classification (15) and are evaluated as cervical intraepithelial neoplasia (CIN) and squamous intraepithelial lesion (SIL). Very mild cervical dysplasia is denoted as atypical squamous cells of undetermined significance (ASC-US), which is characterized by observable abnormalities, but not sufficient to be CIN or SIL. Mild dysplasia is characterized by early changes to the cellular structure and is classified as CIN1 or low-grade SIL (LSIL). Moderate to severe dysplasia is characterized by moderate to severe changes to the cells’ shape and size, with abnormal appearance, and is classified as CIN 2/3 or high-grade SIL (HSIL). CIN3 designation includes carcinoma in situ, which is when cancer cells are found in the cervical tissue but have not spread beyond to the surrounding tissues or to deeper tissue levels of the cervix. The final classification is carcinoma, where invasive cancer is suspected. The most common types of invasive cervical cancer (ICC) are squamous cell carcinoma (cancer of the squamous cells, typically around the transformation zone of the cervix) and adenocarcinoma (cancer of the glandular cells of the endocervix), both of which typically begin as pre-cancerous lesions. Cervical cancer progression is slow and does not always end in invasive cancer; **Figure 2.1.3.1** provides an overview of the progression of cervical cancer. The estimated progression rate from CIN 1 to ICC is approximately 1%, with the rate of progression to ICC rising to 12% from CIN 3 (49). The rate of pre-cancerous lesion progression is difficult to measure in natural history studies; however, estimated average progression times for women infected with oncogenic HPV from ASCUS to LSIL was 5.5 years, and progression from LSIL to HSIL, or worse, was just over 6 years (50). Lesion progression appears slower in women not infected with HPV or infected with non-oncogenic types (50). Pre-cancerous stages of disease can be targeted due to the relatively slow progression from HPV infection to pre-cancerous lesion to invasive cervical cancer.

HPV infections are identified in over 99% of cervical cancers, and in the majority of high-grade lesions (HSIL/CIN3) (25, 51). Identification of HPV in cervical lesions is more common as cytological abnormality increase in severity (36).
2.1.4 HPV Prevalence in the Population\(^1\)

HPV is the most common sexually transmitted infection worldwide, with an estimated general population prevalence ranging from 2–44% in asymptomatic women(52-54). The prevalence and distribution of HPV types vary based on HPV testing methodology, sampling strategy, and geography, with less developed regions typically experiencing higher prevalence (55). Overall, HPV 16 is the most prevalent, accounting for 22% of all HPV infections (55). An important aspect to note is that co-infection with one or more HPV types is common in approximately 20% of HPV positive cases (55, 56). An estimated 10% of asymptomatic women globally are HPV positive at any one time (54).

In Canada the all-type HPV prevalence has been estimated to be between 16.8% and 19% for women eligible for screening (21 – 69 years of age) (2, 57). In regards to cervical cancer risk, data from Quebec, Newfoundland, and British Columbia, found the prevalence of HR-HPV among women 30–69 years of age to be 6.1% (58), and among women 25–65 years of age to be 8% (59). European estimates are comparable with HR-HPV prevalence ranging from 2.2–15.7% (60).

The prevalence of HPV in the female population is heavily age-dependent. In contrast to cervical cancer, the peak prevalence of HPV infection occurs in younger women 20–25 years of age (Figure 2.1.4.1) (61). The peak of HPV infection closely follows after sexual debut (52, 62), even among women who have only had one sexual partner (63). Concordance of HPV infection has been identified in over 40% of newly formed sexual relationships (64).

The age distribution of HPV prevalence varies globally, with three distinct age-prevalence profiles: declining prevalence with age, a U-shape curve with an initial peak followed by a decline and a second smaller peak, and finally, an initial small decline in prevalence followed by continuous plateau with increasing age (54, 61). Among North American population-based prevalence estimates, a strong decline of HPV prevalence is observed with increasing age (61). The decline of HPV in women >25 years of age has been attributed to stabilization of sexual partners resulting in decreased exposure, and resolution of the many transient HPV infections in younger women. Many Canadian prevalence estimates follow this prevalence profile and show a strong decline associated with increasing age (57, 59, 61); however, some evidence of a secondary small prevalence peak (forming a U-shaped curve) for women 45–50 years of age has been observed(2, 56).

\(^1\) All reported HPV prevalence in this section is from the pre-vaccine era.
Figure 2.1.3.1: Progression of Cervical Cancer Disease and interaction with HPV infection. Cancer progression adapted from Woodman et al. (1)) Reprinted and adapted with permission from Macmillan Publishers Ltd: Nature Reviews Cancer. Woodman CB, Collins SI, Young LS. The natural history of cervical HPV infection: unresolved issues. 7(1):11-22. 2007.
Figure 2.1.4.1: Age distribution of HPV types in a population study of Manitoba women illustrating peak prevalence in younger women and a secondary smaller peak amongst women 45-49 years of age. Data abstracted from Demers et al. (2).
The second U-shaped curve has been predominately observed in Latin American regions. The second peak has been hypothesized to be re-infection due to changes in sexual behaviour patterns in women entering new sexual relationships after a long period of monogamy or alternatively, a re-activation of dormant infections in older age (61). Prevalence profiles characterized by an initial decline in HPV prevalence with age, followed by a continuous plateau (i.e. minimal second peak in older women) were predominately observed less developed regions. This prevalence profile has been observed in regions where the HPV prevalence was more stable over time, either due to initially high HPV prevalence (e.g. Africa) or a low overall HPV prevalence (e.g. Asia) (61).

2.1.5 Risk factors for HPV infection and Cervical Cancer

Persistent infection with oncogenic HPV remains the most significant risk factor for the development of cervical cancer. However, other factors have been identified as increasing the risk of cervical cancer, as well as the risk of HPV acquisition. Factors associated with cancer development, mainly age and screening history, also play an important role in the risk of cervical cancer development. Age is an important risk factor, as the development of cervical cancer can take decades from the time of infection to invasive disease. This is exemplified by the increased incidence of cervical cancer after the age of 30, and with the greatest incidence observed in middle-aged women (27) (section 2.1). The other important risk factor related to the physical development of cervical cancer is cervical cancer screening, which will be discussed in section 2.2. Women most at risk for developing cervical cancer are those who do not participate in regular cervical cancer screening (65, 66).

In Canada, some immigrant and ethnic minority populations are at a higher-risk of cervical cancer. Urban immigrant populations have lower screening rates compared to non-immigrant women (67, 68), the degree to which varies across ethnic groups (69). However, time since immigration is an important factor, with women who immigrated to Canada >10 years ago having similar screening rates compared to Canadian-born women (67).

First Nations women in Canada historically have had higher rates of cervical cancer, and are less likely to undergo screening compared to non-First Nations Canadians (70). Over time, the screening gap has decreased; however, screening among First Nations women in Canada remains low (71, 72). In addition, First Nations women are more likely to have an HR-HPV infection compared to non-First Nations women (73).

Environmental factors that increase the risk of cervical cancer and dysplasia include cigarette smoking, hormonal contraception usage, multiparity, and co-infection with other STIs. Many of these factors are also shared with HPV acquisition, which can make it difficult to tease apart the underlying factors individually. As HPV is a sexually transmitted infection, the number of lifetime, as well as recent, sexual partners plays an important role in exposure to HPV and acquisition (Section 2.1.2). Many of these environmental risk factors for cervical cancer have also been shown to be associated with increased number of sexual partners and subsequent exposure to HPV. In general, the risk factors are:

**Cigarette smoking:** Women who currently smoke have been found to have a higher risk of cervical cancer (specifically squamous cell carcinoma), and a dose response is observed for number of cigarettes per day, as well as starting to smoke at younger age (74). The magnitude of that risk is estimated to be roughly two-fold (75); but, the risk estimates for cigarette smoking and cervical cancer can be highly confounded as cigarette smoking, including the number of cigarettes smoked per day, has also been associated with HPV infections and increased number of sexual partners (76). Despite issues of confounding by HPV, cigarette smoking does appear to be an important risk factor for cervical cancer development (74).

**Oral contraception:** Oral contraception use has also been associated with cervical cancer. Risk of cervical cancer appears to be associated with current usage and the length of time of use; women who have been on oral contraception for 5 or more years have about a two-fold increased risk of cervical cancer compared to women who have never been on oral contraception (77, 78). However, 10 years after stopping use of oral contraception this risk is similar to never users. (77).

**Multiparity:** Multiparity and younger age at first pregnancy have been associated with increased risk of cervical cancer, again on the order of about a two-fold increase in risk for women with ≥7 full-term pregnancies compared to nulliparous women, even after controlling for sexual behaviours. The suggested mechanisms include hormonal changes, trauma exposing the underlying epithelium to HPV, or immune suppression (79).

**Co-infection with other STIs:** Immunosuppression due to co-infection with HIV can also increase the risk of cervical cancer development due to the decreased immune function against HPV infections preventing clearance of transient infection (44), although antiretroviral therapy may improve HPV clearance (80). Other sexually transmitted co-infections have also been associated with increased risk of cervical cancer, including *Chlamydia trachomatis* and Human Herpes virus-2, due to chronic inflammation (81).
The relative risk of cervical cancer to most of these aforementioned risk factors is on the order of magnitude of no more than a two-fold increase in risk, compared to a greater than 100-fold increase in risk with a HR-HPV infection (82). Preventing HPV infection is the most effective way to prevent cervical cancer. Preventing HPV infections is difficult, and condoms reduce the risk of transmission but do not prevent HPV infections (40, 41). Since the mid-2000s HPV vaccination has been available for the prevention of some, but not all, HPV types linked to cervical cancer.

2.1.6 HPV Vaccination

There are currently three prophylactic HPV vaccines available (2-, 4-, and 9-valent). The 4-valent (Gardasil®–Merck & Co. Inc.) vaccine was licensed in 2006, the 2-valent (Cervarix® - GlaxoSmithKline Inc.) came to market in 2010, and the 9-valent (Gardasil®–Merck & Co. Inc.) was licenced for use in Canada in 2015. The field of HPV vaccination is rapidly evolving, and tackling issues such as introduction of two doses from three doses (83) for 2- and 4-valent vaccines in children >14 years of age and the introduction of the 9-valent HPV vaccine.

The current HPV vaccines are approved for two or three doses administered over a six-month period and effective against HPV 16 and 18, providing protection against approximately 70% of all cervical cancers³. The 9-valent vaccine includes additional coverage for 5 oncogenic HPV types (HPV 31, 33, 45, 52, and 58), which could provide protection for up to an additional 10% of invasive cervical cancers (23). Vaccine efficacy for three doses is very high with >95% protection against persistent infection, and >90% against pre-cancerous lesions (84, 85). The 4- and 9-valent also provide protection against HPV 6 and 11, which cause the majority of genital wart infections. They are well tolerated with minimal adverse side effects (84, 85). Reduction in genital warts has already been observed in countries that have introduced HPV vaccination programs (86).

In Canada, the 4-valent vaccine was authorized for use in 2006 in women 9–26 years of age. Between 2007 and 2010 all provinces and territories had implemented school-based immunization programs for girls 9–13 years of age, with the vaccination schedule initiating at different ages depending on the province and territory. In addition to school-based programs, catch-up immunization programs are available. The 2-valent vaccine has been authorized for use since 2010. The 9-valent vaccine has been available since 2015, and is currently

³ Some degree of cross-protection against lesions caused by closely related HPV types (45, 31, 33, 35, 52, 58) has been observed, but the level is unknown 84. Lu B, Kumar A, Castellsague X, Giuliano AR. Efficacy and safety of prophylactic vaccines against cervical HPV infection and diseases among women: a systematic review & meta-analysis. BMC infectious diseases. 2011;11:13.
recommended for females and males for the prevention of HPV-associated cancers and genital wart infections (87). Vaccination for boys has been authorized in Canada since 2011, with many provinces now including gender-neutral vaccine programs for school aged children.

Primary prevention is an important component to a comprehensive prevention strategy. However, vaccination alone will not eliminate the need for secondary screening prevention due to an array of potential issues, including: other oncogenic HPV types not covered in the vaccine, the potential for type replacement, potential waning immunity, <100% vaccine efficacy, missed vaccine doses, and the need to protect unvaccinated women (88).

As current and future HPV vaccination continues to lower the prevalence of HPV in the population, the consequence is that screening strategies will need to be reflexive (89). This change in prevalence of HPV in the population will negatively impact the performance (positive-predictive value) of cytology-based population screening (88), resulting in a need for a shift in secondary prevention toward the detection of HPV and identifying women most at risk for disease.

It is important to bear in mind that oncogenic HPV is not only associated with cervical cancer, but also with an estimated 4% of all cancer cases, including a large proportion of anal, vulvar, vaginal, penile, and oropharyngeal cancer cases globally (90) (Figure 2.1.6.1). In 2016 in Canada, an estimated 2.7% of all new cancer cases in women and 1.7% of all new cancer cases in men, will be attributed to HPV-associated cancers (29). Amongst women, cervical cancer represents the highest proportion of new HPV-associated cancer cases (35%), followed by vulvar (11%), anal (9%) and oropharyngeal (7%). Among men, 28% of all new HPV-associated cancer cases are of the oropharynx, followed by anal (4%) and penile (4%) (29).

HPV vaccination is impactful on a range of cancers that do not have secondary screening strategies, such as anal cancer, of which 475 new cases were diagnosed in Canada in 2012 (29). Primary vaccination and secondary screening prevention strategies against oncogenic HPV have applications outside of cervical cancer screening and play an important role in overall cancer prevention.

In Canada, cervical cancer holds a relatively small burden of disease when compared to breast cancer (23.4 deaths per 100,000 women) (29). However, through effective primary and secondary prevention cervical cancer is largely preventable. Currently, the majority of new cervical cancers occur among women who are not adequately screened for the disease. Opportunity exists to continue to reduce the incidence and mortality from cervical cancer in Canada, as well as support developing regions in implementing systems to begin to address one of the leading causes of cancer among women globally.
The next section will highlight the state of cervical cancer screening in Canada, discuss current screening technologies, and outline various cervical cancer screening guidelines. By understanding the screening infrastructure available in Canada and beyond, we can begin to see how HPV testing and self-sampling could be implemented and strengthen existing and future screening programs.

Figure 2.1.6.1: Estimation of the 2008 population attributable fraction (PAF) of HPV by cancer site, data abstracted from de Martel et al. (3)
2.2 Cervical Cancer Screening

Oncogenic HPV is a necessary cause of cervical cancer (25); however, routine screening, follow-up, and treatment can prevent the development of cervical cancer. Currently the majority of cervical cancers detected are in women who do not regularly attend screening programs or who have never been screened (65). The role of screening is to detect the pre-cancerous lesions and intervene through treatment to prevent cancer from ever developing. The success of cervical cancer screening in reducing cervical cancer is in large part due to the identification and treatment of pre-cancerous lesions as opposed to early-stage cancers (9).

Countries that have adopted cervical cancer screening programs have had dramatic reductions in the incidence of cervical cancer (91, 92), and Canada is no exception (Section 2.1.0). British Columbia was the first Canadian province to introduce a cervical cancer-screening program in 1960 and saw early successes in the reduction of cervical cancer. Currently eight provinces (BC, AB, SK, MB, ON, NS, PEI, NFL) have organized or partially organized screening programs, with the Ontario program introduced in 2000. Organized screening programs ensure equal opportunity for everyone, in a defined population, to participate in screening by tracking, monitoring, and evaluating screening participation and outcomes. Organized screening programs are typically managed by external health services organizations and are typically more effective at achieving high levels of screening coverage compared to opportunistic screening. In the absence of organized screening programs, opportunistic screening has been, and continues to be, practiced, with fully funded screening being available in Canada since 1984 with the introduction of the Canadian Health Act (93). Opportunistic screening occurs when an individual requests screening from their healthcare provider. In both organized and opportunistic cervical cancer screening programs, the Pap test has been the method of choice in much of the developed world for the past six decades.

2.2.1 Papanicolaou (Pap) Testing

The Pap test was first introduced, and named after, Dr. Georgios Papanikolaou in the 1940s (94). The Pap test involves the exfoliation and collection of cervical cells, by a trained practitioner. Traditionally the specimen was affixed to a glass slide and examined by a pathologist for abnormal cellular changes. Today, the specimen is either affixed using the traditional method, or more commonly is suspended in liquid medium to undergo liquid-based cytology (LBC). LBC allows for a computerized digital analysis to augment the pathologist’s readings for abnormal cellular changes. Cervical specimens are then assigned a grade to classify their level of abnormal severity (described in Section 2.1.1). The grade assigned to the
cytological specimen is important in the recommended management of cytological abnormalities, with greater severity being managed more aggressively through the diagnostic test of colposcopy and treatments administered during colposcopy.

A review of routine Pap cytology found that sensitivity\(^4\) ranged from 30–87%, with a mean sensitivity of 47%, and specificity\(^5\) ranged from 86–100%, with a mean specificity of 95% for LSIL/CIN-1 threshold. Using a higher severity threshold of LSIL/CIN2-3, Pap cytology sensitivity rose (range 44% - 99%), while specificity was slightly lower (range 91% - 98%)(96).

Overall, Pap test cytology has relatively low sensitivity, which results in false negatives. Due to the slow progression of cervical cancer, serial Pap cytology at pre-determined intervals can be effective for the detection of persistent lesions missed on initial screening rounds (96). The high specificity of Pap cytology is the main utility for screening.

In a Canadian population, Pap test cytology has been shown to have a sensitivity of 55.4% and specificity 96.8% (58), with negative predictive value\(^6\) over 99%, and positive predictive value\(^7\) of 7.1%. However, it has been estimated that in a post-vaccination era that the positive predictive value of the Pap test (assuming sensitivity and specificity remain constant), will decline by 50% as a result of the decline in lesion prevalence in the population (due to the decline in HPV prevalence) (88). Other limitations of cytology include the subjective nature of cytological readings, the need for highly trained personnel and the associated cost to the health care system, and the requirement of visualizing the cervix while collecting a specimen.

Despite the great success that Pap testing has had in reducing the incidence and mortality from cervical cancer, a paradigm shift is underway. Technological advances have allowed for the detection of HPV in women and the introduction of HPV DNA testing as a tool to increase the sensitivity of screening and maximize the specificity of cytology as a triage test.

### 2.2.2 HPV Testing

HPV testing is a molecular test for the detection of HPV DNA. There are a variety of assays that can be used for HPV detection: high-risk signal assays, genotyping assays, and mixed assays.

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\(^4\) Sensitivity is the property of testing positive for the highest possible proportion of people with disease for which the test is performed. 95. Last JM. A Dictionary of Public Health. New York, New York: Oxford University Press, Inc.; 2007.

\(^5\) Specificity is the ability of a test to identify correctly persons who do not have the disease for which the test is done. 95. ibid.

\(^6\) The negative predictive value is the probability that a person whose test result is negative does not have the disease. 95. ibid.

\(^7\) The positive predictive value is the probability that a person whose test result is positive actually has the disease. 95. ibid.
In 2011, the Hybrid Capture II assay (HCII) was the first HPV test approved by Health Canada for primary HPV testing. The HCII is a nucleic hybridization assay that is able to quantitatively detect and amplify the signal from thirteen HR-HPV genotypes (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 68) (97). The major disadvantage of the HCII is that specific HPV genotypes cannot be identified. Being able to identify the specific HPV type is advantageous as carcinogenic properties are not equal among the different types of HPV (42). Specific genotyping assays have been used and continue to be developed to address this issue of HPV-risk stratification (98)\(^8\).

Polymerase chain reaction (PCR) genotyping assays specifically target the HPV DNA for amplification and can be designed to target specific HPV types. The major advantage of genotyping technology is the ability to detect very small amounts of DNA and to identify a multitude of HPV types, both high-risk and low-risk (99, 100). The disadvantage of exclusively using genotype testing for cervical cancer risk is that minute amounts of viral DNA can be detected, which may not indicate a clinically relevant infection. HPV genotyping technology is ideal for surveillance activities, measuring genotype prevalence, or in research settings where high sensitivity is required (100).

In 2014/2015, the Food and Drug Administration in the United States, and Health Canada approved the Cobas®4800 for primary HPV testing. The Cobas® 4800 includes the use of both signal amplification for 12 pooled HR-HPV types and genotyping components for HPV-16 and -18. These mixed test assays leverage both methodologies to allow for improved simultaneous risk-stratification of women.

Current HPV testing platforms require heavy investment in laboratory resources. Next generation HPV testing platforms provide opportunities for advancement in expedited reliable testing, scalability to handle population-based screening volumes, and reduced reliance on additional laboratory investments (101).

In Canada, the National Microbiology Laboratory (NML) of Canada has developed a non-diagnostic genotyping assay for the detection of 46 HPV types (98). This assay has both a high sensitivity (98.8%) and specificity (98.8%) for the detection of HPV infections with multiple types. To date the NML assay has been validated and used in a number of studies (102-105). The cost-effectiveness of the NML assay was a major advantage for this study, given that a specific diagnosis criterion was not required. In addition, at the time of this dissertation work, the NML assay was available for use at the Public Health Ontario Laboratories for research.

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\(^8\) HCII uses nucleic acid hybridization and an enzyme-linked immunooassay to amplify the signal for the detection of 13 types at once. The PCR assay uses a primer target for specific HPV genotypes, and amplifies the HPV DNA associated with each primer.
purposes, which put the study site in the local jurisdiction of the lab and allowed for partnership and capacity building in Ontario.

2.2.3 HPV Testing for Cervical Cancer Screening

The mounting evidence for the use of primary HPV testing for cervical cancer screening has come from both large international trials and Canadian studies (58, 106-109). The Canadian Cervical Cancer Screening Trial (CCCaST) found that in women 30–69 years of age HPV testing was more sensitive than Pap testing (94.6% versus 55.4%) for the detection of high-grade cervical dysplasia CIN 2/3+ (58), which was similar to findings to other trials (106, 110-112). The high sensitivity of HPV testing allows for a large negative predictive value, especially as the prevalence of HPV begins to decline in the population with the introduction and uptake of HPV vaccination (89). In the CCCaST, the negative predictive value was 100% and the positive predictive value was 6.4% (61). The specificity of HPV testing in the CCCaST was found to be slightly lower than the specificity of Pap testing (94.1% versus 96.8%), which again was consistent with other trials (106, 110, 112). The lower specificity of HPV testing is largely age dependent based on the high prevalence of HPV infections in young women, which by and large resolve on their own. Based on the lower specificity, HPV testing has only been recommended in women over 30 years of age (113-115). Cytology triage has been recommended to further improve the specificity, and positive predictive value, of HPV testing for cervical cancer detection (106, 115).

A major, and note-worthy, distinction between Pap testing and HPV testing is that HPV testing provides a risk profile for a woman based on her HPV positivity, as compared to Pap testing that provides an abnormality profile based on cytological examination. This distinction is important, as HPV testing now allows us to risk stratify women, with those who are HPV negative to be at zero risk of cervical cancer at the time of screening. Recent evidence suggests that the screening interval can be safely extended to five years compared to a three-year screening interval with cytology (116). The high negative predictive value of the HPV test is a major factor in the ability to extend the screening interval, which decreases the burden of screening on the system and results in gains in cost-effectiveness for screening programs. Other benefits of HPV testing include that it is automated, and does not require visualizing the cervix to collect a specimen.

2.2.4 Cost-effectiveness of HPV testing

Cost-effectiveness analysis, and modeling, of cervical cancer screening strategies provide tools for decision makers to be able to simultaneously evaluate a multitude of
strategies. Cervical cancer screening cost-effectiveness models have been applied to a variety of settings, and almost unanimously find that strategies employing HPV testing are superior to cytology alone (117-120), and primary HPV testing is more cost-effective compared to HPV co-testing with cytology (121). One of the greatest cost advantages to HPV testing is the ability to safely extend the screening interval and reduce the number of lifetime screens. As costs vary across geo-political boundaries, calculating these models in various settings is important. When applied in a Canadian context, HPV testing on a three-year screening interval with Pap test triage for women 25–30 years and older was more cost-effective than cytology alone (118, 120). Additionally, with the use of HPV testing, a self-sampling strategy (with in-clinic cytology triage) has been explored, and found to be a cost-effective option (122).

Specific costs are not the only aspects that need to be considered when modeling cervical cancer screening strategies. With the introduction of HPV vaccination, cost-analysis will need to take into account the two distinct populations of women – vaccinated and unvaccinated. A Norwegian analysis explored the differences between vaccination status and optimal screening strategies; it found the vaccinated women would be best served with a longer screening interval compared to non-vaccinated women (117).

Introducing program-wide HPV testing to a system that already employs cytology would confer a large investment in infrastructure, training, and funding. Understanding and evaluating the long-term cost-effectiveness of HPV testing, and self-sampling, is an important step in the decision-making process surrounding the implementation of HPV testing in Canada. Despite the large upfront investment required, HPV testing has long-term cost benefits over cytology. The large caveat accompanying the introduction of HPV testing, along with a longer screening interval and self-sampling, is the requirement of an organized tracking system to ensure women are appropriately screened within the interval and all required follow-up can be achieved (117).

2.2.5 Screening Guidelines and Proposed Algorithms
In Ontario, cervical cancer screening is semi-organized and provided as part of the Ontario Health Insurance Program (OHIP). The Pap test is currently the only funded primary screening test for cervical cancer in Canada; however, many provinces are undergoing updates to their cervical cancer screening programs with a paradigm shift towards recommending HPV testing.

In 2012 the Ontario Cervical Screening Program, and clinical practice guidelines, were updated (10). The recommendations include the use of HPV testing for primary screening, for women 30–65 years of age, at five-year intervals, with cytology triage for HPV positive. HPV-
positive women with normal cytology are recommended to undergo repeat HPV testing at 12 months and those with abnormal cytology to be referred for colposcopy (Figure 2.2.5.1). This guideline represents a shift toward better risk stratification, similar to the recommendations made by the US Preventative Task Force Recommendation on Screening for Cervical Cancer (9), and The European Research Organization on Genital Infection and Neoplasia (8).

One of the major barriers to primary HPV testing in Canada is the current lack of infrastructure and funding for implementation. Currently, primary HPV testing is not funded in Ontario, which resulted in interim Provincial Cervical Cancer Screening Guidelines that recommend Pap testing every three years for women 21 – 69 years of age who have been sexually active (10). The lack of logistical preparedness and the subsequent implications of HPV testing at the population level was one of the cited issues of the Canadian Task Force for Preventative Health, which at this time is unable to recommend the use of primary HPV testing (124).

2.2.6 Implementing HPV Testing:

As cervical cancer screening shifts toward the use of HPV testing, many questions arise as to how to implement a primary HPV screening program. Due to the epidemiology of HPV infections, and the high attack rate in younger women, HPV testing for cervical cancer screening in not recommended in younger women. However, there remains a debate as to the effective cut-off age for the use of HPV testing in cervical cancer screening programs. The age cut-off ranges between 25 and 30 years of age up to 69 years of age, with the most recent Ontario guidelines recommending 30 years of age (10).

A longer screening interval has been proposed with the use of HPV testing, which would help mitigate the lower specificity while maintaining safety with a very high negative predictive value. Long-term follow-up in randomized control trials found that the screening interval could be safely extended to five years in women who test HPV negative (125).

Due to the lower specificity of HPV testing, especially in younger women, there is a concern for increased number of false positives and subsequent referrals for colposcopy. Colposcopy has been deemed a harm of cervical cancer screening and should be limited to only those women who have meaningful cytological changes most at risk to develop into...

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9 US Preventative Task Force Recommendation currently includes the use of co-testing of HPV with cytology. However, recent studies have demonstrated that primary HPV testing is non-inferior to co-testing with Pap cytology 123. Wright TC, Stoler MH, Behrens CM, Sharma A, Zhang G, Wright TL. Primary cervical cancer screening with human papillomavirus: end of study results from the ATHENA study using HPV as the first-line screening test. Gynecol Oncol. 2015 Feb;136(2):189-97. and indications are that the next iteration of the US task force guidelines will likely support the use of primary HPV testing (Personal communication – HPV International Conference 2014).
cervical cancer. The unnecessary use of colposcopy in young women also leads to the concern of over-diagnosis of lesion that would never have been clinically meaningful. A recent long-term follow-up of HPV screened women found that the preliminary estimates of over-diagnosis were in fact earlier detection of disease, based on similar cumulative incidence of CIN2+ between HPV testing and cytology at the end of the follow-up period(125). Concerns of over-diagnosis and colposcopy referral have prompted a need to assess algorithms for the management of women undergoing HPV testing. The use of triage Pap testing would prioritize colposcopy to women with cytological abnormalities. Those women who are HPV positive but lack abnormal cytology would be closely followed for either a change in HPV or cytology, depending on which management algorithm is used.
2.2.7 Participation in Cervical Cancer Screening

Participation in cervical cancer screening varies across Canada with the highest participation rate seen on the coasts: Newfoundland and Labrador (74.4%), British Columbia (69.5%) and Nova Scotia, (69.5%), and in Alberta (70.8%). Lower rates of participation are in central Canada, specifically Saskatchewan (64.6%) and Ontario (64.9%) (27). Participation in Ontario has remained steady at between 60–65% of eligible women in the last decade (Figure 2.2.7.1), with slight declines observed in most recent years (126). Current levels of participation are well below the provincial program target of 85% of age-eligible women. Under the current guidelines, women are considered adequately screened for cervical cancer if they are between 21–69 years of age and have received a Pap test in the last three years.

Under-screened women who are not up to date on screening fall into two groups: 1) women who have not received a Pap test in the last three years (based on currently screening guidelines) and 2) women who have never received a Pap test (never-screened).

Under-screened women are more likely to be of low socioeconomic status, immigrants, and uninsured (68, 127). Geographically low rates of cervical cancer screening have been observed in both rural (128, 129) (130) and urban areas (131). In Canada, rural women report having statistically lower rates of Pap testing compared to urban women (21). Over the past decade in Ontario efforts to improve screening in rural areas have improved uptake to 66.7%, which is greater than the provincial average; however, very small communities (<10,000 population) still have an overall low rate of screening (62.9%).

Overall, there are a variety of different under-screened populations in Ontario. The commonality between these under-screened populations is that they represent the majority (~70%) of cervical cancer diagnoses (132).

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10 These are age-standardized rates are for women 20 – 69 years of age who had a Pap test between 2009 – 2011 in the organized screening programs in these provinces. The rates for BC and ON have been corrected for hysterectomy.
Figure 2.2.7.1: Percentage of women 21 – 69 years of age who were eligible and completed a Pap test in the proceeding 3.5 years by age group from 2003 – 2014. Data from the Cancer Quality Council of Ontario (sources: OHIP, CHBD, CytoBase, OCR, RPDB, PCCF+version6a) prepared by the Cancer Screening Evaluation and Reporting, Cancer Care Ontario, December 2015.
2.2.8 Barriers to Cervical Cancer Screening

The many barriers to screening reported in the literature can be categorized into three broad categories: clinic level, procedure level, and personal level barriers (7, 133-135). Clinic level barriers include the lack of a family physician, inconvenient clinic hours, and lack of available transportation to the clinic (7, 136). Barriers at the procedure level are those related directly to the Pap testing and most often are reported as embarrassment, physical discomfort or anticipation of discomfort (134). Personal level barriers include those that pertain to lack of health insurance, religious and cultural beliefs, language barriers, personal trauma, fear of cancer, and lack of knowledge around cervical cancer screening (134, 136).

In communities with socioeconomically disadvantages there are a number of psychosocial barriers to cervical cancer screening participation, which include access to health services (transportation), competing priorities (lack of childcare and unable to get time off work), lower health literacy, and lack of a physician recommendation (137). It is important to acknowledge the interaction between socioeconomic deprivation and cervical cancer screening, particularly when exploring barriers experienced in under-screened communities.

One of the major advantages of introducing primary HPV screening is the option to offer self-sampled vaginal swabs. Self-sampling, whether at-home or in another private location, could address many of these aforementioned barriers. Self-sampling could specifically address barriers related to clinic access and to gynaecological examinations required in Pap testing.

2.2.9 HPV Self-Sampled Testing

Trials validating the use of self-sampling found that self-sampled specimens were just as viable as physician-collected specimens for use in HPV testing (138-141), especially when using a PCR-based HPV test assay (11).

The ability to self-sample for HPV testing, especially when done at home or in another private location, has the potential to remove the dependence on clinic hours, transportation, discomfort with gynaecological exams, and language barriers with a healthcare provider; it could also provide a culturally or religiously acceptable procedure. Removal of these barriers could improve participation in women who are under-screened (142) whether in a rural or urban setting.

High levels of acceptability to self-sampled vaginal swabs have been established among diverse populations of women (105, 141, 143-147), including marginalized and hard-to-reach women (142). Acceptance rates to self-sampling have been estimated to be 75–93% (146). The majority of these studies have been among urban populations, with limited availability of evidence on rural populations (148). Little is presently known about the
acceptability of self-sampling for cervical cancer screening among women living in rural and remote regions in Canada. Enormous potential exists for self-sampling to increase participation in cervical cancer screening programs across a diverse female population, if it is acceptable to women and can address many of the previously reported barriers.

To date, HPV self-sampling uptake has been predominately studied in urban settings (12, 14-17, 19, 20). Select international studies with rural components did not provide definitive findings as to whether offering self-sampling improves uptake among under-screened women, and those that did used a door-to-door recruitment method (13, 149, 150). When mail-delivered self-sampling was examined in a rural community there was no significant difference found in participation between HPV self-sampling and invitation letters for Pap testing. However, there was a significant increase in participation between HPV testing and Pap testing when HPV testing was offered at the clinic (13). The means of providing HPV testing can be done by mail, at the clinic, another private location, or be delivered door-to-door. Unfortunately, door-to-door provision of HPV self-sampling is neither sustainable nor a feasible option for health-care delivery, especially in rural Canadian communities. The use of clinic-based testing has been shown to be an option in rural Ontario (105); however, for highly dispersed rural communities mail delivery may provide the best option to overcome many of the barriers to cervical cancer screening.

Mailed HPV self-sampling kits to eligible women could be an alternative screening option for women living in isolated, rural, or remote communities. At the outset of this dissertation work the extent to which this method was a viable option had not been tested extensively and had not been done within the Canadian context of health-care delivery. The aim, as always, would be to encourage women who are HR-HPV positive to engage in clinic-based Pap testing and appropriate follow-up.

It is important to keep in mind that women have also raised concerns about HPV self-sampling. Concerns raised include being unsure of their ability to self-sample an accurate specimen, the lack of confidence in the test compared to a provider-administered test, and the increased confidence in the ability of health-care providers to provide complete testing (143). These potential barriers to self-sampling should be explored to maximize the potential uptake of self-sampling for HPV testing in rural under-screened women.

2.3 Summary:

The introduction of cervical cancer screening has greatly reduced the mortality and incidence of cervical cancer. To date, screening for cervical cancer has employed cytology for identification of pre-cancerous and cancerous lesions; however, low rates of screening due to a
multitude of barriers has ultimately limited the uptake of screening. Our current understanding of cervical cancer clearly identifies HPV as a causative agent in cancer development. There currently exists the means to test for HPV and identify women most at risk for the development of cervical cancer. By changing the screening paradigm to risk stratification, HPV testing can be utilized and self-sampling can be introduced for women who are reluctant to undergo traditional provider-administered screening. At the outset of this dissertation work, there was limited information on whether offering self-sampling increased participation in rural under-screened women and by how much. The first objective of this dissertation was to measure if self-sampling does, in fact, improve participation in cervical cancer screening in under-screened women. The second objective of the dissertation was to explore barriers to cervical cancer screening in an under-screened rural population and identify educational initiatives that may improve the uptake of self-sampling. The findings from first two objectives were used to support the design and implementation of a randomized HPV self-sampling intervention pilot study to determine the feasibility and acceptability of at-home HPV self-sampling to increase uptake of cervical cancer screening in rural under-screened women (objective 3).
Chapter 3: Methods

3.1 Conceptual Model

The Health Belief Model (HBM) has been used, and discussed at length, as a basis for how cervical cancer screening uptake can be achieved through a psychosocial behavioural change perspective (6, 7, 151). The HBM includes the following dimensions of factors: individual perceptions (perceived susceptibility to cervical cancer and perceived severity of cervical cancer); modifying factors (demographic variables, perceived threat and cues to action); and intention formation factors (perceived benefits and barriers) (6). I have developed a conceptual model describing how the process of cervical cancer screening is undertaken using an adapted HBM framework previously proposed by Waller (7), which separates out the practical barriers to screening attendance (Figure 3.1.1). The validity of the HBM was not tested in this dissertation work. The purpose of the conceptual model was to guide my thinking of how HPV self-sampling could impact a women’s behaviour towards cervical cancer screening.

Self-sampling has the potential to positively impact behaviour change by modifying a number of factors within a HBM for cervical cancer screening. Self-sampling provides an external cue-to-action and could address many of the perceived barriers (procedural, anonymity, privacy, etc.) and could lead to screening uptake by removing practical barriers (access, competing priorities, time pressures, transportation, etc.).

Data collection, variable selection, and interpretation were influenced by the components of the conceptual model, as well as the biological risk factors for disease (as reviewed in Chapter 2).
Figure 3.1.1: Conceptual model for cervical cancer screening behaviour based on the Health Belief Model as adapted from Janz (6) and Waller (7). Reproduced with permission of John Wiley and Sons Inc. and BJOG: An International Journal of Obstetrics and Gynaecology.

3.2 Summary of Study Design

The overarching purpose of this dissertation is to determine if HPV self-sampling can improve participation in cervical cancer screening in rural communities, with a specific focus on under-screened women. This was accomplished through a systematic literature review and meta-analysis, followed by an embedded mixed methods study (Figure 3.2.1).

An embedded mixed methods study design collects and analyzes both qualitative and quantitative data within a major quantitative (or qualitative) design. The embedded design is ideal when a qualitative approach (or strand) is needed to answer secondary, but highly connected, research questions within the primary quantitative study (152). The second, 'embedded', strand is used to supplement the major strand, which can occur concurrently or in sequence, either before or after the major strand. When the embedded strand occurs before the major strand it allows for the results to support the development of interventions, refine recruitment processes, and/or understand participants, context, or environment so that an intervention can be successful. The embedded strand can lend support to a single phase of the
study (either before, during, or after) or during multiple phases of the study, to support the design (before) and provide context for the major strand findings (after) (152).

Prior to conducting the mixed methods study, a systematic literature review and meta-analysis was conducted to determine if cervical cancer screening rates were higher when HPV self-sampling was offered compared to Pap testing (objective 1). The findings provided an estimate as to the uptake of HPV self-sampling in under-screened women, and identified that there was limited evidence available for the use of self-sampling to improve screening uptake in under-screened rural women.

The second and third objectives of this dissertation were answered using an embedded mixed method design comprising of two sequential strands. A qualitative thematic analysis using focus groups (qualitative strand 1) explored barriers to cervical cancer screening, described women’s attitudes towards HPV self-sampling as an option for cervical cancer screening in rural communities, and identified knowledge gaps and educational initiatives that could improve acceptance and uptake of HPV self-sampling and cervical cancer screening, in under-screened rural communities. In addition, factors for improving participation in the randomized control trial (RCT) were explored to help strengthen the design and implementation of a HPV self-sampling pilot study (objective 2). A pragmatic RCT pilot study (quantitative strand 2) determined the feasibility and acceptability of mail-out, at-home HPV self-sampling as a means of increasing uptake of cervical cancer screening in a rural community (objective 3). Findings from the qualitative strand were integrated to support the results from quantitative strand regarding the barriers to cervical cancer screening, and health information and educational outreach initiatives.
Figure 3.2.1: Embedded mixed methods design and timeline for completion of HPV Self-sampling Pilot Study, including qualitative focus group study (strand 1) and pragmatic randomized control trial pilot study (strand 2).
3.3 Objective 1: Systematic Review and Meta-analysis

The first objective of this dissertation was to review the published literature to determine if cervical cancer screening rates were higher when HPV self-sampling was offered compared to clinician-sampled Pap testing in under-screened women. This was accomplished through a systematic review and meta-analysis. Studies exploring the difference in response rates for under-screened women who were offered HPV self-sampling compared to invitation to undergo Pap testing at a local clinic were identified and reviewed.

3.3.1 Study Design:

Medline and Embase databases were systematically reviewed for studies published between January 1990 - July 15, 2012. A total of 242 articles met the search criteria. The key words and medical subject headings for cervical cancer included those related to cervical cancer, HPV infections, self-sampling, and HPV testing. Literature was restricted to peer-reviewed articles that clearly demonstrated a comparison between HPV self-sampling and Pap testing, that were conducted in a population of women who do not routinely participate in cervical cancer screening programs, and that contained screening data at the level of the individual. Inclusion criteria comprised the aforementioned, as well as the need for studies to have clear descriptions of group allocation and compliance for the intervention and control groups. Accepted control groups were those that offered a standard invitation to undergo Pap testing in accordance with normal procedures within their jurisdiction. Ecological studies were excluded due to the inability to calculate individual-level crude rates of screening. Conference abstracts, editorials, commentaries, duplicated datasets, unpublished data, and studies with male participant data were also excluded. There were no language restrictions. One French study was included and a reviewer comfortable in French verified the data extraction. Articles were reviewed in full if the abstract met the inclusion or if the abstract lacked sufficient evidence to be excluded.

3.3.2 Data Collection:

Two independent reviewers abstracted all data (myself and co-author DW). Any discordance was resolved by consensus. Only the most recent article was included for studies that presented on the same dataset. Data abstracted from each article included: first author, publication journal, data of publication, country and city of study, dates of study completion, HPV detection method, sample collection device, population description, age distribution of
participants, definition of under-screened or non-attendees, study design, total number of participants in each group, compliance in each group, and percent positivity of high-risk HPV.

3.3.3 Analysis:

Study quality was assessed for all included studies. I selected the modified Downs and Black tool to facilitate methodological quality assessment (153), which allowed the assessment of both randomized and observational studies by examining both internal and external validity. Randomization, allocation, loss to follow-up, and representativeness of the underlying population were all examined. Studies that met few of the 28-point criteria were deemed low, those that met some (greater than half) were deemed medium and those that met most criteria (more than 20 points) were deemed high.

A single-pooled estimate of the relative uptake of HPV self-sampling was compared to Pap testing. Sensitivity analyses were conducted based on differing study designs to determine the impact of study design on the calculated pooled estimate of relative screening uptake. The study-specific screening uptake and overall pooled estimate of relative screening uptake were calculated using an intention-to-treat analysis of participants’ original allocation, i.e., women randomized to the HPV self-sampling group who elected to undergo Pap testing were analyzed as belonging to the HPV self-sampling group.

A random effects model was used to calculate the pooled relative uptake and 95% confidence intervals. The two models most commonly used in meta-analysis are fixed effects and random effects. A fixed-effects model is commonly used when the pooled estimate is attempting to find the singular effect size with a narrow distribution. The underlying assumption being that there is a one true effect size that is being estimated by all studies. During the analysis, a study with low variance is given more weight in the model as it is seen as being a better approximation to that one true effect. A random-effects model is used when the individual studies are estimating a spectrum of true effects, each within their own distribution. The model allows each study to contribute equally (i.e., equal weights) to the overall mean distribution of a given effect. Given that cervical cancer screening uptake can be impacted by social norms and vary by a country’s culture, it was deemed that each study was estimating the country specific effect and the random-effects model was most appropriate. Statistical heterogeneity was assessed using the I² statistic, which measures variation across studies due to heterogeneity rather than by chance alone (154). All statistical tests were two-sided and performed in Stata 11.2 (Stata Corporation, College Station, TX USA).
3.4 Objectives 2 and 3: HPV Self-Sampling Study Designs

The rural community of Mount Forest, Ontario, was selected as the study setting for the qualitative (objective 2) and quantitative (objective 3) strands of the embedded mixed methods study. Mount Forest was selected as it had a large population of under-screened women residing in the area, and there was strong interest from the local Family Health Team to improve cervical cancer screening and participate in rural community based research (127).

3.4.1 Study Setting:

In 2010 Cancer Care Ontario launched an initiative to address under- and never-screened populations in Ontario. Geographic maps of populations with lower cancer screening rates were identified using geographic information system technology. For cervical cancer screening, recorded Pap tests through the Ontario Health Insurance Plan (OHIP) in 2009 were overlaid with the eligible population (women 30–69 years of age) by the 2006 census dissemination areas. This work was completed in conjunction with the Institute for Clinical Evaluative Sciences.

The Township of Wellington North, in southwestern Ontario was identified as having low rates of cancer screening, specifically cervical cancer screening. Many of the dissemination areas in Wellington North had rates of cervical cancer screening of less than 60% of eligible women (Figure 3.4.1). The town of Mount Forest, approximately 150 kilometres northwest of Toronto, was identified as having a Family Health Team and was approached by the Under-Never-Screened (UNS) Provincial Research Team to discuss the findings of the mapping project and gauge interest in partnering on an initial study to explore the reason for low cancer screening rates in their community.

Small towns and rural landscapes surround the town of Mount Forest. In 2011 the population of Mount Forest was 4,757 with the surrounding township of Wellington North being 11,477 people. The median age of the population was 42.9 years of age (women being 44.6 years of age). Over 60% of households reported being married or living common-law. The ethnic diversity in Wellington North is low, with only 2.4% reporting being a visible minority (155). English is the most common language reported, with 91.9% of the population reporting speaking only English at home. German and Dutch are the top non-English languages reported (156). Wellington North is also home to a number of Older Order Anabaptist groups (Amish and Mennonite).

The 2010 median private household income was $67,071, which was slightly lower than the provincial average ($68,604). The top industries in Wellington North include: manufacturing, agriculture (forestry, fishing, and hunting), health care and social assistance, construction, and
The greatest growth for the area was in manufacturing, health care and social assistance, followed by agriculture (157).

The Mount Forest Family Health Team (MFFHT) is a sole primary care provider for approximately 12,000 patients in Mount Forest and the surrounding Wellington North area. At the time of this dissertation work, the next closest primary care clinics were approximately an hour drive away along rural highways (Fergus, Guelph and Erin-Rockwood)\textsuperscript{11}.

The MFFHT at the Clair Stewart Medical Clinic was comprised of six family doctors, and multi-disciplinary teams comprised of nurse practitioners, nurses, and medical secretaries. As a clinic they offer a variety of specialized programs to combat chronic diseases and provide healthy lifestyle and wellness education programs.

Through the winter and spring of 2011/2012 I formed a partnership with the clinic’s executive director and staff through engagement with the updating of clinic’s electronic medical record system to better identify eligible patients for cancer screening based on updated provincial guidelines. In the spring of 2012, I approached the MFFHT to be the study site for the development and implementation of the HPV self-sampling pilot study.

In January 2012, the clinic implemented a reminder system within the clinic’s electronic medical record (EMR) system, whereby patients who were due for routine cancer screening (breast, colorectal, and cervical cancer screening) had an alert placed on their medical chart. An initial probe found approximately 2,300 women 21 – 70 years of age were due for routine cervical cancer screening.

An advisory group was formed at the clinic, and included the clinic director (Suzanne Trivers), medical director (Dr. Ken Babey), a senior nurse practitioner (Lara Rhiel), and myself. The advisory group provided feedback on the development of the study protocol, advised on issues of practicality in the clinic environment, and provided expertise on the community population.

\textsuperscript{11} In May of 2016, a Family Health Team Clinic was opened in Drayton, approximately 30mins from Mount Forest.
Figure 3.4.1.1: Rates of cervical cancer screening for Waterloo Wellington LHIN for women 30 – 69 years of age in 2009 (Source: Cancer Care Ontario and Institute for Clinical Evaluative Science October 2010)
3.4.2 Objective 2: Barriers and facilitators for cervical cancer screening (Qualitative strand)

The second objective of this dissertation was to explore barriers to cervical cancer screening, describe women’s attitudes towards HPV self-sampling, and identify knowledge gaps and educational initiatives that could improve acceptance of HPV self-sampling, and cervical cancer screening, in an under-screened rural community. In addition, factors for improving participation in the RCT were explored to help strengthen the design and implementation of the RCT pilot study. This objective was accomplished using a qualitative thematic analysis of community focus groups.

3.4.2.1 Study Population and Sample

Focus groups were used to discuss cervical cancer screening, but also included discussions on colorectal screening and breast cancer screening. Women 18–70 years of age without a Pap test in the preceding three years were identified as under-screened using an algorithm in the medical clinic’s EMR. A sample of fifty under-screened women was randomly selected from the EMR to receive an invitation by mail to participate (Appendix 1: recruitment letter). A purposeful sampling approach was used to target under-screened women, and maximize the diversity of women from the under-screened community (158).

Women were also recruited through the use of targeted advertisement posters throughout the community. The clinic’s receptionist facilitated the focus group registration, and participants were compensated financially for their time ($75).

3.4.2.2 Data Collection:

Community focus groups were conducted as part of a larger study that explored who the never- and under-screened were in Ontario and what barriers and facilitators existed for breast, colon, and cervical cancer screening. A subset of these focus groups with rural women included an additional set of semi-structured questions that examined HPV testing and self-sampling as an alternative modality for cervical cancer screening.

Focus group discussions provided flexibility in the data collected by allowing participants to drive the conversation and identify the most meaningful issues to the community. Using a group format maximized the number of women I could speak with, and allowed for cross sharing of ideas to capture a wide range of experiences within the community around cervical cancer screening.
In addressing the second objective of the dissertation, the focus groups served three aims. The first was to explore the barriers to cervical cancer screening experienced in a rural under-screened community. The second was to describe women’s initial perceptions and willingness to try self-sampling if offered. The third was to improve the study design and feasibility of the pragmatic randomized trial by identifying issues that would need to be addressed to maximize the uptake of self-sampling in the community.

The focus groups were age-stratified into two groups to streamline focus group discussions: women 18–39 and women 40+. The age separation was initially based on the number of screening tests women were eligible to receive at the time of the focus group discussions. Women under-40 years were only eligible for cervical cancer screening. In addition, it was hypothesized that women <40 might experience different barriers to cervical cancer screening compared to women >40, due to the increased contact with primary care, and screening, during their childbearing years from prenatal care.

Women under the age of 30 were invited to participate in the focus groups, despite being outside the recommended age for HPV testing because they were the upcoming generation of screeners so their experiences with the current screening program and their perspectives on the use of self-sampling for HPV testing would be valuable for the long-term implementation of a primary HPV-screening program.

Focus groups were offered midweek on two consecutive days in April 2012 in the community room at the Mount Forest Health Clinic. Four focus groups were offered in the evenings (5:30pm and 7:00pm) and two over lunch hour (12:00pm). Multiple times and days were intended to maximize flexibility in participation and account for different life schedules.

Focus group facilitators, myself and another female researcher, were from outside the community and had no prior relationship with participants. All focus groups were facilitated using a semi-structured interview guide. The interview guide included specific discussion questions, as well as potential prompts for facilitating the discussion as needed (Appendix 2).

The semi-structured interview guide was divided into three sections. The first section comprised visual maps of cancer screening rates for the local area and was used to introduce to participants the public health issue of low screening rates. Guided questions promoted participants to discuss why the rates of cancer screening were low compared to provincial.

In late 2011, the Canadian Task Force on Preventative Health Care issued new guidelines for breast cancer screening. Gotzsche PC. Time to stop mammography screening? Cmaj. 2011 Nov 22;183(17):1957-8. They revised the previous recommendation that women 40 – 49 years of age could consider routine mammography, to recommend women 40 – 49 years of age not receive routine mammography. Given the short time period between the release of the new guidelines and focus groups discussions, women 40 – 49 years of age had valuable information about the experience of breast cancer screening.
targets and who the under-screened were in their community. The second section of the interview guide asked participants to reflect upon and identify what barriers and facilitators to cervical cancer screening existed in the community based on personal and community knowledge. The final section of the interview guide began with an overview and introduction to HPV testing and self-sampling. Women were provided with factual information about HPV, the main differences between HPV testing and Pap testing, and were provided with visual prototypes of a self-sampling devices (a Dacron swab and a proprietary self-sampling device HerSwab™ provided by Eve Medical). HPV self-sampling questions asked about initial perceptions and how self-sampling might be accepted at the individual and community levels, if offered. All focus groups were voice recorded and transcribed verbatim.

3.4.2.3 Qualitative Analysis:

Thematic analysis was used to code and identify emergent themes (160, 161). All transcripts were read three times. The first reading identified all possible codes related to HPV testing, self-sampling, and cervical cancer screening, and was conducted by myself, and another research assistant from the UNS Provincial Research Team. Cross checking of coding ensured the most inclusive number of codes, and any disagreements on coding were resolved through consensus building during the cross-checking process. Codes were then aggregated into emergent themes. The second reading of the transcripts re-examined the identified themes and further identified additional emergent themes during this iterative process. The final reading of the complete transcripts identified key supporting quotes and looked for minor, absent, and inter-group differences. In an effort to strengthen the validity of the study findings, I continuously self-reflected during the research process to identify potential researcher bias in the interpretation of the findings, due to my personal experience of living in small rural communities. Additional discussions were had with the larger research team, the research assistant present for the focus groups, and clinic staff to ensure my subjectivity and research bias was minimized during both the thematic coding and interpretation. Coding was completed by NVivo qualitative data analysis software (version 9, 2010, QSR International Pty Ltd., Doncaster, Victoria, Australia).

The preliminary analysis and first reading of the transcripts and field notes were used to shape the methods and approaches of the pragmatic randomized pilot study.
3.4.3 Objective 3: Feasibility and acceptability of HPV self-sampling (Quantitative strand)

The third objective was to determine the feasibility and acceptability of mail-out, at-home HPV self-sampling to increase uptake of cervical cancer screening in an under-screened rural community. A pragmatic randomized trial was piloted to evaluate the effect of offering at-home HPV self-sampling on cervical cancer screening uptake within routine primary care practice. Efficacy and limitations of self-sampling for HPV testing on cervical cancer screening has already been well established in the literature. The knowledge gap exists in the effectiveness of self-sampling for cervical cancer screening uptake under ‘real world’ conditions and within the existing resource structure of primary care. A pilot study was undertaken as there was uncertainty as to whether the methodological approach would succeed in this population.

RCTs are considered the ‘gold standard’ for evaluating the causal effects of a treatment or intervention on an outcome of interest (162). The unit of randomization can either be at the individual level or using a cluster (e.g. a community or a hospital). Cluster randomization is often used with naturally formed groups of people when individual randomization would be unduly difficult. Cluster randomization is also used when high levels of intervention contamination are suspected to be an issue with individual treatment allocation due to proximity/availability of the intervention, which could mask the true effects of the intervention (163).

Individual randomization was possible in the HPV self-sampling RCT pilot study as there was only one medical clinic serving the immediate area, for which all primary care providers were associated, and the threat of intervention contamination was low. HPV self-sampling was only available to women allocated to the HPV self-sampling arm, which limited cross-contamination of that intervention. We were unable to prevent cross-contamination of Pap testing in the HPV self-sampling arm as it is currently recognized as the standard of care for cervical cancer screening. However, contamination of Pap testing in the HPV self-sampling arm was not seen as detrimental as the primary objective of the study was to determine if offering self-sampling as an option affected participation in cervical cancer screening under routine primary care conditions.

3.4.3.1 Study Population, Randomization and Sample Size:

Women were considered eligible for the study if they 1) were 30–70 years of age, 2) currently held a valid OHIP Card, and 3) did not have a Pap test recorded in their medical chart for the preceding 30 months. Women who were enrolled, rostered, or were active at the clinic were considered eligible.
The age range was selected to be in line with current guideline recommendations for HPV testing for cervical cancer screening (4). The OHIP card requirement ensured all participants in the study would not have to pay out of pocket for any necessary follow-up care. The majority of clinic’s active and enrolled patients possessed valid OHIP cards. All Canadian residents are eligible to receive universal access to medically necessary services through a provincially administered program; however, one may decline membership for personal reasons.

The county of Wellington North is home to a number of Old Order Anabaptist communities (Mennonite and Amish). Older Order Anabaptists are eligible to receive OHIP however, typically choose not to use it, and opt-out of receiving an OHIP card. As such, Older Order Anabaptists routinely pay out of pocket for medical expenses. The requirement of an OHIP card for eligibility into the HPV self-sampling pilot study meant members of the Old Order Anabaptist community were excluded from the study. The clinic’s advisory board felt that the Old Order Anabaptists required a separate engagement process around cancer screening due to cultural sensitivity, as well as the ethical implications of having to negotiate payment for the screening test, and any potential follow-up testing. Thus the UNS Provincial Research Team (164) undertook a separate cancer screening study in collaboration with the Old Order Anabaptist communities rather than attempting to integrate into this current study.

Cervical Cancer Screening Guidelines in Ontario defined under-screened as greater than three years since last Pap screening test. Under-screened was redefined as not having had a recorded Pap test in the preceding 30 months to capture women destined to be under-screened during the study period because the clinic had up to a 6-month wait-time for Pap test appointments.

An algorithm was developed within the EMR system to be able to identify all women who met the inclusion criteria. A list of eligible women was extracted and included: name, age, and telephone number. Addresses and stock letters were automatically prepared and printed from the EMR.

Women were randomized in October 2012 to one of three arms: 1) an at-home HPV self-sampling kit, 2) a mailed invitation for Pap testing, or 3) standard of care, specifically, opportunistic Pap test screening. Simple randomization was done using a random number generator, with a 1:1 ratio of allocation to each of the intervention arms with the remainder allocated to the standard of care control arm. Standard of care screening comprised women seeking screening through their own initiative with or without prompting from their health-care provider at a previous medical encounter.
Due to constraints in the EMR system’s algorithm for identifying eligible women, final eligibility was determined post-randomization. A clinic staff member and myself reviewed the list of eligible women. Women were excluded if they resided in a long-term care facility, had a past history of total hysterectomy or another medical condition that was contraindicated with screening (including palliative care), an invalid mailing address, or an inactive medical chart due to leaving the clinic (including women recently deceased). During the eligibility review there was no discretionary impact on the allocation to the study arms, and a set list of excluding criteria was applied equally to all arms.

Sample size was based on an 80% power to detect a difference of 10% between the two active intervention arms, based on an estimated uptake of 20% in the Pap testing arm. I aimed to enroll a minimum of 300 women in each active intervention arm, with a minimum of 100 women in the standard of care opportunist screening control arm. The smaller control arm still maintained power to detect a larger difference (>15%) relative to the HPV self-sampling arm. Estimated screening rates for HPV self-sampling and Pap testing were based on the prior meta-analysis (section 3.3).

3.4.3.2 Data Collection:

Women randomized to the HPV self-sampling arm received a letter from the clinic informing them of the study and provided the option for women to opt-out by contacting the clinic. Two weeks later (November 2012) women were mailed a home self-sampling kit (Appendix 2) that contained a vaginal swab, a collection tube, annotated pictorial instructions (Appendix 4), information sheet on HPV testing and cervical cancer screening (Appendix 5), self-administered questionnaire (Appendix 6), and a clinic-addressed return envelope. The self-administered questionnaires collected demographic, screening history, perceived barriers to screening, preferences for future screening, HPV knowledge, and acceptability of self-sampling. The questionnaire was constructed using demographic and screening barrier questions from a province-wide survey (165) (HPV risk factors, acceptability, and screening preference questions were amended from previous acceptability studies (105, 144)). HPV knowledge was accessed through a previously published knowledge scale (166). The questionnaire was self-administered and condensed as much as possible to reduce participant burden and cost of postage. The content of the questionnaire and instructions for self-sampling were pilot tested by a convenience sample of women aged 25–50 years of age. The women provided feedback on content and clarity, and if they felt other women would be able to follow the instructions.

An HPV and Cervical Cancer information sheet was provided to help address concerns raised during the focus group discussions related to HPV testing and cervical cancer screening.
The information sheet was adapted from the fact sheets publicly available from Cancer Care Ontario. Language and specific concerns about HPV testing were modified to minimize literacy barriers.

Study letters and self-sampling kits that were returned as ‘wrong address’ were removed from the analysis and deemed as non-allocated. Completed self-sampling kits were collected from the MFFHT clinic and hand delivered to the Ontario Public Health Laboratory. HPV testing was performed using the NML linear array HPV test and batched to minimize research costs. The UNS Provincial Research Team paid for all testing costs.

All women had their HPV test results included in their medical chart. Women who tested negative were provided their results by mail. Women who tested positive were notified by phone and/or mail as soon as possible to book a follow-up Pap test appointment.

One month after the distribution of the self-sampling kits, non-responders were given a reminder phone call using a standard message script (December 2012). Only active clinic patients, those enrolled with the clinic or having visited the clinic in the preceding 24 months, received a reminder call.

Women in the invitation for Pap testing arm received an invitation letter for Pap testing from their primary care provider asking them to call the clinic to book an appointment. Women also received a self-administered questionnaire and consent information. Completed questionnaires could be mailed or dropped off at the clinic during their appointment. The questionnaire for the Pap invitation arm was identical to the HPV self-sampling arm with the exception of questions related to the acceptability of self-sampling. After a minimum of one month from the invitation date (starting December 2012), women who had not responded were contacted by phone by a clinic staff member to follow-up and book an appointment if possible.

Women allocated to the control “standard of care” arm received no intervention during the study. At the end of the study, all women who had not attended for Pap testing were mailed an invitation for screening by their primary care provider.

Screening attendance was recorded when completed self-sampling kits were received and/or at the end of the study period (end of July 2013) for all allocated women. Medical charts were reviewed for Pap test completion. In addition, during the review of medical charts any women with predefined medical conditions that were previously not identified, but which excluded them from Pap screening, were removed from the analysis as non-allocated.

HPV testing was performed using a linear array assay targeting both high-risk HPV (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 69) and low-risk types (6, 11, 26, 40, 42, 53, 54, 55, 61, 62, 64, 66, 67, 70, 71, 72, 73, 81, 82, 83, 84, 89) (98). DNA sample quality was
assessed through the detection of human $\beta$-globin in a separate PCR assay. Self-sampling was performed with a Dacron swab and transported in 2mL of PreserCyt. The selection of the self-sampling device was based on previous validation and experience with the system at the Ontario Public Health Lab (personal communications with Dr. Anu Rebbapragada). Validation of self-sampling for HPV testing was not performed in this study. The body of evidence was deemed to be sufficient for the use both HPV testing and self-sampling for cervical cancer screening without including comparisons to cytology or provider-collected samples for HPV testing.

3.4.3.3 Statistical Analysis:

The primary outcome ‘screening response rate’ was analyzed using an intention to treat (ITT) analysis. This was an effectiveness study; therefore, ITT analysis was used since it is thought to best limit bias in randomized trials and provide better pragmatic estimates of an intervention (167, 168). A per-protocol analysis (PPA) of self-sampling uptake was conducted in women who completed HPV self-sampling (in the HPV self-sampling arm) compared to women who underwent Pap testing (in Clinician-sampling Pap test arm) to explore the uptake of self-sampling alone.

Log-binomial regression was used to calculate relative response rates (risk-ratio (RR) of uptake) between the three arms of the study. The primary outcome measure of ‘screening uptake’ was common, which could lead to an overestimation of RR based on the odds ratio (OR) derived from simple logistic regression (162). In addition, log-binomial regression allows for the direct calculation of RRs, which is a more intuitive measure of association compared to ORs.

Differences in demographic characteristics and screening history between questionnaire respondents in the HPV testing arm and the Pap test were explored using Fisher’s Exact Test or ANOVA (all tests were two-sided with level of significance $p<0.05$).

The secondary outcome of ‘HPV self-sampling acceptability’ was explored for all women who submitted a specimen in the HPV self-sampling arm. Univariate and multivariate logistic regression explored acceptability as it related to age, employment, income, education, marital status, prior screening history, HPV knowledge, and reproductive history. Exact logistic regression was used because of sparse data and small sample size (169).

In addition, global measures of acceptability were also collected (proportion of respondents) and included asking if women would recommend HPV self-sampling to family or friends, if they would elect to use self-sampling in the future, and what was their preferred
method HPV testing (e.g., at-home self-sampling, clinic-based self-sampling, clinician-collected sampling).

Acceptability was measured using three parameters. Ease of self-sampling was measured by asking: “How easy was it to take your own swab?”, confidence in self-sampling was captured by asking: “How sure do you feel that you did the test correctly”, and finally, comfort with self-sampling was measured by asking: “How comfortable did you feel when taking your sample today?”. Each parameter was scored on a nine-point Likert-scale. The overall acceptability score was a mean sum of the three parameters, reported with 95% confidence intervals (CI). Reliability of the acceptability parameters was examined using Cronbach's alpha (170, 171). The mean acceptability score was then dichotomized into accepting or hesitant of HPV self-sampling. A conservative cut off for mean acceptability of >80% was thought to be a reasonable delineation of acceptance.

Structural equation modeling and/or path analysis was not performed due to the limited number of components. The number of components was minimized to maintain a short questionnaire. The components of ease, comfort, and confidence have previously been identified in other studies (105, 144) and were consistent with the preliminary findings of the qualitative study.

The tertiary outcome of ‘HPV positivity’ was explored with descriptive statistics, including 95% CIs, for all women who submitted a specimen. Exact logistic regression explored demographic variables and behavioural differences based on HPV status. Model building used previously identified variables related to persistent HPV infection, and included: age, number of sexual partners, and cigarette smoking. Exact logistic regression was used to estimate the logistic model parameters due to the small sample size.

3.5 Ethics Approval
The research ethics board at the University of Toronto approved this study (reference: #28091 Appendix 7).
Chapter 4: Results

4.1 Objective 1: HPV self-sampling improves participation in cervical cancer screening: Systematic review and meta-analysis*

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*A version of this manuscript was published in Canadian Journal of Public Health 2013; 104 (2): e159-e166. Reproduced with permission of the Canadian Public Health Association.

Abstract

Objective: HPV testing has emerged as an effective cervical cancer screening test. The use of HPV self-sampling has the potential to address many barriers to screening and reach at-risk women through engagement in screening. However, there is a need to examine the evidence for whether offering HPV self-sampling in practice increases screening compliance. The objective of this review is to determine to what extent providing HPV self-sampling increases screening participation in women who under or never screened for cervical cancer.

Methods: A systematic literature review conducted in the databases Medline and Embase identified articles examining the use of HPV self-sampling on cervical cancer screening participation. A meta-analysis using a random-effects model was used to calculate the relative compliance, with an intent-to-treat analysis of HPV self-sampling compared to Pap testing, with 95% confidence intervals (CI). All statistical tests were two-sided.

Synthesis: Ten studies were reviewed, with 8 being European and 2 North American. Of the 10 studies, 9 employed a randomized design. In all studies, the relative compliance of HPV self-sampling compared to Pap testing was significantly greater than 1.0. (p<0.01). The overall relative compliance was 2.14 (95% CI 1.30 – 3.52). There was large heterogeneity of screening compliance between studies for both HPV self-sampling and Pap testing.

Conclusion: HPV self-sampling significantly improved the participation of women who did not routinely attend cervical cancer screening programs. New approaches to HPV self-sampling delivery should be considered as HPV testing becomes more widely incorporated as a primary screening tool.

*Note: In 2015 Verdoodt F et al. completed an update (and expansion) to the systematic review and meta-analysis. A synopsis of this updated meta-analysis is on page 71.
Introduction

Cervical cancer screening has dramatically reduced the incidence of cervical cancer in those countries that have implemented screening programs; (1) however, the majority of cervical cancers continue to occur in women who do not attend regular screening (under-screened), or who have never been screened. (2)

The Papanicolaou (Pap) test is one of the standard screening tests used for the detection of cervical cancer. The Pap test, which is administered during a pelvic examination, involves the examination of cervical cells for abnormal histological changes consistent with cervical cell dysplasia and cervical cancer. Barriers to Pap testing can be grouped into three broad categories: clinic-level, test-level, and personal-level barriers. (3-6) Clinic-level barriers include such factors as the lack of a family physician, inconvenient clinic hours and lack of available transportation to the clinic. (5, 7) Barriers at the test-level are reported as physical discomfort or anticipation of discomfort. (6) Personal-level barriers include those that pertain to religious and cultural beliefs, language barriers, and lack of knowledge around cervical cancer screening. (6, 7)

The human papillomavirus (HPV) is a necessary cause, but not a sufficient cause, for cervical cancer. (8) More and more, HPV testing is being considered an important addition to cervical cancer screening programs, either by way of co-testing with the Pap test or as a primary screening test used to triage women for subsequent Pap testing. (9-14) HPV testing seeks to identify the presence of HPV in the vaginal canal. The presence of oncogenic HPV types confers an elevated risk for the future development of cervical cancer. In women over 30 years of age, HPV testing has been shown to be more sensitive than Pap testing for the detection of cervical interstitial neoplasia (CIN) grade 2/3+. (15-17) Due to the lower specificity of HPV testing compared to Pap screening, it has been recommended that HPV testing be used only as a screening modality in women older than 30, as a co-test or that those who test HPV positive be triaged to undergo Pap testing. (9, 16) In order for a two-phase double screening regimen to take place, adequate follow-up procedures and infrastructure are required at the primary care and/or population level.

Trials comparing HPV self-collected samples to that of physician-collected samples, found that both methods provided equally viable samples for detecting HPV. (18-20) In addition, women who performed self-sampling were found to have similar cancer-related outcomes to women who underwent HPV testing by a physician; (21) as such, HPV self-sampling has been investigated as an alternative to physician-collected samples.

Beyond the efficiency and effectiveness of HPV testing as a diagnostic test, studies have also considered women’s attitudes toward self-sampling and found that women have a high acceptance, and positive attitudes, toward the use of HPV self-sampling. (22-25) Being
able to collect one’s own sample has the potential to address many of the current barriers around screening, and improve the participation of women who are most at-risk for cervical cancer, those who are under-screened and/or hard-to-reach. (26) Self-sampling, especially when conducted at-home, removes the dependence on clinic hours, transportation, discomfort with the physical exam, language barriers with a care provider, and could provide a culturally or religiously safe procedure. In short, it appears that the use of self-sampling could play a major role in the use of HPV testing for cervical cancer screening. (27, 28)

While studies have examined and considered many aspects relating to HPV self-sampling, there is a need to examine the evidence for whether HPV self-sampling in practice increases participation and compliance in cervical cancer screening.

The objective of this review is to determine whether the option of HPV self-sampling increases cervical cancer screening participation (through HPV testing) for women living in developed countries who are never or underscreened for cervical cancer.

**Methods**

**Selection of Studies**

A systematic literature review was conducted to identify relevant articles that examined the use of HPV self-sampling for cervical cancer screening in never- and underscreened women. The databases Medline and Embase were systematically searched for peer-reviewed articles published between January 1, 1990 and July 15, 2012, with 87 and 155 relevant citations identified within each respective database.

Keywords and Medical Subject Headings (MeSH) were chosen to capture the constructs of HPV infection, cervical cancer, self-sampling and HPV DNA testing (Table 4.1.1).

The literature search was restricted to peer-reviewed articles that clearly demonstrated the comparison of HPV self-sampling as a primary screening test to standard Pap testing in women who did not routinely participate in cervical cancer screening programs. This review was restricted to developed countries, with the exception of Mexico, where Pap testing is the standard for cervical cancer screening. Mexican studies were also considered due to the importance of Mexico in the North American context both geopolitically and from an immigration perspective.

Studies were included if group allocation was clearly described and compliance was available for both the intervention group and the control group. Accepted control groups where those which offered a standard invitation to undergo Pap testing at a local Health Care Clinic or which offered Pap testing via the normal procedures of the jurisdiction within which the study was conducted.
Studies that employed an ecological design were excluded, as individual level crude rates of compliance in testing could not be determined. Conference abstracts, editorials, commentaries and other unpublished manuscripts were excluded, in addition to articles that included duplicate datasets or male participants. Studies involving male participants were excluded as the objective of this review was to examine compliance specifically in cervical cancer screening.

There were no language restrictions on publications included. Of all the publications only one was published in a foreign language (French). For this paper the data was extracted and confirmed by a second, independent reviewer comfortable in French.

Articles were reviewed in full if the study abstract met the inclusion criteria or if an article lacked sufficient information in the abstract to make an inclusion/exclusion judgment, to minimize errors of omission.

Data extraction and Outcome Measures

The following information was extracted for each study: first author, publication journal, date of publication, country and city of study, dates of study completion, HPV detection method, sample collection device, population description, age distribution of participants, definition of non-attending or underscreened, study design, total number of participants in each group, compliance in each group by test (HPV and Pap), and percent positivity of high-risk HPV.

Two independent abstractors (SR and DW) extracted all data for quality control, and any discordance was resolved by consensus. The most recent article was included for articles that presented on the same dataset.

Methodological Quality of Studies

Study quality was assessed by looking at factors of appropriate randomization, reporting of allocation and loss to follow-up or dropouts, and representativeness of the sample to the underlying target population. A modified Downs and Black Tool (29) was used to guide the quality assessment of the studies. This allowed for the assessment of both randomized and non-randomized health intervention studies, by examining both internal and external validity. The terms low, medium and high referred to a qualitative judgment of whether the studies met few (low), some (medium) or most (high) of the criteria around randomization, reporting of group allocation and loss to follow-up, and representativeness of sample to the underlying target population.
Statistical Analysis

All studies included in this review were used in the analysis to produce a pooled estimate of the relative compliance of HPV self-sampling compared to Pap testing. Additional sensitivity analyses were conducted based on different study designs to ensure that variations in study design did not meaningfully impact the overall pooled estimate. The study-specific relative compliances and the overall pooled relative compliance were calculated using an intention-to-treat-analysis. Women randomized to the HPV arm who elected to undergo Pap testing were analyzed as belonging to the HPV arm. However, for each study the compliance was reported by testing modality for each study arm.

The overall pooled relative compliance, with 95% confidence intervals, between the HPV self-sampling groups and the control groups was calculated using a random-effects model. We had to decide between using a fixed or random effects model for our meta-analysis. A fixed effects model is commonly used when all studies are attempting to estimate one true (fixed) effect size with a narrow distribution. A study with low variance is given more weight in a fixed effect model because it is seen as better estimation of the true effect. A random effects model is used when individual studies are estimating different true effects, with their own distributions. In our meta-analysis, each country has its own true and valid measure of the effect of HPV self-sampling on cervical cancer screening participation, which is impacted by the social norms and values of that country’s culture. To allow the true effect to vary between studies, we selected a random effects model so that each country could contribute equally (i.e. equal weights) to the overarching mean distribution of effect. The statistical heterogeneity was assessed using the $I^2$ statistic, which measures the variation across studies that is due to heterogeneity rather than by chance. (30) All statistical tests were two-sided and analysis was performed using Stata 11.2 (Stata Corporation, College Station TX, USA).

Results

The systematic literature search identified a total of 242 articles, 87 from Medline and 155 from Embase (Figure 4.1.2). After removing duplicate articles, 178 article titles and abstracts were reviewed for inclusion. A total of 21 full text articles were retrieved for full review, of which 10 met both the inclusion and exclusion criteria, and were included in this review (Table 4.1.2).

Study Characteristics

All studies were conducted between 2003 and 2010. The majority of the studies took place in Europe, namely, the Netherlands, (31-33) Italy, (34) United Kingdom, (35) Sweden, (36) Finland, (37) and France. (38) All of the European studies used a randomized controlled
trial design and took advantage of population registries to be able to identify non-attendees to cervical cancer screening programs. Non-attendees were subsequently randomized to either receive a HPV self-sampling kit by mail or receive an invitation to undergo Pap testing.

Two studies were set in North America: one in Mexico (39) and one in the United States. (40) The North American studies differed from the European studies in their design and population definitions. In both North American settings, a door-to-door recruitment approach was used. The US study was non-randomized, and was conducted in a neighborhood that had a low rate of screening. Women, who reported not receiving routine Pap testing, were offered the option of performing HPV self-sampling (delivered to the door) or of receiving a coupon to attend a free Pap testing clinic. The Mexican study targeted underscreened women indicating that women in the study had “limited access to health services”, and would only be screened a few times over their lifetime. (39) Mexican participants were randomized from a database of women enrolled in a community-based program for women with limited access to health services. Randomized women received either an invitation to a free Pap testing clinic or to a HPV self-sampling kit delivered to her home by a study nurse. Despite the differences in study design both these studies employed similar methods for HPV self-sampling and obtained similar HPV positivity results comparable to those found in the European trials.

All of the studies included in the review were similar with regard to targeted age demographic, methods for HPV self-sampling and Pap testing, and urban setting. In addition, all studies targeted women who were considered over-due, or who did not attend regular cervical cancer screening, in their own jurisdictions.

The studies included did differ in the use of the self-sampling device (Table 4.1.2). A wide variety of devices were employed across studies: cervovaginal brush; (31, 33, 39) vaginal swabs; (35, 36, 38, 40) and lavage methods (32, 34, 37).

**Methodological Quality of Studies**

Study quality was deemed to be high in all studies reviewed. All studies reported on allocation of participants and attrition, and 9 out of 10 used a randomized allocation design. The level of compliance in testing was varied between studies but was consistent within a given study, which provided confidence in the study recruitment and internal validity.

**Compliance of HPV self-sampling compared to Pap testing**

The relative compliance of HPV self-sampling compared to Pap testing was significantly greater than 1.0 in all reviewed studies; indicating, that women were significantly more likely to partake in screening if they were offered HPV self-sampling (Table 4.1.3). The pooled relative compliance was 2.14 (1.30 – 3.52 95% CI). These results indicate that women were twice as
likely to participate in cervical screening if they were offered a HPV self-sampling home kit compared to women who were invited to the clinic to undergo Pap testing. A Forest plot of the studies and the pooled effect estimate (Figure 4.1.2) indicated that statistical heterogeneity ($I^2$) was 99.6% ($p<0.0001$), representing significant heterogeneity between studies.

Overall, the compliance in screening varied widely between studies, with compliance reported in the HPV arms between 10.2% and 98.2% and in the Pap test arms between 4.5% and 86.8%. The highest study specific compliances for both HPV testing and Pap testing were reported in the US and Mexico studies. All compliance and relative compliance estimates were unadjusted for any additional covariates, such as age, educational and marital status. Only the non-randomized study (US) examined age and education level, and found that younger age and higher education were associated with HPV self-sampling compliance. (40)

**HPV prevalence**

All of the studies reported high specimen quality from self-collected samples for HPV testing. The percent positivity of high-risk HPV among those who administered the self-sampling ranged from 6.04% to 21.34%. Of the 10 studies, eight used the hybrid-two capture assay for HPV detection, (32-37, 39, 40) and two studies used PCR genotype specific assays. (31, 38)

**Discussion**

To our knowledge, this is the first systematic literature review and meta-analysis that addresses the specific question of whether offering HPV self-sampling, compared to Pap testing, improves participation in cervical cancer screening among women who are never or under-screened for cervical cancer. We found that never/under-screened women offered HPV self-sampling were twice as likely to comply with/participate in cervical cancer screening. A large variety of self-sampling devices were used so it is still unclear what the best HPV self-sampling devices are for collecting reliable samples and maximizing comfort for women.

Many studies have examined the acceptance, reliability, and accuracy of HPV self-sampling. (22-25) Overwhelmingly, HPV self-sampling has been shown to have high acceptance among women and that women are able to collect good samples for testing. (18-20) These factors support the notion that HPV self-sampling has the potential to significantly improve cervical cancer screening compliance in women. Given that the studies reviewed in this analysis studies provided significant evidence that offering HPV self-sampling did improve participation, HPV self-sampling should be pursued as a compliment or alternative to Pap testing in women older than 30, who do not attend regular screening programs.
It is worth noting that HPV testing can potentially produce a relatively larger number of false positives (compared to Pap testing), due to transient infections. Infrastructure to provide timely and effective follow-up is an important component of any health care system that provides wide-scale HPV testing to ensure women who are at an increased risk of cervical cancer are provided with appropriate follow-up care. (10)

**Limitation of the studies reviewed**

Large heterogeneity in compliance was observed between studies with reported compliance of HPV self-sampling as high as 98.2% and others as low as 10.2%. The magnitude of the compliance was study-specific, however the relative compliance between studies was largely similar. This wide difference in observed compliance between studies was the main rationale for selecting a random-effects model. It was theorized that these studies and their populations were measuring different true effects and reflected the possible distribution of participation.

The studies included were predominately conducted in urban settings, with the exception of the US, Mexico, and one sub-study site in rural Italy. The Italian study did find a significantly different relative compliance overall, favoring the use of HPV self-sampling; however, within the rural sub-study site, the compliance was not significantly different between the HPV self-sampling and Pap test. The authors did note that the recruitment time period for this rural site was not optimal and so it is inconclusive whether there are true urban–rural differences. The US and Mexico studies both used door-to-door recruitment methods and had much higher response rates to both HPV self-sampling and Pap testing, however, the door-to-door recruitment may have artificially increased their overall participation rates and unfortunately, screening programs using door-to-door delivery are not sustainable in many areas.

The US and Mexico studies were included in the pooled estimate, despite obvious differences to the European trials. The four main differences being: rural locale, high overall response rate, lack of randomization in the US study, and lack of definitive Pap testing history in the Mexican study. A sensitivity analysis was conducted to estimate the pooled relative compliance without the inclusion of those two studies. The sensitivity analysis yielded an estimated pooled relative compliance of 2.34 (1.47 – 3.70 95% CI), which indicated that the addition of these two community trials did not alter the overall results, and if anything their inclusion provides a more conservative estimate of effect. However, potential differences in compliance between rural and urban women may still exist due to the observed lower relative compliance when both rural studies are taken into account, coupled with the non-significant finding in the rural Italian sub-study site. Differences between rural and urban settings should
continue to be elucidated; especially given rural areas have been shown to have lower screening participation and increased burden of cervical cancer. (41-43)

Limitations of the review

One of the limitations of this review is the scope of articles included. The exclusion of middle/low income study sites led to the omission of four studies, three from India and one from China, that explored HPV self-sampling in a developing country context. (44-46) The authors of the three Indian studies concluded that self-sampling improved screening participation in women. Despite not including the data in the review, the overarching message of increased participation with the provision of HPV self-sampling was echoed throughout these studies. Four additional studies, which examined uptake of HPV self-sampling, were omitted due to a lack of comparison group. (24, 47-49) Within this group of studies the uptake of HPV self-sampling was reported between 32.0% and 58.0%, a comparable estimation to the HPV self-sampling uptake as reported by the studies included in this review.

Another limitation of this review is that studies employing multiple intervention arms were only analyzed based on the comparison between the Pap testing control group and the intervention arm that employed the use of mailed HPV self-sampling test kits. The other interventions arms that were included in some trials consisted of providing HPV testing in a clinic setting or having participants request a self-sampling kit by phone. The restriction to only analyze participants that were provided with HPV self-sampling by mail was done to improve comparability across studies. Additionally, if a study employed a multi-phase or crossover design, only the initial phase of the study was included in the analysis, again to ensure that the comparison groups across the trials were as similar as possible, as participation response in subsequent phases may have been impacted due to increase study exposure from a prior invitation or study information relating to cervical cancer screening. This review attempted to simplify the complexity in many of these trials so that they could be reasonably compared to be able to identify the overarching trend in women’s participation in cervical cancer screening programs when provided with an offer of HPV self-sampling.

Potential publication bias (for null results) was addressed by searching conference proceedings. All conference abstracts were accounted for by identified publications. Despite the potential for outstanding null effect studies, a null effect would not change the pooled effect from these 10 positive studies. A broad search criterion was used to reduce the potential for missing relevant articles. It is unlikely that the literature is missing a large negative study and though one negative study might pull the pooled effect towards the null it would not negate the significantly positive effect.
Conclusion

HPV self-sampling could significantly improve cervical cancer screening participation, especially in those who are under or never screened for cervical cancer. As HPV testing becomes more widely accepted as a primary screening tool or co-testing approach with Pap testing, new approaches to cervical cancer screening delivery should be considered. However, appropriate follow-up and treatment for women who do test high-risk HPV positive needs to develop concurrently to HPV self-sampling delivery. Future research efforts in HPV self-sampling should focus on exploring effective HPV self-sampling delivery methods and infrastructure, and examining the uptake in rural areas, where the use of HPV self-sampling has the potential to make dramatic improvements in those communities.
References


Figure 4.1.1: Flow chart of the systematic search to retrieve studies on the compliance of HPV self-sampling compared to Pap testing for cervical cancer screening from Medline and Embase (January 1, 1990 – July 15, 2012). The number of articles retrieved and removed based on the inclusion and exclusion criteria are provided. Ten articles were included in the review, which met both the inclusion and exclusion criteria.
**Figure 4.1.2:** Forest plot for the pooled estimate of the relative screening compliance of women using HPV self-sampling compared to invitation to Pap testing.

<table>
<thead>
<tr>
<th>Study ID</th>
<th>RR (95% CI)</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gok et al. 2012</td>
<td>4.73 (2.98, 7.49)</td>
<td>9.45</td>
</tr>
<tr>
<td>Szarewski et al. 2011</td>
<td>2.25 (1.71, 2.97)</td>
<td>9.96</td>
</tr>
<tr>
<td>Giorgi et al. 2011</td>
<td>1.41 (1.10, 1.82)</td>
<td>10.01</td>
</tr>
<tr>
<td>Wikstrom et al. 2011</td>
<td>4.27 (3.68, 4.94)</td>
<td>10.18</td>
</tr>
<tr>
<td>Virtanen et al. 2011</td>
<td>1.22 (1.13, 1.31)</td>
<td>10.25</td>
</tr>
<tr>
<td>Castle et al. 2011</td>
<td>1.99 (1.36, 2.92)</td>
<td>9.69</td>
</tr>
<tr>
<td>Lazcano-Ponce et al. 2011</td>
<td>1.13 (1.12, 1.14)</td>
<td>10.27</td>
</tr>
<tr>
<td>Plana et al. 2011</td>
<td>3.66 (3.24, 4.13)</td>
<td>10.21</td>
</tr>
<tr>
<td>Gok et al. 2010</td>
<td>1.67 (1.28, 2.18)</td>
<td>9.99</td>
</tr>
<tr>
<td>Bias et al. 2007</td>
<td>1.94 (1.49, 2.53)</td>
<td>9.99</td>
</tr>
<tr>
<td>Overall (I-squared = 99.5%, p = 0.000)</td>
<td>2.14 (1.30, 3.52)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

**NOTE:** Weights are from random effects analysis.
Tables

**Table 4.1.1:** The key words and Medical Subject Headings (MeSH) used to identify peer-reviewed articles in the databases Medline and Embase from January 1, 1990 – July 15, 2012.

<table>
<thead>
<tr>
<th>Medline</th>
<th>Embase</th>
</tr>
</thead>
<tbody>
<tr>
<td>[Papillomavirus infections OR cervical intraepithelial neoplasia</td>
<td>[Vagina smear OR papilloma virus OR papillomavirus infection OR wart</td>
</tr>
<tr>
<td>OR uterine cervical neoplasmas OR vaginal smears OR</td>
<td>virus OR papilloma OR uterine cervix carcinoma OR uterine cervix</td>
</tr>
<tr>
<td>papillomaviridae] AND</td>
<td>carcinoma in situ] AND</td>
</tr>
<tr>
<td>[Self care OR patient acceptance of health care OR Self-sampl* OR</td>
<td>[Self evaluation OR patient participation OR patient compliance OR</td>
</tr>
<tr>
<td>Self test*] AND</td>
<td>self care OR Self test* OR Self sampling OR Self sampl* OR Self</td>
</tr>
<tr>
<td></td>
<td>sampling Human papillomavirus test] AND</td>
</tr>
<tr>
<td></td>
<td>[Cancer screening OR HPV test*]</td>
</tr>
</tbody>
</table>
Table 4.1.2: Summary study characteristics of reviewed studies published between January 1, 1990 and July 15, 2012 examining HPV self-sampling vs. Pap testing compliance for women who do not normally participate in cervical cancer screening programs.

<table>
<thead>
<tr>
<th>Study (reference), year, country</th>
<th>Number of Participants</th>
<th>Age range Yrs.</th>
<th>Estimated national coverage of cervical cancer screening</th>
<th>Study Characteristics (randomization, HPV detection assay, sampling device and setting)</th>
<th>Description of HPV self-sampling arm and control arm intervention</th>
<th>Definition of under screened population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gok et al. (33), 2012, Netherlands</td>
<td>25,822</td>
<td>30 - 60</td>
<td>77%</td>
<td>Randomized. Hybrid-capture II assay with Cervovaginal brush sampling device. Urban setting.</td>
<td>Mailed HPV self-sampling vs. Pap invitation letter.</td>
<td>Women who had not attended cervical cancer screening in the last year after a reminder invitation for screening.</td>
</tr>
<tr>
<td>Szarewski et al. (35) 2011, United Kingdom</td>
<td>3000</td>
<td>25 - 64</td>
<td>68%</td>
<td>Randomized. Hybrid-capture II assay with swab sampling device. Urban setting.</td>
<td>Mailed HPV self-sampling vs. Pap invitation letter</td>
<td>Women who did not response to 2 invitations for screening.</td>
</tr>
<tr>
<td>Giorgi et al. (34), 2011, Italy</td>
<td>1235</td>
<td>35 - 65</td>
<td>48 - 88%</td>
<td>Randomized. Hybrid-capture II assay with lavage sampling device. Urban and rural settings.</td>
<td>Mailed HPV self-sampling vs. Pap invitation letter</td>
<td>Women who did not respond to 1 regular invitation for screening.</td>
</tr>
<tr>
<td>Virtanen et al. (37), 2011, Finland</td>
<td>8699</td>
<td>30 - 60</td>
<td>70%</td>
<td>Randomized. Hybrid-capture II assay with lavage sampling device. Urban setting.</td>
<td>Mailed HPV self-sampling vs. Pap invitation letter</td>
<td>Women who did not respond to 2 invitations for screening.</td>
</tr>
<tr>
<td>Castle et al. (40), 2011, United States of America</td>
<td>119</td>
<td>26 - 65</td>
<td>*NR</td>
<td>Not randomized. Hybrid-capture II assay with swab sampling device. Rural setting.</td>
<td>Direct-door-to-door offering of HPV self-sampling vs. coupon for free Pap test at local clinic</td>
<td>Women who had not had a Pap test in the last 3 years.</td>
</tr>
<tr>
<td>Lazcano-Ponce et al. (39), 2011, Mexico</td>
<td>22,102</td>
<td>25 - 65</td>
<td>NR</td>
<td>Randomized. Hybrid-capture II assay with Cervovaginal brush sampling device. Rural setting.</td>
<td>Direct door-to-door offering of HPV self-sampling vs. door-to-door invitation to Pap testing at nearest clinic</td>
<td>Women in a poverty-reduction program, with limited access to health services.</td>
</tr>
<tr>
<td>Study</td>
<td>Sample Size</td>
<td>Age Range</td>
<td>Participation</td>
<td>Methodology</td>
<td>Intervention</td>
<td>Outcome</td>
</tr>
<tr>
<td>------------------------------</td>
<td>-------------</td>
<td>------------</td>
<td>---------------</td>
<td>-----------------------------------------------------------------------------</td>
<td>--------------</td>
<td>-------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Piana et al. (38), 2011, France</td>
<td>7,854</td>
<td>35 - 69</td>
<td>60%</td>
<td>Randomized. PCR genotyping assay with swab sampling device. Urban setting.</td>
<td>Solicitation for HPV self-sampling at home vs. Pap invitation letter</td>
<td>Did not participate in cervical cancer screening after invitation</td>
</tr>
<tr>
<td>Gok et al. (32), 2010, Netherlands</td>
<td>27,163</td>
<td>30 - 60</td>
<td>77%</td>
<td>Randomized. Hybrid-capture II assay with lavage sampling device. Urban setting.</td>
<td>Mailed HPV self-sampling vs. Pap invitation letter</td>
<td>Women who had not had a Pap test in 5 years and did not respond to 1 invitation for screening.</td>
</tr>
<tr>
<td>Bias et al. (31), 2007, Netherlands</td>
<td>2624</td>
<td>30 - 50</td>
<td>63%</td>
<td>Randomized. PCR genotyping with Cervovaginal brush sampling device. Urban setting.</td>
<td>Mailed HPV self-sampling vs. Pap invitation letter</td>
<td>Women who did not respond to 2 invitations screening.</td>
</tr>
</tbody>
</table>

*NR – Not reported
Table 4.1.3: Overall results of compliance and relative compliance for all studies reviewed, including high-risk-HPV percent positivity.

<table>
<thead>
<tr>
<th>Study (reference), year, country</th>
<th>Number of Participants</th>
<th>HPV self-sampling arm (n)</th>
<th>HPV self-sampling compliance (%)</th>
<th>Pap test compliance</th>
<th>Total HPV self-sampling compliance (%)</th>
<th>Pap test arm</th>
<th>Pap test compliance (%)</th>
<th>Relative compliance (95% CI)</th>
<th>p-value</th>
<th>% hr-HPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gok et al. (33), 2012, Netherlands</td>
<td>25,822</td>
<td>25,561</td>
<td>7,870 (30.8%)</td>
<td>n/a</td>
<td>7,870 (30.8%)</td>
<td>261</td>
<td>17 (6.5%)</td>
<td>4.727 (2.984 - 7.488)*</td>
<td>&lt;0.000</td>
<td>8.3</td>
</tr>
<tr>
<td>Szarewski et al (35), 2011, United Kingdom</td>
<td>3000</td>
<td>1,500</td>
<td>96 (6.4%)</td>
<td>57 (3.8%)</td>
<td>153 (10.2%)</td>
<td>1,500</td>
<td>68 (4.5%)</td>
<td>2.250 (1.701 - 2.967)*</td>
<td>&lt;0.000</td>
<td>8.4</td>
</tr>
<tr>
<td>Giorgi et al. (34), 2011, Italy</td>
<td>1235</td>
<td>616</td>
<td>103 (16.7%)</td>
<td>18 (2.9%)</td>
<td>121 (19.6%)</td>
<td>619</td>
<td>86 (13.9%)</td>
<td>1.414 (1.098 - 1.821)*</td>
<td>0.0073</td>
<td>21.4</td>
</tr>
<tr>
<td>Wikstrom et al. (36), 2011, Sweden</td>
<td>4060</td>
<td>2,000</td>
<td>679 (34.0%)</td>
<td>100 (5.0%)</td>
<td>779 (39.0%)</td>
<td>2,060</td>
<td>188 (9.1%)</td>
<td>4.268 (3.685 - 4.943)*</td>
<td>&lt;0.000</td>
<td>6.0</td>
</tr>
<tr>
<td>Virtanen et al. (37), 2011, Finland</td>
<td>8699</td>
<td>2,397</td>
<td>663 (27.7%)</td>
<td>93 (3.9%)</td>
<td>756 (31.5%)</td>
<td>6,302</td>
<td>1,631 (25.9%)</td>
<td>1.219 (1.134 - 1.310)*</td>
<td>&lt;0.000</td>
<td>12.2</td>
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<td>Castle et al. (40), 2011, United States of America</td>
<td>119</td>
<td>77</td>
<td>62 (80.5%)</td>
<td>n/a</td>
<td>62 (80.5%)</td>
<td>42</td>
<td>17 (40.5%)</td>
<td>1.989 (1.357 - 2.917)*</td>
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<td>Lazcano-Ponce et al. (39), 2011, Mexico</td>
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<td>9,371</td>
<td>9202 (98.2%)</td>
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<td>11,054 (86.8%)</td>
<td>1.131 (1.123 - 1.139)*</td>
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<td>MI</td>
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<td>Piana et al. (38), 2011, France</td>
<td>7,854</td>
<td>3,552</td>
<td>939 (26.4%)</td>
<td>n/a</td>
<td>939 (26.4%)</td>
<td>4,305</td>
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<td>&lt;0.000</td>
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<td>Gok et al. (32), 2010, Netherlands</td>
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<td>26,886</td>
<td>7,404 (27.54%)</td>
<td>51 (0.19%)</td>
<td>7,455 (27.7%)</td>
<td>277</td>
<td>46 (16.6%)</td>
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<td>Bias et al. (31), 2007, Netherlands</td>
<td>2624</td>
<td>2,352</td>
<td>736 (31.3%)</td>
<td>70 (3.0%)</td>
<td>806 (34.3%)</td>
<td>272</td>
<td>48 (17.6%)</td>
<td>1.942 (1.493 - 2.525)*</td>
<td>&lt;0.000</td>
<td>1 8.0%</td>
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*Statistically significant <0.01
Update:

In 2015, an updated meta-analysis was completed by Verdoost F et al.: “Reaching women who do not participate in the regular cervical cancer screening programme by offering self-sampling kits: A systematic review and meta-analysis of randomised trials” (172). The relative response rate to HPV self-sampling compared to a control (Pap testing or clinician-sampling) was found to be 2.40 (95%CI 1.73–3.33%) by intention-to-treat (ITT), and 2.06 (95% CI 1.44–2.96%) by per-protocol analysis (PPA), when samples were mailed directly. The absolute increase in response was 12.6% (95%CI 9.3–15.9%) between mailed HPV self-sampling and the control group. The revised meta-analysis, with 7 additional studies from 2013 - 2015, confirmed the prior findings of a 2-fold increase in cervical cancer screening (2.14 (95%CI 1.30 – 3.52)) by ITT for direct mailing of self-sampling devices to under-screened women compared to reminder letters for Pap testing. The revised meta-analysis was able to better evaluate the different self-sampling methodologies for delivery: direct mailing, opt-in invitations (calling in to order a self-sampling kit), and door-to-door direct invitation. Similarly, they found the highest overall response to door-to-door invitations. There was no difference in screening uptake when comparing opt-in self-sampling strategies compared to the control group. The delivery method of HPV self-sampling appears to impact the response rate and indicates that more research is needed on optimizing a delivery method that maximizes participation and minimizes waste (172).
4.2 Objective 2: Barriers and Facilitators to Cervical Cancer Screening Among Women in Rural Ontario, Canada: The Role of HPV Self-sampling*

C. Sarai Racey and Dionne C. Gesink


Abstract:

**Purpose:** The addition of human papillomavirus (HPV) testing to primary cervical cancer screening provides an opportunity to employ less invasive cervical cancer screening modalities. The objective of this study was to explore the initial reaction and perception to HPV self-sampling, in the context of current barriers and facilitators to cervical cancer screening, among women in an under-screened community in rural Ontario.

**Methods:** Age-stratified focus groups were conducted with women 18-70 years of age in rural Ontario to discuss cervical cancer screening. Women were recruited using purposive sampling of under-screened women and women in the general community. Qualitative thematic analysis of focus group transcripts identified the barriers, facilitators, and role of HPV self-sampling for cervical cancer screening.

**Results:** Four focus groups were conducted with a total of 25 women. Overall, women were very positive towards HPV self-sampling. HPV self-sampling was felt to address many of the logistical (eg inconvenient clinic hours, lack of time) and procedural barriers (embarrassment, lack of social distance in a small town) to current screening practices. However, HPV self-sampling does not address barriers related to cervical cancer knowledge (eg fear of cancer). Women identified issues related to test reliability, confidence in the ability to self-collect, and education around testing that would need to be addressed prior to implementation. Generational differences were noted in the acceptability of HPV self-sampling between older and younger women.

**Conclusions:** HPV self-sampling was perceived as a facilitator for screening, and was well accepted in this rural community.
Introduction

Cervical cancer incidence and mortality has declined dramatically in Canada since the 1970s. The decline has been attributed to the introduction of the Papanicolaou (Pap) test, allowing for the early detection and treatment of precancerous lesions. Development of cervical cancer is theoretically preventable with early detection of precancerous lesions through routine screening. Despite relatively high participation in cervical cancer screening in the province of Ontario, 1 in 4 women are still not being screened in a timely manner. Women are considered under-screened if they are between 21 – 70 years of age and have not had a Pap test in the preceding three years. Reported barriers to cervical cancer screening within Canada and abroad include: embarrassment about undergoing Pap testing, discomfort with vaginal exam, discomfort with male health providers, inconvenient clinic hours and appointments, transportation, and fear of cancer. Reported facilitators for cervical screening include having a female provider and a healthcare provider recommending screening.

Cervical cancer screening is shifting towards the implementation of human papillomavirus (HPV) testing as a primary cervical cancer screening test, since persistent infection with HPV is a necessary cause of cervical cancer. HPV testing identifies women most at-risk for the development of disease by detecting the presence of HPV. Although primary HPV testing does not directly detect cancer or precancerous lesions, it is still more sensitive at identifying women with precancerous lesions as an endpoint compared to repeat Pap testing. HPV testing is only recommended in women 30 years or older due to the transient nature of HPV infections in younger women.

A major advantage to HPV testing is that it can be self-administered. Self-sampling for HPV testing is comparable to clinician-collected samples with certain assays, and a reliable alternative for women reluctant to undergo the gynecological examination required for Pap testing. Self-sampling has the potential to improve uptake and screening coverage. Acceptability of HPV self-sampling has been explored among diverse groups of women including: urban, immigrant, and hard-to-reach communities. There has been little focus on rural and remote areas for which low rates of cervical cancer screening have been reported. However, available research suggests acceptability is promising for rural populations. Understanding the contextual nuances will be important as we forge a new path forward towards the use of primary HPV testing for cervical cancer screening, and how best we can increase screening coverage.

The purpose of this study was to explore the initial reaction and perception of rural women to HPV self-sampling in the context of current barriers and facilitators to cervical cancer
screening. The results of this study will be used to inform policy makers at the Provincial level on the acceptability of HPV self-sampling, including the feasibility and potential uptake of HPV self-sampling as an alternative screening modality in an under-screened rural community.

Methods

Focus groups discussions and thematic analysis were used to explore rural women’s initial reactions and perception to HPV self-sampling, and contextual barriers and facilitators to cervical cancer screening.

Setting and participant selection:

The community of Mount Forest (population: 4,757), located in the township of Wellington North (population 11,215) in Southwestern Ontario, was identified as a community with low rates of cervical cancer screening. Wellington North is a rural county, with agriculture and manufacturing as primary industries. Mount Forest is the county seat and though it is a very small community, provides the economic, social and health services for the surrounding rural areas. The Mount Forest Family Health Team (MFFHT) is the community’s sole primary healthcare clinic and consists of 6 general practitioner physicians and 3 nurse practitioners, who provide primary, urgent, and low-risk obstetrical care to approximately 12,000 patients in Mount Forest and the surrounding area. Specialist gynecological services are available in the larger metropolitan community approximately an hour away.

A partnership was established with the MFFHT, with the joint intention of improving cervical cancer screening among women within the community. Healthcare providers were not involved in the recruitment, conduct, or analysis of the focus groups. Participant identity was anonymous and the data were treated confidentially.

Focus groups were conducted to discuss cervical cancer screening, in addition to breast and colorectal screening. Participants were recruited using a purposive sampling approach. The clinic’s database was used to identify women 18 – 70 years of age who were over-due for cervical cancer screening based on not having a recorded Pap test in the preceding 3 years. Fifty women under-screened for cervical cancer were selected at random to receive an invitation to participate in a focus group. The number of invitations and the use of random selection were used to decrease administrative burden while purposively targeting under-screened women. In addition, an attempt was made to reach women in the wider community by posting flyers advertising the focus groups at local businesses. Potential participants registered for a focus group by calling reception at the clinic, and were compensated financially ($75) for their time. Younger women (18 – 29) approaching the age
recommended for HPV testing were invited to participate in the focus group discussion because they likely have already participated in cervical cancer screening programs centered around Pap testing and would be aware of both current community barriers to cervical cancer screening and future barriers to HPV testing, which are important to understand from longer term screening program implementation perspectives.

Data collection and analysis:

Six focus groups were offered over 2 days in April 2012 at the Mount Forest health clinic. Four focus groups were offered in the evening and 2 over the lunch hour. Participants were separated by age (18 – 39 and 40+) to group together women who were eligible for a similar number of cancer-screening tests. We also wished to capture women in their childbearing years together as they may have different experiences with cervical cancer screening related to pre-or post-natal health screening and different health priorities, barriers, and facilitators compared to older women.

Two trained female researchers (myself and a member of the UNS Provincial Research Team) from outside the community, with no prior relationship with participants, facilitated all focus groups using a semi-structured interview guide. After an introduction to the study and consent process, participants were asked to identify barriers and facilitators to cervical cancer screening, based on their personal and community knowledge. Women were then provided with a brief information session about HPV self-sampling followed by focused questions about initial perceptions (Eg do you think that women who currently don’t get screened using a Pap test would use an HPV self-test? What issues or concerns do you see arising from using an HPV self-test kit?), and how it might be accepted at the individual and community level if offered (Eg do you think that HPV self-testing should be piloted in your community?).

All focus groups were voice recorded and transcribed verbatim. Thematic analysis was used to code and identify emergent themes. Coding was done using NVivo qualitative data analysis software, QSR International Pty Ltd. Version 9, 2010. All transcripts were read 3 times. The first reading identified all possible codes related to HPV testing and cervical cancer screening, and was conducted by 2 researchers to facilitate crosschecking of codes. Any disagreements in coding were resolved with consensus building during the code crosschecking process. These codes were aggregated into themes. Emergent coding was used to allow all themes to be derived from the data. The second reading re-examined the transcripts for identified themes and allowed other potential themes to emerge during this iterative coding process. The third reading of the transcripts identified key quotes to support themes, and looked for minor, absent, or differences in themes between focus groups. At the conclusion of
the analysis, researcher reflection was conducted to explore potential researcher bias and impact on data interpretation to help strengthen the validity of the findings. The research ethics board at the University of Toronto approved this study (application reference: #28091).

Results:

Four focus groups were conducted, 3 with women 40 years of age or older (FG1-3), and 1 with younger women aged 18 – 39 years of age (FG 4). Focus groups comprised 5 to 9 participants each, with a total of 25 participants. Focus group discussions lasted 1 to 1.5 hours and all women participated in the full length of the focus groups. We have arranged our themes to focus on the use of HPV self-sampling and using a vaginal swab as an alternative primary screening test for women 30 years and older. Barriers and facilitators to screening are discussed within each of these themes for context.

Role for HPV Self-sampling:

**Addressing logistical barriers:**

Women’s positive response to HPV self-sampling was primarily directed at the convenience it could offer by overcoming barriers related to the process of getting screened. Logistical barriers encompassed the themes: *not having time to go to the doctor, inconvenient clinic hours and perceived difficulty of booking and attending appointments.*

Women identified that competing priorities, such as childcare and work responsibilities, prevent women from having time go to the doctor. Most often competing priorities were raised by the older women about the difficulties younger women face today in balancing work, child rearing, and having time to take care of themselves (Table 4.2.1 – 1.a). ‘*Not having time to go to the doctor*’ was perceived to be a major barrier for women and self-sampling was perceived as a way to overcome this barrier (Table 4.2.2 – 2.d). Younger women verified that they did not have time to go to the doctor due to work constraints (Table 4.2.1 – 1.b), but did not identify child rearing as a competing priority. However, few women in the focus group had young children.

Difficulties with timing of appointments due to ‘*inconvenient clinic hours*’ and ‘*perceived difficulty of booking and attending appointments*’ were felt to hinder women’s ability to get screened. Women generally felt that accessing the health care system was inconvenient, and that improving convenience through alternative appointment times or being able to access self-sampling without having to make an appointment might alleviate this barrier (Table 4.2.1 – 1.c). Self-sampling was viewed as a convenient alternative (Table 4.2.2 – 2.b and 2.c) that would
reduce the dependency on fitting into a provider’s schedule and clinic processes (Table 4.2.2 - 2.a and 2.e).

**Addressing procedural barriers:**

HPV self-sampling was perceived to address barriers to the medical procedure (gynecological examination) required for Pap testing. There were a number of themes related to the procedural aspect of screening including *embarrassment, emotional discomfort, physical discomfort,* and *lack of perceived social distance.*

*Embarrassment* was a key barrier that touched on women’s emotional feelings of discomfort with the intimate procedure (Table 4.2.1 – 1.d). Self-sampling was felt to remove the *embarrassment* and *emotional discomfort* that women experienced, by removing the need for another person to perform the exam (Table 4.2.2 – 2.f and 2.h). The perceived discomfort towards Pap testing was enough to stop women from pursuing screening. Critical to note is that this perceived or experienced discomfort (physical or emotional) outweighed the perceived benefits of screening. Self-sampling could provide a more comfortable physical and emotional option, which could address the procedural barriers and be an important facilitator for under-screened women (Table 4.2.2 – 2.g).

During the majority of the focus groups, the themes of embarrassment and discomfort were found in conjunction with the theme ‘Lack of perceived social distance’, meaning feeling a *lack of privacy* and *anonymity* with their healthcare provider. Often in small communities there is little or no separation between the professional and social relationship that a patient has with their healthcare provider. There is no true privacy in this environment because physicians and other health staff are seen under professional circumstance, but are also integrated into their social network (Table 4.2.1 - 1.e). Self-collection was thought to address this barrier by providing “anonymity” (Older women FG1). The ‘lack of social distance’ was primarily identified as a major theme for the older women’s focus groups, and was absent in the younger women’s discussions. Particularly for older women, the ability to self-collect could aid in reducing the physical intimacy currently needed for cervical cancer screening and thus preserve the interpersonal privacy needed to maintain comfort in social relationships and situations (Table 4.2.2 – 2.i and 2.j).

Overall, women were supportive of the prospect of being able to self-sample, and perform self-sampling in their own home. “Yeah. If that’s something I could do at home in my own bathroom and send it off, I’d be much more inclined to do that then” (Older women FG3). The characteristics of self-sampling were perceived to overcome many logistical and
procedural barriers experienced by women in the community and would facilitate cervical cancer screening.

**What the HPV test does not address:**

HPV self-sampling did not address the cervical cancer knowledge barrier. More specifically, the HPV test did not address: ‘fear of cancer’, ‘the lack of awareness about screening’ and ‘waiting to see a doctor until there is something acutely wrong’. The fear of cancer, or finding cancer, was a predominant barrier for accepting or seeking screening. Women perceived that the fear of cancer in their community was rooted in misinformation or a lack of knowledge about cancer survival and treatment. Part of this misinformation included that women perceived cancer to be more prevalent than expected. The perceived prevalence distortion arises from the highly connected nature of social networks in small communities (Table 4.2.1 – 1.f). By knowing personal information, not only about persons proximal in their social network, but also about persons that are socially distant, leads to increased perception of cancer risk.

The lack of knowledge about cancer extended to a ‘lack of awareness about screening’ and the role of screening in preventing cancer and the importance of early detection (Table 4.2.1 – 1.g). Due to this lack of awareness about the importance of early intervention and prevention, women perceived that many in their community do not use medical services unless there is something acutely wrong (Table 4.2.1 – 1.h). This is evidence of misunderstanding the purpose of screening. The lack of preventative healthcare behavior and the fear of cancer are barriers to cervical cancer screening that HPV self-sampling or an alternative screening modality do not address.

**Barriers to HPV self-sampling**

Despite many positive considerations towards HPV self-sampling, women did raise two potential barriers: trusting the reliability of the test and confidence in the ability to self-sample properly.

Trusting the reliability of self-sampling was the biggest barrier identified for using HPV self-sampling. Women’s concerns focused on the reliability of the test and whether a test using self-sampling would be accurate (Table 4.2.2 – 2.m and 2.o). There were also concerns about self-efficacy and the ability to self-sample compared to a healthcare provider “There’s always the disadvantage too. Have you done it correctly?” (Older women FG1).

Women expressed a need for information about HPV testing and self-sampling before they would feel comfortable and confident in taking the test. Women wanted specific
information about the test, including numbers and facts that addressed test accuracy (Table 4.2.2 – 2.p). Women also wanted to know about the process involved in obtaining a test kit, collecting the sample, and what the results would mean. “I would want to know what happens if it’s not a good result” (Older women FG1).

Younger women were more reserved in their response to self-sampling and were more skeptical about the test validity compared to older women (e.g. Table 4.2.2 – 2.m and 2.p). Overall, the need for information from both younger and older women highlighted that more information and knowledge sharing about HPV self-sampling for cervical cancer screening would be needed before women would feel comfortable completing the test. Therefore, providing clear information about self-sampling and HPV testing would be needed to overcome concerns and address issues around trust, and self-efficacy.

Facilitators for Cervical Cancer Screening:

HPV self-sampling was perceived as a facilitator for cervical cancer screening by overcoming identified logistical and procedural barriers. Women also identified a number of additional facilitators for cervical cancer screening. The first was a ‘positive and meaningful relationship with healthcare provider’. This theme encompassed a women’s desire to feel that their health provider really cared for them, and that they had a meaningful relationship. The desire for a meaningful relationship was exemplified during a discussion about returning test results, which demonstrates the commitment of a provider to their wellbeing (Table 4.2.1 – 1.i). Women expressed the desire that all results from self-sampling be actively returned to them, regardless of outcome.

Linked to the concept of a meaningful relationship with the healthcare provider is the emergent theme of a ‘recall system’. Most women agreed that they wanted a due date reminder screening notice from their healthcare provider, and that at-home HPV self-sampling could act as that reminder (Table 4.2.1 – 1.j). A ‘recall’ system was perceived as an action that demonstrated care and engagement on the part of the healthcare team. Women felt that a joint responsibility for timely screening with the patient being actively responsible for health care seeking, and the provider being responsible for knowing and reminding the patient about the timing of screening. The perception of a caring relationship and joint responsibility for screening are important considerations for improving the overall uptake of cervical cancer screening.

Decreasing stigma through awareness and education:

There was much discussion about the lack of open dialogue about cervical cancer screening in families and society in general. There is a perception that cancer is already
stigmatized and intimate cancer sites are further tabooed due to embarrassment (Table 4.2.1 - 1.k). Encouraging open sharing of the benefits and experiences of screening could reduce fear, shame and stigma associated with cancer screening and the “unknown”.

Women perceived that increasing awareness and education would encourage open discussion of screening and foster positive perception of the benefit of screening, empowering women to seek and accept screening. Specifically, there was a desire for more information on the etiology, screening, and treatment of cervical cancer. There was a lack of discussion about the current information available through provincial and national bodies (cancer societies, ministry of health, and non-profit support groups) indicating that women are either unaware of the information available, choosing not to access the information available, not taking up or integrating the information they are exposed to, or the information available does not resonate or otherwise meet their needs.

Discussion

The rural women attending our focus groups were optimistic that HPV self-sampling would increase the uptake of, and participation in, cervical cancer screening by addressing the embarrassment and discomfort of current screening modalities. In addition, self-sampling would decrease intimate contact with providers, allowing the rapport between patients and provider to be maintained while simultaneously facilitating privacy for those patients whose provider is also part of their social interactions, as is often the case in small communities.

HPV self-sampling will not address the knowledge barrier that impacts decisions and intentions around cervical cancer screening. Misinformation and lack of knowledge, combined with perceived lack of risk for cervical cancer, low importance of preventative behaviors,³⁸⁻¹² and the belief that screening is not needed in women who feel healthy⁹ reduce the likelihood that a woman will decide to participate in cervical cancer screening. In addition, the perception of high cancer prevalence in the community, leading to fear and avoidance of screening, will need to be addressed as a potential barrier in small inter-connected communities.³⁴

The barrier associated with the social relationship between patient and provider is significant in small communities. The issue of social relationships impacting the patient-provider relationship has been noted previously in older women, who preferred to have someone other than their local healthcare provider perform intimate screening tests, because their local healthcare provider was also their neighbor and friend.¹² The perceived lack of privacy or need for social distance was important for rural women in our focus groups; however, this barrier might not be an issue for women in larger urban communities. It is important to recognize the multiple roles a healthcare provider may have in the community they are serving.¹³
Furthermore, having a positive and meaningful relationship with a healthcare provider can positively impact a woman’s perspective and participation in screening.

Flexibility, choice, and patient control have previously been found to be important facilitators for cancer screening. The availability of HPV self-sampling allows providers the option of offering self-sampling, or physician-collected, screening to best suit the values and needs of their patients, while maintaining the patient–provider relationship.

Beyond addressing the embarrassment and discomfort of current cervical cancer screening practices, a major perceived benefit of HPV self-sampling was the convenience it could afford, allowing women to undergo screening on their own time at home, avoiding time constrains and inconvenient clinic hours. Many logistical barriers could be addressed from a system perspective (e.g. modifying clinic hours); however, in a rural community it may not always be possible due to limited resources.

There are potential barriers to HPV self-sampling that will need to be addressed prior to implementation. The two main barriers to HPV self-sampling identified in this study include confidence in completing self-sampling properly and perceived test reliability. Similar concerns about self-sampling test reliability and confidence in performing self-sampling have been raised in sexually transmitted infections (STI) studies and self-collection was found to be reliable and efficient. Previous studies have also found HPV self-sampling to be reliably collected.

Unexpectedly, younger women were more skeptical of self-collection and HPV testing than older women, suggesting that factual and clear messaging on HPV self-sampling may be important to younger generations as they approach cervical cancer screening age for HPV testing. This difference in skepticism with age suggests different age groups may require different screening supports, and younger women may need specific messaging about the validity of HPV testing and accuracy of self-sampling. The focus groups discussions did not include an in-depth discussion on the follow-up care needed with HPV testing and women’s perceptions of test results or their interpretation. However, participants were informed about how HPV test results are interpreted and what potential follow-up is necessary, as a part of the information session on HPV self-sampling during the introduction portion of the focus group.

Education and information were identified as important facilitators for screening. There are a wide variety of cervical cancer promotional campaigns distributed by local public health and government organizations targeted at increasing the awareness and uptake of cervical cancer screening, and the link between HPV and cervical cancer, through promotional materials and websites. These public campaigns are in addition to the mass media advertising of the HPV vaccines that are currently licensed for use in Canada. Despite the availability of these resources the call for improved education and awareness of screening was resounding,
and echoed that more education about the relationship between HPV and cervical cancer is needed in cervical cancer screening messaging. Improving the access and dissemination of current high quality educational information available to women is an important consideration for improving screening participation.

Findings from this study were used to advise Cancer Care Ontario’s integrated cancer screening program about rural considerations should HPV testing be offered as a primary screening test, including: what educational materials are needed and how to disseminate them, the potential for generational differences in the acceptance of HPV self-sampling, the barriers that HPV self-sampling would address and the barriers would not address.

One of the limitations of this study was the lack of demographic information collected on participants. Specific data were not collected on ethnicity, marital status, or health insurance status. The community is largely homogeneous, which was reflected in the participants and their disclosure of information during the discussions. In addition, all participants would have had access to cervical cancer screening through universal health care coverage.

Focus group facilitators were from outside the community, which is both a strength and limitation of the study. It is inherently difficult for urban researchers, especially urban researchers who have never lived in a small community, to fully know or understand the nuances of small town rural life which can impact health care seeking behaviors, including ongoing social norms, movement patterns, lifestyle habits, social networks, and culture. This lack of intimate knowledge could result in missing important research findings or misinterpreting findings; however, participants in the focus groups spent significant time contextualizing their responses and teaching the urban researchers about life in small town, rural Ontario. This contextualization increased the thoroughness and completeness of responses, greatly aided analysis and interpretation, and reduced missed interpretations by outsiders. In effect, the time participants spent teaching urban researchers provided an insider’s perspective during the focus group, which resulted in more in-depth probing on topics relevant to the context of small town living, such as privacy, social-connectedness, and access to educational resources, and assisted in the identification of important emerging themes during the analysis.

Conclusions:

HPV self-sampling is a promising modality to improve cervical cancer screening uptake and participation among rural women, especially among those women reluctant to undergo screening because of logistical, procedural, and social barriers towards current cervical cancer screening practices. HPV self-sampling does not address lack of cervical cancer knowledge and our findings suggest significant energy should be devoted to developing cervical cancer
education materials that are easily accessible, resonant, and are applicable to rural women. These educational materials should directly address issues related to self-collection efficacy and test reliability.
References


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<td>Not having time to go to the doctor</td>
<td>1.a</td>
<td>“Do you think time is one of them? I’m just thinking of my oldest daughter too, who, um, and she’s had some problems with her cervix and then, you know, you get so busy raising kids and working or whatever that, and she would try and make her appointment and then she’d end up having to cancel her appointment because of business and all the things that came up, um, and so you keep putting it off and putting it off because there’s a difference, a different lifestyle then when I was in younger years. Like it’s, it’s chaotic. (Older women)</td>
<td>FG1</td>
</tr>
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<td></td>
<td>1.b</td>
<td>“Because people that work, you know, nine to five or aren’t off during the day, it’s real, like, you don’t want to take a day off if you’re paid hourly to go and get [Pap testing] done, right?” (Younger women)</td>
<td>FG4</td>
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<td>Inconvenient clinic hours and appointment bookings</td>
<td>1.c</td>
<td>“Scheduling [is a barrier]. … Well when your appointments have to be a certain distance out time wise, fitting it into your, your monthly calendar can sometimes be challenging. That’s, that’s one factor.” (Older women)</td>
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<td>Embarrassment</td>
<td>1.d</td>
<td>“But we’re so used to it, having babies that, so I guess I’m just kind of like…Yeah, but you’re still ashamed…Oh, I know, it’s embarrassing….Of doing it. … It’s embarrassing….it’s embarrassing to do it. … It’s embarrassing, yeah.” (Exchange between Older women)</td>
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<td>Lack of social distance in a small town (lack of privacy)</td>
<td>1.e</td>
<td>“I think it’s different in a small town then in the bigger cities because you know your doctors more on a personal level. Your kids go to school with their kids and so it’s like ok, I’m going to go in that doctor’s office and take all my clothes off and he’s going to do that examination. It’s kind of uncomfortable. I think that stops people, you know. Even though it’s your doctor. You know. Whereas, when you live in the city, what’s the chance that you’re going to on any other level other than just your doctor? So it’s shouldn’t be uncomfortable. There’s confidentiality. There’s, that’s their job but it is, so, it’s yeah. …Mmhmm. When you hang out with your doctor’s wife, you just don’t…Yeah. [Laugh]…It’s not comfortable.” (Older women)</td>
<td>FG3</td>
</tr>
<tr>
<td>Barriers to the intention to be screened</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fear of Cancer</td>
<td>1.f</td>
<td>“But I think nowadays too, cancer in all forms is out there and it used to be that you’d know a handful of people that were dying of different forms of cancer but now… It’s every month</td>
<td>FG1</td>
</tr>
</tbody>
</table>
you know of someone. You might not be very close to them but it’s family members and acquaintances and friends that are dying of different forms of cancer. Like, it’s a real epidemic now and I think we’re becoming more aware that we should be screened, early prevention is the key”…“But doesn’t that also make us think the odds are higher of bad news? It works that way as well. It should exactly be as you’re saying, that people get screened, but …If you’re finding out something you don’t want to know….Our prevention is fairly limited…Fear…Yeah. “ (Older women exchange)

<table>
<thead>
<tr>
<th>Lack of awareness</th>
<th>1.g</th>
<th>“There’s not enough awareness for, if like, different kinds of cancer. People don’t even think about it. Like, they don’t learn too much about it in school, right? In high school or anything. There’s not much teaching, teaching on, like, I don’t even remember learning that in health class. You learned a lot. Do you remember? “ (Younger women)</th>
<th>FG4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lack of preventative health care behavior</td>
<td>1.h</td>
<td>“I think you are still going to have the women that are headstrong about it, right? Like that lady that I know. Why am I, why would I do it if there’s nothing wrong with me, right?…” (Younger women)</td>
<td>FG4</td>
</tr>
</tbody>
</table>

**Facilitators**

<table>
<thead>
<tr>
<th>Positive and meaningful relationship with care provider</th>
<th>1.i</th>
<th>“Yeah. I think a phone call with results, no matter what the results are, would be very helpful because it just shows that the efforts’ being made and you know that the results have been read, you know that someone’s looked at them and that they’ve not just gone off in a file on a desk in a pile somewhere. (Older women)</th>
<th>FG3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Re-call system</td>
<td>1.j</td>
<td>“But what about at the doctor’s office. I keep thinking back again to that whole thing about getting your notice from the vet. I’m thinking, well, again, if it was all in their little computer and it popped out and said you needed to have your blood pressure taken every three months or and you needed this Pap test, you know. And if it all popped out and they might take another staff and that, to make the phone calls and that but if they constantly were […]…Well, I mean, you know, you’re due for your, your check-up, you know. And a reminder that, you know, it, according to our records with, I mean it can’t, on a, really, on a computer. And how much is the stamp? You’re saying, you know, like maybe with mail. Mind you that’s, that’s why we’re, if they can afford the stamp…[Laughs]” (Older women)</td>
<td>FG2</td>
</tr>
<tr>
<td>Decreasing stigma through awareness and increasing awareness through education</td>
<td>1.k</td>
<td>“It’s part of looking after yourself and don’t think that you’re the only one who’s ever going to do it because chances are half the people in the room have done the same thing [had a Pap test]. So, it’s not, don’t be so shy and embarrassed and it’s all hush-hush. … Yeah, get rid of the stigma.” (Older women)</td>
<td>FG1</td>
</tr>
</tbody>
</table>
### Table 4.2.2: Identified themes for the role of self-sampling and potential barriers identified by rural women

<table>
<thead>
<tr>
<th>Theme</th>
<th>Quote ID</th>
<th>Quote</th>
<th>Focus Group ID</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Addresses logistical barriers</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Improves convenience</td>
<td>2.a</td>
<td>“Or if you only have daytime appointments at your doctor’s office and you can get a prescription over the phone and just pick up [self-sampling kit] at a clinic. “ (Older women).</td>
<td>FG3</td>
</tr>
<tr>
<td></td>
<td>2.b</td>
<td>“There’s also, I think about the convenience and the, uh, those yeast infection commercials. It’s all about convenience and, um, I think that [self-collected testing] would appeal to a huge crowd.” (Older women).</td>
<td>FG1</td>
</tr>
<tr>
<td></td>
<td>2.c</td>
<td>“People may wonder too, like, you know because there’s so much advertising. Do I, would I, could I? And then it’s always in the back of your head so if it was easy to access, you’d think, Oh, that’s [self-collected testing] easy” (Older women)</td>
<td>FG1</td>
</tr>
<tr>
<td></td>
<td>2.d</td>
<td>“I know for myself, our youngest daughter, she has two girls and she has a fulltime job and she travels so she’s up and gone maybe at six o’clock in the morning and she doesn’t get home until six or seven at night. Where she could do that and send if it, well if it come back and there was something the matter, she would look into it.” (Older women)</td>
<td>FG2</td>
</tr>
<tr>
<td></td>
<td>2.e</td>
<td>“I think you are still going to have the women that are headstrong about it, right? Like that lady that I know. Why am I, why would I do it if there’s nothing wrong with me, right? Like, you’re going to have headstrong people but if you have people that like, still want to get it [screening] done but don’t have the time or don’t want to go to the doctor’s office and get it done, right, I think that it would be a success in that way…” (Young women)</td>
<td>FG4</td>
</tr>
<tr>
<td><strong>Addresses Procedural Barriers</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Addresses embarrassment discomfort with physical exam</td>
<td>2.f</td>
<td>“It’s the part you don’t have with you here in the box [self-collection kit]. It’s the other part that’s the problem. It’s not the wee sticky thing…. [Laughs]…Getting up on that table. [Laughs]…Yeah.” (Older women)</td>
<td>FG2</td>
</tr>
<tr>
<td></td>
<td>2.g</td>
<td>“I think this [self-collected testing] is an easy, like, slide into. They might. Realizing that, you know, [Laughs] it’s not as uncomfortable as that [Pap] test.”</td>
<td>FG2</td>
</tr>
</tbody>
</table>
There’s got to be some tests that aren’t uncomfortable, you know. That they, it might just swing them.” (Older women).

| 2.h | “A lot of people would rather do that [self-collected HPV test] than go on a, you know, spread for the doctor.” (Older women) |
| 2.i | “When I wasn’t going [to the doctors for a Pap test] I was feeling guilty so I would say yeah, that [self-collected HPV testing] would have been a nice thing” (Older women) |
| 2.j | “I would have [used self-collected HPV testing] that would have seemed a good, proactive thing for me to do instead of avoiding my doctor” (Older women) |
| 2.k | “So, if you can say, if you don't have time to go see the doctor, then try [self-collection], like you know what I mean? I don't know, it's like your first step to health” (Older Women 180412 pm) |
| 2.l | “If they're not going to come in for a physical and they're not going to get a [Pap test], I mean if they did this, then at least they're doing something” (Older women) |

**Potential Barriers**

| 2.m | “The thing that I’d be skeptical about is what, is this like 100% guaranteed that this is going to catch whatever to find out if I had anything? You know what I mean? Or am I going to send it back and there’s nothing even in it [laugh]” (Younger women). |
| 2.n | “There’s always the disadvantage too. Have you done it correctly?” (Older women) |
| 2.o | “[Concerned the test would be] false” (Older women) |
| 2.p | “Like, that actually, you known, here’s the stats over the test period, not necessarily the test period but these are the stats and this is, you know, 50% did it and 50% are false or whatever” (Younger women). |
| 2.q | “I would want to know what happens if it's not a good result” (Older women) |
4.3 Objective 3: Randomized Intervention of Self-Sampling for Human Papillomavirus Testing in Under-Screened Rural Women: Uptake of Screening and Acceptability*

C. Sarai Racey, Dionne C. Gesink, Ann N. Burchell, Suzanne Trivers, Tom Wong, and Anu Rebbapragada.

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**Abstract**

**Background:** Our aim was to determine if cervical cancer screening uptake would increase among under-screened women living in rural Ontario, Canada if at-home self-collected sampling for human papillomavirus (HPV) testing was offered as a primary cervical cancer screening modality, compared to invited Papanicolaou (Pap) testing or routine opportunistic screening.

**Methods:** Women 30 – 70 years of age who were overdue for cervical cancer screening were randomized to receive either: 1) an at-home HPV self-sampling kit, 2) a reminder invitation for Pap testing, or 3) standard of care opportunistic screening. The first two arms were also asked demographic and screening history questions. Women randomized to arm 1 were asked about acceptability.

**Results:** In total, 818 eligible women were identified in a small rural community in Southwestern Ontario: 335 received a HPV self-sampling kit, 331 received a reminder letter, and 152 received standard of care. In the HPV self-collection arm, 21% (70/335) returned the samples and questionnaire and 11% (37/335) opted to undergo Pap testing. In total, 32% from the HPV self-collection arm, 15% (51/331) from the Pap invitation arm, and 8.5% (13/152) with standard of care were screened. Women receiving the HPV self-sampling kit were 3.7 (95%CI 2.2 – 6.4) times more likely to undergo screening (HPV testing or Pap testing) compared to the standard of care arm. In the HPV self-sampling arm 80% (56/70) of women who underwent self-sampling said they would be very likely to choose self-sampling in the future.

**Conclusions:** Providing self-sampling for HPV testing was more effective than sending reminder letters to increase screening coverage in under-screened women.
Introduction

Cervical cancer is preventable with appropriate screening, and Papanicolaou (Pap) cytology testing has dramatically reduced the incidence of and mortality from cervical cancer in Canada, with age-standardized incidence decreasing 58% between 1972 and 2006 (1). Despite universal access to screening, in 2013 there were approximately 1,450 new cases, and 380 deaths from cervical cancer in Canada (2). Women who remain at greatest risk for cervical cancer are those who do not undergo routine screening (3, 4).

In 2011, the rate of cervical cancer screening in the province of Ontario, Canada, was only 64.9% for women 20-69 years of age over a three-year period (5), well below the provincial population target of 85%. Low rates of screening have been observed across both urban and rural Ontario(6). The goal of our research is to explore alternative screening strategies to improve cervical cancer screening participation among inadequately screened women living in rural Ontario.

Persistent infection with oncogenic human papillomavirus (HPV) is a necessary, but not sufficient, cause of cervical cancer (7). HPV testing is able to identify women most at-risk for the development of cervical cancer. Compared to Pap test cytology, HPV testing has greater sensitivity for the detection of pre-cancerous lesions (8-10), and evidence suggests that HPV testing leads to earlier detection of cervical lesions (11, 12). In addition, increasing HPV vaccination will impact the utility of cytology-based primary screening due to the decline in HPV prevalence resulting in a decreased risk of cervical dysplasia and invasive cancer, and the need to re-examine screening frequency(13). Cost-effectiveness models have found that strategies that employ primary HPV testing, with or without reflexive cytology, are more cost effective than cytology alone (14, 15). Increasingly, HPV testing has been recommended as an alternative to Pap cytology testing for primary cervical cancer screening in women 30 years of age(16-19).

Currently in Ontario, cervical cancer screening is opportunistic and usually conducted in a primary care setting. The Ontario cervical screening guidelines were updated in 2012 to recommend Pap testing for women 21 – 69 years of age, every three years, with the suggested use of HPV testing in women 30 – 69 years of age(18); however, HPV testing is currently not funded. Prior guidelines recommended screening every two to three years after three consecutive negative annual tests.

The introduction of HPV testing provides an opportunity to explore self-sampling strategies. Self-collected samples have been found to be as accurate as physician collected samples for use in HPV testing (20-23), especially when using PCR based HPV test assays (24)(25). HPV self-sampling has the potential to address many of the reported barriers to
current cervical screening, including: dependence on clinic hours (26) (27), transportation, discomfort with gynecological exams (28), and embarrassment (27). Amongst predominately urban women, at-home HPV self-sampling was found to have a two-fold increase in cervical cancer screening participation (29). HPV self-sampling has the potential to address sub-optimal levels of cervical cancer screening (30), particularly in rural populations where many of the barriers to cancer screening exist (31, 32).

HPV testing is a promising alternative strategy to Pap cytology for primary cervical cancer screening (33), with self-sampling having the potential to increase uptake (34). The primary objective of this study was to determine if cervical cancer screening uptake would increase among under-screened women living in rural Ontario, Canada if at-home HPV self-sampling was offered as a primary cervical cancer screening modality, compared to an invitation for Pap cytology testing or no intervention (standard of care opportunistic screening). We also measured acceptability of at-home HPV self-sampling and HPV positivity for this rural population.

**Methods**

**Setting**

This study was conducted between October 2012 and July 2013 in the rural community of Mount Forest in the township of Wellington North in Southwestern Ontario, where low rates (between 56% - 60% of eligible women screened in 2009) of cervical cancer screening have been observed (6). This study was conducted in consultation with the local family health team (FHT) who are the sole primary care providers for the entire region, servicing approximately 12,000 patients. The FHT was comprised of 6 general practitioners and 3 nurse practitioners. The township of Wellington North is a rural region comprised of small towns, where the major industries are manufacturing and agriculture, and mean family income is below the provincial average (35).

**Study Design**

We conducted a pragmatic randomized intervention study targeting under-screened women 30 – 70 years of age. The Clinic identified under-screened women through their electronic medical record (EMR) system. All Canadian residents have access to universal health care insurance administered by the province, unless they decline the insurance for personal reasons. Women were considered eligible for the intervention if they: 1) had a current Ontario Health Insurance Program (OHIP) card, which the majority of active and enrolled patients possessed, and 2) were overdue for cervical cancer screening, which was defined as not
having had a Pap test recorded in the preceding 30-months. Under-screened was redefined to 30-months since their last screening test to maximize the number of women who were under-screened and destined to be under-screening during the study period as the clinic had up to a 6-month wait time for routine cervical cancer screening appointments.

Women were randomized to one of three interventions: 1) an at-home HPV self-sampling kit; 2) an invitation for Pap testing; or 3) standard of care opportunistic screening. Standard of care opportunistic screening entailed women seeking cervical cancer screening through their own initiative, with or without prompting from a health care provider during a prior medical encounter.

Simple randomization was done using a random number generator. Allocation was blinded using a 1:1 ratio for intervention arms 1 and 2 of the study; the standard of care (control) arm consisted of the remaining eligible women not assigned to an active intervention.

Due to constrains in the EMR final eligibility was determined post-randomization. Women were excluded if they resided in a long-term care facility, had a past medical history of a hysterectomy, or another medical contraindication, an invalid mailing address, or had an inactivated medical chart (a standard practice when patients leave the clinic). Age and post-randomization eligibility between arms was used to assess the similarities of the groups.

**HPV self-sampling test arm:**

Women in the HPV test arm received a study information letter from the health clinic two weeks prior to receiving the at-home HPV self-sampling kit. The letter informed women about the study, and provided them the option to opt-out. The at-home HPV self-sampling kit contained a vaginal (Dacron®) swab, collection tube, annotated pictorial instructions, a self-administered questionnaire, an information sheet on HPV and cervical cancer screening, and clinic-addressed return envelope. The self-administered questionnaire asked about acceptability, preference for future screening, demographics, and screening history.

The questionnaire was constructed using demographic and screening barrier questions developed for a provincial wide cancer screening survey (unpublished). HPV risk factors, acceptability, and screening preference questions were amended from previous acceptability studies(36, 37), and HPV knowledge was assessed using a previously developed knowledge scale(38).

A reminder phone call was placed to non-responders one month after distribution of HPV self-sampling kits. Only active clinic patients, women who were enrolled with the clinic or had visited the clinic in the last 24 months, received a reminder call. A standard message script was used.
All women who participated in the HPV self-sampling had their test result recorded in their medical chart. Women who tested negative were provided their result by mail. All women who tested positive for high-risk HPV were notified by phone and/or mail as soon as possible to book a follow-up appointment. In both the HPV self-sampling arm and the Pap invitation arm, the primary care provider followed women who presented for Pap testing, as per standard clinic practice.

**Invitation for Pap testing arm:**

Women in the Pap testing arm were sent an invitation letter for Pap testing that asked women to call their doctor’s office to book an appointment. In addition, they were provided with a self-administered questionnaire and information on HPV and cervical cancer screening. The self-administered questionnaire asked about demographics and screening history. After a minimum of one month from the invitation date women who had not responded were contacted by phone by the clinic’s reception to follow-up and book an appointment if possible.

**Control arm:**

Women in the opportunistic screening arm standard of care were not contacted during the study period. At the completion of the study, all women in the control arm who had not undergone Pap testing were mailed an invitation for Pap screening.

**HPV testing and follow-up:**

Self-sampling was performed with a Dacron swab in 2mL of PreservCyt transport media. The Ontario Public Health Laboratories performed all HPV testing using a linear array assay targeting both HR-HPV (16,18,31,33,35,39,45,51,52,56,58,59,68,69) and LR-HPV types (6,11,26,40,42,53,54,55,61,62, 64, 66,67,70,71, 72,73,81,82,83,84,89) (39). Detection of human β-globin was measured in separate PCR assay to assess DNA sample quality. The research ethics board at the University of Toronto approved this study (reference: #28091).

**Outcomes measures and analysis**

The primary outcome measure was the uptake of cervical cancer screening (HPV self-sampling or Pap smear) between the three arms. Screening with HPV self-sampling was recorded at the time of test submission. Pap test completion was recorded from the medical charts at the end of the study period for all eligible women in the study. A modified intention-to-treat analysis was used for all post-randomization eligible women to calculate the relative response rates (RRs) using log-binomial regression for each arm, with 95% confidence
intervals (CIs). Differences in demographic characteristics and screening history between questionnaire respondents in the HPV testing arm and the Pap test arm were explored using Fisher’s Exact Test or ANOVA (all tests were two sided with level of significance p<0.05).

The secondary outcome of acceptability of HPV self-sampling was measured using three acceptability parameters: ease of self-sampling, confidence in self-sampling, and comfort with self-sampling. Each parameter was scored on a 9-point Likert scale. The overall acceptability score was the mean sum of the three acceptability parameters, reported with 95% CIs. Reliability of the acceptability parameters was examined using Cronbach’s alpha (40, 41). Having a mean score ≥80% was classified as accepting, otherwise women were considered to be hesitant towards self-sampling. The acceptability cut-off was based the mean score data distribution (Appendix 8) Logistic regression analysis explored acceptability as it related to age, prior screening history, HPV knowledge, education, income, and reproductive history. In addition, women were asked if they would recommend HPV self-sampling to family or friends, if they would elect to do it again in future, and to report their preferred delivery of HPV testing.

Sample size calculation:

We aimed to enroll a minimum of 300 women in each of arms 1 and 2, with a minimum of 100 women in the control arm. Sample size was based on 80% power to detect a difference of 10% between the arm 1 and arm 2, based on estimated uptake of 20% in the Pap test arm. The smaller control arm maintained adequate power to detect a larger difference (of greater than 15%) relative to arm 1. Estimated screening rates for arms 1 and 2 were based on a previous meta-analysis of similar comparisons (29).

Results

Identification and randomization

In October 2012, 964 women were identified as under-screened in the clinic: 400 women were randomized to receive at-home HPV self-sampling kits, 400 women to receive Pap test invitation letters, and 164 women to receive the standard of care (controls) (Figure 4.3.1). After adjusting for eligibility a total of 818 women were included in the study: 335 received an HPV self-collection kit, 331 received a reminder letter, and 152 received the standard of care (Figure 4.3.1). No women contacted the clinic to opt-out. Age and post-randomization eligibility was well balanced between the three arms.

In the HPV self-sampling arm, 21% (70/335) returned the self-collected samples and questionnaire and 11% (37/335) opted to undergo Pap testing at the clinic such that in total, 13

Appendix 8 Exploratory and sensitivity analysis for the HPV self-sampling pilot study
32% were screened after receiving a HPV self-sampling kit. Over 60% of the women (43/70) returned the HPV self-sampling kit in the first month. All non-responders active in the clinic in the HPV test arm received a reminder phone call. All women who tested HPV positive were contacted, and received appropriate follow-up care by their primary care provider.

In the Pap test arm, 15.4% (51/331) accepted the invitation for Pap testing. Due to administrative constraints, only 66 (20.0%) women received a reminder phone call. A sensitivity analysis found that receiving a reminder phone call was not associated with undergoing Pap testing (OR=0.8, 95% CI 0.4 – 1.8). In the control arm, 8.6% (13/152) underwent opportunistic Pap testing as standard at the clinic.

In total 171 women received screening (20.9%) in the study. Women receiving the HPV self-sampling kit were 3.7 (95%CI 2.2– 6.4) times more likely to screen (either by HPV or Pap test) compared to the control arm. Women receiving an invitation for Pap screening were 1.8 (95% CI 1.0 – 3.2) times more likely to screen compared to the women who received the standard of care, though this increase was not statistically significant. Women receiving the HPV self-sampling kits were 2.1 (95%CI 1.5-2.8) times more likely to participate in screening (either by HPV or Pap test), compared to women who received a Pap test reminder letter. There was no difference in Pap screening uptake between the assigned HPV or Pap test arms (p=0.097). The mean age of women screened was similar across all three arms (p=0.4; Figure 4.3.1).

In an underpowered exploratory sub-analysis solely examining the uptake of HPV self-sampling, HPV testing uptake remained significantly higher than the control arm (RR = 2.4 95%CI 1.4 – 4.3); however, no significant difference between the HPV self-sampling and clinic-based Pap intervention arms was found (RR=1.4 95%CI 0.98 – 1.9).

**Questionnaire analysis:**

A total of 100 women completed the questionnaire, 76 from the HPV self-sampling arm and 24 from the Pap invitation arm. The two arms of respondents were similar in age, marital status, ethnic background, education, and income (**Supplement Table 4.3.1**)\(^{14}\), although caution should be used in interpreting statistical results due to a small sample size. Most participants (93/97, 95.9%) reported having a family doctor, and over 60% (59/92) of participants had visited their family doctor in the last two years.

Several risk factors for HPV infection were examined and found to be similar across the 100 respondents in the arms. Notable was the high percentage of lifetime cigarette smokers

\(^{14}\) There were two variables that varied significantly (p=0.04) between respondents in the Pap test and HPV self-sampling arm: distribution of lifetime sexual partners and employment status.
among the study participants (63.3%) and the 29.3% of women who reported greater than six lifetime sexual partners (Table 4.3.1).

Lifetime cervical cancer screening was very high, with all but one woman reporting a previous Pap test (99.0%). Having a Pap test three or more years ago was reported by 62.2% of women, with an additional 8.2% unable to recall the date of their last Pap test.

In the HPV self-sampling arm, of the 76 participants, 42.9% of women reported they would not have been screened for cervical cancer if they had not received a self-sampling kit at home (Table 4.3.2 and Supplemental Table 4.3.2). Women reported that they decided to take the HPV self-sampling because it was delivered to their home (84.3%), and they were able to take the test at home (62.9%). Over 90% of women indicated that if they received a positive result they would follow-up as needed.

Respondents were similar to underlying populations in regards to distribution of health care provider (p=0.2); however, HPV self-sampling arm respondents had a slightly older mean age (53.6 years vs. 50.7 years, p=0.04) compared to the sampled population (no significant difference in mean age for the Pap test arm p=0.4).

Acceptability and Future Use

The acceptability parameters had good internal validity and correlation (α= 0.78). The mean acceptability score was 92.6% (SD: 1.5), among the 70 women who elected to undergo self-sampling. The majority of women (89.7%) who completed the questionnaire found HPV self-sampling to be acceptable. Bivariate and multivariate analysis revealed no significant characteristics (age, employment, income, education, marital status, screening history, or HPV knowledge) associated with acceptability. Eighty-eight percent responded that they would recommend HPV testing to a family member or friend, and 90% said they would be likely to use HPV self-sampling in the future. Women also reported that they would prefer to receive an HPV test by mail (78.6%), but were open to receiving HPV testing through other means (Table 4.3.1). Six women in the HPV self-sampling arm completed the questionnaire without submitting a sample for HPV test. The women’s questionnaire responses were included in the overall analysis, as a sensitivity analysis concluded there was no difference between women who did or did not submit a sample for testing. However, questions on acceptability were excluded as they were designed specifically for women who had experienced self-sampling.

HPV Positivity

Among women who underwent HPV testing, 5.7% (4/70) were positive for high-risk HPV, and an additional 12.9% (9/70) tested positive for low-risk HPV (Table 4.3.3). The mean
age of HPV infection women was 48.3 years of age, which was younger than women who tested HPV negative at 54.7 years of age (p=0.05). The self-collected specimens were of high quality with 69/70 being β-globin positive.

Discussion

In a rural community in southwestern Ontario, women under-screened for cervical cancer were three times more likely to participate in cervical cancer screening when offered HPV self-sampling kits compared to women who received no intervention, and twice as likely compared to women who were invited to undergo Pap testing. There was no statistically significant difference in screening uptake between the Pap reminder letter and standard of care arms.

The absolute uptake of cervical cancer screening was 32% of women in the HPV self-sampling arm, 15% in the invitation for Pap test arm, and 9% in the control arm electing to undergo screening. For HPV self-sampling alone, uptake remained significantly higher compared to the standard of care.

The women included in this study all had access and opportunity to be screened for cervical cancer through regular visits to the health clinic, and yet roughly 40% reported they would not have been screened had they not received the HPV self-sampling kit at home. In addition to the prior success HPV self-sampling has had among marginalized and hard-to-reach populations (30), the findings from our study highlight that HPV self-sampling also appeals to women who regularly seek health care.

High acceptability of self-sampling for HPV testing was reported from all women who completed the self-sampling. A limitation was that we only measured acceptability among women who completed a test limiting our ability to generalize findings. However, our findings were consistent with a wide spectrum of population studies on acceptability of self-sampling in women who tried the test (42-45), and among women who were simply described the process(46). Assessing and maximizing acceptability will be important factors for improving screening coverage, as high levels of acceptability have not always been observed (47).

HPV positivity was found to be 6%, which was consistent with previous prevalence estimates in older women in Canada (9, 48). There were no issues with cellular sufficiency, as indicated by the presence of β-globin in all but one sample\textsuperscript{15}.

\textsuperscript{15} Our positivity was relatively low despite the use of a highly sensitive linear array assay. Low positivity could be due either to demographics (older mean age) or methodological (sample integrity) issues. The presence of β-globin in all but one sample indicated that the self-collected samples were of high integrity and there were no issues with cellular sufficiency. This led us to believe the low HPV positivity was due
The two-fold difference in the response rate between self-sampling and Pap invitation was encouraging, and similar to other study findings in urban populations (29). The absolute response rate of 32% in the HPV self-sampling arm was very promising for an under-screened population; however, the response rate also indicated that barriers remain. Future work should focus on identifying and mitigating barriers associated with HPV self-sampling. Barriers to screening may be related broadly to cervical cancer screening, preventative health care behaviors, and/or HPV testing. Barriers to HPV testing may include: lack of education surrounding HPV and cervical cancer, confidence in correctly taking the test, and whether self-sampling is accurate (50). The lack of prior awareness and exposure to HPV testing may have lead to skepticism and contributed to a lower absolute response rate, which may increase over time with increased exposure and familiarity.

Literacy and health literacy limitations may have also impacted the participant response to this study, and others, which employed written recruitment methods, as lower health literacy and education are important factors in the uptake of cancer screening (6, 51), and more prevalent in rural populations (52). Despite efforts made to mitigate literacy issues, by using simple language, pictorial instructions, and reminder phone calls, we cannot disregard the potential impact of health literacy, and it should be addressed prior to implementing at-home HPV self-sampling in areas of lower literacy (53).

Our study used a purposeful population sample of predominately under-screened rural women connected to primary health care, and as such, our findings may not be generalizable to the Canadian population as a whole. The response rate may appear small, however, with minimal encouragement were able to capture data on a group of women who do not routinely participate in screening. Reasons for non-response and uptake of screening are likely heterogeneous within the population and include women who will never elect to undergo screening. Due to data limitations, we were unable to make direct comparisons between our responders and the underlying sampled population, however we feel our findings are representative of a subset of under-screened rural women who are connected to primary care. Future work should focus on identifying and exploring the heterogeneous barriers experienced by different groups of non-responders in an effort to increase uptake of screening using self-sampling.

Another limitation is the potential for non-differential misclassification of screening status (under-, never-, regular-screener), which was ascertained from medical charts.

Approximately 30% of women self-reported having a Pap test in the last two years; resulting from either recall bias (54), or undergoing testing elsewhere. Despite being instructed to inform the clinic if they received Pap testing elsewhere, we did include ‘up-to-date’ screeners in our study, and as such, our findings may have over-estimated the effect compared to a distinctly under-screened population.

There was a change to the protocol for follow-up phone calls to women in the Pap testing arm during the study. Only 20% of the women in the Pap invitation arm received a follow-up phone call due to a shortage of clinical resources. However, sensitivity analysis indicated that this deviation in the protocol did not impact the uptake of screening in this arm. Reminder phone calls were not standard practice at the clinic; however, the novelty of the intervention in this community sparked enthusiasm to test a potential future standard of practice of interest to the clinic should resources and time permit.

Despite a small sample size, we exceeded the 80% power to detect a significant difference in screening uptake between the three arms. A major strength of the study is that it was conducted in community partnership with primary care, using existing resources, while targeting the entire geographically dispersed population. A major limiting factor will be the cost associated with direct distribution of self-collection kits (55); however, improving uptake is one way to minimize waste.

This study adds to a body of literature that suggests home-based delivery of HPV self-sampling can positively impact the uptake of cervical cancer screening among under-screened women. Next steps include exploration of programmatic and logistical pieces needed to maximize uptake in high-risk populations, including addressing health literacy limitations, improving education and awareness, and capitalizing on the current acceptability of this testing platform.

Conclusions:

HPV self-sampling is a viable alternative delivery method of HPV testing in a rural population of under-screened women. HPV testing allows for a variety of distribution methods to suit the needs of the patient and further support patient centered care. We demonstrated that offering at-home HPV self-sampling could increase cervical cancer screening participation among under-screened women in rural settings. However, more needs to be done to identify and mitigate the barriers to screening. HPV self-sampling was acceptable to rural women who accepted the offer to screen; however, greater education and awareness is needed. Self-sampling should be considered when implementing HPV testing into cervical cancer screening programs.
Acknowledgements:
Special thank you to all the women who participated in this study. The Mount Forest Family Health Team and the Claire Stewart Medical Clinic Staff and Doctors for their support and assistance during the development and recruitment of the study. Thank you to the Ontario Public Health Labs for assistance in preparing the HPV self-sampling kits, and laboratory testing and advice. Thanks to the Under/Never-Screened Provincial Research Team for concept development and logistical assistance.

Author Disclosure Statement: No competing financial interests exist for any authors.
References:


attendees as part of RACOMIP, a Swedish randomized controlled trial. International Journal of Cancer. 2014 01 May;134(9):2223-30.
**Figure 4.3.1:** Flow Diagram of the HPV self-sampling pilot study

**IDENTIFIED (n=964)**

- HPV Test Group n=400
  - Did not meet eligibility criteria (n=65)
    - Included: missing or wrong address (48), medical exemption (9), and medical chart inactivated (8)
    - Allocated to HPV Test Group (n=335)
  - Questionnaire Participation (n=76**
    - Numbered Screened (n=107)
      - HPV Self-collected testing (n=70)
      - Pap test (n=37)
    - Screening Participation = 107/335 (31.9%)
    - Mean age of screener: 52.3 years (95%CI 50.3 – 54.2 years)**

- Pap Test Group n=400
  - Did not meet eligibility criteria (n=69)
    - Included: missing or wrong address (45), medical exemption (18), and medical chart inactivated (6)
    - Allocated to Pap Test Group (n=331)
  - Questionnaire Participation (n=24*)
    - Number of Pap tests completed (n=51)
    - Screening Participation = 51/331 (15.4%)
    - Mean age of screener: 50.1 years (95%CI 47.5 – 52.7 years)**

- Control n=164
  - Did not meet eligibility (n=12)
    - Included: medical exemption (10), medical chart inactivated (2)
    - Allocated to Control Group (n=152)

*Only 10/24 underwent Pap testing; ** 6 Women did not submit HPV self-collected sample for testing; *** Not statistically significantly different (p>0.05)
Tables

Table 4.3.1: Demographic information from questionnaire responses and medical charts from participants in the HPV self-sampling arm and Invitation for Pap testing arm.

<table>
<thead>
<tr>
<th>Demographics</th>
<th>HPV arm n(%)</th>
<th>Pap Invitation arm n(%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Submitted questionnaire</td>
<td>76</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>Women screened</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HPV Self-sampling</td>
<td>70 (92.1%)</td>
<td>---</td>
<td></td>
</tr>
<tr>
<td>Pap Test</td>
<td>---</td>
<td>10 (41.7%)</td>
<td></td>
</tr>
<tr>
<td>Mean age in years (95% CI)</td>
<td>53.6 (51.2 - 56.0)</td>
<td>50.5 (46.0 - 55.0)</td>
<td>0.55</td>
</tr>
<tr>
<td>Age distribution (years)</td>
<td>76</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>30 - 39</td>
<td>7 (9.2%)</td>
<td>3 (13.0%)</td>
<td></td>
</tr>
<tr>
<td>40 - 49</td>
<td>22 (29.0%)</td>
<td>8 (34.8%)</td>
<td>0.21</td>
</tr>
<tr>
<td>50 - 59</td>
<td>18 (23.7%)</td>
<td>9 (39.1%)</td>
<td></td>
</tr>
<tr>
<td>60+</td>
<td>29 (38.2%)</td>
<td>4 (16.7%)</td>
<td></td>
</tr>
<tr>
<td>Current health care provider</td>
<td>74</td>
<td>23</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>70 (94.6%)</td>
<td>23 (100%)</td>
<td>1</td>
</tr>
<tr>
<td>No/Unsure</td>
<td>4 (5.4%)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Last visited health care provider</td>
<td>74</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>More than 2 years / unknown</td>
<td>26 (35.1%)</td>
<td>7 (38.9%)</td>
<td>0.79</td>
</tr>
<tr>
<td>In the last 2 years</td>
<td>48 (64.9%)</td>
<td>11 (61.1%)</td>
<td></td>
</tr>
<tr>
<td>Gender of health care provider</td>
<td>76</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>51 (67.1%)</td>
<td>15 (62.5%)</td>
<td>0.79</td>
</tr>
<tr>
<td>Female</td>
<td>22 (29.0%)</td>
<td>8 (33.3%)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>3 (4.0%)</td>
<td>1 (4.2%)</td>
<td></td>
</tr>
<tr>
<td>Risk Factors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Life time smoking history (&gt;100 cigarettes)</td>
<td>75</td>
<td>23</td>
<td></td>
</tr>
<tr>
<td>Life time number of sexual partners</td>
<td>72</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>-----------------------------------</td>
<td>----</td>
<td>----</td>
<td></td>
</tr>
<tr>
<td>1 to 2</td>
<td>34 (47.2%)</td>
<td>4 (20.0%)</td>
<td>0.04</td>
</tr>
<tr>
<td>3 to 5</td>
<td>17 (23.6%)</td>
<td>10 (50.0%)</td>
<td></td>
</tr>
<tr>
<td>6+</td>
<td>21 (29.2%)</td>
<td>6 (30.0%)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Screening History</th>
</tr>
</thead>
<tbody>
<tr>
<td>Past Pap test</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Yes</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Time since last Pap test</th>
<th>75</th>
<th>23</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 years or more</td>
<td>47 (62.7%)</td>
<td>14 (60.9%)</td>
</tr>
<tr>
<td>Less than 2 years ago</td>
<td>24 (32.0%)</td>
<td>5 (21.7%)</td>
</tr>
<tr>
<td>Don't remember</td>
<td>4 (5.3%)</td>
<td>4 (17.4%)</td>
</tr>
</tbody>
</table>

Footnote: To protect the confidentiality of the participants some data has been collapsed or suppressed. *statistically significant difference based on Fisher's Exact Test or ANOVA (p<0.05)
**Supplemental Table 4.3.1**: Demographic information from questionnaire responses and medical charts from participants in the HPV self-sampling arm and Invitation for Pap testing arm.

<table>
<thead>
<tr>
<th>Demographics</th>
<th>HPV arm n(%)</th>
<th>Pap Invitation arm n(%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Submitted questionnaire</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>76</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td><strong>Current living situation</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married/living with a partner/common law</td>
<td>62 (81.6%)</td>
<td>18 (78.3%)</td>
<td></td>
</tr>
<tr>
<td>Divorced/widowed/single or never married</td>
<td>14 (18.45)</td>
<td>4 (17.4%)</td>
<td></td>
</tr>
<tr>
<td><strong>Ethnic identity</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White Caucasian</td>
<td>74 (97.37%)</td>
<td>22 (100.0%)</td>
<td>1.00</td>
</tr>
<tr>
<td><strong>Employment status</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Working full time or part time</td>
<td>43 (56.6%)</td>
<td>15 (65.2%)</td>
<td>0.04</td>
</tr>
<tr>
<td>On disability or social assistance</td>
<td>8 (10.5%)</td>
<td>4 (17.4%)</td>
<td></td>
</tr>
<tr>
<td>Retired</td>
<td>24 (31.6%)</td>
<td>2 (8.7%)</td>
<td></td>
</tr>
<tr>
<td><strong>Household income (Canadian dollars)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less than 19,000</td>
<td>5 (8.2%)</td>
<td>3 (14.3%)</td>
<td>0.34</td>
</tr>
<tr>
<td>20,000 - 49,000</td>
<td>23 (37.7%)</td>
<td>5 (23.8%)</td>
<td></td>
</tr>
<tr>
<td>50,000 - 99,000</td>
<td>22 (36.1%)</td>
<td>11 (52.4%)</td>
<td></td>
</tr>
<tr>
<td>more than 100,000</td>
<td>11 (18.0%)</td>
<td>2 (9.5%)</td>
<td></td>
</tr>
<tr>
<td><strong>Education level completed</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less than High School</td>
<td>13 (17.3%)</td>
<td>2 (9.1%)</td>
<td>0.81</td>
</tr>
<tr>
<td>High School graduate</td>
<td>25 (33.3%)</td>
<td>9 (40.9%)</td>
<td></td>
</tr>
<tr>
<td>Greater than high school</td>
<td>37 (49.3%)</td>
<td>11 (50.0%)</td>
<td></td>
</tr>
<tr>
<td><strong>Risk Factors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age of sexual debut</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>before 18 years of age</td>
<td>33 (50.8%)</td>
<td>13 (61.9%)</td>
<td>0.39</td>
</tr>
<tr>
<td>18 years or after</td>
<td>32 (49.2%)</td>
<td>8 (38.1%)</td>
<td></td>
</tr>
<tr>
<td>Life time pregnancy</td>
<td>73</td>
<td>23</td>
<td></td>
</tr>
<tr>
<td>---------------------</td>
<td>----</td>
<td>----</td>
<td></td>
</tr>
<tr>
<td>Yes 62 (84.9%)</td>
<td>19 (82.6%)</td>
<td>0.75</td>
<td></td>
</tr>
<tr>
<td>No 11 (15.1%)</td>
<td>4 (17.4%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Screening History</th>
<th>75</th>
<th>23</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is cervical cancer screening</td>
<td>75</td>
<td>23</td>
</tr>
<tr>
<td>important to a women's health?</td>
<td>75</td>
<td>23</td>
</tr>
<tr>
<td>Strongly agree</td>
<td>44 (58.7%)</td>
<td>13 (56.5%)</td>
</tr>
<tr>
<td>Agree</td>
<td>24 (32.0%)</td>
<td>7 (30.4%)</td>
</tr>
<tr>
<td>Neutral</td>
<td>5 (6.7%)</td>
<td>3 (13.0%)</td>
</tr>
<tr>
<td>Disagree/Strongly disagree</td>
<td>2 (2.7%)</td>
<td>0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Before receiving information about this study had you ever heard of HPV?</th>
<th>73</th>
<th>23</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes 54 (74.0%)</td>
<td>17 (73.9%)</td>
<td>1.00</td>
</tr>
<tr>
<td>No 19 (26.0%)</td>
<td>6 (26.1%)</td>
<td></td>
</tr>
</tbody>
</table>

Footnote: To protect the confidentiality of the participants some data has been collapsed or suppressed. *statistically significant difference based on Fisher's Exact Test or ANOVA (p<0.05).
Table 4.3.2: Information on self-sampling for HPV testing and acceptability of self-sampling among participants in the HPV self-sampling arm

<table>
<thead>
<tr>
<th>Completed HPV self-test &amp; questionnaire n(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Screening with HPV self-sampling</strong></td>
</tr>
<tr>
<td>What made you decide to take the test today?</td>
</tr>
<tr>
<td>The test came to my house</td>
</tr>
<tr>
<td>Able to take the test at home</td>
</tr>
<tr>
<td>The test was easy</td>
</tr>
<tr>
<td>Other reasons</td>
</tr>
<tr>
<td>Would you have gotten screened if the test was not mailed to you?</td>
</tr>
<tr>
<td>Yes</td>
</tr>
<tr>
<td>No</td>
</tr>
<tr>
<td>Other</td>
</tr>
<tr>
<td>Not sure</td>
</tr>
<tr>
<td>If you test positive, how likely are you follow-up as needed?</td>
</tr>
<tr>
<td>Very likely</td>
</tr>
<tr>
<td>Somewhat likely</td>
</tr>
<tr>
<td>Very unlikely/Don't know</td>
</tr>
<tr>
<td>Acceptability (≥8 being acceptable)</td>
</tr>
<tr>
<td>Acceptable</td>
</tr>
<tr>
<td>Hesitant</td>
</tr>
<tr>
<td>Would you recommend HPV self-testing to a friend or family member?</td>
</tr>
<tr>
<td>Very likely</td>
</tr>
<tr>
<td>Somewhat likely</td>
</tr>
<tr>
<td>Maybe/don't know</td>
</tr>
<tr>
<td>Unlikely/very unlikely</td>
</tr>
<tr>
<td>How likely are you to choose HPV self-testing in the future?</td>
</tr>
<tr>
<td>Very likely</td>
</tr>
<tr>
<td>Somewhat likely</td>
</tr>
<tr>
<td>Maybe/Unlikely/Very unlikely</td>
</tr>
<tr>
<td>How would you like to receive HPV self-testing in future?</td>
</tr>
<tr>
<td>Self-testing at home, delivered by mail</td>
</tr>
<tr>
<td>Self-testing at home, pick up kit at health clinic</td>
</tr>
<tr>
<td>Self-testing at family care provider's clinic (in washroom at clinic)</td>
</tr>
<tr>
<td>Provider-collected sample</td>
</tr>
<tr>
<td>Any of the above</td>
</tr>
</tbody>
</table>
Supplemental Table 4.3.2: Information on self-sampling for HPV testing and acceptability of self-sampling among participants in the HPV self-sampling arm

<table>
<thead>
<tr>
<th></th>
<th>Submitted Completed HPV self-test &amp; questionnaire n(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acceptability of HPV self-sampling</strong>&lt;sup&gt;16&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td><strong>Ease of test</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mean (95%CI)</td>
</tr>
<tr>
<td></td>
<td>&lt;8 - not easy</td>
</tr>
<tr>
<td></td>
<td>≥8 - very easy</td>
</tr>
<tr>
<td><strong>Confidence</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mean (95%CI)</td>
</tr>
<tr>
<td></td>
<td>&lt;8 - not confident</td>
</tr>
<tr>
<td></td>
<td>≥8 - very confident</td>
</tr>
<tr>
<td><strong>Comfort</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mean (95%CI)</td>
</tr>
<tr>
<td></td>
<td>&lt;8 (not comfortable)</td>
</tr>
<tr>
<td></td>
<td>≥8 (very comfortable)</td>
</tr>
<tr>
<td><strong>Overall Acceptability Score (/27)</strong></td>
<td>Mean (95%CI)</td>
</tr>
<tr>
<td><strong>Categorical Acceptability (≥8 being acceptable)</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Acceptable</td>
</tr>
<tr>
<td></td>
<td>Hesitant</td>
</tr>
</tbody>
</table>

Footnote: To protect the confidentiality of the participants some data has been collapsed. a Multiple answers possible.

<sup>16</sup> For all measures of acceptability respondent answers ranged from 1 – 9
### Table 4.3.3: HPV genotype results for all submitted self-collected samples

<table>
<thead>
<tr>
<th></th>
<th>Number of specimens</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of submitted samples</td>
<td>70</td>
<td></td>
</tr>
<tr>
<td>HPV-positive for at least one type</td>
<td>13</td>
<td>18.6%</td>
</tr>
<tr>
<td><strong>High risk Types</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>1</td>
<td>1.4%</td>
</tr>
<tr>
<td>18</td>
<td>1</td>
<td>1.4%</td>
</tr>
<tr>
<td>52</td>
<td>1</td>
<td>1.4%</td>
</tr>
<tr>
<td>45</td>
<td>1</td>
<td>1.4%</td>
</tr>
<tr>
<td><strong>Low risk Types</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>62</td>
<td>5</td>
<td>7.1%</td>
</tr>
<tr>
<td>66</td>
<td>2</td>
<td>2.9%</td>
</tr>
<tr>
<td>84</td>
<td>1</td>
<td>1.4%</td>
</tr>
<tr>
<td>54</td>
<td>1</td>
<td>1.4%</td>
</tr>
<tr>
<td>53</td>
<td>1</td>
<td>1.4%</td>
</tr>
<tr>
<td><strong>HPV Indeterminate Individuals</strong></td>
<td>1</td>
<td>1.4%</td>
</tr>
</tbody>
</table>

*Footnote: A co-infection: one participant was positive for 54 & 62*
4.3.1 Addendum to Results: Integration

Additional results that were not included in any published manuscripts, but hold relevance to the overall dissertation are presented below. Questionnaire data from the HPV self-sampling study reported on barriers to cervical cancer screening, and where women currently receive, and would like to receive, relevant health information. These findings inform what educational outreach activities might be best for disseminating information on cervical cancer screening. The findings from the qualitative strand were integrated with the questionnaire data, and provided contextual information on barriers and the importance of education in screening uptake.

4.3.1.1 Barriers to Screening:

The barriers to cervical cancer screening from the quantitative questionnaire were grouped according to the themes identified from the qualitative analysis. The top barriers women identified were: embarrassment (21.8%), unable to schedule time with their provider (16.1%), Pap testing being too uncomfortable/painful/personal (10.3%), and not feeling comfortable talking to their provider about Pap testing (10.3%) (Table 4.3.1.1). Interestingly, 48.3% of women indicated that ‘nothing stops them’ from getting screened; however, 23 (54.8%) of these women also reported not having received a Pap test in three years prior. These finding indicate that women who report not experiencing logistical, procedural, or lack of information barriers to cervical cancer screening are still not being screened. We can glean some insight through women’s comments as to what ‘other barriers’ might be preventing them from screening, which primarily includes being unable to remember when they were due for screening (Table 4.3.1.1).

The top reported barriers to screening mapped onto the key barriers and concerns raised during the focus group portion of the study (173). The top concerns included logistical and procedural barriers, as well as provider-relationship barriers, which HPV self-sampling could address.
Table 4.3.1.1: Selected barriers to cervical cancer screening from the HPV self-sampling arm and the invitation for Pap testing arm for rural women in the HPV Self-sampling Pilot Study.

<table>
<thead>
<tr>
<th>Potential Barriers to Cervical Cancer Screening*</th>
<th>Total Number of Respondents (n=87)</th>
<th>Total %</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Practical</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I can't get to the doctor's office/clinic (no transportation)</td>
<td>4</td>
<td>4.6%</td>
</tr>
<tr>
<td>I do not have a regular family doctor/nurse practitioner</td>
<td>3</td>
<td>3.4%</td>
</tr>
<tr>
<td>I can't schedule time with a doctor/nurse practitioner</td>
<td>14</td>
<td>16.1%</td>
</tr>
<tr>
<td><strong>Procedural</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>The test is too uncomfortable/painful/personal/complicated</td>
<td>9</td>
<td>10.3%</td>
</tr>
<tr>
<td>A Pap test is embarrassing</td>
<td>19</td>
<td>21.8%</td>
</tr>
<tr>
<td>A past trauma stops me from being examined</td>
<td>3</td>
<td>3.4%</td>
</tr>
<tr>
<td><strong>Intention</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I'm afraid the test will find that something is wrong with me</td>
<td>5</td>
<td>5.7%</td>
</tr>
<tr>
<td>If I am meant to die from cancer, no test is going to change that</td>
<td>1</td>
<td>1.1%</td>
</tr>
<tr>
<td>I am not worried about cervical cancer</td>
<td>4</td>
<td>4.6%</td>
</tr>
<tr>
<td><strong>Provider- Patient Relationship</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>My Doctor/Nurse did not suggest it</td>
<td>8</td>
<td>9.2%</td>
</tr>
<tr>
<td>My Doctor told me I didn't need it</td>
<td>1</td>
<td>1.1%</td>
</tr>
<tr>
<td>There is not enough time to talk about the Pap test</td>
<td>2</td>
<td>2.3%</td>
</tr>
<tr>
<td>I don't feel comfortable talking about the Pap test with my Doctor/Nurse Practitioner</td>
<td>9</td>
<td>10.3%</td>
</tr>
<tr>
<td>I avoid the Doctor because I feel guilty about not doing what they told me to do</td>
<td>4</td>
<td>4.6%</td>
</tr>
<tr>
<td><strong>Other:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nothing stops me from getting a Pap test</td>
<td>42</td>
<td>48.3%</td>
</tr>
<tr>
<td>Other:</td>
<td>11</td>
<td>12.6%</td>
</tr>
<tr>
<td>Forget to book appointment; low risk for cancer; discomfort with male provider; busy schedule; procrastination;</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Previous hysterectomy, cultural and/or religious beliefs, not speaking English well enough, and don’t know enough to decide whether to get the test, were not selected as barriers.*
4.3.1.2 Health information:

During the focus group discussion, emphasis was placed on the need for information and the role of education as a motivator for cervical cancer screening (173). During the HPV self-sampling pilot study, Women were asked about where they currently receive their information about cancer screening, and where they would prefer to receive their information about screening.

The top three places women reported receiving their information about cervical cancer screening were: from the information provided by the study (60.9%), through a health-care provider (39.1%) and through a pamphlet (19.6%) (Table 4.3.1.2).

In contrast, the top three places women reported they wished to receive their information were: directly from a health-care provider (51.1%), watching a video with pictures and verbal explanation (37.8%), general websites (31.1%). Pamphlets were frequently suggested, as were posters and government/public health websites.

This comparison illustrates the importance of the healthcare provider as an integral part of the education and information pathway for women. The use of audio/visual aids also appears to be a desired method of communicating information. It is interesting to note that many women indicated they were receiving their information on cervical cancer screening through the study materials provided. The information sheet that was supplied as a part of the HPV self-sampling pilot study was an openly available government issued pamphlet from the Internet; this demonstrates that having information available is only one part of the process and we need to focus on how best to reach and disseminate available information to women.
Table 4.3.1.2: Where women in the HPV Self-sampling Pilot Study currently receive information on cervical cancer screening and where women would like to receive information on cervical cancer screening

<table>
<thead>
<tr>
<th>Where do you receive your information? (n=92)</th>
<th>Total number of respondents</th>
<th>% of respondents</th>
</tr>
</thead>
<tbody>
<tr>
<td>By reading the information provided in the study</td>
<td>56</td>
<td>60.9%</td>
</tr>
<tr>
<td>Through a Health Care Provider</td>
<td>36</td>
<td>39.1%</td>
</tr>
<tr>
<td>Through a pamphlet</td>
<td>18</td>
<td>19.6%</td>
</tr>
<tr>
<td>Through the newspaper/magazine</td>
<td>10</td>
<td>10.9%</td>
</tr>
<tr>
<td>Through the television</td>
<td>17</td>
<td>18.5%</td>
</tr>
<tr>
<td>Through the internet</td>
<td>15</td>
<td>16.3%</td>
</tr>
<tr>
<td>Through friends and/or relatives</td>
<td>13</td>
<td>14.1%</td>
</tr>
<tr>
<td>Other: Included: Educational environment; work; through the study; friend has it and died; the clinic; doctor said to get a pap test</td>
<td>6</td>
<td>6.5%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>How would you like to receive information? (n=90)</th>
<th>Total number of respondents</th>
<th>% of respondents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Watching a video where pictures are shown and explanations are given verbally</td>
<td>34</td>
<td>37.8%</td>
</tr>
<tr>
<td>Looking at a poster where things are described with pictures and words</td>
<td>25</td>
<td>27.8%</td>
</tr>
<tr>
<td>Directly meeting with a Health Care Provider so I can ask questions</td>
<td>46</td>
<td>51.1%</td>
</tr>
<tr>
<td>Together with my partner</td>
<td>9</td>
<td>10.0%</td>
</tr>
<tr>
<td>In a small group with other women I know</td>
<td>6</td>
<td>6.7%</td>
</tr>
<tr>
<td>In a small group with other women I don't know</td>
<td>7</td>
<td>7.8%</td>
</tr>
<tr>
<td>General Websites</td>
<td>28</td>
<td>31.1%</td>
</tr>
<tr>
<td>By email</td>
<td>17</td>
<td>18.9%</td>
</tr>
<tr>
<td>YouTube</td>
<td>4</td>
<td>4.4%</td>
</tr>
<tr>
<td>Government / Public Health Website</td>
<td>20</td>
<td>22.2%</td>
</tr>
<tr>
<td>None of the above</td>
<td>6</td>
<td>6.7%</td>
</tr>
<tr>
<td>Other Suggestions</td>
<td>10</td>
<td>11.1%</td>
</tr>
</tbody>
</table>

Included: Brochure; by mail; by t.v.; got a letter; not even sure what it is; paper magazine, talk shows; sex education in school, family doctor; Prefer to be educated alone; Pamphlet in hospital or doctors office
Chapter 5: Discussion

5.1 Key Findings and Contributions

The purpose of this dissertation was to determine if HPV self-sampling could improve participation in cervical cancer screening in rural communities, with a specific focus on under-screened women. This purpose was achieved through three objectives using a mixed methods design. The first objective was to review the published literature to determine if cervical cancer screening rates were higher when HPV self-sampling was offered compared to Pap testing in under-screened women. The systematic review and meta-analysis found that overall, under-screened women were twice as likely to participate in screening when HPV self-sampling was offered compared to re-call letters for Pap testing.

The second objective of this dissertation was to explore barriers to cervical cancer screening, describe women’s attitudes towards HPV self-sampling, and identify knowledge gaps and educational initiatives that could improve acceptance and uptake of HPV self-sampling and cervical cancer screening, in under-screened women living in rural communities. In addition, factors for improving participation in the RCT were explored to help strengthen the design and implementation of the HPV self-sampling pilot study. The thematic qualitative analysis (strand 1) found barriers to cervical cancer screening grouped into three categories: logistical, procedural, and knowledge barriers. HPV self-sampling would address logistical barriers, such as attending the clinic or booking an appointment, and procedural barriers to the physical examination, such as embarrassment and lack of privacy. However, self-sampling would not address knowledge barriers, specifically a women’s fear of cancer or lack of awareness of the benefits of screening. Providing women with clear information on HPV testing and cervical cancer screening was identified as an important consideration for the HPV self-sampling pilot study.

The third objective was to determine the feasibility and acceptability of mail-out, at-home HPV self-sampling to increase the uptake of cervical cancer screening in an under-screened rural community. The pragmatic RCT pilot study (quantitative strand) demonstrated that under-screened rural women were twice as likely to be screened with the offer of HPV self-sampling compared to a reminder letter for Pap testing, and 3-times more likely to be screened compared to standard opportunistic Pap testing. The moderate overall participation in HPV self-sampling indicated that barriers to screening remain.

The systematic review and meta-analysis (objective 1) quantified a pooled estimate for the increased uptake of cervical cancer screening with HPV self-sampling, compared to Pap test reminder letters, in under-screened women. In addition, the systematic review highlighted
that there was limited evidence for HPV self-sampling uptake in rural populations, specifically in the Canadian context. The meta-analysis also provided estimates of screening uptake, which had previously been lacking in the literature. Estimated screening uptake is a key parameter for measuring cost-effectiveness of cervical cancer screening modalities. Cost effectiveness for HPV self-sampling hinges on the ability to increase cervical cancer screening participation for under-screened women, who are most at risk for the development of cervical cancer (174).

Uptake of HPV self-sampling in the meta-analysis ranged from 10.2% to 98.2% depending on geography and mode of delivery. Due to the large observed heterogeneity in HPV self-sampling uptake, pilot studies would be advisable for target populations (i.e., under-screened, hard to reach, immigrant populations, etc.) and the self-sampling delivery approach (i.e., opt-in, clinic based, or opt-out) prior to implementing self-sampling in an existing or new cervical cancer screening program (172, 175).

The qualitative strand (objective 2) provided invaluable contextual details regarding how and why self-sampling could increase participation in a rural community. Many of the logistical and procedural barriers reported had previously been identified in the literature, and appear to cut across geography and culture. However, this study was able to explore rural specific barriers to Pap testing (and perhaps other invasive screening exams). A key finding was the perceived lack of social distance and privacy in small communities with healthcare providers, which may not impact screening participation in urban areas. Self-sampling would provide women with the opportunity to undergo screening while maintaining a comfortable relationship with their healthcare provider both inside and outside of the clinic setting. This finding was an important contribution to understanding non-participation in a rural setting and how self-sampling might mitigate this screening barrier.

The qualitative study also contributed to our understanding of potential barriers women may have towards HPV self-sampling. Key issues were test reliability and confidence in one’s ability to self-sample. Knowledge building around self-sampling and HPV testing may help reduce concerns about test reliability, thereby boosting self-efficacy and increasing participation in self-sampling (176). Confidence, comfort, and ease of self-sampling were asked of women who completed self-sampling as part of the HPV self-sampling pilot study. There was a high level of acceptability among women who tried self-sampling; however, confidence in self-sampling scored the lowest on the acceptability scale. Despite any concerns women may have had, over 90% indicated HPV self-sampling as their preferred future screening method. These findings support the premise that a women’s perception about the HPV self-sampling
procedure (to be accurate, safe, protective, and acceptable) is the most predictive characteristic for their intention to participate in self-sampling (177).

Another factor related to the acceptability of self-sampling is the specimen collection device itself. Devices that appear easy to use and comfortable may be more acceptable and improve women’s confidence in self-sampling (178). There are currently a number of commercially available self-collection devices, including swabs, lavages, and brushes with similar acceptability amongst women (179, 180). Identifying, and selecting, a reliable, user friendly, and affordable self-collection device will be paramount to the success of self-sampling within an organized cervical cancer screening program.

Dissemination of information about cancer screening and HPV self-sampled testing could address general concerns toward cervical cancer screening and specific HPV test concerns regarding reliability and confidence in self-sampling. An important finding from the qualitative analysis, as one might expect, was that cancer screening promotion and cancer prevention education are important components to any screening program regardless of which cervical cancer screening test is available.

The HPV self-sampling pragmatic RCT pilot study (objective 3) demonstrated that direct mailing of HPV self-sampling kits is a feasible method for increasing participation in cervical cancer screening for rural under-screened women. Women were twice as likely to participate in screening with self-sampling compared to re-call letters for Pap testing, and three-times more likely to participate compared to standard opportunistic Pap testing. The observed relative increase in cervical cancer screening participation was predicted by the findings of the meta-analysis, and supports the use of self-sampling as a means to increase participation for rural under-screened women. However, a recent study of rural women in 11 First Nations communities in Northern Ontario found that offering HPV self-sampling improved screening uptake by 5.7%, but was not statistically significant different from Pap testing uptake (181). Overall, a lower than expected screening uptake was noted, and large heterogeneity (2.9% - 62.1%) in uptake of HPV self-sampling was observed in participant communities. The difference in these study findings support the use of implementation study designs to identify contextual elements and address potential adaptations needed to maximize feasibility, reach, and uptake of HPV self-sampling for specific under-screened populations.

The absolute participation in the HPV self-sampling pilot study was moderate with 31.9% (95%CI 27.0–37.2%) of women undertaking either form of screening in the HPV self-sampling arm (ITT) and only 20.9% (95% CI 16.7–25.7%) of women selected HPV self-sampling (PPA). These participation rates are similar to many larger studies for the uptake of
HPV self-sampling alone (PPA) (172), and for overall participation in screening (ITT) (12, 14, 19, 182). It is important to note that of the women who underwent screening in the HPV self-sampling arm, a third of these women selected Pap testing. The reasons why women selected Pap testing over HPV self-sampling were likely heterogeneous, and could include simply requiring a reminder for screening or scepticsisms of HPV self-sampling. Regardless of reasoning, the moderate uptake of self-sampling indicated that barriers to cervical cancer screening, and potential impediments to self-sampling, remain.

Overall, offering HPV self-sampling has the potential to increase cervical cancer screening participation in under-screened rural women. This dissertation contributes important findings about the potential uptake of HPV self-sampling among under-screened women, the feasibility and acceptability of HPV self-sampling for reaching under-screened rural women, how HPV self-sampling addresses reasons for non-participation, and reinforced the importance of education and health promotion around cervical cancer screening.

5.2 Limitations of this research

5.2.1 Methodological considerations for RCTs in rural settings

The HPV self-sampling pilot study would not have been possible without the support, expertise, and willingness of the Mount Forest medical community to improve community health. Community-based participatory research (CBPR) is an approach that joins the expertise of community partners with that of academic researchers, in all aspects of the research process, to create knowledge and empower change to the health and wellbeing of the community (183). CBPR approaches can strengthen rural research by mobilizing community expertise and limited community resources, and can build sustainable research infrastructure and knowledge within the community research partners.

The HPV self-sampling project employed some CBPR approaches by having an advisory group made up of medical community and academic partners. The advisory group provided valuable input into the study protocol and workflow to ensure the study and interventions (HPV self-sampling and reminders letters for Pap testing) were feasible within the clinic and community environments. The medical community partners also provided expertise on the community population. Clinic staff were engaged in the follow-up of non-responders in the Pap testing arm, by making phone calls to book appointments within their existing clinic duties. Informal sharing of preliminary findings to healthcare providers and staff helped to validate findings and engage the clinic community in the research process. In the HPV self-
sampling pilot study, the general community was not directly involved in study design, data collection, or analysis. However, findings from the qualitative strand (community focus groups) of the project were used to inform the HPV self-sampling pilot study.

Small communities tend to have limited resources, which is a major barrier to conducting research. Allowances need to be made in the study design and protocol to account for both limited human and financial resources. Using a study design that has the flexibility required to operate an intervention within the confines of the existing system is an important consideration for rural intervention research.

Pragmatic RCTs harness the benefits of randomization while allowing for ‘real world’ outcome measurements. A number of pragmatic design decision were made to accommodate the existing clinic environment and resources.

The electronic medical record (EMR) was used as a patient registry and acted as the sampling frame for the identification and randomization of women. The major advantage of using the EMR was the limited resources (myself) required to identify and confirm participant eligibility, and the ease of collecting end-point Pap testing screening data (184, 185). The disadvantage of using an EMR as a patient registry was the potential for poor data quality and lack of standardization of how patient information was stored and accessed through automated algorithms.

In RCT designs, randomization and allocation to the specific intervention arms are typically conducted at the point of recruitment into the trial once eligibility is confirmed. However, in this instance, the EMR had no standardized location for the documentation of health conditions, and the patient address was exported as a separate file. In some cases, a patient’s address was out of date, and only identified as incorrect when study letter was returned. This limitation in the EMR impacted how the randomization and allocation of women was undertaken. To accommodate this limitation, eligibility was not confirmed until after women were selected into the study. The process of randomization and allocation was completed using a two-step process. First, women who met the inclusion criteria were abstracted from the EMR and randomized, using a random number generator, to one of the three arms. Then, any ineligible women based on the exclusion criteria (i.e., long-term care address, missing address, or palliative/recently deceased) were identified through printed information from the medical chart (i.e., the address label/recruitment letter) or staff knowledge (for palliative or recently deceased patients), were subsequently excluded from allocation to the intervention arm to which they were randomized. This modification ensured that randomization was not biased based on known medical information, while ensuring only eligible women were allocated and
received intervention. Despite the limitations, the EMR was the best tool available for identifying and selecting the target study population, and it provided a platform for measuring Pap test response rate.

Ideally in a randomized study design only the intervention, or variable of interest, is modified between the active arm(s) and the control arm(s) in an effort to measure the true effect of an imposed intervention. During the implementation of the RCT pilot study a modification to the study protocol was needed to accommodate changing staffing demands. In the initial study protocol all women in the active intervention arms (HPV self-sampling or Pap reminder letter) who had not completed HPV self-sampling, or booked a Pap test appointment, at the end of one-month were to receive a reminder phone call. I completed reminder phone calls in the HPV self-sampling arm. However, to facilitate appointment bookings within the EMR the clinic staff were to complete the reminder phone calls in the Pap test reminder arm. Due to changing demands and priorities for the staff, only 20% of women received a reminder phone call in the Pap test reminder arm. A sensitivity analysis was performed and found that the protocol modification did not alter the overall findings and was representative of routine clinical conditions.

HPV self-sampling trials have employed a number of different distribution methodologies, e.g., kit collection at clinic or pharmacy, ordered on-line or by mail, or completed at a clinic or at home. One of the major advantages to self-sampling is the availability of distribution options. In this pilot study, unsolicited direct-to-participant mailing was felt to be the best distribution option to reach this geographically dispersed rural population and overcome previously identified barriers to the current clinic-based screening program, including transportation, appointment wait times, and clinic hours.

Small populations for sampling and statistical analysis are a concern for clinical research in rural and remote communities. Concerns about small sample size were addressed by using the entire female clinic population (between 30 – 70 years of age) as the study sample. Despite using every eligible woman in the community, the sample size for the study was still too small to be able to analyze secondary and tertiary outcomes with sufficient power. The small sample size issue is a learning point for conducting RCTs in small rural settings. How to boost sample size by including additional communities is something to evaluate and consider for future work. Including additional communities would also allow for potential contextual variations to be explored, which may identify important adaptations to maximize uptake of HPV self-sampling.
Conducting clinical research in rural settings can be challenging due to the allocation of limited resources, small sample sizes, and cultural differences in small-town living. Despite these challenges, it is worth the effort to modify and adapt study designs to allow researchers to continue to address important health inequalities experienced by rural populations without compromising data quality (21).

### 5.2.2 Internal validity

For qualitative studies, internal validity is assessed by exploring the credibility of findings with participants, or those who have intimate knowledge of participant’s experience. Participant content checking was not performed in the qualitative study, as we did not collect contact information on participants. However, the preliminary findings and field notes were shared with clinic staff, who felt the findings resonated with their patient’s experiences, and their own observations as to the barriers to cervical cancer screening in the community and those associated with small-town living.

For quantitative studies, internal validity can be assessed through the discussion of selection bias, information bias, and confounding.

#### 5.2.2.1 Selection bias

Selection bias in epidemiological studies occurs when the results are distorted due to how subjects are selected into the study, or allocated to the study arms based on factors that may influence participation (186).

In objective 1, the meta-analysis and systematic review on HPV self-sampling, selection bias may have arisen from a number of sources including publication bias, language bias, and reviewer selection bias (187). Publication bias results from a preference to publish studies with significant results and large effect sizes. Publication bias was minimized by searching for unpublished conference proceedings. All identified conference proceedings were accounted for by published studies identified in the systematic review search. Despite the potential for outstanding unpublished studies, multiple null effect studies would have been needed to alter the estimated effect size from the 10 positive studies included in the meta-analysis.

Language bias arises when studies published in non-English journals are excluded. In the HPV self-sampling meta-analysis there were no restriction of language of publication in an effort to reduce language bias.

Reviewer selection bias occurs when the reviewer selects only a sub-set of available studies that have favourable outcomes. The meta-analysis excluded middle-/low-income countries, which resulted in the omission of four studies - three studies from India and the one from China. Overall, the omitted studies found offering HPV self-sampling improved
participation in cervical cancer screening, and thus would not have impacted the findings from the current meta-analysis.

For objective 3, the randomization of study participants was conducted to minimize selection bias. However, selection bias can be introduced into RCTs when quasi-randomization processes are used (e.g. birth dates, sequential recruitment, etc.), or through a lack of allocation concealment. Allocation concealment refers to whether the investigator or subject has knowledge of which group a participant will be allocated before being enrolled into the study, and thus may influence a participant’s enrolment or eventual study arm allocation, which would invite selection bias (188).

In the HPV self-sampling pilot study (objective 3), selection bias was minimized by using the clinic’s entire population of under-screened women 30 – 70 years of age, and by using a random number generator to assign women to their respective study arm. Allocation concealment was not entirely possible due to the necessity of assessing post-randomization eligibility due to limitations in the EMR registry. However, in an effort to limit allocation bias during post-randomization eligibility assessment (chart review), I blinded the data collection spreadsheet to the allocated study arm, and used the EMR generated personal health number as the personal identifier and linkage variable to subsequent outcome data. Analysis of potential selection bias was not possible due to a lack of information available for all study participants or knowledge of underlying population distributions. I believe that any potential selection bias would be minimal based on proper randomization and concealment of study arm allocation during chart review.

5.2.2.2 Information bias

In the HPV self-sampling pilot study (objective 3), information bias may have been introduced during the ascertainment of participant’s screening status. Information bias, or misclassification, arises due to errors in measurement or in classification of outcome or exposure. Misclassification can be either differential or non-differential. Differential misclassification occurs when the error is dependent on another measured variable or allocation to a study arm. Non-differential misclassification results when the error is independent of other variables (186).

Non-differential misclassification of screening status (under-, never-, regular-screener), ascertained from the clinic’s EMR, may have occurred in the HPV self-sampling pilot study. Eligibility for the HPV self-sampling pilot study was based on having an under- or never-screened status. However, approximately 30% of women who participated in screening
(identified as under- or never-screened) self-reported having had a Pap test in the preceding two years, resulting from either re-call bias or undergoing testing elsewhere. Re-call bias in self-reported cervical cancer screening has been observed, with women typically over-reporting screening (189). To reduce misclassification of screening status women were asked to call the clinic and report previous Pap testing from another location. Women who were up-to-date on cervical cancer screening may have been included in the study, which potentially resulted in an overestimation of the effect of offering HPV self-sampling on screening uptake compared to a distinctly under-screened population.

5.2.2.3 Confounding
Confounding can occur when a variable is associated with both the outcome and exposure, but is not an intermediary on the causal pathway. In the HPV self-sampling pilot study, randomization was used to minimize the effect of confounding by equally distributing confounding variables, both known and unknown, between the groups under study. However, confounding can still occur due to spurious associations, and can be explored using directed acyclic graphs (190). Additionally, imbalances in potential confounders can be assessed between randomized study groups by comparing the distribution of variables between groups (162).

In the HPV self-sampling pilot study, assessing baseline imbalances between study groups was a challenge, as age was the only variable systematically abstracted from the EMR for all eligible women. As such, the post-randomization eligibility criteria (LTC, contraindicated medical conditions, and inactivated medical chart) were also used to assess group balance. The three arms of the pilot study were balanced on mean age, the distribution of male/female physicians, and had similar post-randomization eligibility for the variables available. I felt confident that the randomization achieved balanced study arms and confounding was minimized.

5.2.3 External validity
External validity of qualitative studies focuses on whether findings are transferable to another context or setting. A major limitation of this dissertation is the potential threat to external validity and whether the findings are generalizable to other rural communities or further to other communities in Canada.

The embedded mixed-methods design of this dissertation had a qualitative strand to support the quantitative strand by learning about barriers specific to the community, and identify potential concerns related to HPV self-sampling. In this instance, the external validity in
the qualitative strand was primarily concerned with whether the findings were representative of the larger community. The focus groups may not have captured all the barriers experienced by women in the community, or potential concerns with self-sampling. Demographic information was not collected during the focus group discussions, which limited the ability to compare focus group participants to the overall composition of the community. However, the Mount Forest community is a highly homogenous rural community and since focus group participants were drawn from the community, it would be expected that their observations would largely reflect that of the rest of the community.

Many of the logistical and procedural barriers identified in the focus groups have been previously identified in the literature in a variety of contexts. The barrier of ‘lack of social distance’ was identified as being specific to small communities, and may be transferable to other small community settings in Canada.

Lack of confidentiality and privacy have been cited as barriers to cancer screening in rural and remote First Nations communities (191). Providers often have multiple relationships and roles within the communities (192), which is analogous to the theme of “lack of social distance” identified in Mount Forest. In these communities, issues of privacy and confidentiality have also been described with respect to how health services are accessed, specifically, the social visibility of clinic encounters and inadvertent sharing of private information to the community in waiting rooms (191, 192).

The issues of lack of social distance, confidentiality, anonymity, and privacy are transferable to other rural and remote settings, but could also be transferable to small communities within large urban centers, for example highly connected immigrant communities.

Within these highly connected immigrant populations, I speculate that the multiple relationships and roles providers may have with their patients could lead to a perceived lack of social distance on the part of the patient and/or provider. Although care providers from one’s own cultural and language background have been found to be important facilitators for screening, barriers to screening can arise when care providers do not feel comfortable discussing cervical cancer screening out of respect for cultural modesty and community norms (193, 194).

Overall, the concept of social distance identified in the Mount Forest focus groups is likely transferable to other small communities, and may be extrapolated to both the clinic environment and from the perspective of the provider, depending on the unique characteristics of the community.
In the HPV self-sampling pilot study, generalizability of uptake and acceptability findings were hampered by a lack of information captured on non-responders. There was limited information about the non-responders in all arms of the study; however, on average non-responders were younger compared to those who underwent screening (51.5 years (95% CI 50.0 – 53.0) vs. 49.2 years (95% CI 48.3 – 50.1); p=0.02). Despite the statistically significant age difference, the age gap between screeners and non-responders is minimal. One explanation for this observed age difference is that women at age 50 become eligible for additional cancer screening tests (colorectal and breast cancer screening), which may increase cancer screening as a health priority for both women and/or their health care provider. Other reasons for nonresponse are likely heterogeneous within the population. I hypothesize nonresponse could be due to one or more factors directly related to self-sampling and HPV testing, including being late adopters of novel products/technologies, unappealing packaging, and the women’s relationship with the person recommending screening (i.e. health care provider, family member, trusted friend, etc.). Nonresponse could also be due to barriers identified in the qualitative strand directly related to the topic of cancer, specifically fear of cancer and lack of awareness about the benefits of cancer screening, or women having competing priorities. There will also be a proportion of the population who choose never to undergo screening despite all efforts. Understanding factors for nonresponse may help further improve acceptability of HPV self-sampling and identify activities to further increase uptake. These findings may not be generalizable to all under-screened women living in small rural communities, however, I would anticipate the uptake and acceptability to be generalizable to women living in similar agricultural-based rural communities in Ontario, who are connected to primary health care.

For other small communities, including remote First Nations and highly connected urban immigrant communities, I hypothesize that the absolute uptake of screening and high acceptability of self-sampling observed might not necessarily be generalizable. In remote First Nations communities lower uptake of HPV self-sampling has been observed, due to a number of complex social and historical determinants (181). In immigrant communities, varying degrees of acceptability of self-sampling have been reported (178, 194, 195). However, in both remote First Nations and immigrant communities HPV self-sampling has been reported as favourable over Pap testing (181, 194). Overall, the trend towards increased screening uptake with HPV self-sampling compared to Pap testing is likely generalizable across many small community settings. However, specific implementation strategies should be explored to maximize acceptability and uptake in different communities contexts.
Another limitation of this dissertation work was the lack of information on women who have never been screened for cervical cancer. Women in the qualitative strand expressed previous exposure with cervical cancer screening and overwhelmingly all women who completed a questionnaire in the HPV self-sampling pilot study indicated having had a previous Pap test. It is not surprising that almost all participants had previous screening experience given recruitment was targeted to women about cervical cancer screening, and in the HPV self-sampling pilot study age was restricted to 30 years or older. One question that remains is whether there are true differences in HPV self-sampling uptake between women based on previous screening exposure.

5.3 Strengths of this Research

The major strength of this dissertation was the multiple approaches that were used to examine self-sampling as a means to improve uptake of cervical cancer screening in under-screened women. A mixed-method approach allowed for the integration and support of data findings from different perspectives. The meta-analysis findings were used to identify the knowledge gap in rural under-screened women, and provide cervical cancer screening uptake estimates for the HPV self-sampling pilot study. The qualitative analysis informed the development of the HPV self-sampling pilot study and provided important contextual information related to rural women’s experience with cervical cancer screening. Using an embedded mixed methods approach allowed for a more complete understanding of how HPV self-sampling as an intervention improved uptake of cervical cancer screening in this population.

A second strength of this dissertation was the ability to conduct a population-wide intervention. Despite being a pilot study, the uptake of HPV self-sampling was measured for the entire rural community’s population of under-screened women. Intervention over the course of the study, by way of outreach about cervical cancer screening, was made directly to all under-screened women in the community who received health care at the sole community medical clinic.

Finally, this dissertation work provided an opportunity to build partnerships with the local healthcare providers and bolstered their involvement and capacity for research relevant to their community and to their clinic practice. Communication during study development and of findings promoted continued education, with open discussions of cancer screening guidelines and future clinical directions.
5.4 Implications for Public Health in Canada & Future Research Directions

HPV testing has been shown to reduce the incidence of pre-cancer and cancerous cervical lesions more than Pap testing (109). Self-sampled HPV testing for primary cervical cancer screening is a promising strategy for under-screened women, or those who are reluctant to undergo Pap testing. Prior to the implementation of HPV self-sampling as a cervical cancer screening strategy, funding for HPV testing, and HPV self-sampling, under the provincial health insurance program is required. Cervical Cancer Screening Guidelines in 2012 recommended HPV testing as the primary screening test for cervical cancer, yet Pap cytology has continued as the screening modality in Ontario in the absence of funding for HPV testing.

How best to implement HPV testing algorithms into cancer-screening programs and how best to triage a high-risk HPV positive test continues to be debated. Current options can include triage by cytology, HPV genotyping, and/or immunostaining for specific disease makers (196). The optimal screening interval and age range will also need to be determine, to maximize cost-effectiveness and safety, while minimizing over-diagnosis, and referral for colposcopy. The screening interval can be safely elongated when HPV testing is used (for women who are negative); however, convincing both women and health-care practitioners that less testing is more beneficial can be challenging. Again, having a robust reminder system would provide assurances that screening will not be missed over a longer screening interval. Other programmatic issues with HPV testing will need to be addressed, including how best to screen women under 30 years of age and whether alternate screening algorithms based on vaccination status will need to be evaluated. These programmatic issues around the use of HPV testing in cervical cancer screening will need to be resolved prior to the implementation of HPV testing. Once HPV testing is implemented, there is strong evidence for the inclusion of self-sampling as an option for under-screened women.

Prior to the implementation of HPV self-sampling within a primary cervical cancer screening program a number of logistical factors will need to be determined. The logistical details ranging from identifying the under-screened population, to selecting the self-sampling device, to transportation, to results communication, and follow-up should be detailed and tailored to specific populations to maximize uptake and reduce cost. Education and promotional activities targeted at both women and healthcare providers should be undertaken to maximize the intention of screening and reduce barriers associated with fear, uncertainty, and lack of information.

Resource management, specifically cost, will certainly play a role in the adaptation of self-sampling for HPV testing in screening programs. Self-sampling can be more cost effective
under the conditions of 1) increased uptake of screening, and 2) targeting women who are under-screened, and thus most at risk for developing cervical cancer (174, 197).

The uptake of self-sampling for both women and policy makers may be dependent on the distribution method selected by screening programs. This study used an opt-out approach by way of direct mailing of self-sampling kits. One of the major criticisms of an opt-out approach is the potential for wasted sampling kits due to non-response. Other distribution methods have been explored, namely door-to-door recruitment or an opt-in approach. Door-to-door recruitment has shown great uptake for both self-sampling and Pap test reminders (172); however, as a population strategy it is resource intensive, thus undermining the feasibility and sustainability of such a strategy.

Opt-in strategies (via telephone, on-line, or pick up at pharmacy, or conducted in-clinic) have been considered to reduce sampling kit waste; however, evidence to date indicates the opt-in strategies may not be as effective at increasing screening participation as mailing sampling kits directly to patients (172, 198). That being said, for women who regularly visit their health-care provider, as the women who completed HPV self-sampling in this study were, a clinic-based approach by way of making HPV self-sampling available during a cervical cancer screening appointment or a periodic health exam may be an attractive approach to reduce costs and increase uptake of screening. The clinic could provide a supportive environment for initiating self-sampling where training, education, knowledge transfer between provider and patient can occur. Clinic-based approaches may not alleviate the logistical barriers associated with transportation, booking appointment, or competing priorities for under-screened women. Clinic-based approaches also do not allow for the direct engagement of women who do not have a stable link to primary care. If opt-in approaches do not increase uptake of screening compared to reminder letters, then the cost savings self-sampling confers (due to increased screening) may be lost (197).

The most cost-effective approach for HPV self-sampling for primary cervical cancer screening might be a reminder letter, followed by a self-sampling kit (199). This step-wise approach allows the targeting of under-screened women, while maximizing potential screening uptake by using an opt-out approach. In order to implement such a step-wise approach, a well-organized screening program that monitors both organized and opportunistic screening would be essential to ensure under-screened women could be identified. In the HPV studies (qualitative and quantitative strands) the clinic’s EMR database was used as a primary care registry to track screening attendance due to a lack of an organized screening program registry. In 2015, the Cervical Cancer Screening Program at Cancer Care Ontario began a
provincial initiative to move toward an organized screening program that would track and inform women via letter when they were due for Pap testing. In future, the provincial registry infrastructure would ideally be used to facilitate identification of under-screened women and direct mailing HPV self-sampling initiatives.

Using methods from implementation science to evaluate not only the link between HPV self-sampling and cervical cancer screening uptake, but the components around the implementation of HPV self-sampling in the cervical cancer screening program will be an important step in the scalability of HPV self-sampling to ensure target populations are not only being reached, but uptake across these targeted populations is being maximized.

The availability of self-sampling may also indirectly increase cervical cancer screening participation in under-screened communities. In rural Newfoundland a community-based intervention by Duke et al. found only a 9.5% uptake of HPV self-sampling through their opt-in outreach strategy and promotional campaign (200); however, despite the low uptake of self-sampling the overall community-screening rate increased significantly by 15.2% over two years compared to other communities using promotional campaigns but lacked HPV self-sampling availability (200). In Northern Ontario, a cross-over community-based trial of First-Nations women found increased screening uptake when HPV self-sampling was offered, although large variability in screening uptake was observed between communities (181). Together these findings suggest that screening choice might promote participation in the method deemed most comfortable to the women.

The moderate absolute uptake of HPV self-sampling suggests more can be done to increase cervical cancer screening uptake among under-screened women. Within the HPV self-sampling pilot study, uptake may have been hampered by the novelty and lack of prior exposure to self-sampling. Over time, increased awareness of and experience with self-sampling may bolster uptake. In addition, robust educational and promotional materials from health-care providers, social messaging, and an organized cervical cancer screening program may further normalize and increase uptake among late adopters.

A low-cost self-sampling kit will need to be available prior to implementing HPV self-sampling in an organized cervical cancer screening program. In the HPV self-sampling pilot study a vaginal swab and liquid transport media self-sampling kit was selected based on prior validation by the laboratory, and evidence for effectiveness in the literature. If the goal is to increase uptake of screening, the sampling system (swab, lavage, and brush combined with either dry or wet transport) does not seem to greatly impact overall participation amongst women who elect to undergo self-sampling (201). There are a number of different self-sampling options for HPV testing. In research settings, non-specific vaginal swabs or cotton tampons
have been used due to laboratory experience in working with these specimen collection devices and low cost. These crude sampling methods come with issues of transportation of fixing media, and Canada Post package requirements for biological specimens, as well as potential issues of women’s comfort with a crude collection device. Recent advances in commercially available self-sampling devices may improve women’s confidence and acceptability of collecting their own vaginal sample.

Dry transportation systems are effective for HPV testing and have increased logistical and practical advantages (202) over wet transportation. Dry transportation removes the issues associated with potential spillage and toxicity exposures associated with transport media stabilizers.

Less invasive and easy-to-administer urine sampling has also shown promise as a HPV sampling method (203) and would be an attractive alternative for women reluctant to perform any form of insertive sampling; however, transportation of samples outside of a clinical setting would be an issue.

The results of this dissertation indicate that cervical cancer screening programs should have an affordable, highly acceptable, easily administered, and transportable HPV self-sampling kit, which can be tested rapidly with a high sensitivity and specificity for cervical cancer pre-cancerous and cancerous lesions.

This dissertation demonstrated that HPV self-sampling has the ability to improve participation in cervical cancer screening. The HPV self-sampling pilot study in Mount Forest identified that HPV self-sampling is acceptable to women and that it is feasible to reach women using mail-based home delivery. The qualitative work provided contextualization to the barriers women face with cervical cancer screening in this rural context. Additional research is needed into what barriers remain, and are introduced, with HPV testing and self-sampling, and what additional factors might bolster uptake of screening, especially among women who are currently reluctant to undergo screening. This information might be best achieved through qualitative exploration across a spectrum of communities and include physician and healthcare provider perspectives.

The findings from this dissertation, coupled with further research into the field of optimal self-sampling devices, delivery, and testing platforms, provide a foundation upon which to build larger demonstration studies for the effective use and integration of HPV self-sampling for primary cervical cancer screening within Canada.
Chapter 6: Candidates Contribution to Study Design and Analysis

The candidate was responsible for the identification and development of the three thesis objectives in collaboration with the supervisory committee.

For objective 1, the candidate identified the systematic review research question and search strategy. The search strategy was refined in collaboration with a research librarian. The candidate was responsible for conducting the systematic review, data abstraction, and statistical analysis, including the selection of the random effects model. A co-author performed data abstraction crosschecking.

For the qualitative strand (objective 2), the community of Mount Forest had been previously identified as an under-screened community, and the Mount Forest Family Health Team had been approached by the UNS Provincial Research Team to discuss conducting focus groups with community members. The candidate was responsible for the contribution of the HPV self-sampling specific focus group questions, and facilitation of all community focus groups. A research assistant in the UNS Provincial Research Team transcribed focus group recordings. The candidate completed all thematic analysis, with assistance in the initial analysis phases from UNS Provincial Research Team members, and guidance from supervisor.

For the quantitative strand (objective 3), the candidate was responsible for the design of the HPV self-sampling pilot study with input from the supervisory committee and the clinic’s advisory committee. The candidate was responsible for initiating the clinic’s advisory committee and for maintaining the working relationship with the clinic throughout the study. The candidate designed the algorithm to identify all eligible participants, compiled all study materials and self-sampling kits, and placed all reminder phone calls for the HPV self-sampling arm. The candidate was responsible for collecting all submitted self-sampling kits, conducting chart review, and recording outcome data. A research assistant performed questionnaire data entry. HPV testing was conducted at the Ontario Public Health Lab. The candidate was responsible for liaising with the lab to deliver completed test kits and receive test results. The candidate was responsible for inputting all HPV test results into the EMR, and communicating with clinic providers and staff as to the follow-up procedure for HPV positive women. The candidate was responsible for all statistical analysis in collaboration with the supervisory committee.

The candidate was responsible for drafting all manuscripts, incorporating co-author’s revisions, submission to peer-review and responding to all peer-reviewer comments in collaboration with the supervisory committee. The candidate presented findings at national and international meetings.


Appendices
Appendix 1: Recruitment Letter and Poster for Focus Group

1.1 Recruitment Letter

Dear Resident:

We are looking for people from the Mount Forest area to talk with us about cancer screening and why people in the community don’t get screened for cancer. What we learn will be used to help people get screened for cancer, especially people who don’t normally get screened. At this time, we are most interested in colon, breast and cervical cancer screening.

Will you talk with us?

We will be holding group meetings in April to talk about how to make screening better at the Claire Stewart Medical Clinic/Mount Forest Family Health Team. There will be one men’s group and two women’s groups made up of people from your community.

There are three times when you can be part of the discussion (you only need to pick one): Childcare and food are provided, so please feel free to come early!

**Women 18 – 40 years old:**
- **Wednesday April 18th, 2012**
  - 12:00pm – 1:30pm
  - 5:30pm – 7:00pm
- **Thursday April 19th, 2012**
  - 7:00pm – 8:30pm

**Women aged 40 years or older:**
- **Wednesday April 18th, 2012**
  - 7:00pm – 8:30pm
- **Thursday April 19th, 2012**
  - 12:00pm – 1:30pm
  - 5:30pm – 7:00pm

**Men aged 40 years or older:**
- **Wednesday April 18th, 2012**
  - 7:00pm – 8:30pm
- **Thursday April 19th, 2012**
  - 12:00pm – 1:30pm
  - 5:30pm – 7:00pm

*The meeting will last about 1 hour. You will be compensated $75 for your time.*

Please call 519-323-0255 (Mount Forest Health Care Team) to reserve your spot.

Can’t make it to a meeting but still want to help out? Take our on-line survey at: [www.getscreened.ca](http://www.getscreened.ca)

Learn more about the study or ask questions by visiting our website: [www.getscreened.ca](http://www.getscreened.ca) OR call our Project Manager: Joan Antal at 416-971-6000x ext. 3104

Remember, your participation is voluntary. It’s okay to say no.

Thank you for your time. We hope to hear from you!

Sincerely,

Dionne Gesink, Principle Investigator
University of Toronto
1.2 Recruitment Poster

Why don't people get screened for cancer?
We want to hear from you!

We are looking for people from the Mount Forest area to talk with us about cancer screening and why people in the community don’t get screened for cancer.

We will be holding group meetings for men and women at the Claire Stewart Medical Clinic and the Louise Marshall Hospital. There are three times when you can be part of the discussion (you only need to pick one).

**Women 18 – 40 years old:**
Wednesday April 18\(^{th}\) Th ursday April 19\(^{th}\) 2012 2012 12:00pm – 1:30pm 7:00pm – 8:30pm 5:30pm – 7:00pm

**Women aged 40+ years or older:**
Wednesday April 18\(^{th}\) Th ursday April 19\(^{th}\) 2012 2012 7:00pm – 8:30pm 12:00pm – 1:30pm 5:30pm – 7:00pm

**Men aged 40+ years or older:**
Wednesday April 18\(^{th}\) Th ursday April 19\(^{th}\) 2012 2012 7:00pm – 8:30pm 12:00pm – 1:30pm 5:30pm – 7:00pm

*The meeting will last about 1 hour. Childcare and food are provided and you will be compensated $75 for your time.*

**Please call 519-323-0255 (Mount Forest Family Health Team) or drop by the clinic to reserve your spot.**

Can’t make it to a meeting but still want to help out? Take our on-line survey at www.getscreened.ca

Your participation is completely voluntary.
Questions? Please call our Project Manager: Joan Antal at 416 – 971 – 9800 ext. 3104

We hope to hear from you!
Appendix 2: HPV Self-sampling Kit

2.1 Representation of HPV self-sampling kit participants received by mail
Appendix 3: Focus group Questionnaire Guide

Focus Group Interview Guide

Community Focus Group Interview Guide

[Instructions: Present slides of stats and maps to set context.]

Here’s what we know:
- Participation rates for cervical cancer screening in Ontario have leveled off and are below targets
- Some neighborhoods have lower screening rates than expected suggesting that there are people living in those neighborhoods who have either never been screened or are under screened.

Note: for complete set of statistics, go to: http://csqi.cancercare.on.ca/dimensions/accessible/

Here’s what we don’t know: who is not getting screened, what are their barriers to screening and what might enable them to get screened.

1. What do you think the barriers are to screening for _______. For instance, can you identify any situation or behavior you feel obstructs people from paying attention to the real need for cancer screening? [Instructions: specify group. If there is more than one group, repeat this question for each group].
   a. Probes:
      - At the health center/clinic level?
      - At the neighborhood level (e.g., why don’t people talk about cancer screening and express solidarity or affection through providing support for screening?)
      - At the family level (e.g., why isn’t there more dinner table-type conversation about the need for health-related behaviors, generally, and screening)
      - At the client level?

2. What activities or resources would help increase screening for [this group or name group]? [Instructions: If there is more than one group, repeat this question for each group]
   a. Probes:
      - Looking forward, what would the ideal screening process look like?
      - What would help at the health center/clinic level?
      - What would help at the neighborhood level?
      - What would help at the family level?
      - What would help at the individual level?
      - What are we not doing that you feel we could be doing?

HPV Specific:
One of the barriers to screening is the physical test itself, we would like to now chat about the different testing that is available for cervical screening:

[Ask about knowledge of Pap testing, describe with use of visual aids. Provide HPV test kit for women to see and touch]
A pap test is a pelvic examination that requires a doctor to examine the top of the vagina and to take a small sample of cells to look and see if they are different. If these cells are different it indicates that there might be reason for concern about cervical cancer. The Pap test is looking for cancer.

- Pros: It safe and is able to detect when cells are changing, it is specific, it is conducted during a physical examination and provides an opportunity to talk wit your doctor about other concerns
- Cons: It can be uncomfortable, it requires having a doctors’ appointment

HPV testing is an alternative form of cervical screening. HPV testing identifies if an individual is infected with the virus that may lead to cervical cancer. HPV testing can be self-collected using an at home kit, and then dropped off or mailed to your doctor’s office or directly to the lab for testing. The test is similar to using a tampon. You just insert the q - tip and twirl a few times and then return to the sterile container. Each kit provides a set of instructions on how to use it. Studies that have explored these kits agree that home-users can collect good, reliable samples. Certain types of Human papillomavirus are known to cause cancer in women. The HPV test determines if a woman has an HPV infection. If a woman is positive for HPV she is at higher risk for developing cervical cancer and can be followed more closely. The HPV test is looking for infection with a virus that can cause cancer.

- Pros: It is safe, and can be self-administered, done at home or at the doctors office, it is very sensitive
- Cons: It can only detect the HPV infection and not cancer, many women are able to get rid of their HPV infection before it develops into cancer. If a women is positive she will have to undergo pap testing anyway

3. Do you think that women who currently don’t get screened using a pap test would use an HPV self-test?

Probes:
- If there was a choice between a pap test and an HPV kit what might people choose and why?
- Do you think women would feel confident that they could do an HPV test?
- Do you think HPV testing might remove any current barriers to cervical screening?

4. What issues or concerns do you see arising from using an HPV self-test kit?
   a. Do you think a positive HPV test would encourage or discourage women from following up with their doctor?

5. Based on our discussion so far, do you think that HPV self-testing should be piloted in your community?

6. HPV testing is safe and painless. If we were to pilot the HPV test, what additional information should be include in the HPV home kit?

7. How do we reach women who don’t get tested?
   Probes:
   - What is the best way to reach women to participate in a pilot study?
8. Is there anything else we should be thinking about or that you would like to add?

9. Do you have any questions for us?

Thank you for sharing your thoughts and your time with us. It is greatly appreciated!
Appendix 4: Self-sampling Instructions

INSTRUCTIONS FOR HPV SELF-TESTING

Please read carefully all instructions before you start

→ Do not take your sample within 48 hours of having sex

→ If at any point you feel pain, please stop and remove swab. Please contact your doctor or nurse practitioner to discuss the reason for the pain.

Please return your sample and questionnaire in the pre-paid return envelope.

Keep HPV Testing Kit out of reach of children
HPV Self-test:
The pictures match-up with the written instructions

1. Before you begin, wash your hands with soap and water.
2. Place the swab and collection tube within reach on a hard surface.
3. Unscrew the cap on the collection tube, be careful to ensure it does not tip over and spill.
4. Find a comfortable position, either sitting on the toilet, or one-leg up on the tub.
5. Take the swab and remove the cap. Carefully withdraw the swab with one hand, be sure not to touch the end of the swab to any surfaces.
6. With your free hand spread your labia (opening of your vagina), and insert the tip of the swab into your opening. If you feel pain at any point, stop and remove swab.
7. Continue to insert the swab 2–3 inches into your vagina, and stop if you feel pressure.
8. Twist back and forth 3–4 times. Carefully remove the swab from your vagina, without touching the swab on any surfaces.
9. Place the tip of the swab into the collection tube. Press the shaft of the swab up against the edge of the tube. Using both hands, break the swab off just below the top of the tube.
10. Screw the cap on to the collection tube. Do not force it if the swab is too tall—just shorten the swab shaft until it fits. Make sure the cap is on tight.
11. Throw-out the rest of the swab stick.
12. Place the collection tube into zip-lock bag and seal the bag.
13. Place the zip-lock into return envelope.
14. Complete the questionnaire and place it in the same return envelope & you are all done!

You are all done! Thank you for taking the HPV self-test!
Appendix 5: Cervical Cancer and HPV Information Sheet

**Human Papillomavirus (HPV) & Cervical Cancer**

**What is HPV?**
- HPV is a common virus called Human Papillomavirus
- It is found in both men and women
- There are over 100 types of HPV
  - Some HPV types can cause skin or genital warts
  - Other types of HPV can cause cancer of the cervix

**How do people get HPV?**
- HPV can spread through any sexual activity with a partner (such as skin-to-skin contact, oral or anal sex, sexual intercourse or sharing sex toys)
- Around 8 out of 10 people who have sex will come into contact with HPV at some time in their lives
- Your body’s own defenses (immune system) can often fight off this virus, but that doesn’t always happen
- Most of the time there are no symptoms. You may not even know you have HPV.

**What is the link between HPV and cancer of the cervix?**
- All cases of cervical cancer can be linked to an HPV infection.
- Some types of HPV can cause cell changes (infections) in the cervix.
- Most HPV infections go away on their own
- Sometimes HPV infections do not go away and over time these changes may cause cancer if they are not found early and treated
- Most women with HPV infection do NOT get cervical cancer.

**How can I lower my risk of getting HPV?**
- Limit the number of partners you have sex with
- Use a condom
- Delay your first sexual activity
- Ask your doctor or nurse practitioner if you should get the HPV vaccine

**What is the HPV vaccine?**
- It is a vaccine for girls and women 9 – 26 years old
- It protects against some types of HPV that can cause cancer of the cervix
- Grade 8 females in Ontario may get the vaccine for free at school
- Talk to your doctor or nurse practitioner if you want to get the vaccine

Want more information about HPV and Cervical Cancer Screening:
Visit Cancer Care Ontario:
https://www.cancercare.on.ca/pcs/screening/cervscreening/

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**FACT SHEET**

HPV is a very common family of viruses found in both men and women.

Some HPV types can cause cancer of the cervix (cervical cancer) if these HPV infections are not found and treated...

It is hard to avoid HPV if you are sexually active but you can reduce your risk...

HPV vaccine does not protect you from all types of HPV. That’s why it is very important to get regularly screened for cervical cancer...

**HPV Test:**

What is the HPV Test?
The HPV test is performed using a self-collected swab.
The swab collects cells from your cervix.
The cervical cells are then tested to see if they are infected with HPV.

1. A positive HPV test does NOT mean that you have cancer.
2. A positive HPV test means that you have an HPV infection, which raises your risk of developing cervical cancer.

Updated: September 2012
Appendix 6: Study Questionnaire

QUESTIONNAIRE
This questionnaire asks questions about you, your experience with the HPV self-test, and your previous Cervical Cancer screening experiences.

Please complete all questions as best you can. Your answers are confidential and will not be shared with anyone, not even your health care provider.

Part 1 - General Information Questions

Q1. What is your age? (please check one)
- □ 30 – 34
- □ 35 – 39
- □ 40 – 49
- □ 50 – 59
- □ 60 – 69
- □ 70+

Q2. What best describes your current living situation? (please check one)
- □ Married and/or living with a partner
- □ Divorced
- □ Widowed
- □ Common-law
- □ Single or Never married
- □ Prefer not to answer

Q3. What ethnic group do you identify most with? (please check one)
- □ White/Caucasian (e.g. Australia, Europe)
- □ Mennonite
- □ Aboriginal/First Nation/Metis/Inuit
- □ South Asian (e.g. India, Pakistan, Sri Lanka)
- □ South East Asian (e.g. Philippines, Indonesia, Thailand)
- □ Western Asian (e.g. Armenia, Iran)
- □ Asian (e.g. China, Japan, Korea)
- □ Middle Eastern (e.g. Israel, Saudi Arabia, Iraq)
- □ Central American (e.g. Mexico, Guatemala)
- □ South American (e.g. Brazil, Argentina)
- □ Caribbean
- □ Black African or □ Black Caribbean or □ Black North American
- □ North African
- □ Other (please specify):
- □ Prefer not to answer

Q4. What best describes your current employment status? (please check one)
- □ Working full-time
- □ Working part-time
- □ On disability
- □ On social assistance
- □ Retired
- □ Not working for another reason
- □ Prefer not to answer

Informed Consent:
- □ Yes, I have read the informed consent and agree to participate in this study

__________ (please initial)

Page 1 of 8
Q5. What is your yearly household income (before taxes)? (please check one)
- Less than $19,999
- Between $20,000 – $49,999
- Between $50,000 - $99,999
- More than $100,000
- Don't know
- Prefer not to answer

Q5a. How many people (adults and children) does this income support?
Number of people ________

Q6. Highest level of formal education completed (please check one)
- Less than high school
- High school graduate
- College degree
- University degree
- Other
- Prefer not to answer

Q7. Do you currently have a primary care provider (Family doctor or Nurse practitioner)
- Yes
- No
- Not sure

Part 2 - Cervical Cancer Screening Questions
We are now going to ask you some questions about your reproductive and screening history. Please answer as best as you can.

Q8. Have ever been sexually active (had sex)?
- No → Please go directly to question Q14.
- Yes
- Don't know

Q9. How old were you when you first had vaginal intercourse (sex)?
   Age in years ________
   - Don't remember

Q10. How many sexual partners have you had over your lifetime? (please check one)
- 1 - 2
- 3 - 5
- 6 - 10
- 11+
- Don't know
Q11. How many sexual partners have you had in the past year? (please check one)
- 0
- 1 - 2
- 3 - 5
- 6 - 10
- 11+
- Don't know

Q12. Did you have vaginal sex less than 48 hours before collecting your sample?
- Yes
- No
- Don't know

Q13. Have you ever been pregnant?
- No
- Yes → How many times have you been pregnant in your life, including still births or miscarriages or abortions? ______
- Don't know

Q14. Have you had a hysterectomy (surgery to remove your uterus, ovaries and/or cervix)
- No
- Yes → approximate date (year) of surgery ____________
- Don't know

What is a Pap test?
Your health care provider may have given you a Pap test during a yearly physical or pelvic exam. During a Pap test, you remove your pants and underwear and lie on your back with your legs spread apart and your feet in stirrups or on the exam bed in front of you. The health care provider inserts a metal or plastic instrument into your vagina to take a sample of cells from the opening of your womb (cervix) using a swab.

Q15a. Have you ever had a Pap test (or smear test)?
- No, I have never had a Pap test taken → Please go directly to Q16.
- Yes, I have had a Pap test
- Don't know

Q15b. If Yes, how long ago was your last Pap test? (please check one)
- More than 3 years
- 1-2 years ago
- Within the last year
- Don't remember

Q15c. If Yes, have you ever had an abnormal Pap test result?
- No
- Yes
- Don't know

Q16. Which of the following have ever stopped you from getting a Pap test? (Please check all that apply)

Page 3 of 8
Q16. Which of the following have ever stopped you from getting a Pap test? (Please check all that apply)

☐ I have had a hysterectomy
☐ My cultural/religious beliefs prevent it
☐ I’m afraid the test will find that something is wrong with me
☐ If I am meant to die from cancer, no test is going to change that
☐ I don’t know enough to decide whether to get the test
☐ I don’t speak English well
☐ I can’t get to the doctor’s office/clinic (no transportation)
☐ My doctor/nurse practitioner did not suggest it
☐ I do not have a regular family doctor/nurse practitioner
☐ My doctor told me I didn’t need it
☐ I can’t schedule time with a doctor/nurse practitioner when it is possible for me to go
☐ There is not enough time to talk about the Pap test when I see my doctor/nurse practitioner

Continued...

☐ I don’t feel comfortable talking about the Pap test with my doctor/nurse practitioner
☐ The Pap test is too uncomfortable/painful/personal/complicated
☐ I am not worried about cervical cancer
☐ I avoid the doctor because I feel guilty about not doing what they told me to do (e.g. quit smoking, lose weight, have cancer screening done etc.)
☐ A Pap test is embarrassing
☐ A Past trauma stops me from being examined
☐ Nothing stops me from getting a Pap test
☐ Other (please specify): __________________________________________________________

Q17. How much do you agree with this statement? Cervical cancer screening is important to a woman’s health. (please circle one)

<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agree</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutral</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Disagree</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Strongly Disagree</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Q18. Have you ever been vaccinated for the Human Papillomavirus (HPV)? (Either Gardasil or Cervarix vaccine)

☐ Yes → Yes, when did you have your last injection (year) ____________
☐ No
☐ Not sure

Q19a. Have you smoked at least 100 cigarettes (about 5 packs) in your entire life?

☐ Yes
☐ No → Please go to Part 3
☐ Not sure

Q19b. At what age did you start to smoke regularly?

Age in years _______
Q19c. Do you still smoke regularly?
☐ Yes → Please go to part 3
☐ No
☐ Not sure

Q19d. At what age did you stop smoking regularly?
Age in years ______

Part 3 – HPV Home Test Kit
We are now going to ask you questions about your experience with the HPV self-test. If you choose NOT to take the HPV self-test, please skip to Part 4.

Q20. What made you decide to take the HPV self-test? (Check all)
☐ The test came to me at my home
☐ I was able to do the test at my home by myself
☐ The test was easy
☐ Other (please specify): ________________________________

Q21. Would you have gotten screened if this HPV self-test kit was not mailed to you?
☐ Yes
☐ No
☐ Not sure
☐ Other (please specify): ________________________________

Q22. If HPV testing were offered in the future, how would you prefer to be tested for HPV? (please check all that apply)
☐ Self-testing at home, delivered by mail
☐ Self-testing at home, pick-up kit at health clinic
☐ Self-testing at your family care provider’s clinic (in clinic washroom or exam room)
☐ Provider-collected sample (swab collected by your doctor/nurse practitioner during a pelvic examination)
☐ Any of the above
☐ Don’t know

Q23. If HPV self-testing were offered in the future, how likely would you choose self-testing compared to having a Pap test done by your health care provider? (please check one)
☐ Very likely
☐ Some what likely
☐ Maybe
☐ Unlikely
☐ Very unlikely
☐ Don’t know

Q24. How easy were the instructions to follow? (please circle one)

1  2  3  4  5  6  7  8  9
Not at all easy As easy as possible

Page 5 of 8
Q25. How easy was it to take your own swab? (please circle one)

1 2 3 4 5 6 7 8 9
Not at all easy As easy as possible

Q25a. If you found the HPV self-test difficult (less than 5 on the easy scale), What could be improved? (please check all that apply)
- The instructions could be easier to understand
- What was being asked could be more clear
- How hard it was to physically do the self-test

- Other (please specify): ________________________________

Q26. How sure do you feel that you did the test correctly? (please circle one)

1 2 3 4 5 6 7 8 9
Not sure at all As sure as I can feel

Q27. How comfortable did you feel when taking your sample today? (please circle one)

1 2 3 4 5 6 7 8 9
Not at all comfortable As comfortable as I can expect to feel

Q28. How likely are you to recommend HPV testing to a family member or friend? (please check one)
- Very likely
- Some what likely
- Maybe
- Unlikely
- Very unlikely
- Don’t know

Q29. If your HPV test results turned out to be positive, how likely are you be to make an appointment to follow-up with your primary care provider? (please check one)
- Very likely
- Some what likely
- Maybe
- Unlikely
- Very unlikely
- Don’t know

Q30. Is there anything else you think we should know about your HPV self-test experience?

Page 6 of 8
Part 4 – HPV and Cervical Cancer
Now we will ask you questions about where you go to learn about HPV and cervical health.

Q31. What is the best way for you to receive information about HPV, Cervical Cancer and Sexual Health? (Please check all that apply)
☐ Watching a video where pictures are shown and explanations are given verbally (spoken)
☐ Looking at a poster where things are described with pictures and words
☐ Directly meeting with a Health Care Provider so I can ask questions
☐ Together with my partner
☐ In a small group with other women I know
☐ In a small group with other women I don’t know
☐ General websites
☐ By email
☐ YouTube
☐ Government/public health unit website
☐ None of the above
☐ Other suggestions (please specify): ____________________________

Q32. Where did/do you obtain your knowledge about cervical cancer and screening? (Please check all that apply)
☐ By reading the information provided for this study
☐ Through a Health Care Provider
☐ Through a pamphlet
☐ Through the newspaper/magazine
☐ Through the television
☐ Through the Internet
☐ Through friends and/or relatives
☐ Other (please specify): ____________________________
☐ Don’t know

Q33. Before receiving information about this study, had you ever heard of Human papillomavirus or HPV?
☐ Yes
☐ No
☐ Don’t know

Q34. Please answer True or False to the following statements:

 HPV can be transmitted by kissing ☐ True ☐ False ☐ Don’t know
 HPV can cause genital warts ☐ True ☐ False ☐ Don’t know
 HPV infections can be treated ☐ True ☐ False ☐ Don’t know
 HPV can cause cervical cancer ☐ True ☐ False ☐ Don’t know
 Most people who have HPV have no visible signs or symptoms ☐ True ☐ False ☐ Don’t know
 HPV can be transmitted by oral sex (mount on penis or vagina) ☐ True ☐ False ☐ Don’t know
HPV can cause genital herpes □ True □ False □ Don't know
Most women with HPV will NOT develop cervical cancer □ True □ False □ Don't know
Using condoms during sexual intercourse prevents the spread of HPV □ True □ False □ Don't know
HPV can be transmitted by having unprotected sexual intercourse □ True □ False □ Don't know
HPV can be transmitted by sharing towels or a glass □ True □ False □ Don't know
Multiple sex partners increases the risk of HPV infection □ True □ False □ Don't know
HPV can cause serious health problems for men □ True □ False □ Don't know
HPV is the most common sexually transmitted infection □ True □ False □ Don't know
There is a vaccine that can prevent HPV infections □ True □ False □ Don't know

Q35. Do you have additional comments you would like to share with us about HPV self-testing or cervical cancer screening?

Comments:

***If you decided NOT to take the HPV self-test, why?

Thank you for participating!

If you would like more information about Cancer screening please visit [www.getscreeened.ca](http://www.getscreeened.ca)
Appendix 7: Ethics Approval and Informed Consent

7.1 Ethics Approval Letter

UNIVERSITY OF TORONTO

OFFICE OF THE VICE PRESIDENT, RESEARCH

PROTOCOL REFERENCE # 28091

October 15, 2012

Dr. Dione Gesink
DALLA LANA SCHOOL OF PUBLIC HEALTH
FACTORY OF MEDICINE

Ms. Catherine Saral Raeoy
DALLA LANA SCHOOL OF PUBLIC HEALTH
FACTORY OF MEDICINE

Dear Dr. Gesink and Ms. Catherine Saral Raeoy,

Re: Your research protocol entitled, “Randomized HPV self-testing intervention study in rural Ontario”

ETHICS APPROVAL

Original Approval Date: October 15, 2012
Expiry Date: October 14, 2013
Continuing Review Level: 1

We are writing to advise you that the Health Sciences Research Ethics Board (REB) has granted approval to the above-named research protocol under the REB's delegated review process. Your protocol has been approved for a period of one year and ongoing research under this protocol must be renewed prior to the expiry date.

Any changes to the approved protocol or consent materials must be reviewed and approved through the amendment process prior to its implementation. Any adverse or unanticipated events in the research should be reported to the Office of Research Ethics as soon as possible.

Please ensure that you submit an Annual Renewal Form or a Study Completion Report 15 to 30 days prior to the expiry date of your current ethics approval. Note that annual renewals for studies cannot be accepted more than 30 days prior to the date of expiry.

If your research is funded by a third party, please contact the assigned Research Funding Officer in Research Services to ensure that your funds are released.

Best wishes for the successful completion of your research.

Yours sincerely,

[Signatures]

Judith Friedland, Ph.D.
REB Chair

Daniel Gyewu
REB Manager
7.2 Informed consent for HPV Self-sampling Pilot Study – HPV active arm

UNIVERSITY OF TORONTO
DALLA LANA SCHOOL OF PUBLIC HEALTH

INFORMED CONSENT

Please read carefully. Your participation in the study implies that you have read and understood the following:

What is this project about?
HPV testing is used to identify women who need to undergo Pap testing to screen for cervical cancer. The purpose of this study is to determine if self-collected HPV testing is a way to screen for cervical cancer that works as well as or better than the current way of screening (pap tests only). We would like to see if women are willing to perform the test at home and complete a questionnaire about their experiences with the HPV self-test. The results from this study will be used to determine if HPV self-testing could be used in the future to improve cervical cancer screening.

Why me?
You have been randomly selected to participate in this screening study as a patient of the Mount Forest Family Health Team who has not been in for a Pap Test in more than 2 years. Your participation in this study is completely voluntary and your decision. You may refuse to participate. You may withdraw from the study by refusing to participate. However, you will be unable to withdraw from the study once you have mailed your swab sample and/or questionnaire. Whether or not you decide to participate will not impact in any way the care or treatment that you will receive with the Mount Forest Family Health Team.

What will happen if I agree?
First, you will be asked to collect a vaginal sample using the self-testing device by following the instructions provided. It will only take a few minutes to do the swab. You will then be asked to complete a 10-minute self-administered questionnaire. The questionnaire will ask you about your personal background, your cancer screening history, and your experience with the HPV self-test.

What are the Risk and Benefits?
There is a chance that collecting your own sample may make you feel uncomfortable. If at any point you feel pain you should stop, and we recommend you speak with your care provider about the reason for the pain. There is a chance that testing positive for HPV may make you feel uncomfortable or be stressful. Your health care provider will tell you your results. This process is in place to maintain anonymity and confidentiality for all participants, and to ensure proper follow-up and care for those who test positive. The risk for breach of privacy is the same as what would be experienced through regular clinic visits. There is also a chance that some of our questions in the questionnaire may make you feel uncomfortable. If you wish you may refuse to answer certain questions. The benefit is that you will learn whether or not you have a potentially important HPV infection, which is not currently routinely tested for. You may also learn that you do not have an HPV infection and therefore do not need to be re-tested for 3 years. This may lead to better care for you and other women in Ontario.

How will my identity and privacy be protected?
You will be assigned a unique code which will be used to label swab samples and questionnaire sheets. The unique code will track your questionnaire and test results and your name will not be used at the laboratory. Only the principle investigator will have access to the information that matches your unique study code to your personal information. The principle investigator will only
put this information together if there is an exceptional need to identify you as an individual. The study has been set up so that your information is anonymous when it is analyzed.

**Who will have access to my information?**

Only the research team will have access to data collected for this study. You will receive a copy of your test results. Your primary care provider will be notified of your test results, but will not have access to questionnaire information. All data will be stored at the University of Toronto on a locked computer.

**What will you do with my samples and information?**

Completed individual questionnaires will not be shared with your primary care provider (doctor or nurse practitioner). Questionnaire answers will be entered into a password protected computer and analyzed to figure out what helps or blocks women from getting screened for cervical cancer. All questionnaires will be destroyed once answers have been entered into the computer and verified. The data collected for this study will be entered into a database that is stored on a password-protected computer in a locked office. Computerized data will be archived for five years after the last manuscript is published and stored at the office of Dionne Gesink, University of Toronto. All swabs will be shipped to the Public Health Laboratory at the Ontario Public Health Agency and tested for HPV and you will be given your test results by mail. Your health care provider will only receive a copy of your HPV test results.

**What if I test Positive?**

*Testing positive does not mean that you have cancer. Testing positive means that you need to have a Pap test to look for changes in cervical cells.* If you test positive, your primary care provider will contact you. You will be notified by mail to contact the clinic and you will receive a phone call from your primary care provider’s office. You will be asked to return for a follow up test; however the responsibility for arranging an appointment is ultimately yours. The Family Health Team and Laboratory will treat all information as private and confidential. All swabs will be disposed of after testing has been completed.

**What if I test Negative?**

If you test negative, your results will be sent to you and your primary care provider. You will be notified by mail. If you choose, you may contact your primary care provider’s office to make an appointment to discuss this or any other issue with your doctor or nurse practitioner.

**How will I learn about the results of this study and will they be published or presented somewhere?**

We intend to present the results of this study to health care providers and communities after the data have been analyzed. It is also our intention to publish and make public presentations based on the results of this study. We will gladly send you a summary of the study findings at your request.

**Do you have questions?**

If you have questions during the study, please feel free to ask! If you have questions after the study, please contact someone from the research team. Project Assistant: Sarai Racey, sarai.racey@mail.utoronto.ca, Dionne Gesink, Principle Investigator: Dionne.gesink@utoronto.ca

Questions about ethics can be directed to the University of Toronto Research Ethics Board: Ethics Review Office University of Toronto (416) 946-3273.

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Appendix 8: Exploratory and sensitivity analysis: HPV Self-sampling Pilot Study

8.1 Acceptability:

Acceptability was parameterized based on three measures: comfort, confidence and ease of self-sampling. For each measure the mean score was high (>90%), however the measure of confidence in taking one’s sample was the lowest of the three (Table A8.1.1). Parameterizing acceptability as a mean score of 80% or greater was a reasonable conservative cut off and a natural separation in the observed data (see Figure A8.1.1). However, due to overwhelmingly high acceptability of self-sampling, fitting an explanatory model for acceptability using exact logistic regression was challenging and yielded no significant explanatory variables (manuscript 3). The single predictor model did not provide adequate model fit for the data and so multivariable regression model building was explored as a means to improve model fit. Although models with more parameters improved model fit, there were still no significant predictors of acceptability (Table A8.1.2 and Table A8.1.3).

A sensitivity analysis for the mean acceptability score cut off was then performed using the median means acceptability score of 96%. All predictor variables remained non-significant, however, model fit for the one-predictor models did marginally improve.
Table A8.1.1: Acceptability of at-home HPV self-sampling among participants in the HPV Self-sampling arm

<table>
<thead>
<tr>
<th>Acceptability</th>
<th>Submitted Completed HPV self-test &amp; questionnaire (n=70)</th>
<th>Submitted completed questionnaire (n=6)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>How Easy was it to take your own sample?</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>8.4 (0.16)</td>
<td>5 (4)</td>
</tr>
<tr>
<td>Not Easy - 1</td>
<td>1 (1.5%)</td>
<td>1 (50%)</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>1 (1.5%)</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>1 (1.5%)</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>4 (5.9%)</td>
<td>0</td>
</tr>
<tr>
<td>8</td>
<td>15 (22.1%)</td>
<td>0</td>
</tr>
<tr>
<td>Very Easy - 9</td>
<td>46 (67.7%)</td>
<td>1 (50%)</td>
</tr>
<tr>
<td><strong>How confident did you feel?</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>8.2 (0.2)</td>
<td>5 (4)</td>
</tr>
<tr>
<td>Not Confident - 1</td>
<td>1 (1.5%)</td>
<td>1 (50%)</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>1 (1.5%)</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>2 (2.9%)</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>3 (4.4%)</td>
<td>0</td>
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<tr>
<td>7</td>
<td>3 (4.4%)</td>
<td>0</td>
</tr>
<tr>
<td>8</td>
<td>17 (25%)</td>
<td>0</td>
</tr>
<tr>
<td>Very Confident - 9</td>
<td>41 (60.3%)</td>
<td>1 (50%)</td>
</tr>
<tr>
<td><strong>How comfortable was the test?</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>8.3 (0.2)</td>
<td>7 (2)</td>
</tr>
<tr>
<td>Not Comfortable - 1</td>
<td>1 (1.5%)</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>3 (4.4%)</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>1 (1.5%)</td>
<td>1 (50%)</td>
</tr>
<tr>
<td>6</td>
<td>2 (3.0%)</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>1 (1.5%)</td>
<td>0</td>
</tr>
<tr>
<td>8</td>
<td>11 (16.2%)</td>
<td>0</td>
</tr>
<tr>
<td>As Comfortable as possible - 9</td>
<td>49 (72.1%)</td>
<td>1 (50%)</td>
</tr>
<tr>
<td>Overall Acceptability Score(%)</td>
<td>Mean (SD)</td>
<td>92.4%(1.5)</td>
</tr>
<tr>
<td>Categorical Acceptability (&gt;8 being acceptable)</td>
<td></td>
<td>68</td>
</tr>
<tr>
<td>Acceptable</td>
<td>61 (89.7%)</td>
<td>1 (50%)</td>
</tr>
<tr>
<td>Hesitant</td>
<td>7 (10.3%)</td>
<td>1 (50%)</td>
</tr>
</tbody>
</table>

Figure 8.1.1: Histogram of mean acceptability score (as a percentage)
**Table A8.1.2: Univariable Analysis of Acceptability using Exact Logistic Regression**

<table>
<thead>
<tr>
<th>Univariable Model</th>
<th>OR</th>
<th>Standard Error</th>
<th>p-value</th>
<th>95%CI</th>
<th>(n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (60+ vs. less than 60)</td>
<td>1.6</td>
<td>1.2</td>
<td>0.80</td>
<td>0.3 - 9.3</td>
<td>70</td>
</tr>
<tr>
<td>Marital status (living with a partner vs. alone)</td>
<td>0.8</td>
<td>0.8</td>
<td>1.00</td>
<td>0.0 – 7.0</td>
<td>70</td>
</tr>
<tr>
<td>Employment (Working vs. Not working)</td>
<td>3.6</td>
<td>3.2</td>
<td><strong>0.24</strong></td>
<td>0.5 – 41.0</td>
<td>69</td>
</tr>
<tr>
<td>Education (Post-secondary vs. high-school or less)</td>
<td>0.9</td>
<td>0.6</td>
<td>1.00</td>
<td>0.1 - 5.0</td>
<td>69</td>
</tr>
<tr>
<td>Income (&lt;50,000 vs. &gt;50,000)</td>
<td>0.6</td>
<td>0.6</td>
<td>0.92</td>
<td>0.1 - 4.7</td>
<td>57</td>
</tr>
<tr>
<td>Last Pap test (less than 2 years ago vs. three for more)</td>
<td>1.8</td>
<td>1.5</td>
<td>0.72</td>
<td>0.2 – 12.0</td>
<td>69</td>
</tr>
<tr>
<td>HPV Awareness (Yes vs. no)</td>
<td>0.9</td>
<td>0.8</td>
<td>1.00</td>
<td>0.1 - 5.9</td>
<td>68</td>
</tr>
<tr>
<td>Screening Importance (Agree vs. not)</td>
<td>0.8</td>
<td>n/a</td>
<td>0.81</td>
<td>0.0-5.7</td>
<td>69</td>
</tr>
</tbody>
</table>

**Table A8.1.3: Multivariable Analysis of Acceptability using Exact Logistic Regression**

<table>
<thead>
<tr>
<th>Multivariable Model (N=56)</th>
<th>OR</th>
<th>Standard Error</th>
<th>p-value</th>
<th>95%CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (60+ vs. less than 60)</td>
<td>2.1</td>
<td>2.4</td>
<td>0.86</td>
<td>0.1 - 40.4</td>
</tr>
<tr>
<td>Employment (Working vs. Not working)</td>
<td>2.4</td>
<td>2.7</td>
<td>0.74</td>
<td>0.2 - 47.6</td>
</tr>
<tr>
<td>Income (&lt;50,000 vs. &gt;50,000)</td>
<td>0.3</td>
<td>0.3</td>
<td>0.48</td>
<td>0.0 – 3.0</td>
</tr>
<tr>
<td>Last Pap test (less than 2 years ago vs. three for more)</td>
<td>3.8</td>
<td>3.6</td>
<td>0.33</td>
<td>0.4 - 47.5</td>
</tr>
</tbody>
</table>
8.2 HPV positivity:

A series of models were used to investigate the relationship between HPV positivity and known risk factors in this study population. Due to the small number of HPV positive women, the model was very underpowered, with very wide confidence intervals. This exploratory analysis found increased number of lifetime sexual partners and a lifetime history of smoking increased the odds of testing HPV positive. A multivariable model with explanatory variables age, lifetime sexual partners, and lifetime history of smoking yielded significant model fit, however, only lifetime history of smoking remained significant (Table A8.2.1 and Table A8.2.2). The findings from the model building should be interpreted with caution due to the wide confidence intervals as a result of the small sample size. The model building yielded no new information, but was consistent with a large body of research documenting risk factors for HPV infection (52).

<table>
<thead>
<tr>
<th>Univariable Model</th>
<th>OR</th>
<th>Standard Error</th>
<th>p-value</th>
<th>95%CI</th>
<th>(n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (60+ vs. less than 60)</td>
<td>2.7</td>
<td>1.9</td>
<td>0.24</td>
<td>0.6 - 16.8</td>
<td>70</td>
</tr>
<tr>
<td>Number of lifetime partners (less than 3 vs. 3+)</td>
<td>4.3</td>
<td>3.1</td>
<td>0.05</td>
<td>1.0 – 27.0</td>
<td>67</td>
</tr>
<tr>
<td>Lifetime smoking history</td>
<td>9.8</td>
<td>10.5</td>
<td>0.02</td>
<td>1.3 - 445.2</td>
<td>69</td>
</tr>
<tr>
<td>Currently smoking</td>
<td>3.4</td>
<td>2.3</td>
<td>0.12</td>
<td>0.8 - 16.1</td>
<td>49</td>
</tr>
<tr>
<td>Age of first sexual encounter (less than 18 years old)</td>
<td>2.4</td>
<td>1.6</td>
<td>0.29</td>
<td>0.6 - 12.2</td>
<td>61</td>
</tr>
<tr>
<td>Ever pregnant</td>
<td>0.4</td>
<td>0.3</td>
<td>0.31</td>
<td>0.1 - 2.1</td>
<td>68</td>
</tr>
</tbody>
</table>

Table A8.2.1: Univariable Analysis of HPV Positivity using Exact Logistic Regression

<table>
<thead>
<tr>
<th>Multivariable Model (N=66)</th>
<th>OR</th>
<th>Standard Error</th>
<th>p-value</th>
<th>95%CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>2.2</td>
<td>1.7</td>
<td>0.44</td>
<td>0.4 - 15.5</td>
</tr>
<tr>
<td>Lifetime smoking history</td>
<td>9.3</td>
<td>10.1</td>
<td>0.03</td>
<td>1.2 - 436.1</td>
</tr>
<tr>
<td>Number of life time partners</td>
<td>3.6</td>
<td>2.7</td>
<td>0.13</td>
<td>0.8 - 23.8</td>
</tr>
</tbody>
</table>

Table A8.2.2: Multivariable Analysis of HPV Positivity using Exact Logistic Regression