Evaluating the effectiveness of cervical cancer screening invitation letters

By

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Abstract

The purpose of this study was to evaluate the effectiveness of an invitation letter on cervical cancer screening participation among unscreened Manitoba women 30 to 69 years of age. A cluster randomized trial design was used in which unscreened women (n=31,452) were randomly assigned by the forward sortation area (FSA) of their postal code to an intervention group that was sent an invitation letter (n=17,068) or a control group that was not sent an invitation letter (n=14,384). In order to ensure access to screening, a Pap test clinic was held by a health centre in 20 of the 27 FSAs in the intervention group two to three weeks after the invitation letters were mailed.

Six months after the letters were mailed, 1,010 women in the intervention group (5.92%) and 441 women in the control group (3.06%) had a Pap test. Women who were sent an invitation letter were significantly more likely to have had a Pap test in the next six months compared to women who were not sent an invitation letter (Odds Ratio (OR) = 2.05, 95% Confidence Interval (CI) 1.78-2.37, $p<0.001$). However, women who had a Pap test clinic in their FSA were not significantly more likely to have had a Pap test compared to women who did not have a Pap test clinic in their FSA (OR = 1.04, 95% CI 0.82-1.32, $p=0.76$).

Using the Behavioural Model of Health Services Use as a theoretical framework, predisposing, enabling, and need factors that might influence screening participation were also included as covariables in multivariable logistic regression Generalized Estimating Equation (GEE) models. There was a significant main effect of age group ($p<0.001$), average household income ($p=0.01$), area of residence ($p=0.01$), residential mobility ($p=0.05$), and access ($p=0.001$). Interactions between the invitation letter and each

significant variable were tested. The interaction between the invitation letter and age group remained significant (p=0.02); therefore, the effectiveness of the invitation letter was related to age.

Of the 1,451 women who had a Pap test in the next six months, 21 women (1.45%) had a high-grade Pap test result. It is recommended that invitation letters continue to be sent to unscreened Manitoba women 30 to 69 years of age and that other provincial screening programs consider sending invitation letters to unscreened women.

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The results and conclusions presented are those of the author. No official endorsement by Manitoba Health is intended or should be inferred.

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List of Acronyms

ACG	adjusted clinical groups
AGC	atypical glandular cells
AJCC	American Joint Committee on Cancer
ASC-H	atypical squamous cells - high grade
ASC-US	atypical squamous cells - undetermined significance
BMHSU	Behavioural Model of Health Services Use
CA	Community area
CCHS	Canadian Community Health Survey
CIN	cervical intraepithelial neoplasia
CRT	cluster randomized trial
DA	dissemination area
DNA	deoxyribonucleic acid
FIGO	International Federation of Gynecology and Oncology
FSA	forward sortation area
GEE	generalized estimating equation
GLM	generalized linear model
HMO	Health Maintenance Organization
HPV	human papillomavirus
HSIL	high-grade squamous intraepithelial lesion
IARC	International Agency for Research Against Cancer
ICC	intraclass correlation coefficient
ICD-9	International Classification of Diseases 9th version

ICD-10-CA	International Classification of Diseases 10th version
ICD-O	International Classification of Diseases - Oncology
ITT	intention-to-treat
LBC	liquid-based cytology
LSIL	low-grade squamous intraepithelial lesion
MHPR	Manitoba Health Population Registry
MHSC	Manitoba Health Services Commission number
MISCAN	MIcro-simulation SCreening Analysis
NACI	National Advisory Committee on Immunization
NHIS	National Health Interview Survey
OR	odds ratio
PHIN	personal health identification number
PPV	positive predictive value
RCT	randomized controlled trial
RHA	regional health authority
RR	relative risk
RUB	resource utilization band
TNM	tumour, nodes, and metastases
WHO	World Health Organization
95% CI	95% confidence interval

Chapter 1. Introduction

1.1 Background

The incidence of cervical cancer is low in Canada primarily because of wide-spread screening using the Papanicolaou test (Pap test) (Liu S, Semenciw R, Probert A, & Mao Y, 2001; Miller AB et al., 2000). The Pap test identifies pre-cancerous cervical lesions that can be treated before the development of invasive cancer. Several analyses have found that approximately half of women diagnosed with invasive cervical cancer had not been screened in the previous five years or had never been screened (Ackerson K, Pohl J, & Low LK, 2008; Decker KM, McLachlin CM, Kan L, Rose J, Onysko J, Ahmad R, et al., 2011; Parboosingh EJ et al., 1996). Therefore, women who are not screened at the recommended interval or who have never been screened have a higher risk of developing cervical cancer and are more frequently diagnosed at an advanced stage (Decker KM, McLachlin CM, Kan L, Rose J, Onysko J, Ahmad R, et al., 2011; Health Canada, 2002; Woltman KJ & Newbold KB, 2007).

Invitation letters are used by organized cervical cancer screening programs in many developed countries to encourage participation among under-screened and unscreened women (Hakama M, Chamberlain J, Day NE, Miller AB, & Prorok PC, 1985; International Agency for Research on Cancer, 2005; Mitchell H et al., 1991; Patnick J, 2000). The aim of this study was to evaluate the effectiveness of cervical cancer screening invitation letters among unscreened women in Manitoba. Several previous studies from Europe, Australia, and North America have assessed the effectiveness of invitation letters with mixed results. Most of these studies were not population-based but focused on sub-groups such as women who belonged to a health maintenance

organization (HMO) or family practice, women who lived in an inner-city area, low-income women, or women from one ethnic group. Many studies had small sample sizes, did not use an intention-to-treat analysis (ITT), did not exclude women who were ineligible for screening, and did not use accurate address information.

In addition to these studies, three meta-analyses have examined the effect of invitation letters on cervical cancer screening participation. The Task Force on Community Preventive Services in the United States reviewed eight cervical cancer screening invitation letter studies; the median post-intervention increase in Pap test use was 9.8% (Baron RC et al., 2008). A meta-analysis by Tseng et al. (2001) that included ten randomized controlled trials (RCTs) (n=20,722) found that women who were sent an invitation letter were significantly more likely to have a Pap test compared to women who were not sent a letter (odds ratio (OR) =1.64, 95% confidence interval (CI) 1.49-1.80) (Tseng DS, Cox E, Plane MB, & Hla KM, 2001). In a Cochrane Systematic Review, Everett et al. (2011) reviewed twelve RCTs that compared the cervical cancer screening participation of women who were sent an invitation letter to women who were not sent a letter (n=99,651) (Everett T et al., 2011). Women who were sent an invitation letter had a significantly higher uptake of cervical cancer screening than women who were not sent an invitation letter (Relative Risk (RR) =1.44, 95% CI 1.24-1.52).

Within Canada, invitation letters have been used by only two cervical cancer screening programs (Saskatchewan and the Calgary Health Region in Alberta) (Performance Indicators Working Group, Cervical Cancer Prevention and Control Network, 2009). Although Manitoba has used various community-level interventions to improve screening rates such as posters, pamphlets, mass-media advertising, and an

annual, province-wide Pap test week, at least one third of Manitoba women have not had a Pap test in the last three years and 10% have no Pap test record in the screening registry (CervixCheck CancerCare Manitoba, 2011).

In order to increase participation, the screening program decided to mail invitation letters to unscreened Manitoba women 30 to 69 years of age. Unscreened was defined as a woman who had no cytology or colposcopy record in the screening registry, had never been diagnosed with an invasive gynaecological cancer, had not had a hysterectomy that included removal of the cervix, and had been a part of the screening registry for at least five years.

1.2 Purpose of the study and research questions

The purpose of this study was to evaluate the effectiveness of an invitation letter on cervical cancer screening participation among unscreened Manitoba women. The research questions addressed in this thesis are as follows:

1. To what extent does an invitation letter increase the cervical cancer screening participation of unscreened Manitoba women?
2. Is an invitation letter more effective for certain groups of women?
3. For women who were screened, does an invitation letter result in the identification of high-grade cervical abnormalities which could be treated before progression to invasive cancer?

A cluster randomized trial (CRT) was used in which all unscreened Manitoba women 30 to 69 years of age were randomly assigned by the forward sortation area (FSA) of their postal code (the first three digits) to an intervention group that was sent an invitation letter or a control group that was not sent an invitation letter. In addition, to

ensure access to screening, a Pap test clinic was held by community health centers in several of the FSAs that were sent invitation letters.

The theoretical framework used to guide the study was based on the Behavioural Model of Health Services Use (BMHSU) developed by R.M. Anderson (Andersen R, 2008; Andersen RM, 1995; Phillips KA, Morrison KR, Andersen R, & Aday LA, 1998). The BMHSU states that predisposing, enabling, and need factors at contextual and individual levels influence health care use (Andersen R, 2008). In this study, predisposing factors included visible minority status, immigration status, education, income, age, and health status. Enabling factors included area of residence, residential mobility, continuity of care, and opportunity to be screened. Need was measured by the baseline cervical cancer screening rate among women 30 to 69 years of age for each FSA.

This study is the first population-based randomized evaluation of the effectiveness of cervical cancer screening invitation letters in Canada. Unlike previous research, this study used a theoretical framework to guide the study and operationalize factors that might influence the relationship between an invitation letter and screening participation.

1.3 Organization of thesis

This thesis is presented as follows:

Chapter 1 provides an introduction to the thesis.

Chapter 2 reviews cervical cancer etiology, diagnosis, staging, treatment, and descriptive epidemiology.

Chapter 3 provides background information about international and Canadian cervical cancer screening including the screening process, screening delivery, and future developments that may affect cervical cancer screening.

Chapter 4 reviews factors that influence cervical cancer screening participation, previous cervical cancer screening invitation studies, and the limitations of these studies.

Chapter 5 provides background information about the CRT and the impact of choosing this type of study design. Options for analysis are also provided.

Chapter 6 provides background information about the BMHSU and how this theoretical framework was used to guide the study.

Chapter 7 explains the methods used to conduct this research.

Chapter 8 describes the study results including the characteristics of the study participants, screening rates, the time to Pap test, and the results of univariable and multivariable logistic regression models. Screening outcomes and the cost of the invitation letters are provided.

Chapter 9 summarizes the main study findings and compares this research to previous cervical cancer screening invitation letter studies. The study's strengths, limitations, generalizability, and unique contributions to the literature are also discussed.

Chapter 10 discusses the policy recommendations that arise from this research and future research questions.

Chapter 2. Cervical Cancer Etiology and Epidemiology

2.1 Introduction

Cervical cancer is caused by infection with the human papillomavirus (HPV) (Dawar M, Deeks S, & Dobson S, 2007; Trottier H & Franco EL, 2006). Over 530,000 women world-wide are diagnosed with cervical cancer each year including 1,300 Canadian women (Canadian Cancer Society & National Cancer Institute of Canada, 2010; International Agency for Research on Cancer, 2008). Approximately 275,000 women die from cervical cancer each year including 370 Canadian women (Canadian Cancer Society & National Cancer Institute of Canada, 2010). In developed countries such as Canada that have wide-spread cervical cancer screening, cervical cancer incidence and mortality have decreased dramatically over the past 40 years. This chapter reviews cervical cancer etiology, diagnosis, staging, treatment, and descriptive epidemiology.

2.2 Etiology

The cervix is the cylindrically-shaped lower third of the uterus that extends into the vagina. Cervical cancer is a malignancy of the cells that line the surface of the cervix. Cervical cancers that arise from the squamous cells that cover the outer surface of the cervix are called squamous cell carcinomas and those that arise from the glandular (columnar) cells in the cervical canal are called adenocarcinomas (Schiffman M & Hildesheim A, 2006). Approximately 80% of cervical cancers are squamous cell carcinomas, 15% are adenocarcimomas, and 5% are mixed adenosquamous cell carcinomas and other rare histological types (Schiffman M & Hildesheim A, 2006).

Cervical cancer begins locally and then extends into the paracervical tissues (those adjacent to the cervix), the pelvic organs, regional lymph nodes, and finally, distant organs (Benedet JL, Pecorelli S, Ngan HYS, & Hacker NF, 2000).

Interest in cervical cancer etiology began in the mid-nineteenth century. Cervical cancer was believed to be a "disease of poverty" that occurred exclusively among women who were "chronically overworked and underfed, poor, prolific, harassed, worried, drained by lactation, and reposeless" (Moscucci O, 2005). Physicians also found that the rate of cervical cancer was higher among prostitutes and women married to men whose first wives had died from cervical cancer and lower among nuns who had never been sexually active (Shepherd LJ & Bryson P, 2008). From these observations, they concluded that cervical cancer was caused by a sexually transmitted agent (Shepherd LJ & Bryson P, 2008). It is now known that all cervical cancers and pre-cancerous changes can be attributed to infection with HPV (Dawar M et al., 2007; Trottier H & Franco EL, 2006).

HPV deoxyribonucleic acid (DNA) sequences in cancerous cervical cells were initially observed in 1985 (Zur Hausen H, 1985). In 1994, the first of several studies found that HPV infection was a strong risk factor for the development of cervical cancer (Munoz N, Bosch FX, & Shah KV, 1994). More than 118 different HPV types have since been isolated and sequenced; 40 infect the genital tract and 12 are classified as carcinogens (Bouvard V et al., 2009; de Villiers E-M, Fauquet C, Broker TR, Bernard H-U, & zur Hausen H, 2004). In 2002, the International Agency for Research Against Cancer (IARC) coordinated a study of invasive cervical cancer etiology that included over 20 countries. Over 90% of cervical cancers from each country contained HPV DNA

with the inclusion of "possible" infections raising the likelihood to 100% (Bosch FX, Lorincz A, Munoz N, Meijer C, & Shah K, 2002; Munoz N et al., 2003). The most common HPV types involved in cervical cancer are types 16, 18, 31, 33, 35, 45, 52, and 58 (de Sanjose S et al., 2010). In an analysis of the distribution of HPV genotypes among women with invasive cervical cancer in 38 countries, de Sanjose et al. (2010) found that HPV types 16 and 18 caused 70% of cervical cancers, HPV type 45 caused 6% of cervical cancers, HPV types 31, 33, 35, 52, and 58 caused 15% of cervical cancers, and other HPV types caused the remaining 9% of cervical cancers (de Sanjose S et al., 2010). HPV types 16, 18, 31, 33, and 45 account for 80% of squamous cell carcinomas and HPV types 16, 18, 33, 45, and 59 account for 94% of adenocarcinomas (Bosch FX & de Sanjose S, 2003).

HPV infections are transmitted sexually by direct epithelial (skin or mucosa) to epithelial contact (National Advisory Committee on Immunization, 2007). Cervical infection with HPV is very common; 2% to 20% of the world's female population has detectable HPV DNA on the cervix at any time (Bosch FX & de Sanjose S, 2003). The primary risk factors for HPV infection are an increasing number of sexual partners, early age at onset of sexual intercourse, and the likelihood that each sexual partner also had an HPV infection (Bosch FX, 2003).

Although it has been well established that HPV infection is the necessary cause of cervical cancer, it may not be sufficient as a very small number of infected women develop cervical cancer. Therefore, other co-factors such as oral contraceptive use, parity (number of children), and smoking influence the risk of progression from a transient infection to invasive cervical cancer. In a pooled analysis of case-control IARC studies

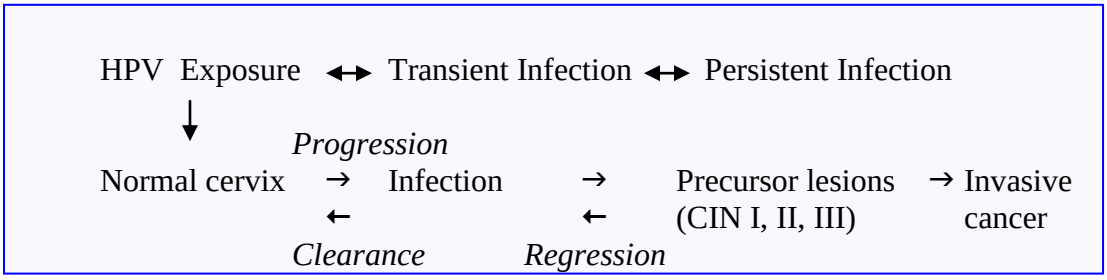
of women who tested positive for HPV infection, the use of oral contraceptives for longer than five years was significantly associated with the likelihood of being diagnosed with cervical cancer (OR=3.4, 95% CI 2.1-5.5) (Moreno V et al., 2002). The odds of being diagnosed with invasive cervical cancer in women with seven or more full-term pregnancies was almost four times greater compared to nulliparous women (OR=3.8, 95% CI 2.7-5.5) and the risk increased with increasing number of full-term pregnancies (Munoz N et al., 2002). Hormonal, nutritional, and immunologic mechanisms have been hypothesised as the biological explanation for the associations (Castellsague X & Munoz N, 2003).

The effects of smoking have been examined in many case-control studies; all consistently show a significant association between smoking and cervical cancer (ORs from 2 to 5) (Castellsague X & Munoz N, 2003). Women who smoke have cervical HPV infections of longer duration with a lower probability of clearance than women who do not smoke (Giulian AR et al., 2002).

Figure 1 illustrates the progressive development of cervical cancer. The prevalence of HPV infection peaks during adolescence and the early 20s after the initiation of sexual activity and HPV exposure (National Advisory Committee on Immunization, 2007). HPV infections are usually transient but if the infection cannot be cleared by the immune system, it may become persistent leading to mild dysplasia (cervical intraepithelial neoplasia (CIN) I) and, if clearance still does not occur, eventually to moderate or severe dysplasia (CIN II and CIN III). The risk of a pre-cancerous lesions peaks six to 12 months after initial infection but approximately 90% of women who are infected with HPV will clear the infection within 24 months without

progression to cervical cancer (National Advisory Committee on Immunization, 2007; Woodman CB, Collins S, Winter H, & et al., 2001).

Figure 1 Cervical cancer development



Source: Adapted from International Agency for Research on Cancer, 2005; Schiffman M & Hildesheim A, 2006. Used with permission from the World Health Organization Press and the New England Journal of Medicine.

2.3 Diagnosis, staging, and treatment

Diagnosis

Cervical cancer is diagnosed following an abnormal cytology result or after the development of clinical symptoms. Women who have an abnormal high-grade cytology result or symptoms are usually referred for colposcopy. A colposcopy is a stereoscopic, magnified examination of the cervix using a colposcope. The aim is to examine the cervical transformation zone and identify abnormal areas. A biopsy of the abnormal area is often performed in order to histologically confirm the diagnosis.

Staging

Staging describes the extent or severity of cancer based on tumour size and whether the cancer has metastasized to lymph nodes or distant sites. Staging for cervical cancer is based on histology and clinical examination (Benedet JL et al., 2000; International Agency for Research on Cancer, 2005). Two staging systems are used: the

International Federation of Gynaecology and Obstetrics (FIGO) staging classification system and the American Joint Committee on Cancer (AJCC) tumour, node, and metastases (TNM) staging system (Benedet JL et al., 2000; Edge SB et al., 2009). The systems are similar and assign a stage of disease from I to IV; stage I is the earliest stage where the cancer has invaded the cervix but it is not growing outside the uterus, stage II describes disease that has extended beyond the cervix to adjacent organs or structures, stage III represents more extensive involvement, and stage IV is the most advanced stage where the cancer has spread to nearby organs or other areas of the body (Benedet JL et al., 2000).

Treatment

Treatment depends on the stage at diagnosis, the importance of preserving fertility, the woman's age, and her health status (Benedet JL et al., 2000). For early stage cancers (stages I and II), the recommended treatment includes conization, hysterectomy, and pelvic lymphadenectomy with the option of radiation therapy (Benedet JL et al., 2000; International Agency for Research on Cancer, 2005). Conization of the cervix is the excision of a cone-shaped or cylindrical wedge from the cervix that includes the transformation zone and all or a portion of the endocervical canal. Conization can be performed by scalpel (cold-knife), laser, or electrosurgical excision. Because the risk of recurrence increases with the presence of positive nodes, chemotherapy may also be recommended (Benedet JL et al., 2000). The standard treatment for more advanced cervical cancers (stages III and IV) is primary radiation with concurrent chemotherapy (Benedet JL et al., 2000; International Agency for Research on Cancer, 2005).

2.4 Descriptive Epidemiology

Descriptive epidemiology is a depiction of the place and time of disease occurrence and the characteristics of the persons who are affected by the disease. By observing these trends in time, place, and persons, information can be learned about the nature and risk of disease. The extent of disease in a population is measured by incidence, mortality, survival, and prevalence rates. The quality of these measures depends on the completeness and type of disease surveillance. In Manitoba, surveillance is active and legislation exists that requires the reporting of all cancers leading to a high level of case completeness. In other areas of the world, passive surveillance is used which may influence case completeness by either overestimating or underestimating the number of cases (Parkin DM & Bray F, 2009). Therefore, the quality of information needs to be taken into consideration when comparing disease rates between areas.

2.4.1 International

Incidence and mortality

Incidence is the number of new cases of disease in a population over a period of time. Mortality is the number of individuals who have died from the disease over a period of time. Incidence and mortality rates are the fundamental measures of disease surveillance because they are a direct indication of disease risk. By comparing incidence and mortality rates between different groups, factors that might influence the risk of disease and death can be identified.

Cervical cancer is the third most common cancer in women world-wide with an estimated 530,000 new cases and 275,000 deaths in 2008 (International Agency for Research on Cancer, 2008). This equates to an age-standardized incidence rate of 15.3

per 100,000 women and an age-standardized mortality rate of 7.8 per 100,000 women (International Agency for Research on Cancer, 2008). Approximately 80% of cervical cancers occur in developing countries where it accounts for 13% of all female cancers (International Agency for Research on Cancer, 2008). In developed countries, cervical cancer accounts for 3.6% of female cancers (Parkin DM, Bray F, & Pisani P, 2005).

Table 1 shows age-standardized incidence and mortality rates per 100,000 person-years and the mortality-to-incidence rate ratio (MR:IR) for 1993 to 2002 by region from the GLOBOCAN database developed by IARC (Kamangar F et al., 2006). The MR:IR ratio is an indirect measure of cancer survival; an MR:IR ratio that approaches 1.0 suggests limited survival.

Table 1 Age-standardized incidence and mortality rates per 100,000 person-years and mortality to incidence rate ratio by region, 1993-2002

Region		**Incidence**		**Mortality**		**MR:IR**
		Number	Rate	Number	Rate	Ratio
World	More developed	83,437	10.3	39,512	4.0	0.39
	Less developed	409,269	19.1	233,727	11.2	0.59
Continent	Oceania	1,063	7.4	330	2.0	0.27
	Europe	59,931	11.9	29,812	5.0	0.42
	Central and South America	65,493	29.0	29,524	13.4	0.46
	Asia	265,744	15.4	142,679	8.4	0.55
	Africa	78,887	29.3	61,671	23.1	0.79

Note: Age-standardized to the world standard population (Segi M, 1960). Person-years are the sum of the periods of time-at-risk for each person.

Source: Kamangar F et al., 2006. Used with permission from the American Society of Clinical Oncology.

In more developed regions (Europe, Australia, New Zealand, North America, and Japan), the age-standardized cervical cancer incidence rate was 10.3 per 100,000 person-years and the age-standardized mortality rate was 4.0 per 100,000 person-years. In less developed regions (Africa, Central America, South America, Asia except Japan, Caribbean, Melanesia, Micronesia, and Polynesia), the age-standardized incidence rate was 19.1 per 100,000 person-years and the age-standardized mortality rate was 11.2 per 100,000 person-years. Age-standardized incidence and mortality rates were highest in Africa (29.3 per 100,000 person-years and 23.1 per 100,000 person-years respectively) and lowest in Oceania (7.4 per 100,000 person-years and 2.0 per 100,000 person-years respectively). The MR:IR ratio was 0.39 in more developed regions and 0.59 in less developed regions. The MR:IR ratio varied from 0.27 in Oceania to 0.79 in Africa.

In less developed countries, invasive cervical cancer rates are low at young ages but subsequently increase and, after 40 years of age, exceed the rates in more developed countries (Bhurgri Y et al., 2008; Kamangar F et al., 2006). In developed countries, rates plateau after the age of 40 (Kamangar F et al., 2006).

Survival

Survival is the proportion of individuals diagnosed with a disease alive at the beginning of a time interval who survive to the end of the interval (i.e. a five-year period). Relative survival is the ratio of the observed survival to the expected survival in the general population of the same age and sex.

Cervical cancer survival depends primarily on stage and age at diagnosis (Henley SJ, King JB, German RR, Richardson LC, & Plescia M, 2010). In developing countries, 60% to 80% of cases are diagnosed at stage III or IV and have a low probability of

survival (Sankaranarayanan R et al., 2010). The five-year age-standardized relative survival for women diagnosed with cervical cancer from 1990 to 2001 using data from 25 cancer registries in 12 countries was 13% in Uganda, 22% in Gambia, 37% in the Philippines, 46% in India, 53% in Costa Rica, and 61% in Thailand (Sankaranarayanan R et al., 2010). When including the stage at diagnosis, the five-year age-standardized relative survival (in Costa Rica, India, Philippines, and Thailand) was 73.2% for women diagnosed with localized cervical cancer, 47.2% for women diagnosed with regional cervical cancer, and 7.4% for women diagnosed with metastasized cervical cancer (Sankaranarayanan R et al., 2010).

In contrast, the five-year age-standardized relative survival for women diagnosed with cervical cancer from 1995 to 2002 using data from 82 cancer registries in 23 European countries was 66.7% (Sant M et al., 2009). Relative five-year age-standardized survival ranged from 51.5% in Poland to 66.9% in France (Sant M et al., 2009). Survival was significantly higher than the European mean in northern Europe and significantly lower in Poland, Portugal, England, and Wales (Sant M et al., 2009). Survival among European women decreased with increasing age from 80.4% for women 15 to 44 years of age to 36.9% for women 75 years of age or older (Sant M et al., 2009). When including the stage at diagnosis, the five-year age-standardized relative survival for women in the United States (US) diagnosed from 1999 to 2006 was 92% for women diagnosed with localized cervical cancer, 58% for women diagnosed with regional cervical cancer, and 17% for women diagnosed with metastasized cervical cancer (Henley SJ et al., 2010).

Although a few studies have found no difference in survival by cervical cancer morphology, the majority of studies have shown that the five-year survival rate is 10% to

20% lower for adenocarcinoma compared to squamous cell carcinoma (Gien LT, Beauchemin M-C, & Thomas G, 2010; Sant M et al., 2009). The difference may be related to the presence of more adverse prognostic factors in cases of adenocarcinoma such as the size of the tumour and lymph node metastases (Gien LT et al., 2010).

2.4.2 Canada

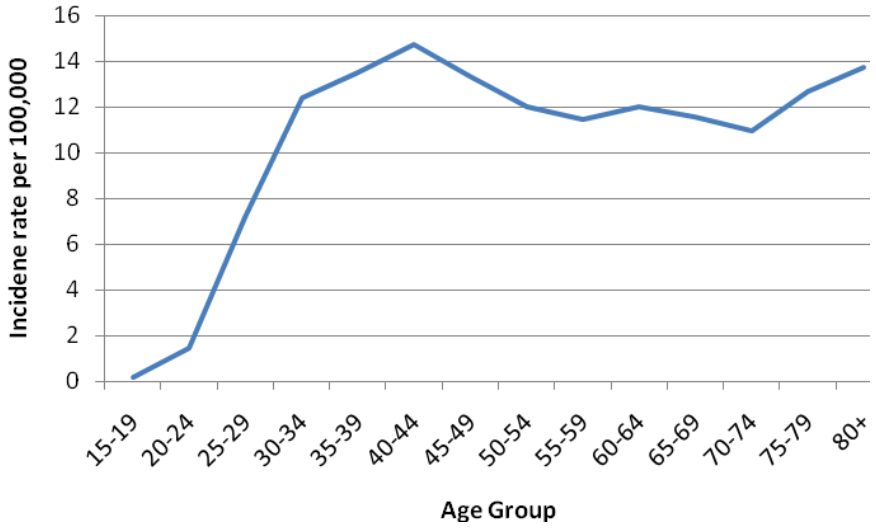
Incidence and mortality

In Canada, cervical cancer accounts for approximately 1.7% of new cancer cases and 1.1% of deaths due to cancer in women (Canadian Cancer Society's Steering Committee on Cancer Statistics, 2011). In 2007, 1,401 Canadian women were diagnosed with invasive cervical cancer and 375 women died from the disease (Canadian Cancer Society's Steering Committee on Cancer Statistics, 2011). The lifetime risk of developing cervical cancer among Canadian women is 0.7% (1 in 138.2) and the lifetime risk of dying from cervical cancer is 0.3% (1 in 384.6) (Canadian Cancer Society & National Cancer Institute of Canada, 2006). The age-standardized incidence rate was 8 per 100,000 in 2007 and the age-standardized mortality rate was 2 per 100,000 in 2006 (Canadian Cancer Society's Steering Committee on Cancer Statistics, 2011).

Figure 2 shows invasive cervical cancer incidence by age group from 1998 to 2007. Cervical cancer incidence peaks at 40 to 45 years of age (14.7 per 100,000), gradually declines (10.9 per 100,000 for women 70 to 74 years of age), and then increases slightly for women over 80 years of age (13.7 per 100,000) (Surveillance and Risk Assessment Division, PHAC, Statistics Canada, & Canadian Council of Cancer Registries, 2009). Additionally, the incidence of cervical cancer is approximately three times higher among First Nations and Inuit women than the general population (Hislop

TG, Deschamps M, Band PR, Smith JM, & Clarke HF, 1992; Hislop TG et al., 1996; Martin B, Smith W, Orr P, & Guijon F, 1995).

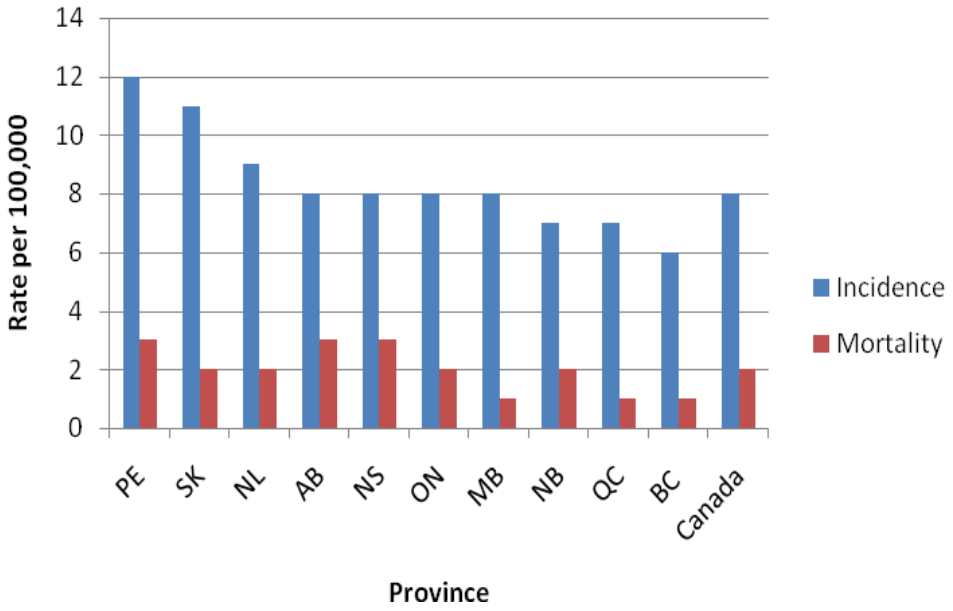
Figure 2 Invasive cervical cancer incidence by age group, Canada, 1998 to 2007



Data source: Surveillance and Risk Assessment Division, PHAC et al., 2009.

Figure 3 shows the age-standardized incidence for 2007 and 2008 and mortality for 2006 for Canada and each province (Canadian Cancer Society's Steering Committee on Cancer Statistics, 2011). Incidence varied from 12 per 100,000 in Prince Edward Island to 6 per 100,000 in British Columbia. Mortality varied from 3 per 100,000 in Prince Edward Island, Alberta, and Nova Scotia to 1 per 100,000 in Manitoba, Québec, and British Columbia.

Figure 3 Age-standardized invasive cervical cancer incidence (2007 and 2008) and mortality (2006) by province

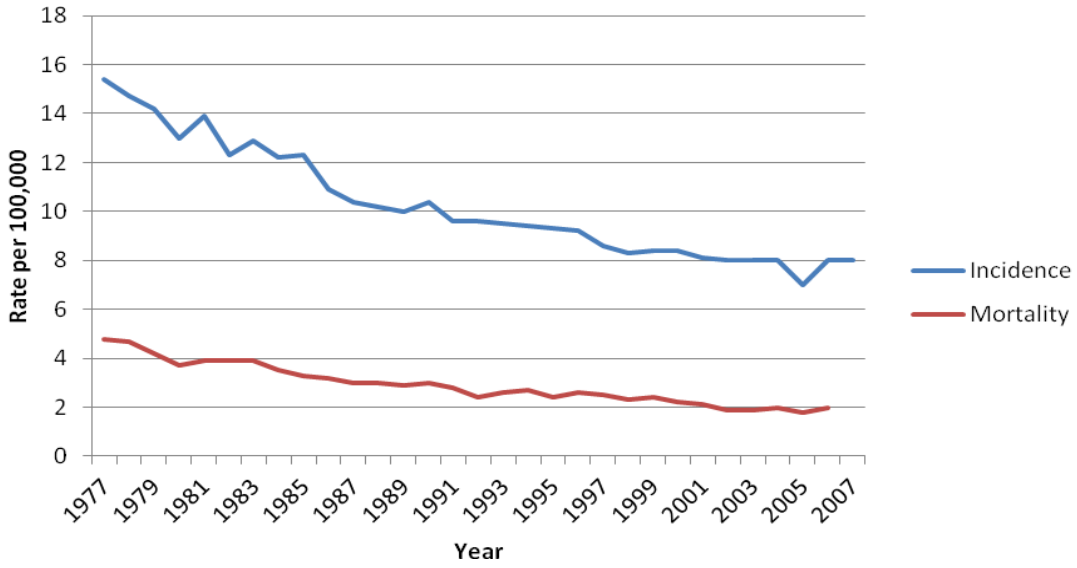


Notes: For incidence, 2007 for Canada, Ontario, Québec, Newfoundland and Labrador and 2008 for British Columbia, Alberta, Saskatchewan, Manitoba, New Brunswick, Nova Scotia, Prince Edward Island; For mortality, 2006 for Canada and all provinces.

Data source: Canadian Cancer Society's Steering Committee on Cancer Statistics, 2011.

Cervical cancer incidence and mortality has declined in Canada since the 1970s (Figure 4) (Canadian Cancer Society's Steering Committee on Cancer Statistics, 2011; Liu S et al., 2001). The age-standardized incidence rate declined from 15.4 per 100,000 in 1977 to 8.0 per 100,000 in 2007 and the age-standardized mortality rate declined from 4.8 per 100,000 in 1977 to 2.0 per 100,000 in 2006.

Figure 4 Age-standardized invasive cervical cancer incidence and mortality, Canada, 1977 to 2007



Data source: Canadian Cancer Society's Steering Committee on Cancer Statistics, 2011.

Prevalence

Prevalence is the number of individuals who have a disease at a given point in time. Prevalence depends on disease duration and incidence; therefore, prevalence indicates the burden of the disease in a population. However, high prevalence does not necessarily signify high risk; it may be a reflection of high survival. Similarly, low prevalence may reflect a highly fatal disease or a rapid cure as well as low incidence.

As of 2005, the five-year age-standardized cervical cancer prevalence rate in Canada was 24.6 per 100,000 (Ellison LF & Wilkins K, 2009). This represents three percent of all ten-year prevalent cancer cases among Canadian women (Ellison LF & Wilkins K, 2009). The five-year prevalence rates in 2005 by age group were 32.3 per 100,000 for women 20 to 39 years of age, 61.2 per 100,000 for women 40 to 49 years of age, 49.9 per 100,000 for women 50 to 59 years of age, 45.6 per 100,000 for women 60 to 69 years of

age, 40.4 per 100,000 for women 70 to 79 years of age, and 34.8 per 100,000 for women 80 years of age and older (Ellison LF & Wilkins K, 2009).

Survival

The estimated five-year age-standardized relative survival for Canadian women diagnosed with invasive cervical cancer from 2004 to 2006 was 73% (Ellison LF & Wilkins K, 2010). Ten-year survival decreased slightly to 70% which suggests that the prognosis is very good for women who survive for five years after diagnosis (Ellison LF & Wilkins K, 2010). However, the estimated five-year relative survival decreased with increasing age at diagnosis (84% for women 15 to 44 years of age, 71% for women 45 to 54 years of age, 69% for women 55 to 64 years of age, 57% for women 65 to 74 years of age, and 42% for women 75 years of age and older) (Ellison LF & Wilkins K, 2010).

2.4.3 Manitoba

Incidence

In 2008, invasive cervical cancer was the 11th most common cancer in Manitoba women and accounted for 1.7% of all cancers detected (Epidemiology and Cancer Registry, CancerCare Manitoba, 2011). The age-standardized incidence rate was 8.2 per 100,000 women. Table 2 shows the number of cervical cancer cases and the incidence rates per 100,000 by age group for 2008 (Epidemiology and Cancer Registry, CancerCare Manitoba, 2011). Cervical cancer was very low in women less than 29 years of age (1.3 per 100,000) and highest for women 30 to 39 years of age (21.8 per 100,000).

Table 2 Number of cervical cancer cases and age-specific incidence rates per 100,000 women in Manitoba, 2008

Age Group	Number of cases	Incidence rate per 100,000
0-29	3	1.3
30-39	17	21.8
40-49	12	13.4
50-59	6	7.4
60-69	3	5.5
70-79	4	10.7
80+	5	15.0
Total	50	8.2

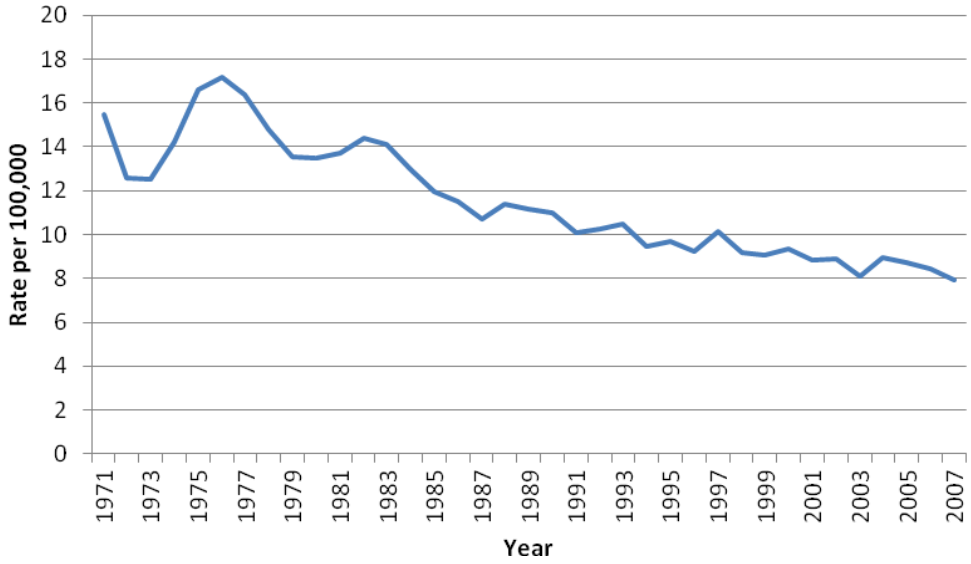
Note: The age groups with five or fewer cases have been published previously by CancerCare Manitoba.

Data source: Epidemiology and Cancer Registry, CancerCare Manitoba, 2011.

In 2008, 46% of women diagnosed with invasive cervical cancer were diagnosed at stage I, 14% were stage II, 16% were stage III, 12% were stage IV, and 12% had an unknown stage (Epidemiology and Cancer Registry, CancerCare Manitoba, 2011).

Figure 5 illustrates the change in cervical cancer incidence in Manitoba from 1971 to 2007 (Demers A, Harrison M, Musto G, Decker KM, & Lotocki R, 2003; Department of Epidemiology and Cancer Registry, CancerCare Manitoba, 2010). A three-year moving average was used to smooth out short-term fluctuations and highlight long-term trends (Porta M, 2008). The age-standardized incidence rate declined from 15.5 per 100,000 in 1971 to 8.5 per 100,000 in 2006 although the rate remained fairly stable from 1995 onward.

Figure 5 Age-standardized cervical cancer incidence rate per 100,000 for Manitoba, 1971 to 2007

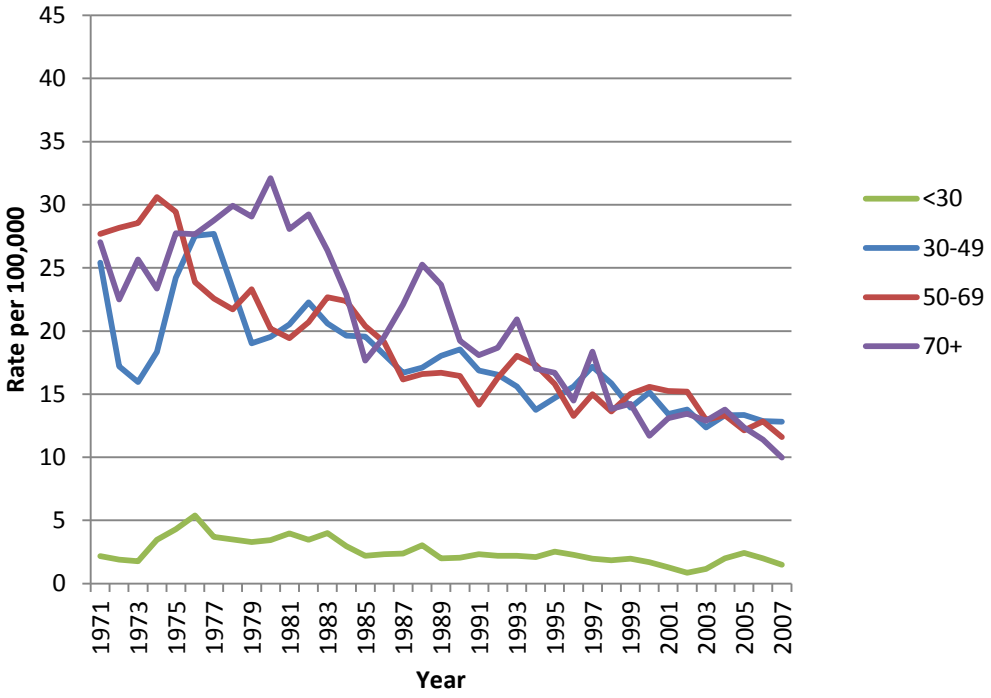


Notes: Three-year moving average.

Data sources: Demers A et al., 2003; Epidemiology and Cancer Registry, CancerCare Manitoba, 2011.

Figure 6 shows the change in cervical cancer incidence by age group from 1971 to 2007 (Demers A et al., 2003; Department of Epidemiology and Cancer Registry, CancerCare Manitoba, 2010). Cervical cancer incidence remained low for the less than 30 age group and declined slightly over time from 2.2 per 100,000 in 1971 to 2.0 per 100,000 in 2007. The incidence rates for women 30 to 49, 50 to 69, and 70 years of age and older declined significantly (25.4 per 100,000 to 12.9 per 100,000 for the 30 to 49 age group, 27.7 per 100,000 to 12.8 per 100,000 for the 50 to 69 age group, and 27.0 per 100,000 to 11.4 per 100,000 for 70 years of age and older) and have converged over time.

Figure 6 Cervical cancer incidence rates per 100,000 for Manitoba by age group, 1971 to 2007

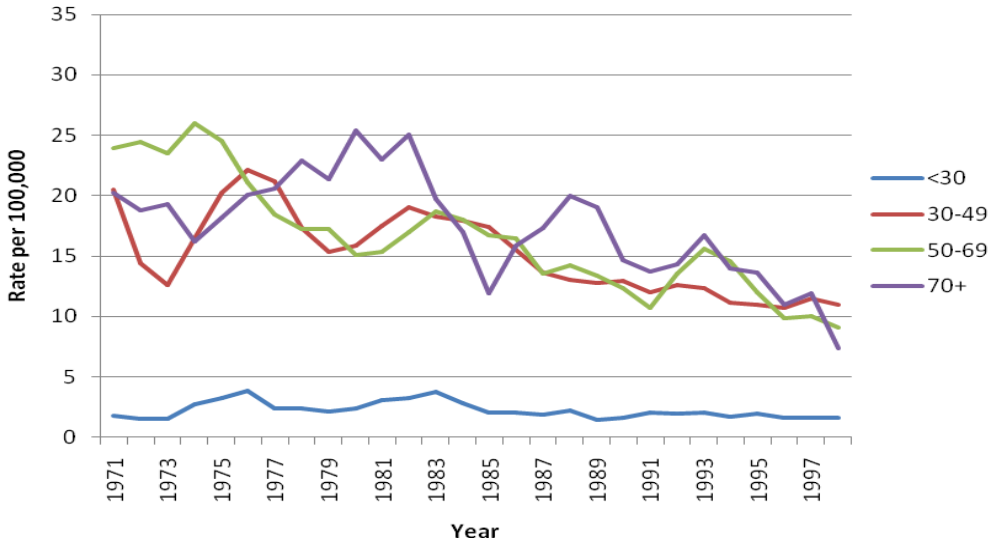


Note: Three-year moving average.

Data sources: Demers A et al., 2003; Epidemiology and Cancer Registry, CancerCare Manitoba, 2011.

The age-standardized incidence rate of squamous cell carcinoma decreased from 12.6 per 100,000 in 1971 to 6.2 per 100,000 in 1998 (Demers A et al., 2003). Figure 7 shows the incidence rate of squamous cell carcinoma by age group (Demers A et al., 2003). The incidence rate decreased slightly for the less than 30 age group (from 1.8 per 100,000 to 1.6 per 100,000) and decreased significantly for the other age groups (20.5 per 100,000 to 10.9 per 100,000 for the 30 to 39 age group, 23.9 per 100,000 to 9.1 per 100,000 for the 50 to 69 age group, and 20.2 per 100,000 to 7.4 per 100,000 for 70 year of age and older).

Figure 7 Squamous cell carcinoma incidence rate per 100,000 by age group for Manitoba, 1971 to 1998

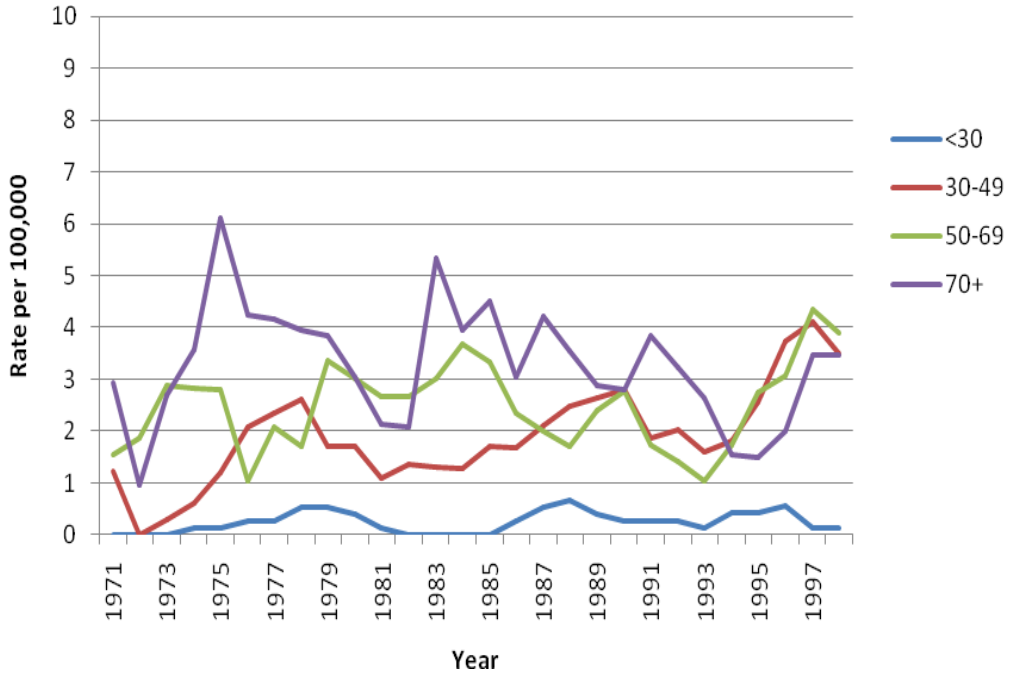


Notes: Three-year moving average.

Data source: Demers A et al., 2003.

In contrast, the age-standardized incidence rate of adenocarcinoma increased from 0.9 per 100,000 in 1971 to 2.1 per 100,000 in 1998 (Demers A et al., 2003). Figure 8 shows the incidence rate of adenocarcinoma by age group (Demers A et al., 2003). The incidence rate remained close to zero for the less than 30 age group and increased for all other age groups (1.2 per 100,000 to 3.5 per 100,000 for the 30 to 49 age group, 1.5 per 100,000 to 3.9 per 100,000 for the 50 to 69 age group, and 2.9 per 100,000 to 4.5 per 100,000 for the 70 year and older age group). Overall, the proportion of women diagnosed with adenocarcinoma increased for all age groups from 7% to 11% between 1970 and 1994 and from 11% to 22% between 1994 and 1998 (Demers A et al., 2003).

Figure 8 Adenocarcinoma of the cervix incidence rate per 100,000 by age group for Manitoba, 1971 to 1998



Notes: Three-year moving average.

Data source: Demers A et al., 2003.

Cervical cancer incidence in Manitoba differs by geography and ethnicity. From 1985 to 2002, cervical cancer incidence ranged from less than 2.2 to 7.8 cases per 100,000 women in the southern, rural areas of the province and the non-core neighbourhoods of Winnipeg to 20.4 to 39.9 cases per 100,000 women in northern Manitoba and the central core of the Winnipeg (Green C, Demers A, & Decker KM, 2006). In addition, the risk of invasive cervical cancer was higher in the northern part of the province (RR=1.74) and the central core of Winnipeg (RR=1.50) and lower in southern, rural Manitoba (RR=0.53) (Green C et al., 2006). From 1984 to 1997, the age-standardized cervical cancer incidence rate was significantly higher among First Nations,

Inuit, and Métis women compared to non-Aboriginal women living in Manitoba (34.1 per 100,000 compared to 9.5 per 100,000) (Young TK, Kliewer E, Blanchard J, & Mayer T, 2000).

Mortality

In 2008, invasive cervical cancer was the 10th most common cause of cancer deaths in Manitoban women (Epidemiology and Cancer Registry, CancerCare Manitoba, 2011). The age-standardized mortality rate was 3.3 cases per 100,000 (Epidemiology and Cancer Registry, CancerCare Manitoba, 2011). Table 3 shows the number of deaths due to cervical cancer and the mortality rates per 100,000 by age group for 2008 (Epidemiology and Cancer Registry, CancerCare Manitoba, 2011). The total number of deaths was 20 and the mortality rate was highest for the 70 to 79 age group (10.8 per 100,000).

Table 3 Number of cervical cancer deaths and age-specific mortality rate per 100,000 women, Manitoba, 2008

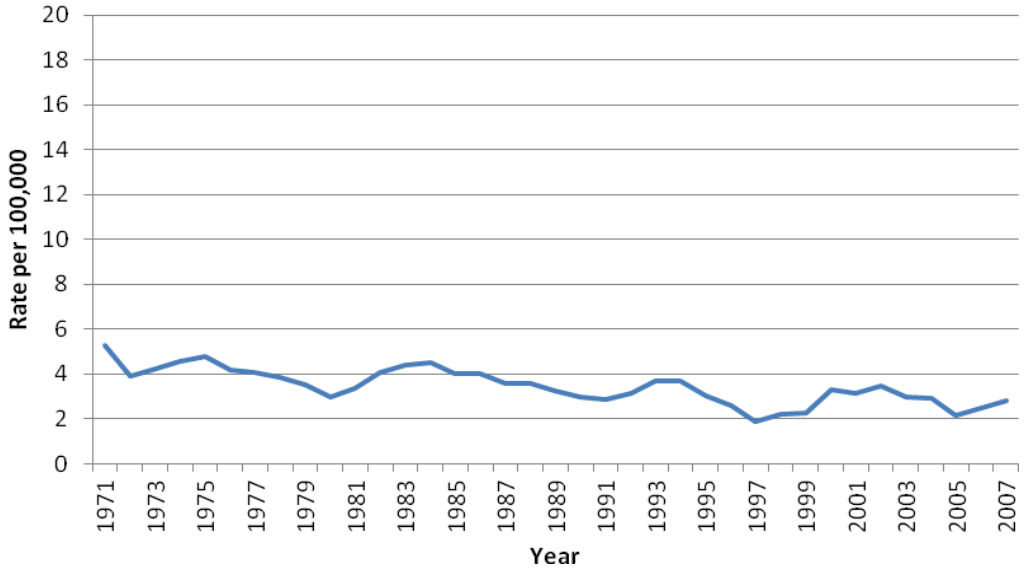
Age Group	Number of deaths	Mortality rate per 100,000
0-29	1	0.4
30-39	2	2.6
40-49	3	3.4
50-59	6	7.4
60-69	1	1.8
70-79	4	10.8
80+	3	9.0
Total	20	3.3

Note: The age groups with five or fewer cases have been published previously by CancerCare Manitoba.

Data source: Epidemiology and Cancer Registry, CancerCare Manitoba, 2011.

Figure 9 illustrates the change in the age-standardized cervical cancer mortality rate from 1971 to 2007 (Demers A et al., 2003; Epidemiology and Cancer Registry, CancerCare Manitoba, 2011). This information is displayed by age group in Figure 10 (Demers A et al., 2003; Epidemiology and Cancer Registry, CancerCare Manitoba, 2011). The age-standardized mortality rate declined from 5.3 per 100,000 in 1971 to 2.5 per 100,000 in 2007. Mortality for women less than 30 years of age has remained consistently low over time (0.3 per 100,000 in 1971 and 0.1 per 100,000 in 2007). Mortality rates decreased significantly from 1971 to 2006 for all other age groups (6.1 per 100,000 to 2.3 per 100,000 for the 30 to 49 year age group, 12.9 per 100,000 to 3.9 per 100,000 for the 50 to 69 age group, and 14.6 per 100,000 to 7.1 per 100,000 for the 70 years of age and older age group).

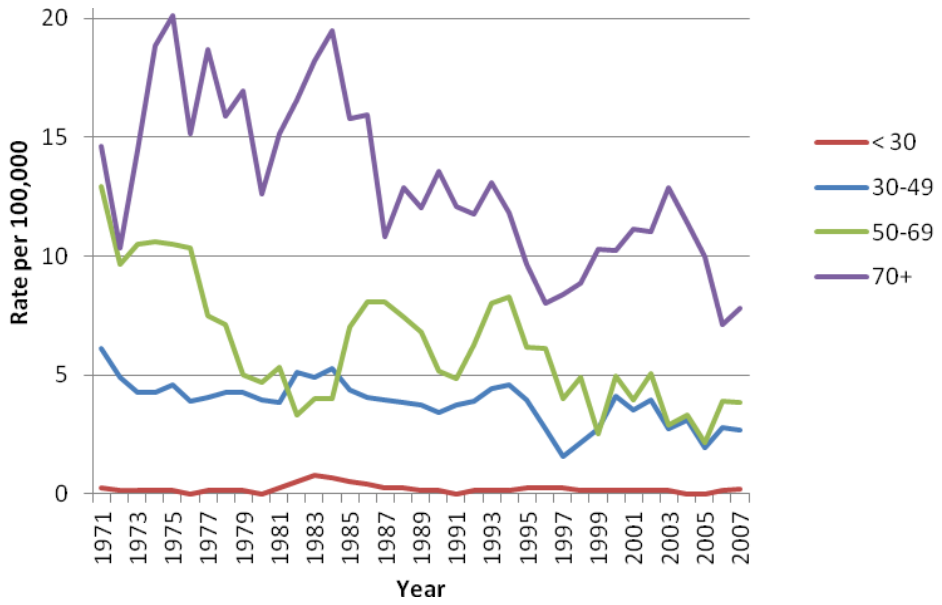
Figure 9 Age-standardized cervical cancer mortality rate per 100,000 for Manitoba, 1971 to 2007



Note: Three-year moving average.

Data sources: Demers A et al., 2003; Epidemiology and Cancer Registry, CancerCare Manitoba, 2011.

Figure 10 Cervical cancer mortality rates per 100,000 by age group for Manitoba, 1971 to 2007

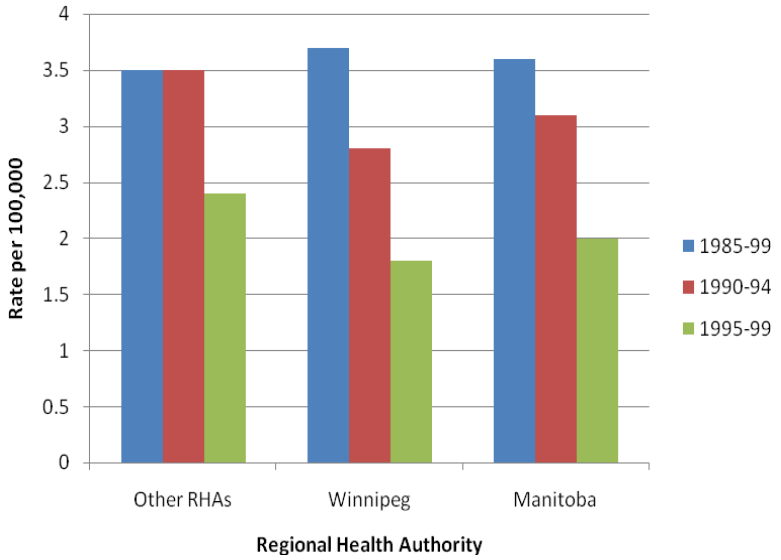


Note: Three-year moving average.

Data sources: Demers A et al., 2003; Epidemiology and Cancer Registry, CancerCare Manitoba, 2011.

Figure 11 shows the age standardized mortality rates for the Regional Health Authority (RHA) of Winnipeg, all other RHAs combined (because of the small number of deaths), and Manitoba for 1985-1989, 1990-1994, and 1995-1999 (Demers A et al., 2003). Approximately half of the population of Manitoba resides in the RHA of Winnipeg. The mortality rate for the RHA of Winnipeg decreased from 3.7 per 100,000 in 1985-1989 to 2.8 per 100,000 in 1990-1994 to 1.8 per 100,000 in 1995-1999. Mortality rates all other RHAs also decreased from 3.5 per 100,000 in 1985-1989 and 1990-1994 to 2.4 per 100,000 in 1995-1999 but remained higher than rates for the RHA of Winnipeg. Mortality rates in the other RHAs and Winnipeg were not significantly different than the Manitoba rate for each of the three time periods.

Figure 11 Age standardized invasive cervical cancer mortality rates by Regional Health Authority in Manitoba, 1985 to 1989, 1990 to 1994, and 1995 to 1999



Data source: Demers A et al., 2003.

Survival

The five-year cumulative relative survival rate for Manitoba women diagnosed with invasive cervical cancer was 68% from 1985 to 1989, 65% from 1990 to 1994, and 72% from 1995 to 1999[1](Demers A et al., 2003). Compared to the 1985 to 1989 period, five-year survival was not significantly different from 1990 to 1994 or 1995 to 1999.

Five-year survival was highest for women 20 to 29 years of age (88%) and decreased with age (84% for 30 to 39 years of age, 64% for 40 to 49 years of age, 66% for 50 to 59 years of age, 63% for 60 to 69 years of age, and 42% for 70 years of age and older) (Demers A et al., 2003). Compared to women 20 to 29 years of age, survival was

[1] Cumulative relative survival describes the cancer-specific risk of death over five years after diagnosis. It is the relative survival (the ratio of the observed survival to the survival expected in the general population of the same age and sex) multiplied over five consecutive years.

significantly lower for women 40 to 49, 50 to 59, 60 to 69 and 70 years of age and older. Women diagnosed with adenocarcinoma had a slightly lower five-year survival rate than women diagnosed with squamous cell carcinoma (65% versus 68%) although the difference was not significant (Demers A et al., 2003).

Prevalence

The number of women diagnosed with cervical cancer between 1985 and 1999 and still alive and living in Manitoba in 1999 was 539 (Demers A et al., 2003). Between 1989 and 1999, the five-year prevalence rate of cervical cancer decreased from 44.6 per 100,000 women to 39.8 per 100,000 women (Demers A et al., 2003). This decrease was principally observed in the 50 to 69 and 70 years of age and older age groups (Demers A et al., 2003).

2.5 Chapter Summary

This chapter reviewed the etiology, diagnosis, treatment, staging, and descriptive epidemiology of cervical cancer. Cervical cancer is caused by HPV, a sexually transmitted virus that is very prevalent in the population. However, most HPV infections are transient and are cleared by the immune system. Rarely, the infection cannot be cleared leading to the development of pre-cancerous lesions and, if left untreated, invasive cervical cancer. Pre-cancerous lesions and invasive cancer are diagnosed following abnormal cytology or clinical symptoms. Treatment includes surgery, radiation, and chemotherapy.

In Canada, cervical cancer incidence has decreased dramatically in the past 40 years from 15.4 per 100,000 in 1977 to 8.0 per 100,000 in 2007. Mortality has also declined from 4.8 per 100,000 in 1977 to 2 per 100,000 in 2006. In Manitoba, cervical

cancer incidence remained low for women less than 30 years of age and declined slightly over time from 2.2 per 100,000 in 1971 to 2.0 per 100,000 in 2008. However, the incidence rates for women 30 to 49, 50 to 69, and 70 years of age and older have declined significantly (25.4 per 100,000 to 12.9 per 100,000 for the 30 to 49 age group, 27.7 per 100,000 to 12.8 per 100,000 for the 50 to 69 age group, and 27.0 per 100,000 to 11.4 per 100,000 for 70 years of age and older). These decreases are largely attributed to cervical cancer screening. The following chapter provides information about cervical cancer screening world-wide and within Canada and Manitoba.

Chapter 3. Cervical Cancer Screening

3.1 Introduction

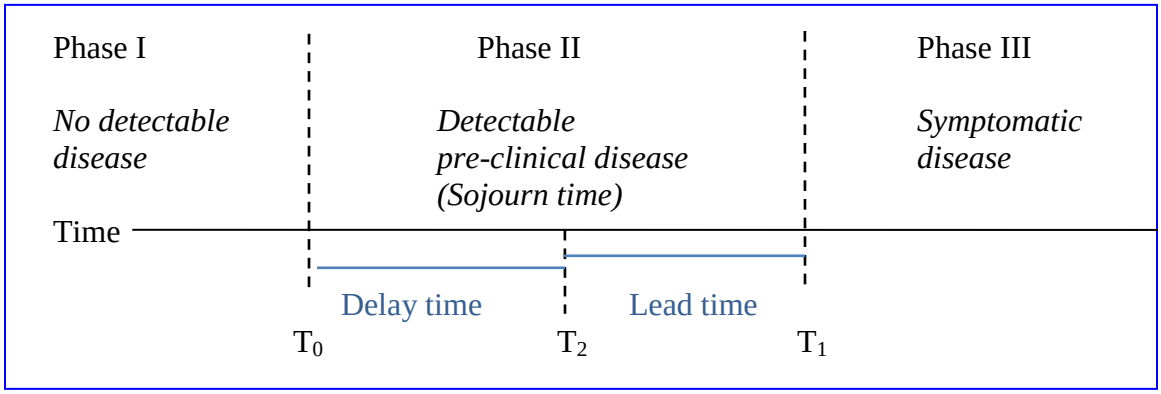
Screening is the systematic application of a test to identify asymptomatic individuals at risk of a disease who will benefit from further investigation or preventive action (Wald NJ, 2006). The goal of cancer screening is to detect pre-cancerous lesions or early stage cancer thereby improving the likelihood of successful treatment and reducing disease incidence and mortality (Strong K, Wald N, Miller A, Alwan A, & WHO Consultation Group, 2005). The introduction of cervical cancer screening using the Pap test has been associated with significant decreases in cervical cancer incidence and mortality. This chapter reviews a model of screening for chronic diseases, screening strategies, the organized cancer screening process, cervical cancer screening effectiveness, cost effectiveness, the potential harms of screening, and cervical screening policies world-wide, within Canada, and Manitoba.

3.2 Model of screening

Figure 12 illustrates a model of screening for chronic diseases. The central premise of the model is that early detection offers the opportunity to change the disease's progression and prognosis. In phase I (no detectable disease), the disease cannot be detected although early malignant changes may have taken place. Phase II (detectable pre-clinical disease) begins when the disease can be detected by screening but is still asymptomatic and ends when the disease is clinically present (T_0 to T_1). This period is also called the sojourn time and is a function of the delay time and the lead time. Delay time is the period of time that has passed before the screening test detects the disease (T_0

to T_2). Lead time is the period of time between when the disease is found by screening and when the disease would have developed in the absence of screening or the time gained in treating the disease earlier than usual (T_2 to T_1). The sojourn time varies within a population and is affected by the frequency of screening. Phase III (symptomatic disease) begins when symptoms appear.

Figure 12 Model of screening for a chronic disease



Source: Adapted from International Agency for Research on Cancer, 2005. Used with permission from the World Health Organization Press.

The performance of a screening test is also influenced by the test's sensitivity, specificity, and positive predictive value (PPV). Sensitivity is the ability of a test to identify correctly individuals who have the disease. Specificity is the ability of a test to identify correctly individuals who do not have the disease. PPV is the probability that an abnormal test result correctly indicates the disease. Sensitivity and specificity are generally constant across populations and settings but PPV varies with the prevalence of disease in the population (i.e. PPV is lower and the chances of a false positive result is higher when the prevalence of disease is lower). Table 4 illustrates the two by two table used to calculate sensitivity, specificity, and PPV.

Table 4 Screening sensitivity, specificity, and positive predictive value

Screening test results	**True disease state**	
	Positive	Negative
Abnormal	TP	FP
Normal	FN	TN

TP = True Positive - diseased individuals detected by the test

FP = False Positive - non-diseased individuals positive by the test

FN = False Negative - diseased individuals not detected by the test

TN = True Negative - non-diseased individuals negative by the test

$$\text{Sensitivity} = \frac{TP}{TP + FN} \qquad \text{Specificity} = \frac{TN}{FP + TN} \qquad \text{PPV} = \frac{TP}{TP + FP}$$

3.3 Screening strategies

Two primary strategies have been used to reduce disease incidence and mortality through screening: organized screening and opportunistic screening. The goal of organized screening is to reduce disease incidence and mortality at the population level; it is a collectivistically-oriented health and social policy (McKinlay JB & Marceau LD, 2000). Organized screening occurs on a population-basis and includes the following key components (Strong K et al., 2005):

- A clear definition of the objectives of the program and the expected health benefits;
- The ability to identify individuals in the population who will benefit;

- Measures that encourage high coverage and participation such as health education, invitation, and reminder letters;
- Adequate resources to register health information to be used for program evaluation and monitoring;
- Adequate facilities to perform and interpret the test;
- An organized, quality control program for the screening test and the test's interpretation;
- Adequate facilities for diagnosis and treatment;
- A referral system for the management of abnormal tests and to provide information about normal tests and;
- Available program data so that program evaluation and monitoring is done regularly.

In contrast, the goal of opportunistic screening is to reduce disease incidence and mortality at the individual level; it is an individualistically-oriented health and social policy (McKinlay JB & Marceau LD, 2000). Opportunistic screening includes any unsystematic screening activity and typically occurs when an individual presents for a routine medical examination or a consultation for an unrelated condition (Hakama M et al., 1985; Strong K et al., 2005). Therefore, eligible individuals in the target population are not identified or invited to be screened before they interact with a health care provider.

Both organized and opportunistic screening strategies have lead to decreased disease incidence and mortality (International Agency for Research on Cancer, 2005). However, there is evidence that organized screening maximizes population coverage,

minimizes the harms of screening by inviting and reminding women to be screening based on a longer screening interval, and is more cost-effective and efficient (Ronco G & Rossi PG, 2008). In addition, because opportunistic screening is not centrally coordinated, quality assurance and evaluation are often not possible. Opportunistic screening can also lead to the high coverage of young, healthy individuals who have a lower risk of developing the disease and the low coverage of older, hard-to-reach, and socio-economically disadvantaged individuals who have a higher risk of developing the disease (Nygard JF, Skare GB, & Thoresen SO, 2002). Appendix A provides a summary of the similarities and differences between organized and opportunistic screening. Several key Canadian reports have recommended that cervical cancer screening be implemented as part of an organized screening process (Miller AB et al., 1991; Walton RJ et al., 1976).

3.4 The organized cancer screening process

The organized cancer screening process involves four stages: identify and invite the target population, provide the screening test, investigate abnormal results, and recall individuals for re-screening (Figure 13).

1. Identify and invite the target population

The identification of the appropriate population to be screened is based on an evaluation of the screening test's effectiveness for different age groups. Eligible individuals within the target population are then identified by the government, public health units, physicians, or other health care providers (Strong K et al., 2005). Letters of invitation are the primary method used to encourage individuals to be screened although

other forms of promotion such as small media (brochures, ads) and mass media are also used.

2. Provide the screening test

Screening tests are usually applied to a large population of individuals. The screening test is chosen to be as sensitive and specific as possible. The process of screening results in two groups: individuals who have a normal screening result who do not require further action and individuals who have an abnormal screening result who require further action.

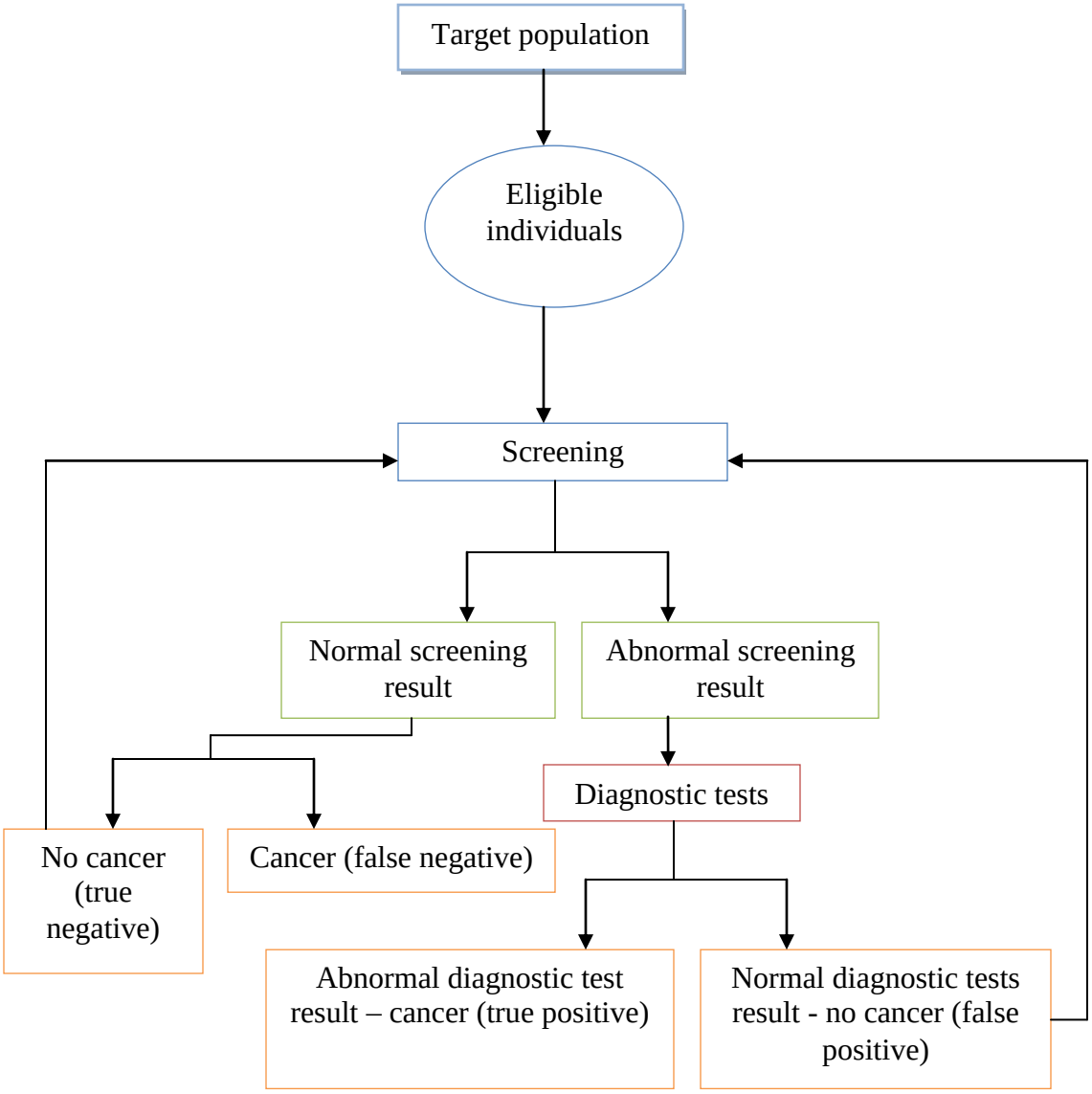
3. Investigate abnormal results

Because screening tests yield preliminary results, individuals who have an abnormal screening result require further diagnostic tests. Diagnostic tests provide a more definitive finding but are frequently more invasive and incur greater harms. Most individuals with an abnormal screening result will have a normal diagnostic test result (false positive outcome) while a few individuals will have an abnormal diagnostic test result (true positive outcome) and be diagnosed with a pre-cancerous lesion or invasive cancer.

4. Recall individuals for re-screening

Because the sensitivity of most cancer screening tests is moderate, individuals need to be recalled for screening on a regular basis. Individuals who had a normal screening result or an abnormal screening result followed by a normal diagnostic test result are re-screened according to a recommended screening interval. The small number of individuals who are diagnosed with cancer between screening intervals (interval cancer or false negative outcome) are not recalled for screening.

Figure 13 The organized cancer screening process



3.5 Cervical Cancer Screening

3.5.1 The Pap test

Cervical cancer is ideal for screening because of its natural history, long pre-invasive period, and the availability of a simple test – the Pap test (International Agency for Research on Cancer, 2005; Mayrand M-H et al., 2007). Epithelial changes in the

cervix were first described in 1886 and cervical carcinoma in situ was identified in 1908 (Morrison AS, 1992). In 1928, Dr. George Papanicolaou published the results of a study of normal and malignant cells shed from the cervix (Lippman SM & Hawk ET, 2009). The New York World newspaper reported that "Although Dr. Papanicolaou is not willing to predict how useful the new method will be in the actual treatment of malignancy itself, it seems probable that it will prove valuable in determining cancer in the early stages when it can be more easily fought and treated" (Vilos GA, 1998). The Pap test was validated in 1943 and introduced into routine practice in the late 1940s (Traut HF & Papanicolaou GN, 1943).

A conventional Pap test is performed by sampling cervical cells using a brush or spatula, fixing the cells on a slide, and examining the cells for abnormalities. Each Pap test slide contains between 50 and 300,000 cervical cells (Shepherd LJ & Bryson P, 2008). In the last 10 years, liquid-based cytology (LBC) has been introduced as an alternative to the conventional Pap test. When using LBC, cells are sampled using a brush and are collected in a liquid vial, filtered by machine during which extraneous matter is removed, and transferred to a slide. The cells are distributed in a single layer on the slide making interpretation easier.

The Pap test is examined under a microscope by a cytotechnologist or cytopathologist and classified as either satisfactory or unsatisfactory. A Pap test is unsatisfactory if obscuring factors such as red blood cells, white blood cells, or mucus are present or if there are insufficient epithelial cells or cytolysis (CervixCheck CancerCare Manitoba, 2009). Satisfactory Pap test results are classified using the 2001 Bethesda System as normal or (in order of severity) atypical squamous cells of undetermined

significance (ASC-US), low-grade squamous intraepithelial lesions (LSIL), atypical glandular cells (AGC), atypical squamous cells-high grade (ASC-H), high-grade squamous intraepithelial lesions (HSIL), adenocarcinoma in situ or squamous cell carcinoma in situ, or adenocarcinoma or squamous cell carcinoma (Nayar R & Solomon D,). Women who have a low-grade Pap test result (ASC-US or LSIL) are usually monitored with repeated Pap tests. Women who have a high-grade Pap test result (AGC, ASC-H, and HSIL) are referred for a colposcopy.

The conventional Pap test is inexpensive, easy to perform, has a high specificity (approximately 98%), and a moderate sensitivity (approximately 51%) (Shepherd LJ & Bryson P, 2008). Sensitivity may be increased slightly by using LBC instead of conventional cytology (Shepherd LJ & Bryson P, 2008). Because of the moderate sensitivity of the Pap test, women must be screened repeatedly over a lifetime to decrease the probability that an abnormality is missed (i.e. a false negative result). Unfortunately, the likelihood of a false positive result also increases with the number of screens per lifetime. Approximately 30% of women who are screened every five years will experience a false positive result compared to 50% of women who are screened every three years and 75% of women who are screened every two years (Raffle A & Gray M, 2007). False positive results are an important consideration in the screening process and should be limited as much as possible because they can lead to anxiety, additional diagnostic tests, and unnecessary costs (Bennetts A et al., 1995; Idestrom M, Milsom I, & Andersson-Ellstrom A, 2003; Peters T, Somerset M, Baxter K, & Wilkinson C, 1999).

The reduced probability of a cervical cancer diagnosis after a negative screening test is high for three years after the last Pap test and then declines by 4% per year (Colditz

GA et al., 1997). Therefore, even six to nine years after a negative test, considerable protection remains for screened women compared to unscreened women regardless of other risk factors (Colditz GA et al., 1997).

3.5.2 Effectiveness of cervical screening

At the population level, screening effectiveness is primarily assessed by a reduction in cancer mortality. Because cervical cancer screening can detect pre-cancerous lesions that can be treated to prevent invasive cancer, a reduction in cervical cancer incidence can also be used as a measure of screening effectiveness. RCTs that assess reductions in incidence and mortality due to screening are the most valid method for measuring screening effectiveness. However, unlike mammography for breast cancer or fecal occult blood testing for colorectal cancer, screening for cervical cancer became an accepted part of health care before RCTs were implemented to evaluate cervical cancer mortality (Morrison AS, 1992). Consequently, evidence of effectiveness comes from three sources: 1) trends in cervical cancer incidence and mortality over time in relation to the rate of cervical cancer screening; 2) observational studies of screening outcomes; and 3) modeling of screening policies and practices that estimate effectiveness.

Several studies have used survival as the outcome when measuring screening effectiveness. However, survival is not an appropriate measure because survival is influenced by three biases: lead-time bias, length-time bias, and volunteer or selection bias. Lead-time bias is the overestimation of survival time due to a backward shift in the starting point for measuring survival that occurs when a disease is detected early because of screening (Porta M, 2008). Length-time bias occurs because screening is better at finding long-lasting, non-progressive or slowly progressive cancers (i.e. cancers that exist

for a long length of time) than detecting rapidly progressive cancers with a poor prognosis (Raffle A & Gray M, 2007). Therefore, the survival in a group of screen-detected individuals is automatically better than the survival in a group of clinically-detected individuals whose cancer presented with signs or symptoms even if the final outcome (i.e. death) is not different. Volunteer or selection bias refers to the fact that individuals who choose to participate in screening may be different in important ways from individuals who do not choose to participate. Previous studies have found that individuals who attend screening tend to be healthier than those who do not attend screening which may influence survival (Raffle A & Gray M, 2007). The best way to avoid the effects of lead-time, length-time, and volunteer or selection bias is to not use survival as a measure of screening effectiveness but use incidence and mortality measures.

Incidence and mortality trends over time

When screening begins without RCT evidence, incidence and mortality trends over time in relation to the rate of screening become an important way to examine screening effectiveness. However, several limitations must be considered when interpreting trends. The effect of screening may be difficult to separate from the effect of other factors that influence incidence and mortality such as changes in the classification of cancer, improvements in treatment, hysterectomy prevalence, and HPV prevalence. Some cervical cancer risk factors such as sexual behaviours may be similar within a cohort of women which influences cervical cancer incidence as the cohort of women ages. Finally, trends may also be difficult to interpret if information is lacking on the extent and quality of screening particularly when the screening strategy is opportunistic.

Despite these limitations, trends in cervical cancer incidence and mortality from several developed countries are useful in assessing cervical cancer screening effectiveness because of accurate screening participation rates and the availability of national incidence and mortality data from before and after the implementation of screening programs. For example, decreases in cervical cancer incidence and mortality have been observed in the Nordic countries where it is possible to examine trends between comparable regions with and without screening. By the end of the 1960s, Finland had a national organized screening program that covered the entire population (International Agency for Research on Cancer, 2005). From the early 1960s to the 1990s, the age-standardized cervical cancer incidence rate decreased by 77% from 14.8 per 100,000 to 3.4 per 100,000 and the age-standardized mortality rate decreased by 80% from 6.6 per 100,000 to 1.2 per 100,000 (International Agency for Research on Cancer, 2005; Nygard JF et al., 2002).

In comparison, Norway had organized screening in only one county that covered approximately five percent of the population (International Agency for Research on Cancer, 2005). During the same time period (1960s to 1990s), the age-standardized cervical cancer incidence rate decreased by 26% from 18.1 per 100,000 to 13.3 per 100,000 and the age-standardized mortality rate decreased by 41% from 5.7 per 100,000 to 3.4 per 100,000 (International Agency for Research on Cancer, 2005; Nygard JF et al., 2002). Therefore, although partial coverage in Norway did decrease cervical cancer incidence and mortality, the decrease in Finland with full population coverage was much greater.

Strong time trend evidence for cervical cancer screening effectiveness is also available from the United Kingdom (UK). Organized cervical cancer screening began in the UK in the 1960s (Patnick J, 2000). Cervical cancer incidence rates were fairly stable from the 1960s to the mid 1980s (14 and 16 per 100,000 respectively) during which time screening participation was less than 50% (Quinn M, Babb P, Jones J, & Allen E, 1999). In order to improve participation, a national invitation and recall system was established in 1988 (Patnick J, 2000; Quinn M et al., 1999). Screening participation rose from 42% in 1988 to 85% in 1994 (Quinn M et al., 1999). By 1995, the age-standardized incidence rate in England decreased by 37% to 10 per 100,000 (Quinn M et al., 1999). Age-standardized mortality decreased by 40% from 6.1 per 100,000 in 1987 to 3.7 per 100,000 in 1995 and by 74% to 1.6 per 100,000 in 2000/2002 (Comber H & Gavin A, 2004; Quinn M et al., 1999). This decrease has been attributed to the organized cervical screening program (Quinn M et al., 1999; Sasieni P & Adams J, 1999; Sasieni P, Castanon A, Cuzick J, & Snow J, 2009).

In 1999, Sasieni and Adams examined trends in cervical cancer mortality in England and Wales after taking into account age and cohort effects (Sasieni P & Adams J, 1999). Women born after 1935 had higher mortality rates than women born earlier. The increased mortality risk coincided with changes in sexual behaviours in the 1960s and the subsequent wide-spread use of oral contraceptives. They found no significant change in cervical cancer mortality until the mid 1980s when screening coverage improved. The mortality reduction was greatest in the youngest age groups and the least in women over 70 years of age.

Limited information exists on cervical cancer time trends in Eastern European and developing countries. In countries such as Bulgaria, Romania, and Russia with little or no screening, cervical cancer mortality rates have risen since the 1970s (International Agency for Research on Cancer, 2008). There is evidence of recent declines in mortality in more affluent Eastern European countries such as the Czech Republic, Hungary, and Poland; it appears that mortality peaked among women born between 1945 and 1960 then started to decrease (International Agency for Research on Cancer, 2008). Latin American countries exhibit large variation in cervical cancer incidence and mortality which partly reflects different access to cervical cancer screening and treatment. Chile, Costa Rica, Cuba, and Mexico have limited cervical cancer screening and the age-standardized cervical cancer mortality rate from 1960 to 1994 in each country has remained stable or increased (International Agency for Research on Cancer, 2005; Robles SC, White F, & Peruga A, 1996). This may be because in most Latin American countries, cervical cancer screening programs are linked to family planning and prenatal care programs that focus on women less than 30 years of age; consequently, older, higher-risk women are not screened (Robles SC et al., 1996).

The age-standardized incidence of invasive cervical cancer has declined in India where screening is opportunistic and not widely available from 25 per 100,000 in 1960 to approximately 20 per 100,000 in 2000. In contrast, cervical cancer incidence has decreased significantly in China from 26.7 per 100,000 in 1972 to 1974 to 2.5 per 100,000 in 1993 to 1994 which is attributed to screening, better treatment, and changes in sexual behaviours decreasing exposure to HPV (International Agency for Research on Cancer, 2005; Jin F et al., 1999). There are very few data on time trends in Africa; in

general, the incidence rate of cervical cancer appears to be stable or increasing and screening is very limited (International Agency for Research on Cancer, 2005).

Case-control studies

A case-control study compares the cervical cancer incidence and mortality for women who have been screened with women who have not been screened. Although differences between the groups suggest that screening may reduce cancer risk, a case-control study does not provide evidence of a causal relationship because the results may be due to confounding (i.e. factors that reduce the likelihood of developing the disease may also increase the likelihood of screening such as socio-economic status) and other biases such as section and recall bias. However, several high-quality[2] cervical cancer screening case-control studies from a variety of settings have been conducted and have found that cervical cancer screening with the Pap test is highly effective and decreases invasive cervical cancer incidence by 60% to 90% (Eddy DM, 1990; Raffle A & Gray M, 2007).

In 1986, IARC combined several case-control studies to estimate the reduction in cervical cancer incidence in women 35 to 65 years of age who had one previous Pap test by various screening intervals (Table 5) (IARC working group on evaluation of cervical cancer screening programmes, 1986; International Agency for Research on Cancer, 2005). Screening once every 10 years reduced the incidence of invasive cancer by 64.1%, every five years by 83.6%, every three years by 90.8%, every two years by

[2] A high-quality case-control study is large enough to detect differences between the groups, has a good definition of the population, an explicitly defined time period, does not rely on self-reported information, and includes all or most of the cases (Raffle A & Gray M, 2007).

92.5%, and every year by 93.5%. The difference in incidence reduction between screening every two years and every three years was 1.7%. The lifetime number of Pap tests ranged from 30 for annual screening to three for screening every 10 years. They concluded that the benefit of screening every year instead of every two years (a 1.7% reduction in incidence) was low relative to the cost (five additional Pap tests) per woman.

Table 5 Percentage reduction in cervical cancer incidence and lifetime number of Pap tests

Screening interval (years)	% reduction in cancer incidence	Lifetime number of Pap tests
10	64.1	3
5	83.6	6
3	90.8	10
2	92.5	15
1	93.5	30

Notes: Includes women 35 to 65 years of age who had one prior Pap test.

Source: IARC working group on evaluation of cervical cancer screening programmes, 1986; International Agency for Research on Cancer, 2005. Used with permission from the World Health Organization Press.

Colditz et al. (1997) used the 1986 IARC study results and participation rates from the US National Health Interview Survey (NHIS) to estimate the reduction in cervical cancer incidence by frequency of screening among American women (Table 6) (Colditz GA et al., 1997). According to the NHIS, 49% of women in the US are screened annually, 16% are screened every three years, and 35% have not been screened in at least three years. Colditz et al. (1997) assumed that the 35% of women who were not screened in the past three years received a Pap test every 10 years. Applying the estimates of cervical cancer incidence reduction from IARC, the overall reduction in cervical cancer

incidence was 82.8%. If the 49% of women who undergo annual screening were screened every three years instead, the lifetime number of tests for these women would drop from 45 to 15. The reduction in cervical cancer incidence would decrease slightly from 93.5% to 90.8%. If the 35% of women who are screened once every 10 years were screened every three years, the lifetime number of tests for these women would increase from 5 to 15 and the reduction in cervical cancer incidence would increase from 64% to 90.8%. Therefore, if all American women were screened but less frequently (i.e. every three years), the lifetime number of Pap tests would decrease to 15 and the reduction in cervical cancer incidence would be 90.8%. They concluded that increasing screening coverage among women not regularly screened while reducing the frequency of screening in other groups is the most effective screening strategy.

Table 6 Frequency of Pap tests and reduction in cervical cancer in the United States using data from the International Agency for Research Against Cancer

Screening pattern	**Lifetime number of Pap test per woman**	**Reduction in incidence (%)**
Current		
49% annual	45	93.5
16% every 3 years	15	90.8
35% every 10 years	5	64.1
Population average	26.2	82.8
Whole population every 3 years	15	90.8
Change from current	-11 tests per woman	8% reduction in cervical cancer

Notes: Includes women 20 to 65 years of age.

Source: Colditz GA et al., 1997. Used with permission from John Wiley and Sons.

In 2009, Sasieni et al. published the results of a large case-control study that examined the age-specific effectiveness of cervical cancer screening (Sasieni P et al.,

2009). Participation in the UK cervical screening program by a woman 35 to 64 years of age reduced her risk of cervical cancer over the next five years by 60% to 85% and her risk of advanced cervical cancer by 90%. However, screening women 20 to 24 years of age had little or no impact on cervical cancer incidence under the age of 30.

Modeling of screening strategies

Statistical models have been used to examine the effect of different cervical screening strategies on incidence and mortality. The models use observed data based on the natural history of cervical cancer, Pap test performance, the effectiveness of different treatment options for pre-cancerous cervical lesions, and the results of previous case-control studies. Overall, these modeling study results indicate that cervical cancer screening, even at a screening interval of five years, significantly reduces invasive cervical cancer incidence and mortality (Eddy DM, 1990).

Van Ballegooijen et al. (2000) used the MIcro-simulation SCreening ANalysis (MISCAN) simulation model to evaluate the effectiveness of different screening strategies (age ranges, screening interval, participation rates, and proportion of abnormal Pap tests) from various European countries on the reduction in life-years lost due to cervical cancer (van Ballegooijen M et al., 2000). MISCAN compares screening strategies by generating a large population (i.e. 40 million women) of fictitious individual life histories in which some women develop cancer and some women die from the disease (Habbema JDF, van Oortmarssen GJ, Lubbe JT, & van der Maas PJ, 1985). The model produces age-specific and time-specific cancer incidence and mortality rates. The fictitious population then undergoes simulated screening which may change some of the life histories. For example, pre-cancerous lesions will be detected by screening for some

women preventing the development of invasive disease and subsequent cancer-related death. The aggregate change of all the life histories comprises the screening program's effectiveness.

The estimated reduction in incidence ranged from 75% in the Netherlands and Finland with a lifetime number of screens of seven to 96% in Germany with a lifetime number of screens of 53 (Table 7). The results suggest that screening successfully reduces cervical cancer incidence but high coverage and restricted screening intensity are also key factors in determining screening effectiveness.

Table 7 Estimated reduction in incidence and mortality by country and screening policy

Screening policy	**Netherlands and Finland**	**United Kingdom**	**Sweden**	**Belgium, France, Greece, Italy, and Spain**	**Germany**
Starting age	30	20	23	25	20
Interval	5 years	5 years	3 years (ages 23-49) 5 years (ages 50-60)	3 years	1 year
Ending age	60	64	60	64 (65 for France)	72
Lifetime number of screens	7	10	12	14	53
Incidence reduction (%)	75	90	84	87	96
Mortality reduction (%)	76	88	80	86	95

Note: Assumes 100% coverage.

Source: van Ballegooijen M et al., 2000. Used with permission from Elsevier.

3.5.3 Cost-effectiveness

An evaluation of cervical cancer screening should also include an analysis of cost-effectiveness. The goal of a cost-effectiveness analysis is to determine the balance between the resources used (costs) and the outcomes achieved (effectiveness). The cost-effectiveness of cervical cancer screening depends on the screening interval, the age range, and the number of excess Pap tests (i.e. Pap tests that occur outside the age range or recommended screening interval) (Anderson R, Haas M, & Shanahan M, 2008). Cost-effectiveness models from developed countries have found a wide range of costs per life year due to differences in model specifications, estimates of the unit costs, duration of operation of the screening program, and organized program operating costs (Ginsberg GM, Tan-Torres Edejer T, Lauer JA, & Sepulveda C, 2009). However, the models consistently support three conclusions: cervical cancer screening is cost-effective, organized screening is more cost-effective than opportunistic screening, and increasing coverage is more cost-effective than using resources in other areas of the cervical cancer screening.

Ginsberg et al. (2009) evaluated the cost-effectiveness of different cervical cancer screening strategies in 14 World Health Organization (WHO) regions of the world (Ginsberg GM et al., 2009). They found that screening was cost-effective in regions with high income, low mortality, and high existing treatment coverage.

In 2002, Van den Akker-van Marle et al. estimated the cost-effectiveness of 500 different cervical cancer screening policies using MISCAN (van den Akker-van Marle E, van Ballegooijen M, van Oortmarssen GJ, Boer R, & Habbema D, 2002). Screening policies differed with respect to the recommended number of lifetime screens, screening

interval, and age range. The analyses used demographic, epidemiologic, screening, and treatment data from the Netherlands. The costs varied from $US 0.5 million to $US 9.5 million per 1,000,000 women and the effects ranged from 50 to 350 life-years gained per year of the screening program. The cost per life-year gained increased from $15,500 for the three-year screening interval (one more life-year for each additional $15,500 spent on cervical cancer screening) to $23,900 for the one and a half year screening interval (one more life-year for each additional $23,900 spent on cervical cancer screening)[3]. The additional reduction in cervical cancer incidence from three-year screening to one and a half year screening was 2.7%. They concluded that cervical cancer screening cost-effectiveness can be improved by reducing the number of tests, starting screening at a later age, and lengthening the screening interval.

3.5.4 Potential harms of screening

While there is evidence that screening with the Pap test effectively reduces cervical cancer incidence and mortality, there are also potential harms from screening a large number of healthy, asymptomatic women in order to prevent invasive disease in a few. These harms include the psychological consequences of screening, adverse outcomes associated with treatment including unnecessary treatment or over-treatment, and economic costs (Alibhai SMH, 2006; International Agency for Research on Cancer, 2005).

[3] Interventions that cost less than $50,000 to $60,000 per quality adjusted life-year gained are considered reasonably efficient (Owens DK, 1998).

When cervical cancer screening began in the 1940s, it was expected that only a very small percentage of women would have clearly abnormal cervical cells and all others would be normal (Raffle A & Gray M, 2007). However, abnormal Pap test results range from mildly abnormal to severely abnormal yet all require some form of follow-up from repeated screening to colposcopy and biopsy. Studies have found that women who are screened repeatedly following a low-grade abnormality may experience inconvenience, anxiety, and uncertainty (Barratt AL, 2006; Korfage IJ, van Ballegooijen M, Huveneers H, & Essink-Bot M-L, 2010). In addition, colposcopy has been associated with raised anxiety levels before and during the procedure.

Cervical cancer screening may also lead to the diagnosis of pre-invasive cancers that would never have caused a health problem (over-diagnosis) but their treatment may cause significant harm. The seriousness of the harm depends on the invasiveness of the treatment. Meta-analyses have found that some treatments following an abnormal Pap test, such as conization, are associated with adverse obstetrical outcomes including preterm delivery and low birth weight (Arbyn M et al., 2008; Kyrgiou M, Martin-Hirsch P, Arbyn M, Prendville W, & Paraskevaidis E, 2006).

Lastly, economic harms may occur at the personal or health care system level including lost income due to time off from work for treatment and the shifting of health care resources away from one area to pay for repeated testing and follow-up (Alibhai SMH, 2006).

3.5.5 Cervical cancer screening policies world-wide

Cervical cancer screening policies differ considerably by country (Appendix B). The European Code Against Cancer recommends that women should participate in

cervical cancer screening beginning at 20 to 30 years of age but preferably not before 25 years of age depending on the burden of disease in the population and the available resources (Arbyn M et al., 2010; Boyle P, Autier P, Bartelink H, & et al., 2003). Screening should continue at three or five year intervals until 60 to 65 years of age. However, the recommended screening interval varies across Europe from every year in countries with opportunistic screening to every five years in countries with organized screening (European Commission, 2003). As a consequence, the lifetime number of tests ranges from six to more than 50. Population coverage varies from 50% in countries with opportunistic screening such as Germany to over 80% in countries with organized screening such as the UK, Finland, Iceland, and the Netherlands (International Agency for Research on Cancer, 2005; Patnick J, 2000; Schenck U & von Karsa L, 2000; Sigurdsson K & Sigvaldason H, 2006).

The National Cervical Screening Program in Australia recommends that women 20 to 69 years of age have a Pap test every two years while the New Zealand Cervical Screening Program recommends screening every three years (Australian Institute of Health and Welfare, 2009; National Cervical Cancer Screening Programme, 2005). In the US, various organizations and government agencies provide guidelines and funding for screening (Fahs MC, Plichta SB, & Mandelblatt JS, 1996; Swan J, Breen N, Coates RJ, Rimer BK, & Lee NC, 2003). Historically, the recommended screening interval has been every year. However, in 2009, the American College of Obstetricians and Gynaecologists updated its guidelines to recommend screening every two years for women 21 to 29 years of age and every three years for women 30 years of age and older (The American College of Obstetricians and Gynecologists, 2009). The US Preventive

Task Force recommends organized screening within three years of the onset of sexual activity or age 21 years (whichever comes first) followed by screening every three years (after three consecutive normal Pap tests) up to 64 years of age (United States Preventive Services Task Force, 2011).

3.5.6 Cervical cancer screening policies in Canada

In Canada, each province and territory is mandated to establish its own screening program and guidelines. Table 8 summarizes the characteristics of cervical cancer screening by province and territory. Participation rates are from the 2005 Canadian Community Health Survey (CCHS) which is an annual cross-sectional survey of approximately 65,000 Canadians 12 years of age and older. The CCHS excludes individuals who live on First Nations communities, institutional residents, full-time members of the Canadian Forces, and residents of certain remote regions (Statistics Canada, 2012).

British Columbia began the country's first cervical screening program in 1960 followed by Manitoba in 1963 (Cervical Cancer Screening Program, BC Cancer Agency, 2010; Choi NW & Nelson NA, 1986). Currently, Canadian cervical screening programs vary in their extent of organization from opportunistic screening in Québec, New Brunswick, Prince Edward Island, and the three Territories to partially organized screening in British Columbia, Alberta, Ontario, Nova Scotia, and Newfoundland and Labrador. Saskatchewan, the Calgary Health Region in Alberta, and Manitoba have recently implemented invitation letters and now include all the components of an organized screening program.

In 1989, the Canadian National Workshop on Screening for Cancer of the Cervix recommended a three-year screening interval if an organized screening program exists (Miller AB et al., 1991). Presently, the screening interval varies from annual screening in Newfoundland and Labrador to triennial screening following several consecutive negative annual Pap tests in Alberta and Saskatchewan. As Canadian programs become more organized, the recommended age at which screening should start has changed from 18 years of age to 21 years of age or within three years of becoming sexually active (Cervical Cancer Prevention and Control Network, 2010). Since most women over 60 years of age who are diagnosed with invasive cervical cancer have not been adequately screened, most Canadian provinces recommend screening until 69 years of age (Cervical Cancer Prevention and Control Network, 2010).

Table 8 Summary of cervical cancer screening in Canada

Territory or Province	Type	Start	Target age group	Screening interval	CCHS 3-year participation rate (2005)
Yukon	S	NA	NA	NA	79.2
Northwest Territories	S	NA	NA	NA	83.5
Nunavut	S	NA	NA	NA	79.3
British Columbia	PO	1960	After becoming sexually active to 69 if 3 or more normal results in last 10 yrs.	Biennial after 3 annual normal.	72.6
Alberta	PO	2000	21 or within 3 years of becoming sexually active to 69 if 3 or more normal results in last 10 yrs.	Triennial after 3 annual normal.	76.6
Saskatchewan	O - 2009	2003	After becoming sexually active.	Triennial after 2 annual normal.	77.1
Manitoba	PO, O -2010	1963-74 2001	3 years after becoming sexually active to 70 if 3 or more normal results in the last 10 years.	Biennial.	75.1
Ontario	PO	2000	3 years after becoming sexually active to 70 if 3 or more normal results in last 10 yrs.	Biennial or triennial after 3 annual normal.	72.9
Québec	S	NA	NA	NA	68.5
New Brunswick	S	NA	NA	NA	76.5
Nova Scotia	PO	1991	3 years of becoming sexually active or age 21 to 75 if 3 normal in past 10 yrs.	Biennial after 3 normal.	81.0
Prince Edward Island	PO	2001	20-69	Biennial	79.9
Newfoundland and Labrador	PO	2003	All women	Annual	75.8

Notes: S – opportunistic; PO – partially organized; O – organized; NA – not available because guidelines are under development; CCHS – Canadian Community Health Survey

Data sources: Cervical Cancer Prevention and Control Network, 2010; Statistics Canada, 2009.

According to the 2005 CCHS, 72.8% of Canadian women 18 to 69 years of age reported having had a Pap test in the previous three years (Statistics Canada, 2009). The percentage of women screened ranged from 68.5% in Québec to 83.5% in the Northwest Territories (Statistics Canada, 2009). These rates were not adjusted by excluding women who had a hysterectomy which may increase screening rates depending on the underlying hysterectomy rate in the region and age group (Snider JA & Beauvais JE, 2000).

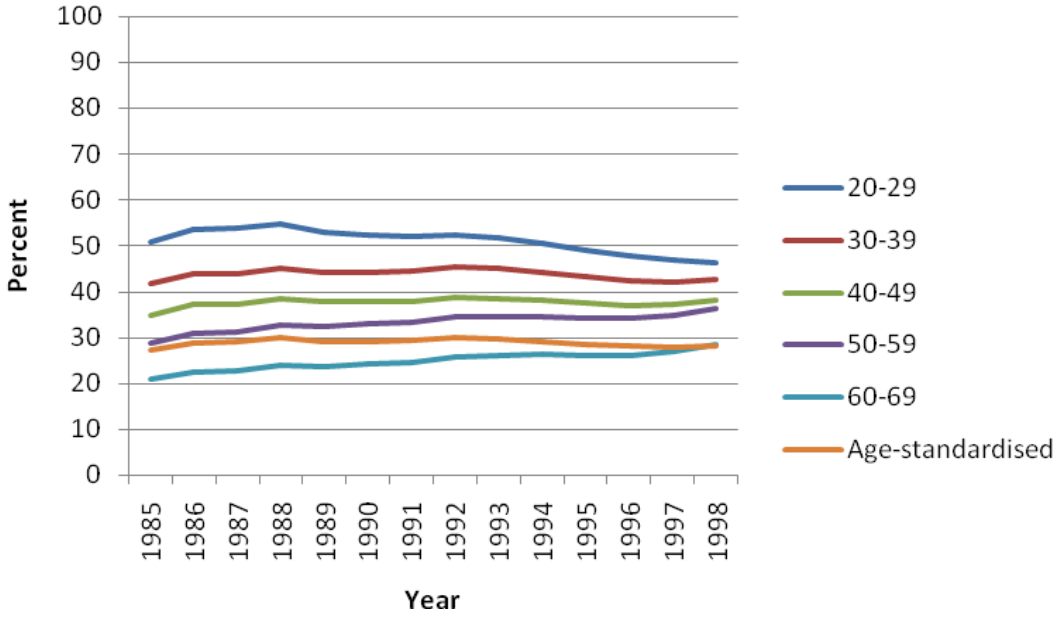
3.5.7 Cervical cancer screening in Manitoba

A province-wide cervical cancer screening registry was initiated in Manitoba in 1963 and continued until 1974 (Choi NW & Nelson NA, 1986). The registry collected all Pap test results for Manitoba women. In 2001, a provincial cervical cancer screening program (CervixCheck) was implemented with a mandate to ensure that Manitoba women receive organized, high quality, cervical cancer screening services. The program includes a registry that collects Pap test, colposcopy, and histology information, a fail-safe strategy to ensure that the appropriate follow-up tests are performed after an abnormal Pap test, and on-going quality assurance and evaluation. The program recommends that women should be screened every two years within three years after first sexual activity (CervixCheck CancerCare Manitoba, 2012). Screening can be discontinued once a woman turns 70 years of age and has at least three negative Pap tests in the previous 10 years (CervixCheck CancerCare Manitoba, 2012).

Figure 14 shows the age-standardized and age-specific annual Pap test rates for Manitoba women from 1985 to 1998 unadjusted for hysterectomy (Demers A et al.,

2003). The age-standardized Pap test rate remained stable from 27.2% in 1985 to 28.2% in 1998. Annual Pap test rates decreased in the 20 to 29 age group (50.9% to 46.3%) and increased in all other age groups (30 to 39 – 41.6% to 42.5%, 40 to 49 – 34.7% to 38.0%, 50 to 59 – 28.8% to 36.2%, and 60 to 69 – 20.8% to 28.3%).

Figure 14 Age-standardized and age-specific annual Pap test rates, 1985-1998

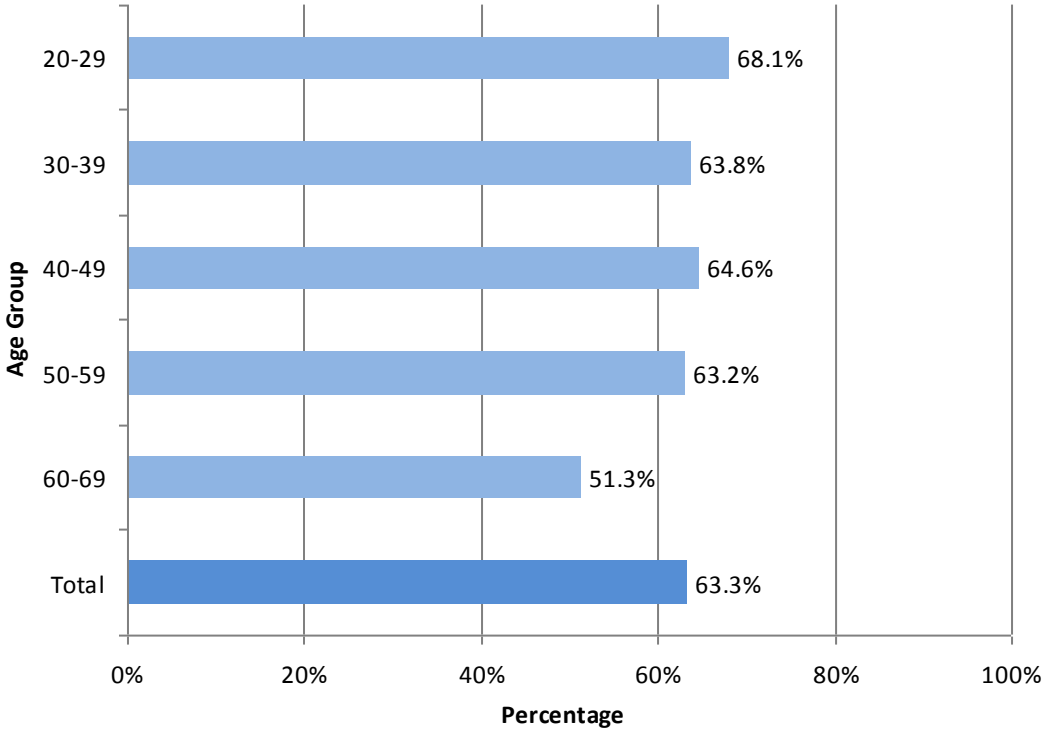


Note: Three-year moving average.

Data source: Demers A et al., 2003.

Excluding women who had a hysterectomy, the percentage of women 18 to 69 years of age who had at least one Pap test in a three year period between 1995/96 and 2003/04 was 69.4% (Martens P et al., 2008). Figure 15 shows three-year screening rates by age group adjusted for hysterectomy and previous invasive cervical cancer for women screened from April 2008 to March 2011 (CervixCheck CancerCare Manitoba, 2011). The percentage of women 20 to 69 years of age who had at least one Pap test was 63.3%. Screening rates were highest for women 20 to 29 years of age (68.1%) and lowest for women 60 to 69 years of age (51.3%).

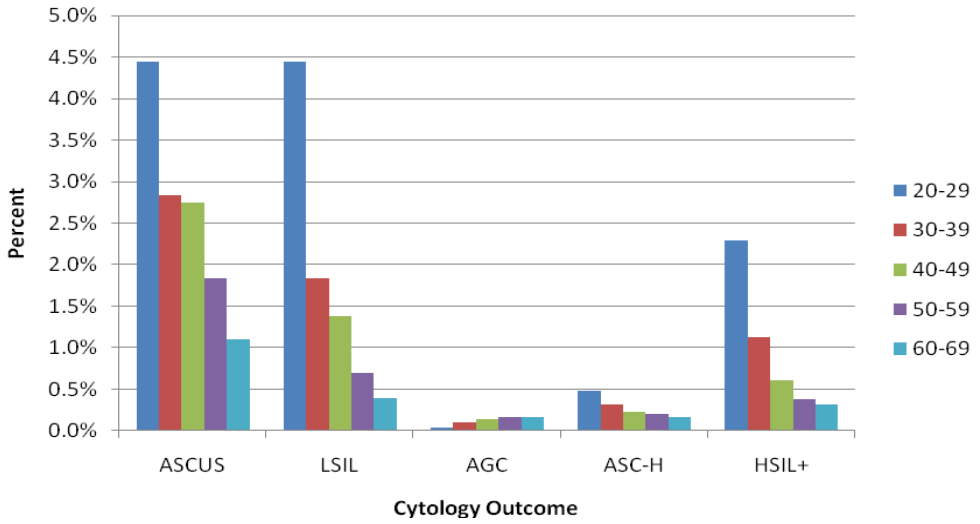
Figure 15 Age-specific three-year Pap test rates, 2008 to 2011



Data source: CervixCheck CancerCare Manitoba, 2011.

Figure 16 shows the distribution of abnormal cytology results by age group from 2007 to 2009 (CervixCheck CancerCare Manitoba, 2011). During this time, 93.7% of cytology outcomes for women 20 to 69 years of age were normal. The percentage of normal results increased with age (88.0% for 20 to 29 years, 93.7% for 30 to 39 years, 94.8% for 40 to 49 years, 96.8% for 50 to 59 years, and 98.1% for 60 to 69 years). Abnormal cytology results were highest in the 20 to 29 age group (ASC-US 4.8%, LSIL 4.6%, AGC 0.1%, ASC-H 0.5%, and HSIL+ 2.0%) and decreased with age. The overall lifetime risk of being diagnosed with a cervical abnormality for Manitoba women was 24.2% (Demers A, 2009).

Figure 16 Abnormal cytology outcomes by age group, 2007 to 2009



Data source: CervixCheck, CancerCare Manitoba (2011).

3.5.8 Future of cervical cancer screening

Two important factors will influence the future of cervical cancer screening. First is the availability of more sensitive and specific cervical cancer screening tests such as HPV DNA tests. HPV DNA detection can be used for primary screening alone or in combination with cytology, for the triage of women with equivocal cytology results (i.e. ASC-US), and for the follow-up of women treated for high-grade cervical abnormalities to predict the success or failure of treatment (Arbyn M et al., 2010). HPV DNA testing has been evaluated in a number of trials (Kim JJ, Wright TC, & Goldie S, 2005; Mayrand M-H et al., 2006; Mayrand M-H et al., 2007; Vijayaraghavan A, Efrusy MB, Mayrand M-H, Santas CC, & Goggin P, 2010). The Canadian Cervical Cancer Screening Trial found that the sensitivity of HPV testing for detecting high-grade lesions was 95% compared to a sensitivity of 54% for the Pap test (Mayrand M-H et al., 2007).

However, because HPV infections are common and frequently clear spontaneously particularly in younger women, HPV DNA testing in younger women can

lead to unnecessary diagnostic tests and over-diagnosis (Arbyn M et al., 2010). HPV DNA testing may be most effective when used as a triage for equivocal results in women less than 30 years of age and as the primary screening method in women 30 years of age and older (Goldie S, 2006; Tota J, Mahmud SM, Ferenczy A, Coutlee F, & Franco EJ, 2010). Women with both normal cytology and the absence of HPV DNA have an extremely low risk of developing cervical cancer in the next 10 years (Bosch FX, 2003). Currently, Canadian guidelines recommend HPV testing for women over the age of 30 with an ASC-US result (Shepherd LJ & Bryson P, 2008).

Second is the development of two vaccines that prevent infection with HPV types 16 and 18 which cause 70% of cervical cancers: Cervarix®, a bivalent vaccine and Gardasil®, a quadrivalent vaccine. The quadrivalent vaccine also protects against HPV types 6 and 11 which are responsible for most external anogenital warts and low-grade cervical lesions. The vaccines have been evaluated in RCTs and are considered to be nearly 100% effective in preventing new infections by the targeted HPV types (Tota J et al., 2010; Villa LL, Costa RL, Petta CA, & et al., 2006). The WHO states that the HPV vaccine should be included as a part of a coordinated prevention strategy for cervical cancer (World Health Organization, 2009).

In Canada, the National Advisory Committee on Immunization (NACI) recommends the use of Gardasil® for females between nine and 13 years of age prior to sexual activity (National Advisory Committee on Immunization, 2007). However, because approximately 30% of all cervical cancers are caused by types other than the types targeted by the vaccines, HPV vaccination will reduce but not eliminate the risk of cervical cancer (Goldie S, 2006). Infection with non-vaccine HPV types will continue to

occur and if screening is discontinued, some women will develop cervical cancer. Therefore, cervical cancer screening is still required. Nevertheless, cervical cancer screening policies will need to be updated for the appropriate surveillance of women who have been protected by the HPV vaccination (i.e. later start age and longer screening interval) (Franco EL & Harper DM, 2005).

3.6 Chapter Summary

This chapter reviewed a model of screening for chronic disease, screening strategies, the organized cancer screening process, cervical cancer screening effectiveness, cost-effectiveness, cervical cancer screening policies, and future developments that will influence screening. The screening model suggests that early detection offers the opportunity to change the disease's progression and prognosis by identifying disease during the asymptomatic phase.

Two different strategies have been used to reduce disease incidence and mortality through screening: organized screening and opportunistic screening. The organized screening process includes identifying and inviting the target population for screening, providing the screening test, investigating abnormal screening results, and recalling individuals to be screened on a regular basis.

The evidence for the effectiveness of cervical cancer screening using the Pap test is non-experimental and comes from trends over time in cervical cancer incidence and mortality in relation to screening, observational studies, and modeling of screening policies and practices. Given the uniformity of the evidence assembled by different methods from a variety of sources, it is clear that screening decreases cervical cancer incidence and mortality.

Screening policies differ around the world from annual screening to screening every five years. In Canada, 72.8% of Canadian women 18 to 69 years of age report having had a Pap test in the previous three years (Statistics Canada, 2009). The percentage of Manitoba women 20 to 69 years of age who had a Pap test from 2008 to 2011 is 63.3% and has remained stable for the past 10 years (CervixCheck CancerCare Manitoba, 2011). The introduction of new technologies such as HPV DNA testing and HPV vaccination will impact future screening policy decisions but because the risk of cancer is not eliminated, screening will still be necessary. The following chapter reviews factors related to screening participation, previous cervical cancer screening invitation letter studies, and the limitations of these studies.

Chapter 4. Cervical Cancer Screening Participation and Invitation Letters

4.1 Introduction

Despite the availability of screening in developed countries and its effectiveness in decreasing cervical cancer incidence and mortality, some women are rarely or never screened. Reasons women give for not participating in cervical cancer screening include a lack of knowledge about the Pap test, believing screening unnecessary or of no benefit, considering oneself not to be at risk of developing cervical cancer, and fear of embarrassment or pain (Fylan F, 1998). These reasons are often related to socio-economic status, ethnicity, age, health status, and access to the health care system (Fylan F, 1998).

In order to increase screening rates, a variety of strategies have been used including small media (brochures, flyers), mass media (radio advertisements, bus stop advertisements), group education, one-on-one education, and invitation letters (Task Force on Community Preventive Services, 2008). Invitation letters are printed messages advising women that they are due or late for screening. They have been used in a variety of studies to encourage women to be screened for cervical cancer with varied results. This chapter reviews factors that are related to screening participation and the results and limitations of previous invitation letter studies.

4.2 Factors related to screening participation

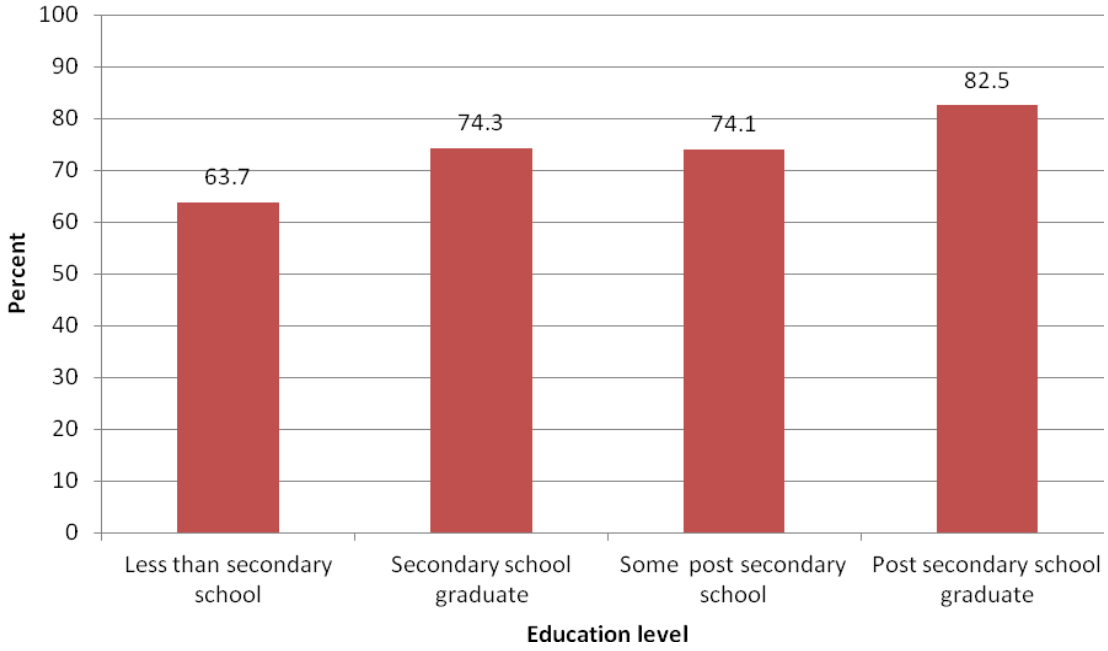
4.2.1 Education and income

Several studies have found that education level is directly related to cervical cancer screening participation (Harlan LC, Berstein AB, & Kessler LG, 1991; Jennings-

Dozier K, 1999; Katz S & Hofer TP, 1994; Simoes EJ et al., 1999; The National Cancer Institute Cancer Screening Consortium for Underserved Women, 1995; Woltman KJ & Newbold KB, 2007). Education is associated with health literacy skills which include the ability to obtain, process, and understand health information (Lockwood-Rayermann S, 2004; Paasche-Orlow MK, Parker RM, Gazmararian JA, Nielsen-Bohlman LT, & Rudd RR, 2005; Schillinger D, Barton LR, Karter AJ, Wang F, & Alder N, 2006; von Wagner C, Knight K, Steptoe A, & Wardle J, 2007; von Wagner C, Steptoe A, Wolf MS, & Wardle J, 2009; von Wagner C, Good A, Whitaker KL, & Wardle J, 2011). Davis et al. (2002) found that individuals with low health literacy skills struggle to understand the concept of early detection and the value of screening (Davis TC, Williams MV, Marin E, Parker RM, & Glass J, 2002). Previous research has found that Canadian and American women who have less than a high school education are less likely to have heard of a Pap test or, if they have heard of the Pap test, to be less compliant with screening recommendations (Harlan LC et al., 1991; Katz S & Hofer TP, 1994).

The 2008 CCHS found that 63.7% of women who had less than a secondary school education reported having had a Pap test in the previous three years compared to 74.3% of women who had graduated from secondary school, 74.1% of women who had some post-secondary school education, and 82.5% of women who were post-secondary school graduates (Figure 17) (Statistics Canada, 2009). Woltman et al. (2008) also found that women with less than a high school education were half as likely to have ever had a Pap test compared to women who were high school graduates (Woltman KJ & Newbold KB, 2007).

Figure 17 Percentage of women 18 to 69 years of age who reported having had a Pap test in the previous three years by education level



Data source: Statistics Canada, 2009.

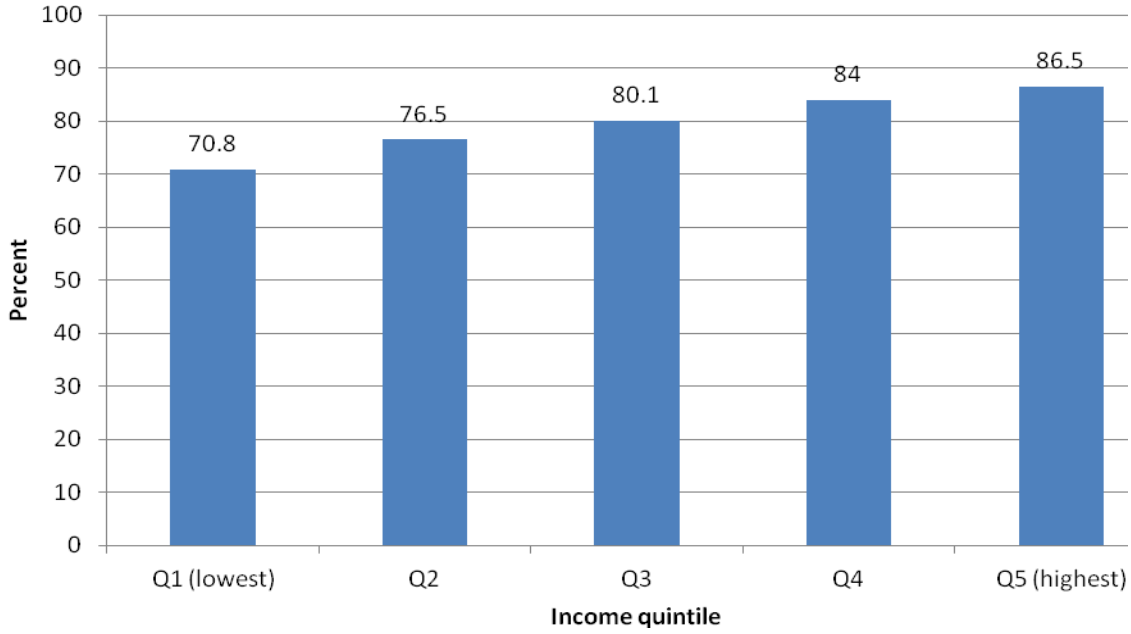
Notes: The CCHS excludes individuals who live on First Nations communities, institutional residents, full-time members of the Canadian Forces, and residents of certain remote regions.

Like education, lower income levels have been associated with decreased awareness of the benefits of participating in screening, expecting screening tests to be unpleasant and embarrassing, increased worry about following a screening invitation, and stronger beliefs in the role of chance in health (Niederdeppe J & Levy AG, 2007; Wardle J & Steptoe A, 2003; Wardle J et al., 2004; Wardle J, McCaffery K, Nadel M, & Atkin W, 2004). Women with lower incomes may experience a higher frequency of stressful events, have fewer social or economic resources available to help cope with stress, or have less time available to practice preventive health behaviours such as screening (Hatch

SL & Dohrenwend BP, 2007; Marmot M, Friel S, Bell R, & et al., 2008; Wardle J et al., 2003).

Inequalities in cervical screening participation by income level have been shown in several studies in countries with and without universal health care insurance (Harlan LC et al., 1991; Jennings-Dozier K, 1999; Katz S & Hofer TP, 1994; Paskett ED et al., 2010; Simoes EJ et al., 1999). In 1994, Katz et al. found that women with higher incomes were more likely to have a Pap test in both Canada and the US after controlling for age, education, marital status, and history of previous pregnancies (Katz S & Hofer TP, 1994). According to the 2008 CCHS, 70.8% of women in the lowest income quintile reported having had a Pap test in the previous three years compared to 76.5% of women in the second quintile, 80.1% of women in the third quintile, 84.0% of women in the forth quintile, and 86.5% of women in the highest income quintile (Figure 18) (Statistics Canada, 2009). Therefore, it appears that personal expenses such as transportation costs, availability of sick leave or paid time off from work, and child or elder care fees can pose significant barriers to screening participation for low income women (Katz S & Hofer TP, 1994).

Figure 18 Percentage of women 18 to 69 years of age who reported having had a Pap test in the previous three years by income quintile



Data source: Statistics Canada, 2009.

Notes: The CCHS excludes individuals who live on First Nations communities, institutional residents, full-time members of the Canadian Forces, and residents of certain remote regions.

Information on cervical cancer screening by income level is also available for Manitoba. In 2003 to 2004, women who lived in a Winnipeg neighbourhood that had a higher average household income had an increased likelihood of cervical cancer screening compared to women who lived in the rest of Manitoba (Martens P et al., 2008). Other research has found that Métis women living in Winnipeg also had a greater likelihood of having a Pap test if they lived in a neighbourhood with a higher household income (Martens P et al., 2010). Women who live in a more affluent neighbourhood may be more likely to know other community members who have attended screening, be more aware of cancer prevention strategies, and may have higher self-efficacy for using cancer

screening services (Moser K, Patnick J, & Beral V, 2009; Webb R, Richardson J, & Pickles A, 2004).

4.2.2 Visible minority and immigrant women

Several Canadian studies have found that visible minority women are significantly less likely to be screened for cervical cancer (Amankwah E, Ngwakongnwi E, & Quan H, 2009; Gupta A, Kumar A, & Stewart DE, 2002; Johnston GM, Boyd CJ, & MacIsaac MA, 2004; Lofters A, Glazier RH, Agha MM, Creatore MI, & Moineddin R, 2007; McDonald JT & Kennedy S, 2007; Quan H et al., 2006). Barriers such as a lack of knowledge about the importance of the Pap test, language issues, beliefs and attitudes (for example, the belief that health care is unnecessary in the absence of symptoms), concern about the gender of the health care provider, and not having a regular health care provider are more common among visible minority women (Amankwah E et al., 2009; Redwood-Campbell L, Fowler N, Laryea S, Howard M, & Kaczorowski J, 2011).

Not knowing where to go for screening is also a common barrier particularly if the woman is a recent immigrant (Wu Z, Penning MJ, & Schimmele CM, 2005). Woltman et al. (2007) found that immigrant women were significantly less likely to have ever had a Pap test compared to Canadian-born women after controlling for age, marital status, socio-economic status, and health-related characteristics (Woltman KJ & Newbold KB, 2007). In addition, many recent immigrant women do not speak English or French and face a language barrier in communicating with health care providers (Gentleman GF, Lee J, & Parsons GF, 1998; Lee M, 2000; Maxwell CJ, Bancej CM, Snider J, & Vik SA, 2001; Woltman KJ & Newbold KB, 2007).

Cervical cancer screening rates among Aboriginal women (Métis, Inuit, and First Nations) have historically been lower than among non-Aboriginal women (Hislop TG et al., 1996; Young TK et al., 2000). More recently, higher three-year screening rates have been reported for Aboriginal women and range from 69% to 85% depending on the source of data and the populations that were included (Demers A et al., 2012). In addition, from 2004/05 to 2006/07, Métis women 18 to 69 years of age living in Manitoba had similar cervical cancer screening rates compared to all other women (69.0% versus 67.8%) (Martens P et al., 2010). After controlling for geographic area, age, income, mental and physical co-morbidities, and continuity of care, Métis women were more likely than other Manitoba women to have had a Pap test (Martens P et al., 2010).

4.2.3 Age

Women over the age of 40 have higher incidence and mortality rates from cervical cancer than younger women (the median age at diagnosis is 45) (Surveillance and Risk Assessment Division, PHAC et al., 2009). This higher rate may be associated with decreased participation in cervical cancer screening (Gentleman GF et al., 1998; Lockwood-Rayermann S, 2004). In Canada, women over 65 years of age are more likely than younger women to have never had a Pap test and are less likely to have received one in the past three years (Maxwell CJ et al., 2001). Older women may perceive screening to be of less value because of beliefs about life expectancy, quality of life issues, or the presence of other illnesses (von Wagner C et al., 2011). It is important to note that a cohort effect could be taking place in which women are less likely to be screened not because of their age but because of other factors common to the entire cohort of women.

4.2.4 Health status

Health status has been associated with both decreased and increased participation in cancer screening (Ackerson K & Preston SD, 2009; Lewis CL, Kistler CE, Amick HR, & et al., 2006; Martens P et al., 2008; Martens PJ et al., 2009). From 1995/96 to 2003/04, cervical cancer screening rates in Winnipeg were 79% in community areas (CAs) that had the best overall health status (a premature mortality rate that was statistically lower than the Manitoba mortality rate) compared to 68% in CAs that were the least healthy (a premature mortality rate that was statistically higher than the Manitoba mortality rate) (Martens P et al., 2008).

Canadian women who are obese are less likely to be screened for cervical cancer (Cohen SS et al., 2008; Mitchell RS, Padwal RS, Chuck AW, & Klarenbach SW, 2008). Obese women may suffer from restricted mobility and may be less able to undergo screening (Mitchell RS et al., 2008). Healthcare providers and obese women may perceive screening to be more physically difficult, less accurate, or less important because of other health concerns (Cohen SS et al., 2008). Negative stereotypes may also affect the decision to perform a Pap test (Mitchell RS et al., 2008). In addition, obesity disproportionately affects those of lower income and these economic barriers may prevent access to care (Mitchell RS et al., 2008).

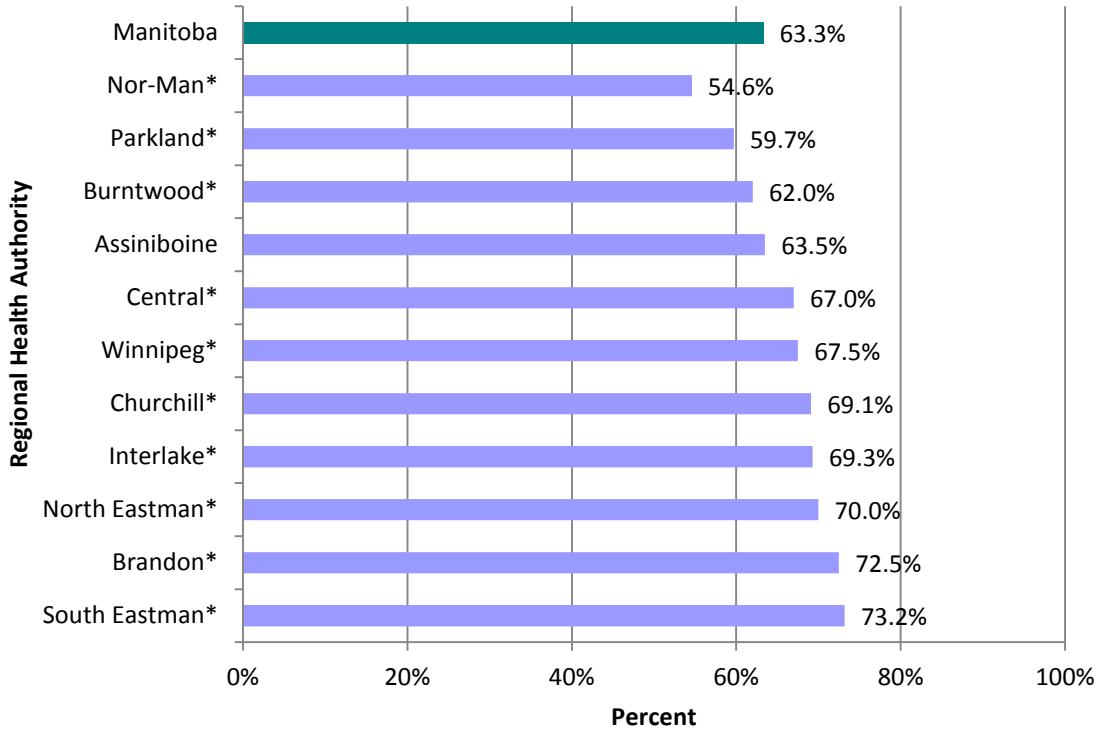
Research in mental health has found that Manitoba women who were diagnosed with any type mental health illness (including depression) were more likely to have had a Pap test perhaps because of more interactions with the same health care provider (Martens P et al., 2008; Martens PJ et al., 2009). However, women who were diagnosed with schizophrenia were less likely to have had a Pap test (Martens P et al., 2008;

Martens PJ et al., 2009). Women diagnosed with schizophrenia, a mental illness that can lead to many serious issues including social isolation, may be less likely to see a health care provider who performs Pap tests or screening might be considered less important in the context of other health issues.

4.2.5 Area of residence

In Manitoba, cervical cancer screening rates vary by area of residence. Figure 19 shows the percentage of women who had at least one Pap test by RHA from April 2008 to March 2011. Screening participation ranged from 54.6% in the RHA of Nor-Man to 73.2% in the RHA of Brandon (CervixCheck CancerCare Manitoba, 2011). All RHAs except Assiniboine differed significantly from the Manitoba rate. Overall, screening rates were lower in northern Manitoba and higher in southern Manitoba.

Figure 19 Percentage of women 20-69 years of age who had at least one Pap test from by Regional Health Authority, 2008 to 2011

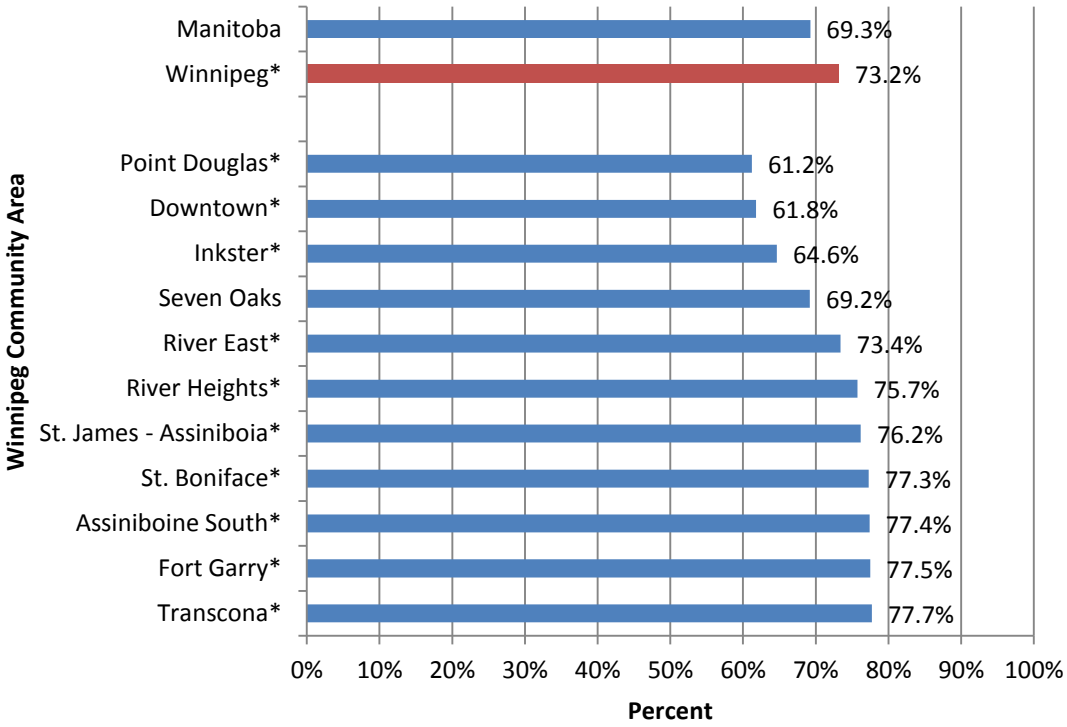


Notes: *Significantly different from the Manitoba rate ($p<0.05$).

Data source: CervixCheck CancerCare Manitoba, 2011.

Within the city of Winnipeg, screening rates differ by CA. Figure 20 shows the percentage of women 18 to 69 years of age who had at least one Pap test from 2003/04 to 2005/06 by Winnipeg CA (Fransoo R et al., 2009). Screening rates ranged from 78.3% in St. Vital (a more affluent Winnipeg CA) to 61.2% in Point Douglas (a low-income, inner-city CA). All CAs except Seven Oaks differed significantly from the Manitoba rate.

Figure 20 Age-adjusted percentage of women 18 to 69 years of age who had at least one Pap test by Winnipeg Community Area, 2003/04 to 2005/06



Notes: *Significantly different from the Manitoba rate ($p<0.05$).

Data source: Fransoo R et al., 2009.

However, the 2008 CCHS found that the percentage of women who reported having had a Pap test by location of residence was not significantly different (78.3% urban, 76.2% rural, 76.1% rural isolated, and 79.2% rural very isolated) (Statistics Canada, 2009). These different results may be due to the source of the data (self-reported versus administrative), the use of different populations (Canada versus Manitoba), or the exclusion of some individuals such as First Nations communities from the CCHS.

4.2.6 Residential mobility

Residential mobility is the movement of individuals within the province that results in a change of address. Although residential mobility itself may not be a direct factor in a woman's health, changing one's address may lead to lack of continuity with a health care provider despite the total number of interactions with the health care system (Lix L et al., 2006). In Manitoba, Lix et al. (2006) found that the odds of having at least one address change was associated with older age, gender (higher for males than females), marital status (higher for single and widowed individuals), income (higher for lower income), and the use of hospital and physician services (higher for those who used more services) (Lix L et al., 2006). Frequent changes in residence may also indicate financial instability which may influence the use of screening services (Lix L et al., 2006).

4.2.7 Continuity of care and opportunity to be screened

Continuity refers to the degree to which a series of health care events is experienced as coherent and connected (Haggerty JL et al., 2003). Continuity of care has been previously used as an indicator of the level of health care available to an individual (Litaker D, Koroukian S, & Love T, 2005). The availability of care over time from a usual source of health care better enables an individual to resolve health care issues when they arise, benefit from the coordination of care across multiple settings, and receive preventive services (Litaker D et al., 2005). Continuity of care is also important because it is potentially modifiable through health system-level interventions (Martens PJ et al., 2009).

Lack of continuity of care with a primary care physician has been identified as an important risk factor for never having had a Pap test (Bazargan M, Bazargan SH, Farooq M, & Baker RS, 2004; Grunfeld E, 1997; Martens P et al., 2008; Martens PJ et al., 2009). In Manitoba, having continuity of care has been found to increase the likelihood of having a Pap test regardless of income level or whether a woman had a diagnosis of schizophrenia (Martens P et al., 2008; Martens PJ et al., 2009). Continuity of care may also relate to an individual's level of satisfaction with their health care provider. Previous research has found that women who report less satisfaction (poorer communication or distrust of the health care provider) have lower rates of screening participation (Ackerson K & Preston SD, 2009).

Related to continuity of care is the concept of opportunity to be screened. Opportunity is the number of visits to a health care provider during which screening could take place. However, a high number of visits may not necessarily indicate higher screening participation particularly if the visits took place to multiple health care providers. A review of 245 women who developed invasive cervical cancer in Kingston, Ontario found that there was no difference in access to the health care system for women who had never been screened or not screened recently compared to women whose screening history was considered satisfactory (Carmichael JA, Jeffrey JF, Steele HD, & Ohlke ID, 1984). In addition, a Manitoba study found that although women diagnosed with invasive cervical cancer had fewer Pap tests, their opportunities to be screened were as frequent as women not diagnosed with cervical cancer (Decker KM et al., 2009).

4.3 Cervical cancer screening invitation letter studies

4.3.1 Overview of previous studies

Invitation letters have been evaluated in several previous studies (Binstock MA, Geiger AM, Hackett JR, & Yao JF, 1997; Bowman J, Sanson-Fisher R, Boyle C, Pope S, & Redman S, 1995; Buehler SK & Parsons WL, 1997; Burack RC et al., 1998; de Jonge E et al., 2007; Del Mar C, Glasziou P, Adkins P, Hua T, & Brown M, 1998; Eaker S, Adami H-O, Granath F, Wilander E, & Sparen P, 2004; Hunt JM, Gless GL, & Straton JAY, 1998; Johnston GM, Boyd CJ, MacIssac MA, Rhodes JW, & Grimshaw RN, 2003; McDougall L & Linehan M, 2011; McDowell I, Newell C, & Rosser W, 1989; Morrell S et al., 2005; Pierce M, Lundy S, Palanisamy A, Winning S, & King J, 1989; Pritchard DA, Straton JA, & Hyndman J, 1995; Somkin C et al., 1997; Stein K, Lewendon G, & Davis C, 2005; Vogt TM, Glass A, Glasgow RE, La Chance PA, & Lichtenstein E, 2003).

Four Canadian studies have examined the impact of an invitation letter on cervical cancer screening participation (Buehler SK & Parsons WL, 1997; Johnston GM et al., 2003; McDougall L & Linehan M, 2011; McDowell I et al., 1989). The Nova Scotia cohort study was population-based (n=114,426) and used the provincial cervical screening registry to identify unscreened women (no Pap test in 10 years) and under-screened women (no Pap test in three years) who were 18 years of age and older (Johnston GM et al., 2003). Invitation letters were sent to 15,691 unscreened and 6,995 under-screened women who lived in Cape Breton Island. Unexposed women included 61,510 unscreened and 32,996 under-screened women who lived in mainland Nova Scotia. After six months, 6.9% of women who were sent an invitation letter had a Pap

test compared to 4.6% of women in the unexposed group for an absolute difference in screening of 2.3%. Overall, the study found that women who were sent an invitation letter were more likely to have a Pap test in the next six months compared to women who were not sent a letter (OR=1.64, 95% CI 1.53-1.74).

In an unpublished study from Alberta, 30,738 women from the Calgary Health Region who had not had a Pap test in five years were randomly assigned to one of four groups: a control group (n=11,312), a loss-framed invitation letter group (n=6,616), a gain-framed invitation letter group (n=6,260), and a standard invitation letter group (n=6,650) (McDougall L & Linehan M, 2011). The standard letter stated that cervical cancer can be prevented through routine screening. The loss-framed letter stated that the risk of cervical cancer is increased if screening is not regular and the gain-framed letter stated that Pap tests can prevent cervical cancer. Six months after the invitation letters were mailed, 13.7% of women 21 to 34 years of age in the invitation letter group had a Pap test compared to 12% of women in the control group (1.7% difference, p=0.01). Among women 35 to 49 years of age, 11.2% of women in the invitation letter group had a Pap test compared to 8.9% of women in the control group (2.3% difference, p=0.001). Lastly, among women 50 to 69 years of age, 6.6% of women in the invitation letter group had a Pap test compared to 5.0% of women in the control group (1.6% difference, p=0.001). There was no difference in participation between the three invitation letter groups.

Two small RCTs have also been conducted in Canada in family medicine clinics in St. John's, Newfoundland and Ottawa, Ontario (Buehler SK & Parsons WL, 1997; McDowell I et al., 1989). Buehler et al. (1997) (n=441) found that 10.7% of women 18

to 68 years of age who had no Pap test in the previous three years who were sent an invitation letter had a Pap test in the next six months compared to 6.2% of women in the control group (Buehler SK & Parsons WL, 1997). The difference between the groups (4.5%) was not statistically significant (OR=1.17, 95% CI 0.87-3.36). However, McDowell et al. (1989) (n=1,366) found a statistically significant 12.2% difference in Pap test use over the next year among women 18 to 35 years of age who had not had a Pap test in the previous year who were sent an invitation letter (25.9% screened in the letter group versus 13.7% screened in the control group, OR=1.89, 95% CI 1.13-3.18) (McDowell I et al., 1989).

Five Australian RCTs have evaluated the effect of an invitation letter on cervical cancer screening participation (Bowman J et al., 1995; Del Mar C et al., 1998; Hunt JM et al., 1998; Morrell S et al., 2005; Pritchard DA et al., 1995). The largest study, a population-based RCT that included 90,247 women, found that 4.4% of women 20 to 69 years of age who had not had a Pap test in the previous four years and who were sent an invitation letter had a Pap test in the next three months compared to 2.9% of women in the control group (2% difference, OR = 1.54, 95% CI 1.43-1.67) (Morrell S et al., 2005). An RCT (n=689) that took place in a Vietnamese community did not find a difference in screening between women 18 to 67 years of age who had not had a Pap test in the previous two years who were sent an invitation letter and a control group (RR=0.85, 95% CI 0.55-1.3) (Del Mar C et al., 1998).

One Australian RCT focused on Aboriginal women 18 to 70 years of age who had not had a Pap test in the previous three years (Hunt JM et al., 1998). Women were randomized to be contacted by the health clinic (n=119), to be sent an invitation letter

(n=125), or to the control group (n=122). Eight women who were contacted by the health clinics (6.7%), three women in the invitation letter group (2.4%), and no women in the control group had a Pap test.

Two additional Australian RCTs took place in family medicine clinics (Bowman J et al., 1995; Pritchard DA et al., 1995). Bowman et al. (1995) (n=878) found that 22.6% of women 18 to 70 years of age who had not had a Pap test in the previous three years who were sent an invitation letter from the health clinic had a Pap test in the next six months compared to 24.5% of women who were not sent an invitation letter (a decrease of 1.9%). However, 36.9% of women who were sent an invitation letter from their family physician had a Pap test (12.4% difference, OR=1.81, 95% CI 1.13-2.91) (Bowman J et al., 1995). Pritchard et al. (1995) (n=757) found a statistically significant 8.9% difference in screening in the next year among women 36 to 69 years of age who had not had a Pap test in the previous two years who were sent a letter (25.7% screened) compared to controls (16.8% screened) (OR=1.67, 95% CI 1.01-2.77) (Pritchard DA et al., 1995).

Four European studies found a statistically significant difference in screening following an invitation letter while one study did not find a difference (de Jonge E et al., 2007; Eaker S et al., 2004; Pierce M et al., 1989; Stein K et al., 2005). A population-based, quasi-randomized study by De Jonge et al. (2008) in Belgium included 87,654 women 25 to 64 years of age who had not had a Pap test in the previous 30 months (de Jonge E et al., 2007). In the quasi-randomized design, invitation letters were mailed for eight age-specific units within five-year age groups. An accurate population-based registry was used to determine study eligibility and Pap test use. The difference in the percentage of women screened in the next 12 months was 6.4% (95% CI 5.9-6.9).

In 2005, Stein et al. randomly selected 1,140 women 39 to 64 years of age who had not been screened in at least 15 years from the county of Devon, UK to receive a telephone call (n=285), letter from a celebrity (n=285), letter from the screening program (n=285), or no intervention (n=285) (Stein K et al., 2005). After three months, 4.6% (95% CI 2.5-7.7%) of women in the program letter group had been screened compared to 4.0% (95% CI 0.38-3.6%) of women in the telephone group, 1.8% (95% CI 0.57-4.0%) of women in the celebrity letter group, and 1.8% (95% CI 0.57-4.0%) of women in the control group. The difference in screening between women who were sent an invitation letter and women in the control group was 2.8% (p=0.09). They concluded that social marketing using a celebrity did not have an impact on a woman's decision to participate in cervical cancer screening.

In a large population-based RCT in Sweden (n=10,569), Eaker et al. (2004) found that 15.5% of women 25 to 59 years of age who had not had a Pap test in the previous three years who were sent an invitation and a reminder letter had a Pap test in the next six months compared to 6.6% of women who were sent an invitation letter and no reminder (9.2% difference, OR=2.7, 95% CI 2.4-3.2) (Eaker S et al., 2004). However, no control group was included in this study so the effect of the invitation and reminder letters could not be compared to women who were not sent a letter.

The final European RCT was small (n=274), included women 35 to 62 years of age who had not been screened in five years, and took place in a family medicine clinic in the UK in a lower socio-economic area (Pierce M et al., 1989). Overall, 32% of women who were sent a letter had a Pap test in the next year compared to 15% of women in the control group (difference 17%, OR=2.15, 95% CI 1.35-3.45).

Two American RCTs found a statistically significant difference in Pap test rates while two RCTs did not find a difference (Binstock MA et al., 1997; Burack RC et al., 1998; Somkin C et al., 1997; Vogt TM et al., 2003). Vogt et al. (2003) included 600 women who had not had a Pap test in the previous three years who belonged to an HMO in Oregon (Vogt TM et al., 2003). Women who were sent an invitation letter had an 18% participation rate in the next 12 weeks compared to 16% for controls (2% non-significant difference).

Burack et al. (1998) included 1,928 women 18 to 40 years of age from an HMO in Michigan who had not had a Pap test in the previous year (Burack RC et al., 1998). Overall, 29% of women who were sent an invitation letter had a Pap test in the next year compared to 28% of women in the control group (1% difference, OR=1.07, 95% CI 0.88-1.30). However, Binstock et al. (1997) did find a statistically significant 10.1% difference in Pap test use among women 25 to 49 years of age who belonged to a Southern California HMO and had not had a Pap test in the previous three years (n=653) (26.4% screened in the letter group compared to 16.3% screened in the control group in the next year, OR=1.84, 95% CI 1.54-2.19) (Binstock MA et al., 1997). Somkin et al. (1997) (n=3,564) found that 19.4% of women 20 to 64 years of age who had not had a Pap test in three years who belonged to an HMO in Northern California and were sent an invitation letter had a Pap test in the next six months compared to 9.1% of controls (10.3% difference, OR=2.40, 95% CI 1.89-3.05) (Somkin C et al., 1997).

One additional American study by Lantz et al. (1995) found a statistically significant 17.9% difference in screening among women who received an invitation letter and telephone call (21.7% screened) compared to women who received neither (3.8%

screened) (OR=6.9, 95% CI 1.9-25.6) (Lantz PM et al., 1995). However, the sample size was small (n=139) and the setting was an HMO where the woman's telephone number was available. In a population-based setting, this is often not the case nor is it feasible to telephone each woman. Appendix C provides summarized information about previous cervical cancer screening invitation letter studies.

4.3.2 Meta-analyses

The range of findings in the previous studies suggests that invitation letter effectiveness varies by population and study methodology. In order to address this variability, three meta-analyses have evaluated the effectiveness of invitation letters on cervical cancer screening participation (Baron RC et al., 2008; Everett T et al., 2011; Tseng DS et al., 2001). A meta-analysis combines the results from different studies to draw general conclusions by estimating the central tendency and variability in effect size across the studies (Baghi H, Noorbaloochi S, Moore JB, 2007; Nakagawa S, 2007). The quality of the meta-analysis depends on the validity of the studies included in the review. Appendix D provides a summary of the studies included in each meta-analysis.

Baron et al. (2008) and the US Task Force on Community Preventive Services reviewed 21 studies that examined client reminders for cervical cancer screening (letters, postcards, or telephone calls) (Baron RC et al., 2008). Eight higher quality studies included in the final meta-analysis found a 9.8% median absolute increase in screening participation.

Tseng et al. (2001) reviewed ten RCTs that assessed the effectiveness cervical cancer screening invitation letters (n=22,722) (Tseng DS et al., 2001). They found that women who were sent an invitation letter were significantly more likely to have a Pap

test compared to women who were not sent a letter (OR=1.64, 95% CI 1.49-1.80). This effect varied by socioeconomic status; the OR for the two studies that included Medicaid eligible women from the US (low socioeconomic status) was 1.16 (95% CI 0.99-1.35) and the OR for the eight studies that included all other populations (mixed socioeconomic status) was 2.20 (95% CI 1.79-2.28). They concluded that invitation letters may be less effective for low socioeconomic populations.

In a Cochrane Systematic Review, Everett et al. (2011) reviewed twelve RCTs that compared the cervical cancer screening participation of women who were sent an invitation letter to women who were not sent a letter (n=99,651) (Everett T et al., 2011). The meta-analysis found that women who were sent an invitation letter had a significantly higher screening rate than women who received usual care or no invitation letter (RR=1.44, 95% CI 1.24-1.52). The review concluded that there is sufficient evidence to support the use of invitation letters in increasing cervical cancer screening participation.

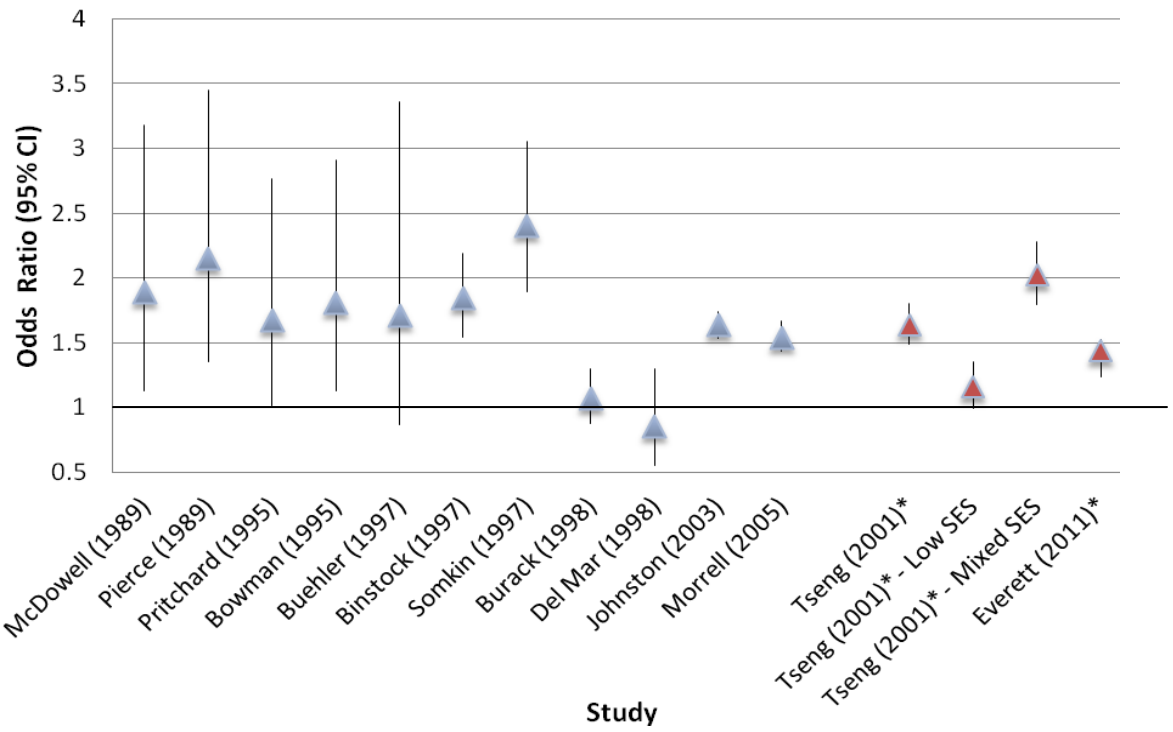
4.3.3 Summary of previous studies

Figure 21 shows the ORs and 95% CIs for previous invitation letter studies and meta-analyses. An OR was not available for the following studies: Hunt, 1998, De Jong, 2008, Stein, 2005, Eaker, 2004, Vogt, 2003, and McDougall, 2009. Three studies in Figure 21 have a 95% CI that includes one which means there was no statistically significant difference in the Pap test rate of women who were sent an invitation letter compared to women who were not sent a letter (Buehler SK & Parsons WL, 1997; Burack RC et al., 1998; Del Mar C et al., 1998). Eight studies had wide confidence intervals most likely due to a small sample size (Binstock MA et al., 1997; Bowman J et

al., 1995; Buehler SK & Parsons WL, 1997; Del Mar C et al., 1998; McDowell I et al., 1989; Pierce M et al., 1989; Pritchard DA et al., 1995; Somkin C et al., 1997). Due to these wide intervals, there is less confidence in the study results; the effect of the invitation letter could be larger or smaller than the observed effect (Baghi H, Noorbaloochi S, Moore JB, 2007; Nakagawa S, 2007).

Three studies show narrow confidence intervals and therefore provide a more confident effect of the invitation letter: Johnston et al. (2003) (OR=1.64, 95% CI 1.53-1.74), Morrell et al. (2005) (OR=1.54, 95% CI 1.43-1.67), and Burack (1998) (OR=1.07, 95% CI 0.88-1.33) (Burack RC et al., 1998; Johnston GM et al., 2003; Morrell S et al., 2005).

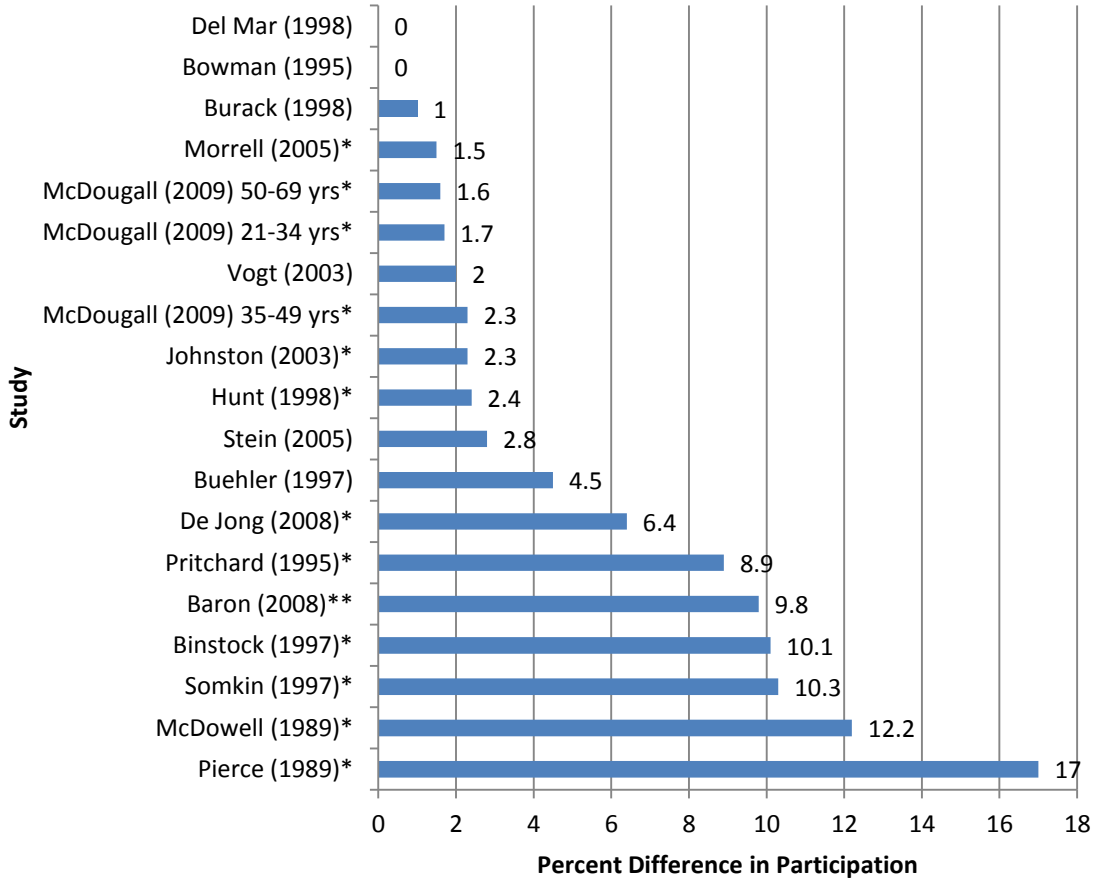
Figure 21 Odds ratios and 95% confidence intervals for previous invitation letter studies and meta-analyses



Notes: * Meta-analyses.

Figure 22 shows the difference in participation between the invitation letter group and the control group for the previous invitation letter studies. The difference in participation ranged from 0% to 17%.

Figure 22 Difference in screening participation between the invitation letter and control groups for previous invitation letter studies and meta-analyses



Notes: *Statistically significant difference between the intervention and control groups; ** Meta-analysis

Based on these results, there is still some uncertainty about the effectiveness of an invitation letter on cervical cancer screening participation in Manitoba. The effectiveness appears to be influenced by characteristics of the population, health care system, environment, and the study methodology. Consequently, when answering the question

"is this intervention effective?" it is necessary to consider the intervention, the outcome, and the context in which the intervention takes place. Although meta-analyses provide better evidence about the effectiveness of invitation letters, issues of study heterogeneity (variations in study outcomes between studies) and quality must be considered when interpreting the findings. These limitations emphasize the importance of assessing invitation letter effectiveness in a Manitoban context.

4.3.4 Lessons and limitations

Although the methodological differences in the previous studies make comparisons between them difficult, some lessons can be learned. Most of the studies included younger women (18 to 30 years of age) who had not had a Pap test in the previous one to three years. Few studies focused on women over 30 years of age and on women who had not had a Pap test in the previous five years or who had never had a Pap test all of whom are at a higher risk of developing invasive cervical cancer.

The outcome measure in all studies was the number of women who had a Pap test. However, methods for determining Pap test use varied from HMO databases, family practice rosters, and self-reported data to population-based databases. The quality of these data sources was frequently not stated. For example, self-reported Pap tests may not accurately reflect a woman's screening history because of recall and volunteer bias (Bowman J, Redman S, Dickinson JA, Gibberd R, & Sanson-Fisher R, 1991). When the method for determining screening participation was not population-based, women could have had a Pap test at a location that was not included in the study which would underestimate in the effect of the invitation letter on screening participation.

The follow-up time from the date the invitation letter was mailed until the assessment of screening participation varied from three months to two years. The evaluation of participation should be close enough to the date of the invitation letter to reduce the effect of secular trends, cohort effect, or other unknown confounding factors while allowing enough time for women to make an appointment with a health care provider and have a Pap test. Morrell et al. (2004) found that after 180 days, the number of women who had a Pap test in the invitation letter group changed very little (Morrell S et al., 2005). Therefore, studies that had a very short follow-up period such as three months may not have included all Pap tests while studies that had a long follow-up period (one or two years) may not be able to attribute the Pap test to the invitation letter. In addition, Pritchard et al. (1995) followed women for one year but the recommended screening interval was two years so some women may have been not included in the study follow-up (Pritchard DA et al., 1995). Finally, the HMO in Burack et al.'s study (1998) recommended annual screening but some physicians disagreed and may have carried out biennial screening.

Five previous studies were population-based, and of these, three were RCTs that found contradictory results. Eleven of the RCTs had a small or moderate sample size. Most of these studies focused on sub-groups of women such as inner-city visible minority women, low income women, and immigrant women. The generalizability of these results is uncertain because the participants may not be representative of other populations.

Several RCTs randomized women without assessing their screening eligibility leading to the exclusion of women post-randomization. The most common reason for excluding women from the analysis was because of a hysterectomy. Women who have

had a total hysterectomy do not need a Pap test and should not be invited to be screened. By excluding these women post-randomization, the study results may be biased.

Three studies did not use accurate address information which is crucial when evaluating the effectiveness of invitation letters. Pierce et al. (1989) found that 74% of women received the invitation letter (Pierce M et al., 1989). Similarly, Hunt et al. (1998) found that 30% of the invitation letters were undelivered or returned to the health clinic (Hunt JM et al., 1998). In addition, Eaker et al. (2004) did not have information on the number of women who had moved which may have underestimated the effect of the letter (Eaker S et al., 2004). Address information quality and completeness was not available for several other studies.

Contamination in an RCT occurs when women who are randomized to the control group are exposed to the intervention either through discussions with women in the intervention group or through health care providers who are caring for women in both groups. Only one RCT addressed the issue of contamination. Del Mar et al. (1998) suspected contamination between women who received an invitation letter and those who did not because of the presence of a mass media campaign which may have reduced the ability to detect a significant difference between the two groups (Del Mar C et al., 1998).

Overall, the evaluation of cervical cancer screening invitation letters should take into consideration the contamination that can occur when using an RCT, use a population-based registry to identify the study population, accurately exclude women who are not eligible for screening before randomization (i.e. women who have had a hysterectomy or have been diagnosed with invasive cervical cancer), not rely on self-

reported Pap tests, and ensure that the sample size and power are sufficient to detect a difference between the intervention and control groups.

4.4 Chapter Summary

This chapter reviewed the factors that influence screening participation including education, income, visible minority status, immigrant status, age, health status, area of residence, residential mobility, continuity of care, and the opportunity to be screened.

This chapter also reviewed the design, results, and limitations of previous cervical cancer screening invitation letter studies and meta-analyses. Invitation letter interventions have been evaluated in a variety of settings from HMOs in the US and private clinics in Australia to nationally funded, population-based programs with centralized procedures and registries in Europe and Canada.

The difference in screening participation between women who were sent an invitation letter and women who were not sent a letter ranged from 0% to 17% with ORs from 0.85 to 2.40. The variability of previous study results suggest that cervical cancer screening invitation letter effectiveness is influenced by the characteristics of the population, health care system, environment, and the study methodology. Therefore, there is still some uncertainty about the effectiveness of an invitation letter on cervical screening participation in Manitoba. The next chapter provides background information on the CRT design which was used to evaluate the effectiveness of cervical screening invitation letters in Manitoba.

Chapter 5. Cluster Randomized Trials

5.1 Introduction

A CRT is an RCT in which the unit of randomization is a cluster or group instead of an individual. The units of randomization can vary from small clusters such as households or families to large clusters such as classrooms, worksites, or communities. Because the allocation of clusters is random, confounding factors should be distributed equally between the two groups. Hence, a CRT retains a high level of internal validity. In addition, a CRT minimizes contamination between the intervention and control groups, increases the practicality of the study design, permits the inclusion of contextual or environmental information in the analysis, and can be designed to cope with multifaceted interventions (Donner A & Klar N, 2000).

However, CRTs are more difficult to design, require more participants to obtain equivalent statistical power, and necessitate more complex analyses (Campbell MK, Elbourne DR, Altman DG, & Consort Group, 2004). This chapter reviews the most commonly used CRT designs, the impact of choosing a CRT, and methods used to analyze CRTs.

5.2 The cluster randomized trial study design

The most commonly used CRT designs include the completely randomized design, the matched-pair design, the stratified design, and the stepped wedge design (Donner A & Klar N, 2000). The completely randomized design involves no pre-stratification or matching of clusters according to baseline characteristics. The strength of the completely randomized design is its simplicity in execution and analysis. This

study design is most suited to studies with a large number of clusters to ensure that there are no systematic differences between the intervention and control groups (Donner A & Klar N, 2000).

The matched-pair design matches or pairs the clusters in the intervention and control groups on potentially important factors. The most commonly used matching factors are cluster size and geographic area. The main advantage of the matched-pair design is the ability to balance baseline factors which may enhance the credibility of the study conclusions and increase the power to detect intervention effects (Donner A & Klar N, 2000). The power of the matched-pair design compared to the completely randomized design improves as the effectiveness of the matching increases (Donner A & Klar N, 2000). The limitation of this study design includes selecting the most appropriate variables to be matched (Donner A & Klar N, 2000). In addition, if the number of pairs available to be matched is small, any loss to follow-up of a single cluster in a pair means that both clusters in the pair must be discarded from the study when testing the intervention (Donner A & Klar N, 2000).

The stratified design is an extension of the matched-pair design in which several clusters rather than just one are randomly assigned within strata to the intervention and control groups. Stratification should occur on cluster-level factors that are known to be strongly associated with the outcome (Donner A & Klar N, 2000). The stratified design provides some baseline control on factors thought to be related to the outcome without the difficulty of finding appropriate pair matches or the analysis challenges of the matched-pair design but has been used less frequently than other CRT designs (Donner A & Klar N, 2000).

Lastly, a stepped wedge design is a crossover study in which different clusters switch treatments at different points in time. The advantage of this design is the ability to increase study power. However, potential gains in power are realized only when stringent assumptions are satisfied which limits the usefulness of the design as applied to CRTs (Donner A & Klar N, 2000).

5.2.1 Impact of the study design

The decision to use a CRT impacts the power of the study and the required sample size. A fundamental assumption of the RCT is that the outcome for an individual participant is completely unrelated to that for any other participant (i.e. they are independent) (Eccles M, Grimshaw JM, Campbell M, & Ramsay C, 2003). This assumption is violated with cluster randomization because two individuals within a cluster may be more likely to respond in a similar manner to an intervention than two individuals from different clusters (Eccles M et al., 2003). For example, women within one community may be more alike because of similar socio-economic status or ethnic background and may therefore respond to an intervention in a similar manner. The statistical measure of the extent of clustering or the degree to which responses within a cluster are similar is called the intraclass correlation coefficient (ICC) or rho (ρ) (Eccles M et al., 2003). The ICC is based on the relationship of the between-cluster to within-cluster variance and takes a value between 0 and 1 (Eccles M et al., 2003).

ICC (rho) = $s^2_{bw}/(s^2_{bw} + s^2_{wi})$ where bw= between clusters and wi=within clusters

Because of clustering, a CRT has reduced power to detect an intervention effect relative to an RCT that randomizes the same number of individuals (Donner A & Klar N, 2004). To retain power equivalent to an RCT, the number of individuals in a CRT must

be increased by 1+(n-1) ρ where n is the average cluster size and ρ is the ICC (Campbell MK, Mollison J, Steen N, Grimshaw JM, & Eccles M, 1999). Therefore, a larger sample size is always required for a CRT (Donner A & Klar N, 2004). A number of rules of thumb have been proposed such as at least 25 observations from 25 clusters are required to detect a significant relationship in a multi-level model (Campbell MK, Fayers PM, & Grimshaw JM, 2005).

5.2.2 Impact on the study analyses

The analysis of an RCT in which the individual is both the unit of randomization and the unit of analysis is fairly straightforward. This is not the case for a CRT for two reasons: the unit of analysis must be selected (cluster or individual) and an appropriate analytic method must be chosen that takes into account the clustered nature of the data.

Although randomization occurs at the cluster level, in a CRT, analyses can occur at the cluster or individual level. Cluster-level analyses are appropriate when the research question focuses on the randomized unit as a whole rather than on the individual (for example clinics or hospitals) (Donner A & Klar N, 2000). Analyses at the cluster level are easy to conduct and explain, can be applied to any outcome variable, permit the construction of exact statistical inferences, can be adapted to adjust for baseline imbalances in cluster size, and when weighted properly, can provide power comparable to individual-level analyses (Donner A & Klar N, 2000). Basically, a summary statistic such as a mean or proportion is calculated for each cluster (Eccles M et al., 2003). As each cluster provides only one data point, the data can be considered independent which permits the use of standard statistical tests such as un-weighted or weighted regression (Eccles M, Grimshaw J, Walker A, Johnston M, & Pitts N, 2005; Ma J et al., 2009; Peters

TJ, Richards SH, Ades AE, & Sterne JAC, 2003). Unfortunately, a cluster-level analysis does not permit any adjustment for individual-level characteristics (Eccles M et al., 2005; Ma J et al., 2009).

Individual-level analyses are appropriate when the research question focuses on the individual. Analyses at the individual level allow a more direct examination of the joint effects of cluster-level and individual-level predictors, can be extended to permit the analyses of multi-level data, yield estimates of the extent of clustering, and provide more efficient estimates of the effect of the intervention when there are many clusters or when the cluster sizes are variable (Donner A & Klar N, 2000).

At the individual level, standard statistical analyses such as individual-level logistic regression are not appropriate because they do not take into account the clustered nature of the data (Austin PC, 2007). For example, the results of a standard logistic regression will be inaccurate because the between-cluster variance is averaged across the sample producing underestimated standard errors, confidence intervals that are too narrow, and *p* values that are smaller than their actual value (Christie J, O'Halloran P, & Stevenson M, 2009). This may lead to concluding that there is a difference between the control and intervention groups when there is none (i.e. a type I error) (Christie J et al., 2009).

Individual-level analytic methods that are appropriate for a CRT include a standard logistic regression with an adjusted standard error to allow for clustering and hierarchical models such as generalized estimating equations (GEE), random-effects logistic regression, and Bayesian random-effects logistic regression (Ma J et al., 2009; Peters TJ et al., 2003). GEE is a hierarchical model that extends the standard logistic

regression to allow for clustering by specifying a correlation matrix that describes the association between different individuals in the same cluster. The GEE also permits the incorporation of additional cluster or individual characteristics into the model and has a high power for detecting a statistically significant intervention effect (Austin PC, 2007).

Random-effects logistic regression is a hierarchical linear model that includes a cluster-level random effect in the model which is assumed to follow a normal distribution. Bayesian random-effects logistic regression is a traditional hierarchical random-effects logistic regression but is based on different assumptions about the variance of the cluster-level random-effect.

Of these hierarchical models, the GEE estimates the population-averaged effect while random-effects logistic regression and Bayesian random-effects logistic regression estimate the subject-specific effect (Austin PC, 2007). Population-averaged models are most frequently used in studies in which the difference in the population-average responses between two groups with different risk factors is the focus instead of the change in an individual's response (a subject-specific model) (Zeger Sl, Liang K-Y, & Albert PS, 1988). For example, if the independent variable is whether or not a woman was sent an invitation letter and the dependent variable is screening participation, a population-averaged model estimates the difference in screening rates between women who were sent an invitation letter and those who were not sent a letter. In contrast, the subject-specific model estimates the expected change in a woman's probability of being screened if she was sent an invitation letter.

Therefore, the choice of analysis method also depends on the research question. For this study, the question is "What is the difference in screening participation for women

sent an invitation letter compared to those who were not sent a letter or what is the population-average effect of the invitation letter?" Based on this research question, the GEE is the appropriate analysis approach for this study.

5.3 Generalized estimating equations

The GEE approach was developed by Liang and Zeger (1986) to produce more efficient and unbiased regression estimates for use in analyzing longitudinal or repeated measures with non-normal outcome variables (Zeger Sl & Liang K-Y, 1986; Zeger Sl et al., 1988). The GEE is an extension of the generalized linear model (GLM) to correlated data but unlike the GLM, which is based on maximum likelihood theory for independent observations, the GEE is based on quasi-likelihood theory (Cui, 2007). Using a GEE model requires the specification of a link function, the distribution of the dependent variable, and the correlation structure of the dependent variable.

The link function depends on the distribution of the dependent variable; the logit link is the standard linking function for binary dependent variables (Ballinger GA, 2004). The goal of specifying the working correlation structure is to estimate the regression parameters as efficiently as possible and depends on the nature of the data (Ballinger GA, 2004). The working correlation matrix can be unstructured, autoregressive, exchangeable, or independent (Ballinger GA, 2004). An unstructured correlation matrix assumes that correlations are different for each pair of observations and estimates all possible correlations between within-subject responses. An autoregressive correlation matrix is used when data are correlated within a cluster over time. An exchangeable correlation matrix is appropriate when data are clustered within a particular subject but are not time-series data or there is no logical ordering of observations within a cluster.

Finally, an independent correlation matrix is chosen when the responses within subjects are independent of each other.

In summary, GEE accounts for correlations among outcomes within a cluster when estimating regression coefficients and standard errors. The main limitation of GEE occurs when the number of clusters is small (less than 20). In this case, the variance estimate that is produced may be biased and a correction is necessary (Ma J et al., 2009).

5.4 Intention-to-treat and per-protocol analyses

An additional step in the analysis of a CRT is determining which participants should be included in the analyses. There are two options: the ITT and the per-protocol analysis. Analysis by ITT includes all participants as intended upon randomization regardless of whether or not they actually received the invitation letter (i.e. once randomized, always analyzed). An ITT analysis has three advantages: it retains the balance between the groups from randomization and therefore limits potential biases created by differences in baseline participant characteristics, it provides an unbiased estimate of the effect, and it reflects the effectiveness of the intervention in the real world by including non-compliance and protocol deviations which support the generalizability of the intervention (Heritier SR, Gebski VJ, & Keech AC, 2003; Moncur RA & Larmer JC, 2009). The main disadvantage of an ITT analysis is that it provides a conservative estimate of the size of the treatment effect.

An alternative to the ITT analysis is the per-protocol analysis which includes only those individuals who completed the study. A per-protocol analysis reflects the maximum potential benefits of the intervention or the efficacy of the intervention in an ideal situation (Moncur RA & Larmer JC, 2009). However, a per-protocol analysis is

subject to bias because by excluding individuals who did not complete the study, the original comparability of groups achieved after randomization is not maintained (Sedgwick P, 2011). Therefore, any differences between the intervention and control groups at the end of the study may not be due to differences in the intervention but a result of differences between the groups in their baseline characteristics. For this reason, if non-compliance rates are small, an ITT analysis should be used (Heritier SR et al., 2003).

5.5 Chapter Summary

A CRT randomizes clusters or groups of individuals such as families, schools, or communities instead of individuals to an intervention or control group. The most commonly used CRTs include the completely randomized design, the matched-pair design, the stratified design, and the stepped wedge design. Although each has strengths and weaknesses, all CRT designs reduce contamination and often increase study practicality. However, compared to a RCT, CRTs are more complex to design, require more participants to obtain equivalent statistical power, and require more intricate analyses. The analysis of a CRT needs to take into consideration the clustered nature of the data and can occur at the cluster or individual level.

GEE is a hierarchical model that extends a standard logistic regression to allow for clustering by specifying a correlation matrix that describes the association between different individuals in the same cluster. GEE permit the estimation of population-averaged effects, have a high power for detecting a statistically significant intervention effect, and lead to more precise standard errors, confidence intervals, and *p* values (Austin PC, 2007). One final step in the analysis of a CRT is determining which

participants should be included in the analysis. The options include an ITT analysis which includes all participants as intended upon randomization or a per-protocol analysis which includes only those individuals who completed the study. Since a per-protocol analysis is subject to bias, an ITT analysis is preferred.

In addition to the study analyses, the framework that forms the foundation of the study must be carefully considered. The next chapter describes the theoretical framework for used for this study, the Behavioural Model of Health Services Use.

Chapter 6. Theoretical Framework

6.1 Introduction

This chapter reviews the evolution of behaviour change theories from a focus on the individual to population-level theories that reflect multiple determinants of health behaviour. The use of a population-level theory is particularly important when examining cervical cancer screening because whether or not a woman is screened depends on her individual characteristics as well as the health care system and environment in which she lives.

The theoretical framework chosen to evaluate the effectiveness of cervical cancer screening invitation letters was the Behavioural Model of Health Services Use (BMHSU) developed by Ronald Andersen in the 1960s and revised over time in response to new issues and developments in health care delivery (Andersen R, 2008; Phillips KA et al., 1998). This population-level model includes four components: a contextual level, an individual level, health behaviour, and health outcomes. Predisposing, enabling, and need factors that occur at the contextual and individual levels influence health care use.

6.2 The evolution of behaviour change theories

There are more than 30 theories of behaviour change (Michie S, 2008). The first generation of theories was an extension of clinical medicine into public health and therefore had an individualistic orientation. These theories were developed to explain an individual's health and illness behaviours and include the Health Belief Model (HBM), the Theory of Reasoned Action (TRA) and the Theory of Planned Behaviour (TPB), the Transtheoretical model (TTM), and the Precaution Adoption Process Model (PAPM)

(Glanz K, Rimer BK, & Lewis FM, 2002). The HBM, TRA, and TRB have a cognitive perspective and propose that individuals choose an action that will lead to a positive outcome (Austin LT, Ahmad F, NcNally M-J, & Stewart DE, 2002). The TTM postulates that change occurs as an individual progresses through six stages: pre-contemplation, contemplation, preparation, action, maintenance, and termination (Reyna VF, 2008). The PAPM is also a cognitive theory of behaviour change but it emphasizes the role of risk perception (Weinstein ND, 1988).

The next generation of theories incorporated key components from earlier theories but expanded the concept of individualism by including some external variables. An example is Integrative Theory (IT) which suggests that behaviour is most likely to occur if one has a strong intention to perform the behaviour, if one has the necessary skills and abilities required to perform the behaviour, and if there are no environmental constraints preventing the behaviour (Fishbein M, 2000). However, system-wide variables that influence health behaviour were not included in these mid-level theories. Therefore, individual and mid-level theories are increasingly viewed as necessary but not sufficient to explain health behaviour (McKinlay JB, 1998).

Population-level theories evolved next as an understanding of the social and economic influences on health progressed (Rose G, 1985). Population-level theories reflect the multiple determinants of health behaviour such as individual, interpersonal, organizational, community, and public policy factors and the multiple levels of intervention (i.e. down-stream, mid-stream, and up-stream prevention efforts) that are required to achieve desired health outcomes (McKinlay JB, 1998). All of these factors interact in complex ways to produce the "causes of the causes" (McKinlay JB & Marceau

LD, 2000). Population-level theories also take into account the possibility of reciprocity between individuals and their environments; behaviour both influences and is influenced by an individual's environment.

Examples of population-level theories include the Interactive Model of Client Health Behaviour (IMCHB) and the BMHSU. The IMCHB consists of three major elements: client singularity (demographic characteristics, social influences, previous health care experience, and environmental resources), client-professional interaction, and health outcomes (Cox CL, 1982). The objective of the IMCHB is to identify and suggest explanations for relationships between these three major elements. The IMCHB has previously been used because its ecological components are appropriate for health disparity studies where socio-environmental factors are an important consideration (Ackerson K et al., 2008). Ackerson et al. (2008) used the IMCHB to guide the analysis of women's perceptions about cervical cancer screening (Ackerson K et al., 2008). The BMHSU includes four components: a contextual level, an individual level, health behaviour, and health outcomes (Andersen R, 2008; Andersen RM, 1995; Phillips KA et al., 1998). Predisposing, enabling, and need factors that occur at the contextual and individual levels influence health care use.

Over the past 40 years, individual and mid-level theories have contributed considerably to the development of new knowledge about health behaviour. However, with respect to cervical cancer screening, an important impact on incidence and mortality has occurred in organized programs that focus on the system as well as the individual (International Agency for Research on Cancer, 2005). This is because whether or not a woman has a Pap test is influenced by her individual characteristics, the characteristics of

the health care providers in her community, the health care system policies that are in place, and the environment in which she lives. Individual and mid-level theories provide some understanding of cervical cancer screening participation but may miss factors that shape women's beliefs, determine what screening barriers women face, and influence the screening options that are available. Further limitations of individual-level theories include a focus on individual risk factors that diverts resources away from upstream healthy public policy, blaming the victim, producing a life-style approach to health policy instead of a social policy approach to healthy lifestyles, overlooking ways in which behaviours are culturally generated and maintained, and underestimating the contribution of social and behavioural factors (McKinlay JB, 1998).

Therefore, a theory that helps explain cervical cancer screening participation must include the context in which screening occurs. The IMCHB explicitly addresses the client-provider interaction and the role of the professional in influencing client behaviour (Cox CL, 1982). Although health care provider behaviour is an important part of the screening process, measuring the elements of the client-provider relationship was not the objective of the cervical cancer screening invitation letter study. The BMHSU, however, considers many of the factors that might interact with an invitation letter to influence a woman's screening participation. The BMHSU is different from other theories of health care use that either focus solely on how an individual's characteristics influence health behaviour or include some external variables but not the context in which health care use occurs (Austin LT et al., 2002; Glanz K et al., 2002; Munro S, Lewin S, Swart T, & Volmink J, 2007; Painter JE, Borba CPC, Hynes M, Mays D, & Glanz K, 2008; Ricketts TC & Goldsith LJ, 2005). Therefore, the BMHSU was chosen as the theoretical

foundation for this study and was used to organize and operationalize factors that influence screening.

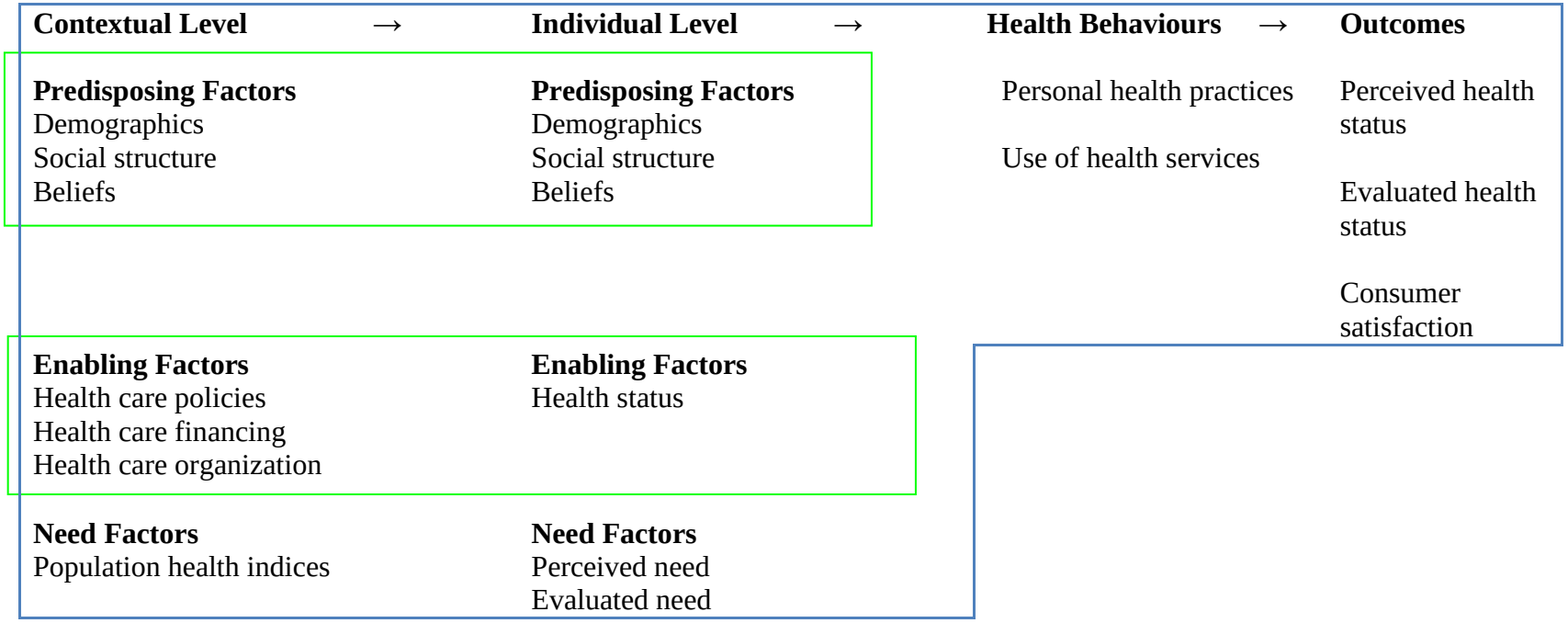
6.3 The Behavioural Model of Health Services Use

The BMHSU was developed in the 1960s to understand why families used health services, define and measure health care use, and assist is developing policies to promote equitable access to care (Andersen RM, 1995). The original model states that an individual's use of health services is a function of their predisposing characteristics, factors which enable use, and their need for care (Andersen RM, 1995). The model has been revised over time in response to new health care policy and health services delivery issues, developments in health services research, and critiques of the early version of the model (Andersen R, 2008).

Figure 23 illustrates the most recent phase of the model (Andersen R, 2008). The model includes four components: the contextual level, the individual level, health behaviour, and health outcomes. Predisposing, enabling, and need factors occur at the contextual and individual levels. Predisposing factors at the contextual and individual levels include demographics, social structure, and beliefs. At the contextual level, enabling factors include health care policies, financing, and organization. At the individual level, enabling factors include health status. Predisposing and enabling factors influence the need for health care use. Need at the contextual level is measured using population health indices and may be influenced by health education programs or by changing incentives to seek or provide care. Need at the individual level includes the individual's perceived and evaluated need for health services. Predisposing, enabling, and need factors influence health behaviours which, in turn, influence health outcomes.

Health behaviours include personal health practices and the use of health services such as screening. Health outcomes include perceived health status, evaluated health status, and consumer satisfaction.

Figure 23 Behavioural Model of Health Services Use



Source: Adapted from Andersen R, 2008. Used with permission from Wolters Kluwer Health.

6.4 Theoretical framework for evaluating cervical cancer screening invitation letters

Although the BMHSU has been used as the theoretical framework for health care research in a variety of settings, it has not been used in cervical cancer screening invitation letter research (Ricketts TC & Goldsith LJ, 2005). No previous studies that have examined the relationship between cervical cancer screening participation and invitation letters have stated a theory that formed the foundation of the research or provided a framework for the study design and analysis. This is not uncommon; research in population health often lacks a theoretical basis and behavioural interventions seldom use theory to guide research (Carpiano RM & Daley DM, 2006; Michie S & Abraham C, 2004). However, there is increasing recognition that behaviour change interventions should be based on a theoretical foundation (Michie S, 2008).

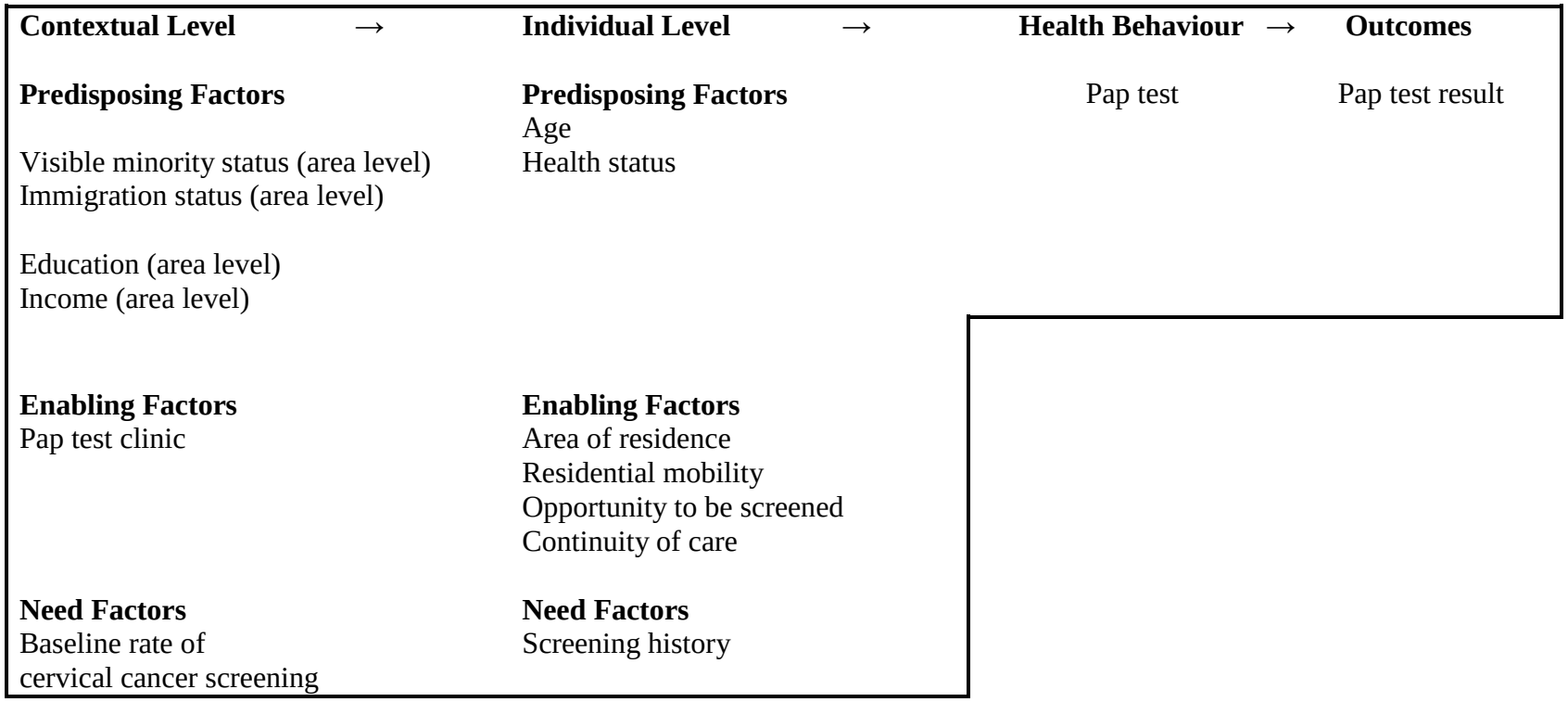
The BMHSU was chosen as the framework for this research because it is a population-level framework that recognizes that individuals exist within a broader social context (Hawe P, Shiell A, & Riley T, 2009). Figure 24 illustrates the application of the BMHSU to evaluating the effectiveness of cervical cancer screening invitation letters in Manitoba. Predisposing factors at the contextual level included area-level measures of visible minority status, immigration status, education and income. Predisposing factors at the individual level included age and health status. Enabling factors at the contextual level included whether or not a Pap test clinic was held in an intervention group FSA. Enabling factors at the individual level included area of residence, residential mobility, continuity of care, and opportunity to be screened. Need factors at the contextual level included the baseline cervical cancer screening rate in each FSA. Need factors at the individual level included a woman's screening history which was used to determine her

study eligibility. The health care behaviour of interest was the Pap test and the outcome was the Pap test result.

6.5 Chapter summary

Behaviour change theories have evolved from a focus entirely on the individual to population-level theories that include the influence of individual, organizational, community, and public policy factors. The BMHSU was selected as the theoretical foundation to evaluate the effectiveness of cervical cancer screening invitation letters among unscreened Manitoba women because it is a population-based theory that recognizes that individuals exist within a broad social context. This is important when studying cervical cancer screening because screening participation is influenced by multiple factors such as demographics (age, socioeconomic status, and health status), health care system policies (access issues), and the community in which a woman lives. The next chapter describes the methods used to carry out this research including operationalizing the dimensions of the BMHSU.

Figure 24 Cervical cancer invitation letter study theoretical framework



Chapter 7. Methods

7.1 Introduction

This chapter describes the methods used to evaluate the effectiveness of an invitation letter on cervical cancer screening participation in Manitoba using a CRT. Unscreened Manitoba women 30 to 69 years of age were randomized by FSA to an intervention or control group. Unscreened was defined as a woman who had no cytology or colposcopy record in the screening registry, had never been diagnosed with an invasive gynaecological cancer, had not had a complete hysterectomy, and had been a part of the screening registry for at least five years.

The intervention was a personally addressed invitation letter that provided information about cervical cancer screening from the screening program accompanied by a brochure. One to three weeks before the invitation letters were mailed, the screening program contacted a health centre in each intervention FSA to ask if the centre would hold a Pap test clinic to ensure screening access. The databases used for this study included the Cervical Cancer Screening Registry, the Manitoba Health Population Registry (MHPR), the Medical Claims Database, the Hospital Abstracts Database, and Statistics Canada 2006 Census data.

Descriptive statistics were used to describe the characteristics of the study participants. The Kaplan-Meier estimate of the survival curve was used to determine the cumulative Pap test incidence for each study group during the six month follow-up period. A univariable ITT logistic regression GEE model was used to determine if the invitation letter was predictive of having a Pap test. The ITT analysis included all

participants as intended upon randomization regardless of whether or not they actually received the invitation letter.

Based on the BMHSU, five multivariable ITT logistic regression GEE models were used to model Pap test use as a function of predisposing, enabling, and need factors. A final multivariable ITT logistic regression GEE model was performed that included all variables in the study's theoretical framework and significant interactions.

A per-protocol univariable logistic regression GEE model was also performed that included in the model women who died, had an end of coverage flag from Manitoba Health, or who had a mail return flag (their invitation letter was returned to the screening program undelivered).

7.2 Setting

The cervical cancer screening program in Manitoba (CervixCheck) was established in 2001 to ensure that Manitoba women receive organized, high-quality, cervical cancer screening services. The goal of the program is to reduce cervical cancer incidence and mortality. Program guidelines recommend biennial screening beginning three years after the onset of sexual activity until 70 years of age if the woman had three normal Pap test results in the previous ten years (CervixCheck CancerCare Manitoba, 2012).

In Manitoba, Pap tests are performed by primary care physicians, midwives, and nurse practitioners. Follow-up tests after an abnormal Pap test are also coordinated by the woman's health care provider. The screening program monitors Pap test results for women 18 years of age and older (approximately 482,922 women in 2011). When appropriate follow-up after an abnormal Pap test does not occur, the screening program

sends a letter to the woman's health care provider indicating the proper course of action. If no response is received, a letter is sent directly to the woman.

7.3 Study design

A completely randomized CRT design was used for this study (Figure 25). As discussed in Chapter five, a CRT was chosen to minimize contamination between the intervention and control groups and to increase the practicality of the study design by allowing letter distribution to occur by cluster. To determine if matching or stratification was required, cluster-level factors known to be strongly associated with the outcome can be compared between the intervention and control groups. In this study, the baseline rate of cervical cancer screening among the intervention clusters was compared to the rate among the control clusters. There was no difference between the groups (64.44% in the intervention group versus 64.04% in the control group, p=0.58). Therefore, the clusters were not stratified prior to randomization.

A cluster was defined as the FSA of the postal code. A FSA is a geographical region in which all postal codes start with the same three characters. FSA maps for Manitoba, Brandon, and Winnipeg can be accessed from the following link: http://www.canadapost.ca/cpc2/addrm/hh/current/indexm/cmMB-e.asp. Randomization at the FSA level was practical because letters could be batched by postal code. In addition, the FSA is used by the screening program to plan interventions in communities with lower screening rates.

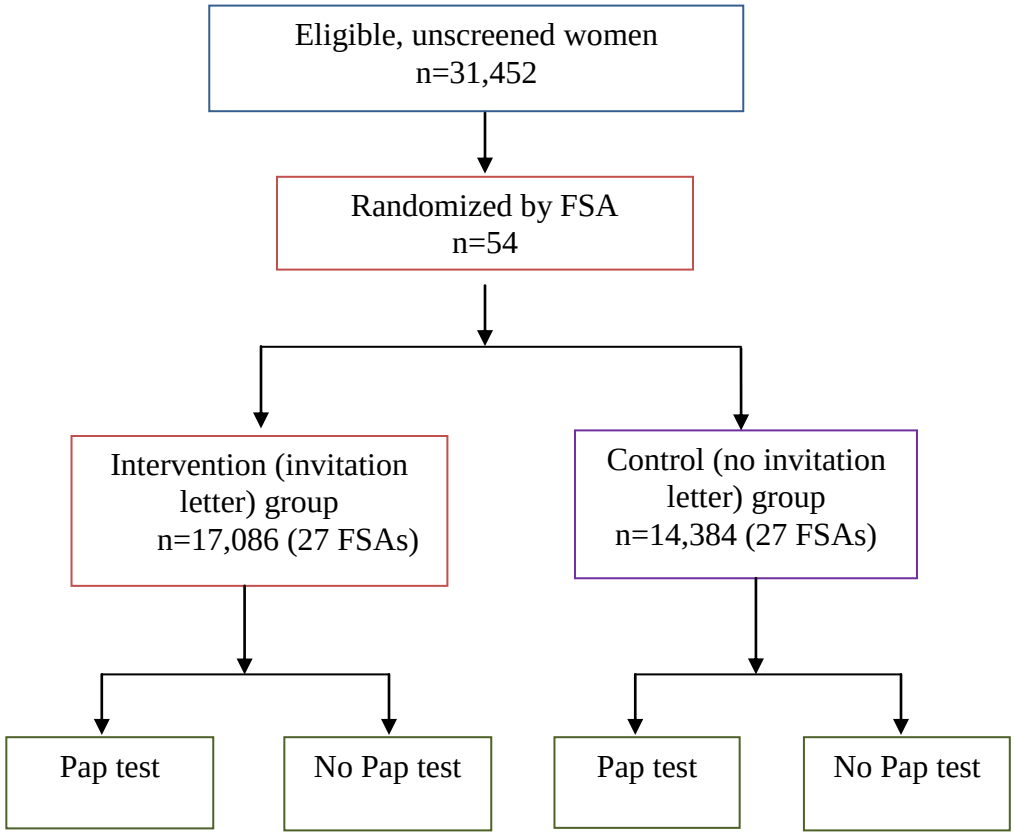
Two weeks before the start of the study, the screening registry was refreshed with address and health coverage information from the MHPR. Eight FSAs had a small number of unscreened women and were therefore combined with a geographically

adjacent FSA. Overall, 54 FSAs were randomized to either the intervention or control group using a random number generator in EXCEL. The average number of women per FSA cluster was 582.

In the intervention group (n=17,068), women were mailed an invitation letter inviting them to be screened for cervical cancer accompanied by a brochure about screening. Invitation letters were mailed over 13 weeks from May 31st, 2010 to August 23rd, 2010. Eligible women were determined at the start of each week. Women in the control group (n=14,384) were not mailed an invitation letter but had an index date that matched the invitation letter date.

Pap test information was abstracted from the screening registry in September, 2011 in order to capture all Pap tests that occurred in the six month time frame after the invitation letter was mailed. This takes into account any delay between the date the Pap test was performed and the date the Pap test was entered into the screening registry ensuring a high a Pap test capture rate as possible. A six month follow-up period was selected because it was considered unlikely that any Pap test performed greater than six months after the invitation letter could be attributed to the letter.

Figure 25 Flow chart of the cluster randomized trial of cervical cancer screening invitation letters



7.4 Study population

The study population included all women in the screening registry who were eligible to receive an invitation letter (n=31,452). Eligible women included unscreened women who were 30 to 69 years of age at the date of the invitation letter (index date for the control group), had a complete Manitoba postal code, were eligible for health care insurance in Manitoba (i.e. did not have an end-of-coverage date from the MHPR), and did not have a mail return flag from the MHPR. A mail return flag occurs when correspondence from Manitoba Health is returned undelivered. The total sample size represents approximately 10% of the Manitoba female population 30 to 69 years of age.

Unscreened is often defined as no Pap test in the previous five years. For this study, unscreened was defined as any woman who had no cytology or colposcopy record in the screening registry since its inception in 2001, had never been diagnosed with an invasive gynaecological cancer, had not had a complete hysterectomy, and had been registered in the screening registry for at least five years. Women who were diagnosed with an invasive gynaecological cancer were excluded because they may require closer follow-up and often more frequent Pap tests. A woman had to be registered in the screening registry for at least five years to ensure that women without any Pap test record who had been added in the last five years (i.e. women who recently moved to the province) were excluded from the study. Therefore, the unscreened women in this study included the following:

- Women who had never had a Pap test;
- Women who had no Pap test from August 22, 2001 (the date the first Pap test was registered in the screening registry) to June 2010 but had a Pap test before this time period; and
- Women who had no Pap test in the registry, were registered in the screening registry for at least five years, but had a Pap test in another province more than five years ago.

Unscreened women were chosen as the target group because the risk of invasive cervical cancer is greater in women who have not been screened and the risk increases with the amount of time since the last Pap test (Decker KM et al., 2009). Women between 30 and 69 years of age were chosen because the incidence of invasive cervical cancer is highest at approximately 45 years of age and the progression from a cervical

abnormality to an invasive cancer primarily occurs over a ten-year time period (Demers A et al., 2003; International Agency for Research on Cancer, 2005).

7.5 Sample size

In order to determine if the number of clusters (n=54) and participants (n=31,452) were large enough to detect a significant difference between the intervention and control groups, the ORs were estimated for different ICC values with a power of 80% and α=0.05 using results from a simulation study of multi-level logistic modeling (Chateau D, 2010; Moineddin R, Matheson FI, & Glazier RH, 2007). Three different ICC values were used: ρ=0.04, ρ=0.17, and ρ=0.38. The estimated ORs were 1.20, 1.70, and 2.20 respectively. The effect observed in this study must be at least this large depending on the value of the ICC to detect a significant difference between the two groups. Previous meta-analyses have found ORs of 1.64 and 1.44 (Everett T et al., 2011; Tseng DS et al., 2001). Therefore, if the ICC is less than 0.17, the number of clusters and participants should be sufficiently large to detect a significant difference between the intervention and control groups.

7.6 Intervention

The invitation letter used by the screening program was a personally addressed, low-literacy (grade five to six reading level) letter with English on one side and French on the other side. The letter stated that the woman had not had a Pap test in at least five years, described the benefits of screening, suggested where a woman could go to obtain a Pap test, and provided the program's telephone number. No appointment time was provided because the screening program does not provide Pap tests. The letter was signed by the program medical director and the program manager. The letter was

accompanied by a Pap test brochure that provided information about the screening program, Pap tests, HPV infections, and colposcopy. The brochure also included the following paragraph in 12 additional languages including Ojibwa and Cree – "Pap tests help prevent cervical cancer. All women who have ever been sexually active should have a Pap test at least every two years. Book your appointment today." The program's telephone number, website, and e-mail address were included in the brochure. Appendix E shows a copy of the invitation letter and brochure.

One to three weeks before the invitation letters were mailed to women in the intervention group, the screening program contacted a health centre in each FSA to ask if the centre would hold a Pap test clinic to ensure screening access. A Pap test clinic includes dedicated staff and time to provide Pap tests either by appointment or on a walk-in basis. Most of the health centers that were contacted had previously held a Pap test clinic in conjunction with the annual Pap test week held each October. Although the provision of a Pap test clinic was not part of the study design, it was taken into account in the analysis.

7.7 Data sources and variables

The data sources used for this study were the Cervical Cancer Screening Registry, the MHPR, the Medical Claims Database, the Hospital Abstracts Database, and Statistics Canada 2006 Census data. To protect confidentiality, the linkages in this study were performed via a scrambled PHIN using anonymized versions of the MHPR, Medical Claims Database, and Hospital Abstracts Database.

Cervical Cancer Screening Registry

The screening program operates a population-based registry as outlined in the Cervical Cancer Screening Registry Regulation under the Public Health Act. The Act requires the reporting of all cervical cancer screening tests (Pap test, colposcopy, and biopsy results) regardless of service location and provider to the screening registry. Pap tests are electronically submitted to the registry by each of the cytology laboratories in Manitoba on a daily basis. The first Pap test report was entered into the screening registry on August 22, 2001. Once a female turns 18 years of age, the screening registry is populated with her name, address, personal health identification number (PHIN), and Manitoba Health Services Commission (MHSC) number from the MHPR. The registry is updated with new population information, coverage data (end of coverage date and cancel code), address information, and vital statistics data each month from the MHPR. Information on gynaecological cancers (diagnosis date, International Classification of Diseases for Oncology (ICD-O) topography and morphology codes, and stage) is added to the screening registry each month from the Manitoba Cancer Registry. Hysterectomy information (tariff code and service date) is added to the screening registry from the Manitoba Physician Claims database monthly.

The following variables were collected from the screening registry for each woman in the study: invitation letter date for women in the intervention group or corresponding index date for women in the control group, postal code, date of birth, age at invitation or index date, date the woman was registered in the screening registry, Manitoba Health cancel code, Pap test date(s), Pap test outcome(s), cancer diagnosis date, cancer ICD-O topography code, cancer ICD-O morphology code, and whether or not the

invitation letter was returned to the screening program by Canada Post (a mail return flag).

Manitoba Health Population Registry

All Manitoba residents covered by provincial health insurance are included in the MHPR which is maintained by Manitoba Health for the purpose of administering the Manitoba Health insurance program. This excludes individuals whose health care is federally funded such as military personnel, RCMP members, and individuals incarcerated in a federal institution. Since eligible Manitoba residents are not required to pay premiums for health insurance, virtually everyone is included in the MHPR. The MHPR includes a MHSC number, PHIN, coverage dates, and cancel codes for each individual.

Each woman in the study (previously identified using the screening registry) was linked to the MHPR via a scrambled PHIN to determine the number of postal code changes she had during the five-year period before the start of the study (April 1, 2005 to March 31, 2010).

Medical Claims Database

The Medical Claims database is generated by claims filed by physicians for payment of services and includes a billing tariff code, service date, an International Classification of Diseases 9th version (ICD-9) diagnosis code, and provider identification. Approximately seven percent of physicians in Winnipeg and 40% of physicians outside of Winnipeg are salaried but are asked to submit a shadow claim for administrative purposes (Katz A, 2011).

Each woman in the study was linked to the Medical Claims database via a scrambled PHIN to identify all tariff codes, tariff code service dates, ICD-9 diagnosis codes, physician number associated with each tariff code (scrambled), and physician specialty code that occurred during the two-year period before the start of the study (April 1, 2008 to March 31, 2010).

Hospital Abstracts Database

The Hospital Abstracts database includes demographic and clinical information (gender, postal code, up to 25 International Classification of Diseases 10th version (ICD-10-CA) diagnoses codes, and procedure codes) for all separations from acute and chronic care facilities in Manitoba. The database also includes information for all Manitobans admitted to out-of-province facilities. Each woman in the study was linked to the Hospital Abstracts database via a scrambled PHIN to identify ICD-10-CA diagnosis codes for each hospital separation that occurred during the one-year period before the start of the study (April 1, 2009 to March 31, 2010).

Statistics Canada 2006 Census Data

Statistics Canada 2006 census data contains socio-economic information on the population by dissemination area (DA). The 2006 census data files were obtained from the University of Manitoba through the data liberation initiative. A postal code conversion file was used to link DA information to the woman's postal code at the time the invitation letter date was sent or the index date. Multiple DAs linked to a single postal code were resolved by choosing the most recently active DA.

7.8 Operationalizing the theoretical framework

Outcome variable

The primary outcome in this study was whether or not a woman had a Pap test in the six months following the invitation letter date or index date. The secondary outcome was the Pap test result for women who were screened.

Predictor variable

The predictor variable was whether or not an invitation letter was sent.

Covariables

Based on the study's theoretical framework, 12 factors were included as covariables in the relationship between the invitation letter and a Pap test: visible minority status, immigration status, high school education, average household income, Pap test clinic, baseline rate of cervical cancer screening, age, health status, area of residence, opportunity to be screened, continuity of care, and residential mobility. Visible minority status, immigrant status, education, and average household income were measured at the DA level that corresponded to each woman's postal code. Baseline screening rate was measured at the FSA level. Therefore, these area-level measures were used as proxy measures for individual-level measures. For example, if the average household income in a DA was $50,000, this value was assigned to each woman who lived in that DA. Similarly, if the baseline screening rate in an FSA was 45%, this value was assigned to each woman who lived in that FSA. The remaining variables were measured at the individual level.

Predisposing Factors – Contextual level

Visible minority status

Visible minority status was measured as the percentage of individuals who identified themselves as a visible minority by DA using Statistics Canada 2006 census data. The percentage of individuals who identified themselves as a visible minority was calculated by dividing the total visible minority population for the DA by the total population for the DA.

Immigration status

Immigration status was measured as the percentage of individuals who identified themselves as an immigrant by DA using Statistics Canada 2006 census data. An immigrant was defined as an individual who was not a Canadian citizen at birth. The percentage of individuals who identified themselves as an immigrant was calculated by dividing the total immigrant population for the DA by the total population for the DA.

High school education

Education was measured as the percentage of individuals that graduated from high school by DA using Statistics Canada 2006 census data. The percentage of individuals who identified themselves as having a high school or greater level of education was calculated by dividing the total population that had a high school certificate, college diploma, or university degree by the total population of individuals 25 to 64 years for the DA.

Average household income

Income was measured using average household income by DA from Statistics Canada 2006 census data.

Predisposing Factors – Individual level

Age

Age at the time the invitation letter was mailed or the index date was determined using the date of birth and the date of the invitation letter or index date from the screening registry.

Health status

Health status was measured using the Resource Utilization Band (RUB) that was calculated for each woman using The Johns Hopkins Adjusted Clinical Groups (ACG) System software developed by The Johns Hopkins University (The John Hopkins University Bloomberg School of Public Health, Health Services Research and Development Centre, 2003). ACG values indicate an individual's level of morbidity based on their utilization of physician and hospital services over the previous year as well as their age and sex (Finlayson GS, Ekuma O, Yogendran M, Burland E, & Forget E, 2010). ACGs were designed to represent clinically logical categories for individuals expected to require similar levels of health care resources (The Johns Hopkins University Bloomberg School of Public Health, Health Services Research and Development Centre, 2009). However, individuals with similar health care use may be assigned different ACGs because they have different epidemiological patterns of morbidity (The Johns Hopkins University Bloomberg School of Public Health, Health Services Research and Development Centre, 2009). Previous research in Manitoba has found a strong association between ACG values and premature mortality rates (the gold standard for measuring population health status) providing evidence for the use of ACGs as an

indicator of health status (Reid R, MacWilliam L, Roos NP, Bogdanovic B, & Black C, 1999).

In this study, the ACG value for each individual was calculated and then collapsed by The Johns Hopkins ACG System software into one of six summary RUB categories: no use, healthy user (no morbidity), low user (low morbidity), moderate user (moderate morbidity), high user (high morbidity), and very high user (very high morbidity). The RUB combines the full set of mutually exclusive ACG values into fewer categories making it possible to identify which individuals have more (or less) morbidity based on their resource use (The Johns Hopkins University Bloomberg School of Public Health, Health Services Research and Development Centre, 2009). Therefore, RUB is a measure of the overall morbidity burden for each individual from no use which includes women who did not use the health care system, to healthy user which included women who did use the health care system but did not experience any morbidity to women who experienced low, moderate, high, and very high levels of morbidity.

In order to calculate a RUB value for each woman, age, sex, ICD-9-CA codes for all physician claims and ICD-10-CA codes for all hospital separations that occurred during the year before the study (April 1, 2009 to March 31, 2010) were entered into the ACG software.

Enabling factors – Contextual level

Pap test clinic

Health centers in the intervention group FSAs were asked by the program to hold a Pap test clinic two to three weeks after the invitation letters in their FSA were mailed.

Pap test clinics were not held in the control group FSAs as these women were not sent an invitation letter. This information was recorded by the screening program.

Enabling factors – Individual level

Area of residence

Residence was defined using each woman's postal code from the screening registry. Five aggregate areas were included: North (RHAs of Churchill, Burntwood, and Nor-Man), Mid (RHAs of North Eastman, Interlake, and Parkland), Rural South (RHAs of South Eastman, Central, and Assiniboine), Brandon (RHA of Brandon), and Winnipeg (RHA of Winnipeg).

Opportunity to be screened

Opportunity to be screened was defined as the total number of visits to a general practitioner, family practitioner, internal medicine specialist, pediatrician, general surgeon, obstetrician, or gynaecologist in the two years prior to the invitation letter or index date. A previous analysis of Pap test frequency and physician type found that these physician specialties provide 99.9% of all Pap tests (Decker KM et al., 2009). Opportunity to be screened was calculated using the number of physician visits for each woman in the study from the Medical Claims database for the two years prior to the invitation letter date or index date (April 1, 2008 to March 31, 2010).

Continuity of care

Continuity of care was measured by determining the individuals with at least 50% of visits to the same physician among those with at least three visits in the previous two-year period (Martens P et al., 2008). Continuity of care was calculated using the number of physician visits for each woman to a general practitioner, family practitioner, internal

medicine specialist, pediatrician, general surgeon, obstetrician or gynaecologist from the Medical Claims database for the two years prior to the invitation letter date or index date (April 1, 2008 to March 31, 2010).

Residential Mobility

Residential mobility was defined as the total number of postal code changes during the five years prior to the invitation letter date or index date. Within the city of Winnipeg, a single postal code occupies a small area such as one side of a residential block or a medium-sized apartment building (Lix L et al., 2006). Outside of Winnipeg, postal codes cover a larger geographic area (Lix L et al., 2006). Residential mobility was categorized as no change in postal code or one or more changes in postal code in the five years prior to the invitation letter date or index date (April 1, 2005 to March 31, 2010).

Need Factors

Baseline rate of cervical cancer screening

The baseline rate of cervical cancer screening by FSA was measured as the proportion of women who had at least one Pap test in the previous three-year period. The baseline screening rate was calculated using the screening registry.

Table 9 operationalizes the study's theoretical framework including the variables used to measure each construct at the contextual and individual levels, the operational definition, and the data source.

Table 9 Operationalizing of the cervical cancer invitation letter study

Theoretical construct	Variable	Operational definition	Data source
Predisposing Factors (Contextual Level)	Visible minority status	The percentage of individuals who identify themselves as a visible minority by DA.	Statistics Canada 2006 census data
	Immigration status	The percentage of individuals who identify themselves as an immigrant by DA.	Statistics Canada 2006 census data
	High school education	The percentage of individuals who had a high school education or greater by DA.	Statistics Canada 2006 census data
	Average household income	Average household income by DA.	Statistics Canada 2006 census data
Predisposing Factors (Individual Level)	Age	Age at the time the invitation letter was sent for the intervention group or index date for the control group.	Cervical screening registry
	Health status	The RUB calculated from the ACG value for each individual for the previous year.	Cervical screening registry, Medical Claims database, Hospital Abstracts database
Enabling Factors (Contextual Level)	Pap test clinic	Whether a Pap test clinic was held in the FSA two to three weeks after the invitation letter was mailed for the intervention group only.	Cervical screening program
Enabling Factors	Area of residence	Area of residence based on postal code.	Cervical screening

(Individual level)		Grouped as North, Mid, Rural South, Brandon, and Winnipeg.	registry
	Opportunity to be screened	The maximum number of visits to the same physician in the two years prior to the invitation letter date or index date.	Medical Claims database
	Continuity of care	At least 50% of visits to the same physician among individuals with at least three visits in the two years prior to the invitation letter date or index date.	Medical Claims database
	Residential mobility	Number of postal code changes in the five years prior to the invitation letter date or index date (one versus more than one).	Manitoba Health Population Registry
Need (Contextual level)	Baseline rate of cervical cancer screening	The percentage of women who had at least one Pap test in the previous three-year period by FSA.	Cervical screening registry
Health Behaviour	Pap test	A Pap test that occurred in the six month follow-up period after the invitation letter date or index date.	Cervical screening registry
Outcome	Pap test result	The result of the Pap test that occurred in the six month follow-up period after the invitation letter date or index date.	Cervical screening registry

7.9 Ethical considerations

Approval from the Research Resource Impact Committee at CancerCare Manitoba was received on April 26, 2010 (RRIC 21-2010). Approval from the Health Research Ethics Board at the University of Manitoba was received on July 13, 2010 and re-approved in June 2011 and 2012 (H2010:223). Approval from the Health Information Privacy Committee at Manitoba Health was received on October 28, 2010.

7.10 Statistical analyses

Descriptive statistics were used to illustrate the characteristics of the study participants. Differences between the intervention group (invitation letter) and control group (no invitation letter) were assessed using the non-parametric Wilcoxon test (the Kruskal-Wallis test) when the covariable was continuous and not normally distributed or when the variable was in rank order. A t-test was used to test for differences between the intervention and control groups when the covariable was continuous and normally distributed. For categorical variables, differences between the intervention and control groups were assessed using the chi square (χ^2) statistic. For the descriptive statistics, the threshold *p* value was set to 0.05.

The Kaplan-Meier estimate of the survival curve was used to describe the cumulative Pap test incidence during the six month follow-up period for each of the study groups. A univariable logistic regression GEE model with an exchangeable correlation matrix to account for clustering within the dataset was used to determine if the invitation letter was predictive of having a Pap test in the six month follow-up period. The exchangeable correlation matrix was chosen because there was no logical ordering of observations within a cluster and the data were not a time-series (Ballinger GA, 2004). A

binomial distribution type was used because the outcome was binary (Pap test or no Pap test). The invitation letter was the predictor variable and a Pap test in the six months following the letter was the outcome variable.

The ICC was calculated by dividing the between-cluster variance intercept (the variance from the regression parameter covariance matrix) by the between-cluster variance plus the within-cluster variance (the variance of a logit model which is equal to $pi^2/3$).

The theoretical framework for this study, the BMHSU, identifies predisposing, enabling, and need factors at contextual and individual levels as important factors in health care use. Therefore, five multivariable logistic regression GEE models with an exchangeable correlation matrix and a binomial distribution type were used to examine Pap test use as a function of predisposing, enabling, need, contextual-level, and individual-level factors separately.

In order to ensure that the models were appropriate and accurate, continuous variables were tested for linearity. Variables for which there was not a linear relationship between the predictor variable and the outcome were converted to categorical variables. To test for multicollinearity (a relationship between two or more independent variables), frequency distributions between suspected collinear variables were examined followed by logistic regression GEE models that included the two variables separately and then together. All variables were tested for homoscedasticity (constant variance of the error) by examining logistic regression diagnostic statistics (standardized deviance residuals and leverage values). A final multivariable logistic regression GEE model was

performed that included all variables in the theoretical framework. Interactions between the invitation letter and significant variables were examined.

For women who were sent an invitation letter (the intervention group), a univariable logistic regression GEE model was used to determine if the presence of a Pap test clinic was predictive of having a Pap test. The Pap test clinic was the predictor variable and a Pap test in the six months following the invitation letter was the outcome variable.

Analyses were performed on an ITT basis in which all participants were analyzed as intended upon randomization regardless of whether or not they received the invitation letter. Since the ITT analysis gives a conservative estimate of the treatment effect, a per-protocol logistic regression GEE model was also performed to reflect the maximum potential benefits of the intervention. For this study, the per-protocol analysis included in the model women who died, had an end-of-coverage date from Manitoba Health, or whose letter was returned to the program in the six months after the invitation letter date.

For all logistic regression models, the unit of analysis was the individual and the threshold *p* value was set to 0.10 (0.05x2) because the research questions and hypotheses were one-tailed. All analyses including the logistic regression GEE models (PROC GENMOD) were conducted in SAS 9.2 (SAS Institute Inc., 2010).

Lastly, the costs required for the intervention letter were determined including the average cost per woman, average cost per woman screened, and average cost per high-grade lesion detected. In order to avoid a breach of confidentiality, all counts and rates were suppressed if the count upon which the rate was based represented five events or less unless the rate was truly 0 or if the count could be determined by subtraction. The letter "s" in brackets (s) indicates a suppressed rate.

7.11 Chapter Summary

This chapter reviewed the methods used to evaluate the effectiveness of an invitation letter on cervical cancer screening participation. A CRT was used in which 31,452 unscreened Manitoba women 30 to 69 years of age were randomly allocated by FSA to an intervention (invitation letter) or control group (no invitation letter).

The data sources for the study included the cervical cancer screening registry, the MHPR, the Medical Claims database, the Hospital Abstracts database, and Statistics Canada 2006 census data. The primary outcome in the study was whether or not a woman had a Pap test in the six months following the invitation letter or index date.

Based on the study's theoretical framework, the BMHSU, the following variables were included in multivariable logistic regression GEE models: visible minority status, immigration status, education, income, Pap test clinic, baseline cervical cancer screening rate, age, health status, area of residence, residential mobility, opportunity to be screened, and continuity of care. The next chapter describes the study results.

Chapter 8. Results

8.1 Introduction

This chapter summarizes the results of the CRT that evaluated the effectiveness of invitation letters on cervical cancer screening participation among unscreened Manitoba women 30 to 69 years of age. The descriptive characteristics of the study participants are reviewed including predisposing factors (visible minority status, immigration status, high school education, average household income, age, and health status), enabling factors (Pap test clinic, area of residence, opportunity to be screened, continuity of care, and residential mobility), and need factors (FSA baseline cervical cancer screening rate).

Screening rates by FSA, region of residence, and age group for each study group are described followed by an assessment of the contamination that occurred in the study. The time from the invitation letter to the Pap test and the cumulative Pap test incidence is provided. The results of a univariable and six multivariable ITT logistic regression GEE models based on the study's theoretical framework, the BMHSU, are shown. Two additional models are also presented: a univariable logistic regression GEE model that evaluated the influence of a Pap test clinic on screening participation for women who received an invitation letter and a per-protocol analysis that included in the model women who died, had an end of coverage date, or whose mail was returned to the screening program.

Lastly, the screening outcomes are presented for the women who had a Pap test in the six month follow-up period after the invitation letter was sent and the cost of the invitation letter intervention is determined.

8.2 Descriptive characteristics

A total of 31,452 unscreened women were included in the study. The intervention group (invitation letter) included 17,068 women (54.11%) and the control group (no letter) included 14,384 women (45.73%). A total of 112 telephone calls were received by the cervical screening program regarding the invitation letter. Seventy-nine women (0.25%) who were sent an invitation letter stated that they had previously had an hysterectomy. Hysterectomy information may have been missing for these women because they had a hysterectomy in another province or they had a hysterectomy before 1984 when hysterectomy information began to be collected in the Medical Claims database by Manitoba Health. Seven women (0.02%) reported cognitive or physical disabilities that prevented them from having a Pap test and nine women (0.03%) opted out of the registry. Previous cytology and colposcopy reports for women who opt out are removed from the registry, future reports are not added to the registry, and these women do not receive correspondence from the program.[4] Two women (0.01%) requested additional information about where to go for a Pap test.

Table 10 summarizes the descriptive characteristics of the study participants for each predisposing, enabling, and need factor at the contextual and individual levels by study group.

[4] As of January, 2012, 39 women had opted out of the cervical screening registry completely and 107 women had requested that no correspondence be sent to them.

Table 10 Descriptive characteristics of the study participants for predisposing, enabling, and need factors at the contextual and individual levels by study group[5]

Descriptive Characteristic	**Group**		
PREDISPOSING FACTORS	**Intervention**	**Control**	***P* value**
Total	17,068	14,384	
Contextual level			
Visible minority status, n (%)	16,681 (97.73)	14,325 (99.59)	<0.001
Median percentage	3.63	6.31	
Mean percentage	10.97	12.87	
Standard deviation	15.29	16.69	
Immigration status, n (%)	15,430 (90.40)	14,113 (98.11)	0.17
Median percentage	11.96	11.76	
Mean percentage	15.50	15.63	
Standard deviation	12.12	12.87	
High school education, n (%)	16,681 (97.73)	14,325 (99.59)	<0.001
Median percentage	80.28	81.03	
Mean percentage	77.12	79.03	
Standard deviation	15.99	13.78	
Average household income, n (dollars)	17,022 ($50,757)	14,365 ($51,926)	<0.001
Individual level			
Age, n (%)			
30-39	3,020 (17.69)	2,547 (17.71)	0.53
40-49	4,392 (25.73)	3,770 (26.21)	
50-59	4,868 (28.52)	4,125 (28.68)	
60-69	4,788 (28.05)	3,942 (27.41)	
Health status (RUB), n (%)			
No use	5,823 (34.12)	4,872 (33.87)	0.79
Healthy use – no morbidity	1,292 (7.57)	1,126 (7.83)	
Low morbidity	3,061 (17.93)	2,555 (17.76)	

[5] Predisposing factors include demographics, social structure, and beliefs. Enabling factors include health care policies, financing, organization, and health status. Need factors include perceived and evaluated need for health services.

Moderate morbidity	5,879 (34.44)	4,979 (34.61)	
High morbidity	769 (4.51)	668 (4.64)	
Very high morbidity	244 (1.43)	184 (1.28)	
ENABLING FACTORS			
Contextual level			
Pap test clinic, n (%)			
Yes (20 FSAs)	14,078 (82.48)	NA	NA
No (7 FSAs)	2,990 (17.52)	NA	
Individual level			
Area of residence, n (%)			
Brandon	377 (2.21)	535 (3.72)	<0.001
Non-Winnipeg	7,563 (44.31)	3,928 (27.31)	
Winnipeg-core	2,283 (13.38)	3,398 (23.62)	
Winnipeg non-core	6,845 (40.10)	6,523 (45.35)	
Residential mobility (postal code changes), n (%)			
0	13,108 (76.80)	10,920 (75.92)	0.07
1 or more	3,960 (23.20)	3,464 (24.08)	
Opportunity to be screened, n (%)			
0 visits	4,879 (28.59)	4,174 (29.02)	0.01
1 to 5 visits	4,650 (27.24)	3,707 (25.77)	
6 or more visits	7,539 (44.17)	6,503 (45.21)	
Continuity of care, n (%)			
Yes	7,181 (42.07)	6,287 (43.71)	0.003
No	9,887 (57.93)	8,097 (56.29)	
NEED FACTORS			
Contextual level			
Baseline screening rate (%)	64.44	64.05	0.58

Predisposing Factors – Contextual level

Visible minority status

The percentage of individuals who reported being a visible minority by DA from Statistics Canada 2006 census data was used as a proxy measure for each woman's visible minority status. Therefore, if the woman lived in a DA with a 5% visible minority population, her visible minority status was set to 5%. Visible minority status information was available for 31,006 women (98.58%) - 16,681 women in the intervention group (97.73%) and 14,325 women in the control group (99.59%). Visible minority information was missing from the census data for 446 women (1.42%) - 387 women in the intervention group (2.27%) and 59 women in the control group (0.41%). The median percentage of visible minority women was 4.81% - 3.63% in the intervention group and 6.31% in the control group. The percentage of visible minority women was not normally distributed. There was a significant difference in the percentage of visible minority women between the intervention and control groups ($Z=12.69$, $p<0.001$).

Immigration status

The percentage of individuals who reported being an immigrant by DA from Statistics Canada 2006 census data was used as a proxy measure for each woman's immigration status. Immigration status information was available for 29,543 women (93.93%) - 15,430 women in the intervention group (90.40%) and 14,113 women in the control group (98.11%). Immigrant status information was missing from the census data for 1,909 women (6.07%) - 1,638 women in the intervention group (9.60%) and 271women in the control group (1.88%). The median percentage of immigrant women was 11.92% - 11.96% in the intervention group and 11.76% in the control group. The

percentage of women by immigration status was not normally distributed. There was no difference in the percentage of women who reported being an immigrant between the intervention and control groups (Z=-1.36, p=0.17).

High school education

The percentage of individuals who reported having a high school education or greater by DA from Statistics Canada 2006 census data was used as a proxy measure for each woman's education level. Education information was available for 31,006 women (98.58%) - 16,681 women in the intervention group (97.73%) and 14,325 women in the control group (99.59%). Education information was missing from the census data for 446 women (1.42%) - 387 women in the intervention group (2.27%) and 59 women in the control group (0.41%). The median percentage of women who had a high school level of education or greater was 80.70% - 80.28% in the intervention group and 81.03% in the control group. The percentage of women who had a high school level of education or greater was not normally distributed. There was a significant difference in the percentage of women who had a high school level of education or greater between the intervention and control groups (Z = 7.70, p<0.001). However, the absolute difference in the median percentage of women who had a high school education between the intervention and control groups was 0.75%. Therefore, it is likely that the statistical significant difference between the groups is due to the large sample size (Baghi H, Noorbaloochi S, Moore JB, 2007).

Average household income

Average household income by DA from Statistics Canada 2006 census data was used as a proxy measure for each woman's income. Average household income was

available for 31,387 women (99.79%) - 17,022 women in the intervention group (99.73%) and 14,365 women in the control group (99.87%). Income was missing for 65 women (0.21%) - 46 women in the intervention group (0.27%) and 19 women in the control group (0.13%). The median average household income by DA was $51,037 - $50,757 in the intervention group and $51,926 in the control group. Average household income was not normally distributed. There was a significant difference in average household income between the intervention and control groups (Z=7.56**,** $p<0.001$). The absolute difference in the average household income the intervention and control groups was $1,169. Therefore, as with high school education, the statistical significant difference between the groups is likely due to the large sample size.

Predisposing factors – Individual level

Age

The average age at the time the invitation letter was mailed was 51.24 years for the intervention group and 51.13 years for the control group. Overall, 17.70% of women were 30 to 39 years of age, 25.95% were 40 to 49 years of age, 28.59% were 50 to 59 years of age, and 27.76% were 60 to 69 years of age. In the intervention group, 3,020 women (17.69%) were 30 to 39 years of age, 4,392 women (25.73%) were 40 to 49 years of age, 4,868 women (28.52%) were 50 to 59 years of age, and 4,788 women (28.05%) were 60 to 69 years of age. In the control group, 2,547 women (17.71%) were 30 to 39 years of age, 3,770 women (26.21%) were 40 to 49 years of age, 4,125 women (28.68%) were 50 to 59 years of age, and 3,942 women (27.41%) were 60 to 69 years of age. There was no difference in age distribution between the intervention and control groups ($\chi^2 = 1.93$, $p=0.59$, $df=3$).

Health status

From April 1, 2009 to March 31, 2010 (one year prior to the start of the study), 34% of the women had no health care use, 7.69% had healthy use with no morbidity, 17.86% had low morbidity, 34.52% had moderate morbidity, 4.57% had high morbidity, and 1.36% had very high morbidity. In the intervention group, 5,823 women (34.12%) had no use, 1,292 women (7.57%) had healthy use with no morbidity, 3,061 women (17.93%) had low morbidity, 5,879 women (34.44%) had moderate morbidity, 769 women (4.51%) had high morbidity, and 244 women (1.43%) had very high morbidity. In the control group, 4,872 women (33.87%) had no use, 1,126 women (7.83%) had healthy use with no morbidity, 2,555 women (17.76%) had low morbidity, 4,979 women (34.61%) had moderate morbidity, 668 women (4.64%) had high morbidity, and 184 women (1.28%) had very high morbidity. There was no difference in the distribution of RUB between the intervention and control groups ($Z=0.27$, $p=0.79$).

Enabling factors – Contextual level

Pap Test Clinic

In order to ensure access to screening, the screening program contacted health centres in the intervention group FSAs to request that the centre hold a Pap test clinic two to three weeks after invitation letters were mailed. In total, 20 of the intervention group FSAs had a Pap test clinic. Seven of the intervention group FSAs did not have a Pap test clinic; health centres in four FSAs declined to participate and three FSAs had no health centre located in the area. None of the control FSAs had a Pap test clinic because the women in these FSAs were not sent an invitation letter. A total of 14,078 women

(82.48%) who were sent an invitation lived in an FSA that had a Pap test clinic and 2,990 women (17.52%) lived in an FSA that did not have a Pap test clinic.

Enabling factors – Individual level

Area of Residence

Area of residence was originally defined in the analysis as north, mid, rural south, Brandon, and Winnipeg (section 7.8). However, because most of the women who live in the north were randomized to the intervention group, area of residence defined in this manner was confounded with the intervention. Therefore, area of residence was re-defined using the woman's postal code at the time the invitation letter was sent or the index date into four new categories: Brandon, rural/Northern, Winnipeg-core, and Winnipeg non-core. The Brandon category includes the Brandon city postal codes (R7A, R7B, and R7C). The rural/Northern category includes all rural and northern areas (i.e. all postal codes outside of Winnipeg or Brandon). The Winnipeg-core category includes postal codes from the following FSAs: R2L (Elmwood), R2W (North end), R2X (North end), R3A, (city centre), R3B (city centre), R3C (city centre), R3E (city centre-west end), and R3G (city centre-west end). The Winnipeg core is characterized by lower socioeconomic status while the non-core neighbourhoods of Winnipeg are generally associated with higher socioeconomic status (Deverteuil G et al., 2007). The Winnipeg non-core includes all other Winnipeg postal codes.

Overall, 2.90% of women lived in Brandon, 36.54% lived outside of Winnipeg or Brandon, 18.06% lived in the core area of Winnipeg, and 42.50% lived in the rest of Winnipeg (non-core). In the intervention group, 377 women (2.21%) lived in Brandon, 7,563 women (44.31%) lived in a rural or northern area, 2,283 women (13.38%) lived in

the Winnipeg core, and 6,845 women (40.10%) lived in the rest of Winnipeg (non-core). In the control group, 535 women (3.72%) lived in Brandon, 3,928 women (27.31%) lived in a rural or northern area, 3,398 women (23.62%) lived in the Winnipeg core, and 6,523 women (45.35%) lived in the rest of Winnipeg (non-core). There was a significant difference in area of residence between the intervention and control groups (χ^2 =1183.42, p<0.001, df=3).

Residential mobility

Residential mobility was defined as the number of women who changed their postal code during the five-year period before the invitation letters were mailed (April 1 2005 to March 31, 2010). Most women (76.4%) did not have a postal code change while 23.6% of women had one or more postal code changes. In the intervention group, 13,108 women (76.80%) had no postal code change and 3,960 women (23.20%) had one or more postal code changes. In the control group, 10,920 women (75.92%) had no postal code change and 3,464 women (24.08%) had one or more postal code changes. There was no difference in residential mobility between the intervention and control groups (χ^2 =3.36, p=0.07, df=1).

Opportunity to be screened

An opportunity to be screened was defined as the total number of visits to a general practitioner, family practitioner, internal medicine specialist, pediatrician, general surgeon, obstetrician, or gynaecologist in the two-year period before the invitation letters were mailed (April 1, 2008 to March 31, 2010). The number of visits ranged from 0 to 431. The median number of visits was 4 and 99% of women had fewer than 69 visits.

Opportunity to be screened was categorized as no visits, one to five visits, and six or more visits. Overall, 28.78% of women had no visits, 26.57% had one to five visits, and 44.65% had six or more visits. In the intervention group, 4,879 women (28.59%) had no visits, 4,650 women (27.24%) had one to five visits, and 7,539 women (44.17%) had six or more visits. In the control group, 4,174 women (29.02%) had no visits, 3,707 women (25.77%) had one to five visits, and 6,503 women (45.21%) had six or more visits. The percentage of women who had no, one to five, and six or more visits was significantly different between the intervention and control groups (χ^2 =8.76, p=0.01,df=2). However, the absolute difference in the percentage of women by number of visits between the two groups was small (a difference of 0.43% for no visits, 1.44% for one to five visits, and 1.04% for six or more visits). Therefore, the statistical significant difference between the groups is likely due to the large sample size.

Continuity of care

Continuity of care was defined as the number of women who had least 50% of visits to the same physician among those with at least three visits in the two-year period before the invitation letters were mailed (April 1, 2008 to March 31, 2010). Overall, 42.82% of women had continuity of care and 57.18% of women did not have continuity of care. In the intervention group, 7,181 women (42.07%) had continuity of care and 9,887 women (57.93%) did not have continuity of care. In the control group, 6,287 women (43.71%) had continuity of care and 8,097 women (56.29%) did not have continuity of care. Although continuity of care was significantly different between the two groups (χ^2 =8.53, p=0.003, df=1), the absolute difference in continuity of care between the intervention and control groups was small (a difference of 1.64% for women

who had continuity of care and 1.64% for women who did not have continuity of care). Therefore, the statistical significant difference between the groups is likely due to the large sample size.

Need factors – Contextual level

Baseline screening rate

The average baseline cervical cancer screening rate was 64.26% - 64.44% in the intervention group and 64.05% in the control group. The baseline rate of screening ranged from 52.72% to 79.06% in the intervention group and from 48.48% to 80.26% in the control group. The baseline screening rate was close to being normally distributed. Since the baseline screening rate was an FSA-level measurement (i.e. all women in the FSA had the same baseline screening rate), a t-test was conducted at the FSA level. There was no difference in the baseline screening rate between the intervention and control groups (t=-0.55, p=0.58).

8.3 Screening rates

Figure 26 shows the flow of participants through the cervical cancer screening invitation letter CRT. Overall, 31,452 unscreened, eligible women 30 to 69 years of age were randomly assigned by FSA to the intervention group (N=17,068) or the control group (N=14,384). In the intervention group, 1,010 women (5.92%) had a Pap test and 795 women (4.66%) died, had an end of coverage date, or their mail was returned to the screening program in the six months following the date the invitation letters were mailed. In the control group, 441 women (3.06%) had a Pap test and 298 women (2.07%) died or had an end of coverage date in the six-month follow-up period. The absolute difference

in the percentage of women who had a Pap test between the intervention and control groups was 2.86%.

Figure 26 Flow of participants through the cervical cancer screening invitation letter cluster randomized trial

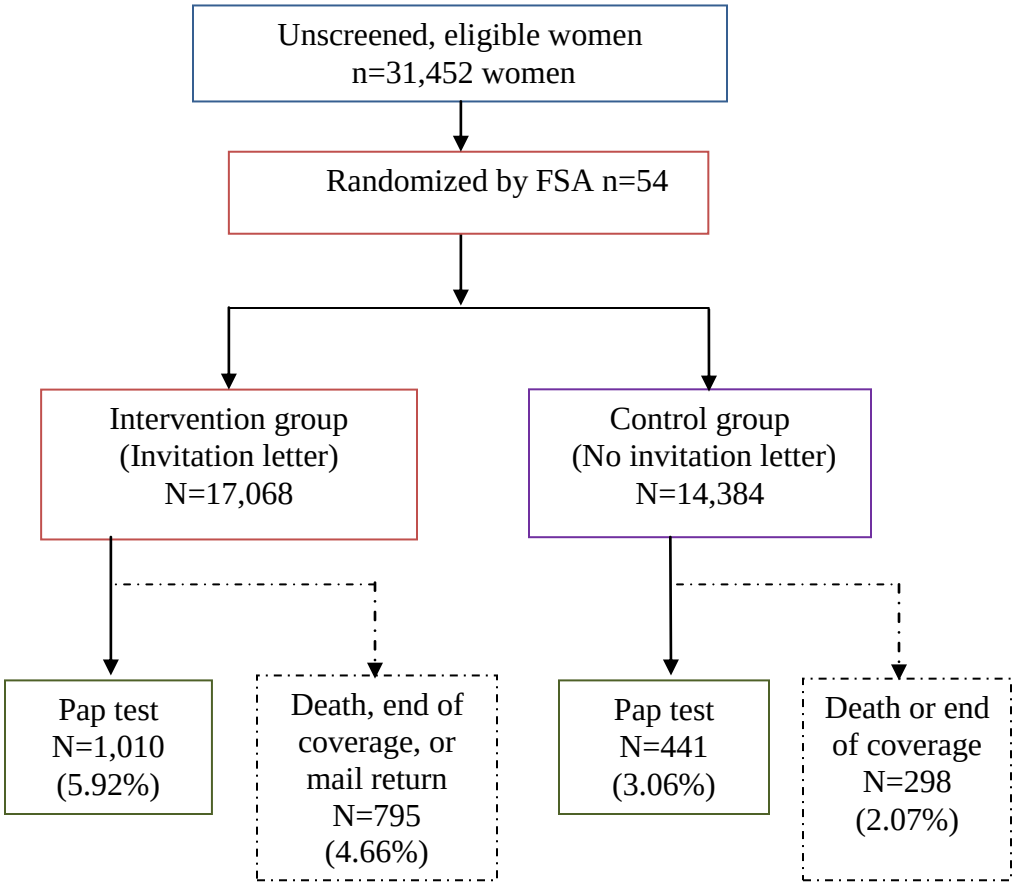


Table 11 shows the number and percentage of women who had a Pap test by FSA for the intervention and control groups in the six month follow-up period. In the intervention group, the percentage of women who had a Pap test ranged from 3.75% in R3K (Assiniboia) to 12.66% in R8N (Thompson). The percentage of women screened in the FSAs of R0A/R5A (South Eastman), R3C (city centre), and R8N (Thompson) were significantly different than the group mean. In the control group, the percentage of

women who had a Pap test ranged from 1.35% in R0H (Central) to 4.26% in R6M (Morden). The percentage of women screened in the FSA of R0H (Central) was significantly different than the group mean.

Table 11 Number and percentage of women screened by Forward Sortation Area for each study group

FSA	Community description	Unscreened women	Women screened	Percent screened
	Intervention group			
R0A/R5A	South Eastman - excluding Steinbach and Ste Anne /St. Adolphe	739	66	8.93
R0B	Burntwood, Nor-Man, Churchill - excluding Thompson, Flin Flon, and The Pas	1,236	75	6.07
R0C	Interlake	1,353	72	5.32
R0E	North Eastman	997	61	6.12
R0J	Parkland - South part including Erikson, Hamiota, Birtle, Rossburn, Waywayseecappo, Russel	809	47	5.81
R0K	Assiniboine - East part including Souris	640	33	5.16
R2C	Transcona - Canterbury Park, Regent	701	34	4.85
R2G	North Kildonan	780	37	4.74
R2H	St. Boniface - North St. Boniface, Norwood, Norwood Flats	373	22	5.90
R2K	East Kildonan	878	41	4.67
R2L	East Kildonan - East Elmwood, Glenelm	485	30	6.19
R2M	St. Boniface St. Vital - Glenwood, Worthington	931	48	5.16
R2P	North West - Maples, Mandalay West	978	59	6.03
R3C	City centre - Daniel McIntyre, West Alexander	907	28	3.09
R3E	West End - Daniel McIntyre, West Alexander	891	44	4.94
R3J	St. James	640	33	5.16
R3K	Assiniboia - Kirkfield Park,	293	11	3.75

	Westwood, Glendale, The Oaks			
R3T	Fort Garry - Fort Richmond, Waverley Heights, Montcalm	1,034	68	6.58
R3W	Transcona - Harbour View, Meadows, Peguis	68	8	11.76
R3X	Island Lakes	168	13	7.74
R5G	Steinbach	419	40	9.55
R5H	Ste Anne	120	9	7.50
R6W	Winkler	390	28	7.18
R7B/R7C	Brandon	377	17	4.51
R7N	Dauphin	251	22	8.76
R8N	Thompson	316	40	12.66
R9A	The Pas	294	24	8.16
Total		**17,068**	**1,010**	**5.92**
	Control group			
R0G/R3S	South Central - from the border to the outside of the city	909	33	3.63
R0H	Central - excluding Portage la Prairie, St-Francois de-Xavier, Winkler, Cartier	518	7	1.35
R0L	Parkland - excluding Dauphin	1,041	32	3.07
R0M	Assiniboine – West part including Virden, Griswold, Melita	734	27	3.68
R1A/R1B	Selkirk, Lockport	498	19	3.82
R1N	Portage La Prairie	553	20	3.62
R2E	East St. Paul - River East Estates, Pritchard Farm, Birds Hill	137	(s)	(s)
RJ2	St. Boniface - Windsor Park, Southdale, Maginot, Niakwa Place	536	17	3.17
R2N	St. Vital - River Park South, Dakota Crossing	478	14	2.93
R2R	North West - Tyndall Park, Brooklands	740	30	4.05
R2V	West Kildonan - Garden City, Jefferson	881	27	3.06
R2W	North End - Dufferin, North Point Douglas	1,093	27	2.47
R2X	North End - Dufferin, North Point Douglas	651	16	2.46
R2Y	Assiniboia - Sturgeon Creek, Heritage Park, Crestview, Buchanan	494	16	3.24
R3A	City centre - Centennial, Logan	195	(s)	(s)
R3B	City centre - Exchange district, South Point Douglas, Spence	522	15	2.87

R3G	West End - Sargent Park, Wolseley, St. Mathews, Minto	937	28	2.99
R3L	Fort Rouge - River Osborne, Lord Roberts, Roslyn, Riverview	531	22	4.14
R3M	River Heights Fort Rouge - Cresentwood, Grant Park	530	14	2.64
R3N	River Heights - Sir John Franklin, J.B.Mitchell, Mathers	370	11	2.97
R3P	Tuxedo - Tuxedo, Linden Woods, Brockville, Fort Whyte	386	9	2.33
R3R	Charleswood	536	15	2.80
R3V	St. Norbert- Park la Salle, Richmond Lakes	132	(s)	(s)
R4J/R4H/R4K/R4L	Headingley/Cartier/St-Francois de-Xavier	70	(s)	(s)
R6M	Morden	188	8	4.26
R7A	Brandon	535	17	3.18
R8A	Flin Flon	189	(s)	(s)
Total		**14,384**	**441**	**3.06**

Notes: (s) indicates a suppressed rate.

Table 12 shows the number and percentage of women who had a Pap test by region of residence for the intervention and control groups in the six-month follow-up period. In the intervention group, 17 women (4.51%) who lived in Brandon had a Pap test compared to 517 women (6.83%) who lived in a rural or northern area, 102 women (4.47%) who lived in the Winnipeg core, and 374 women (5.46%) who lived in the rest of Winnipeg (non-core). In the control group, 17 women (3.18%) who lived in Brandon had a Pap test compared to 123 women (3.13%) who lived in a rural or northern area, 88 women (2.59%) who lived in the Winnipeg core, and 213 women (3.26%) who lived in the rest of Winnipeg.

Table 12 Number and percentage of women screened by region for each study group

Region	Intervention Group			Control Group		
	Unscreened women	Women screened	Percent screened	Unscreened women	Women screened	Percent screened
Brandon	377	17	4.51	535	17	3.18
Rural or Northern	7,563	517	6.83	3,928	123	3.13
Winnipeg core	2,283	102	4.47	3,398	88	2.59
Winnipeg – non core	6,845	374	5.46	6,523	213	3.26
Total	17,068	1,010	5.92	14,384	441	3.06

Table 13 shows the number and percentage of women who had a Pap test by age group for the intervention and control groups in the six-month follow-up period. In the intervention group, 162 women (5.36%) 30 to 39 years of age had a Pap test compared to 305 women (6.94%) 40 to 49 years of age, 282 women (5.79%) 50 to 59 years of age, and 261 women (5.45%) 60 to 69 years of age. In the control group, 91 women (3.57%) 30 to 39 years of age had a Pap test compared to 144 women (3.82%) 40 to 49 years of age, 126 women (3.05%) 50 to 59 years of age, and 80 women (2.03%) 60 to 69 years of age.

Table 13 Number and percentage of women screened by age group for each study group

Age Group	Intervention Group			Control Group		
	Unscreened women	Women screened	Percent screened	Unscreened women	Women screened	Percent screened
30-39	3,020	162	5.36	2547	91	3.57
40-49	4,392	305	6.94	3770	144	3.82
50-59	4,868	282	5.79	4125	126	3.05
60-69	4,788	261	5.45	3942	80	2.03
Total	17,068	1,010	5.92	14,384	441	3.06

8.4 Contamination

One of the strengths of the CRT is the ability to reduce the amount of contamination between the intervention and control groups. In order to explore the impact of contamination in this study, all women 30 to 69 years of age in the cervical screening registry who were unscreened and eligible to be sent an invitation letter as of December 1, 2009 were identified. This cohort of women (n=33,041) was followed for six months to determine the percentage of women who "spontaneously" had a Pap test. December 1, 2009 was chosen because invitation letters had not yet been sent to any women in the province by the screening program.

A total of 1,092 women (3.30%) had a Pap test between December 1, 2009 and June 1, 2010 (a six-month follow-up period) which represents a baseline spontaneous Pap test rate. This baseline rate is close to the percentage of women in the control group who had a Pap test (3.06%). Therefore, contamination between the intervention and control groups in this study was very unlikely.

8.5 Time to Pap test

Figure 27 shows the number of weeks from the date the invitation letter was mailed or the index date to the date of the Pap test for the 1,010 women in the intervention group and the 441 women in the control group who had a Pap test in the six-month follow-up period. The percentage of women who had a Pap test in the intervention group was highest during weeks three and four (7.52%), declined over time, and then increased again at week 14 (5.9%). The percentage of women who had a Pap test in the control group was highest during week one (6.12%). The major impact of the invitation letter occurred three to eight weeks after the letters were mailed.

Figure 27 Number of weeks from the date the invitation letter was mailed to the date of the Pap test by study group

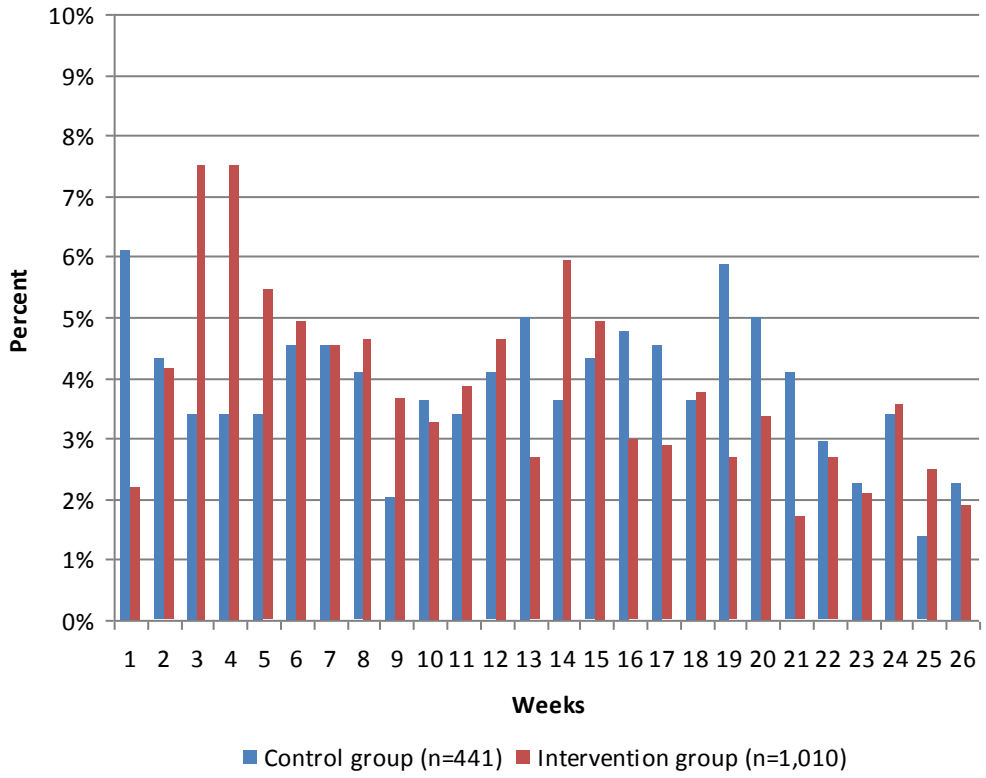
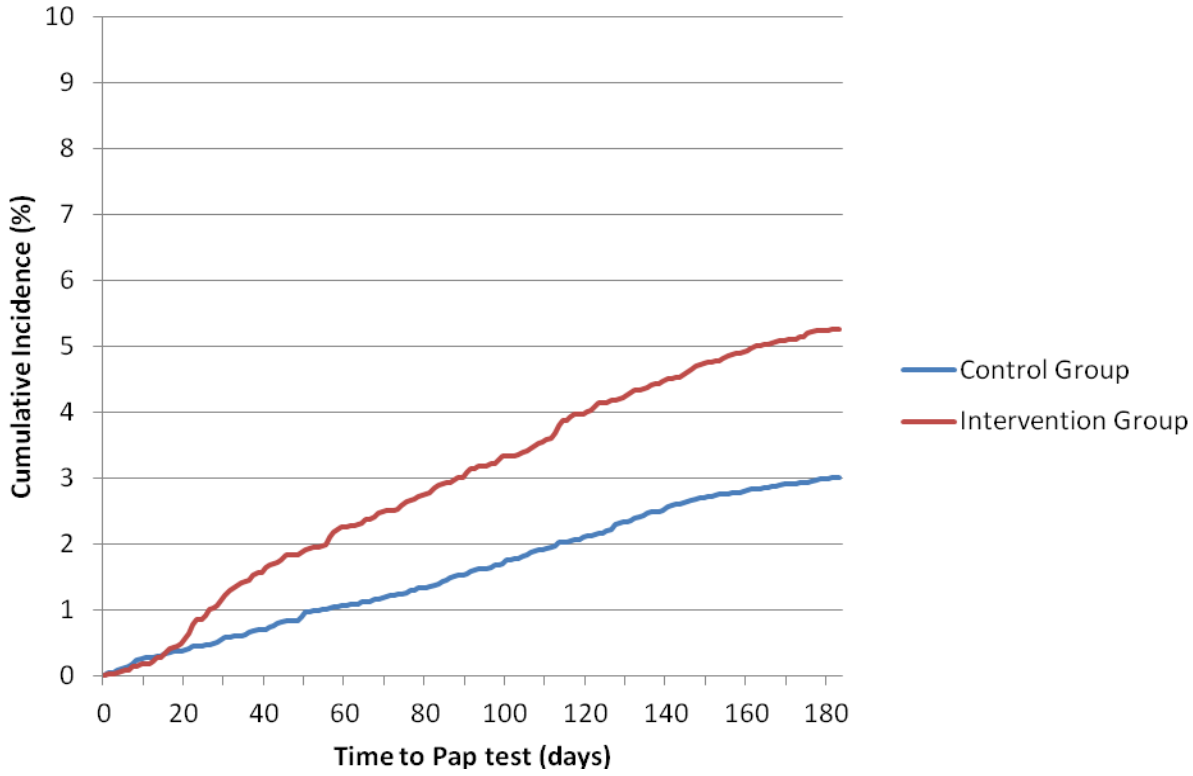


Figure 28 shows the cumulative Pap test incidence at ten day intervals for the intervention and control groups. At 20 days, the intervention and control curves diverge which suggests that women began to have Pap tests following the invitation letter at this point in time.

Figure 28 Cumulative Pap test incidence by study group



8.6 Univariable model

A univariable logistic regression GEE model using an exchangeable correlation matrix to account for clustering within the dataset was conducted. The analysis included 54 clusters based on the FSA. The dependent variable was a Pap test within six months of the invitation letter date or index date and the independent variable was the invitation letter (yes or no). In total, 1,010 women (5.92%) in the intervention group had a Pap test compared to 441 women (3.06%) in the control group. Women who were sent an invitation letter were significantly more likely to have had a Pap test in the next six months compared to women who were not sent an invitation letter (OR= 2.05, 95% CI 1.78-2.37, $p<0.001$).

An additional sensitivity analysis was performed because two FSAs (R4A and R3Y) that included 194 unscreened women were not randomized to the intervention or control group. In these two FSAs, nine women (4.64%) had a Pap test during the six month follow-up period. When these two additional FSAs were included in the control group in the univariable logistic regression GEE model with 56 clusters instead of 54 clusters, 1,010 women (5.92%) in the intervention group had a Pap test compared to 460 women (3.15%) in the control group. The OR was 2.03 (95% CI 1.76-2.35, $p<0.001$). Since this OR is extremely close to the model that included 54 clusters, it is unlikely that the exclusion of the 194 women influenced the study results.

8.7 Intraclass correlation coefficient

The ICC was 0.001. This ICC indicates that the variation due to clustering was negligible. This was confirmed by running a standard logistic regression model that did not take into account the clustered nature of the data. The results for both models were very similar. The confidence intervals were slightly narrower for the standard logistic regression model (OR=1.99, 95% CI 1.77-2.23, $p<0.001$) than those observed with the GEE (OR=2.03, 95% CI 1.76-2.35, $p<0.001$) and the p value was the same.

8.8 Multivariable models

8.8.1 Linearity

The linearity of each continuous variable in relation to the outcome was tested. Visible minority status, immigration status, high school education, average household income, and the baseline screening rate were not linearly related to the outcome. Therefore, each continuous variable was categorized as follows:

Visible minority status

Over 25% of women lived in a DA that had a visible minority status of 0%. Fifty percent of women lived in a DA that had a visible minority status of 1% to 25%. In order to capture areas with no, low, or high visible minority population levels, visible minority status was categorized to 0% visible minority population, 1% to less than 25% visible minority population, and 25% or greater visible minority population.

Immigration status

The median level of immigration status was 12%. Therefore, immigration status was categorized to less than 10% immigrant population and 10% or greater immigrant population.

High school education

The median level of high school education was 80%. Only 5% of women lived in a DA that had less than 50% of the population completing high school. In order to capture areas with a low level of high school education compared to moderate or high levels, high school education was categorized as less than 50% of individuals with at least a high school education, 50% to less than 75%, and 75% or greater.

Average household income

The median average household income was $51,000. The following three categories were chosen to provide an even distribution of average household income: less than $40,000, $40,000 to less than $60,000, and $60,000 or greater.

Baseline screening rate

The median baseline screening rate was 65%. The following three categories were chosen to provide an even distribution of baseline screening rate: less than 60%, 60% to 69%, and 70% or greater.

Table 14 shows the number and percentage of women for each new categorical variable by study group. There was a significant difference in visible minority status between the intervention and control groups (χ^2=111.31, p<0.001, df=2), high school education (χ^2=158.33, p<0.001, df=2), average household income (χ^2=68.20, p<0.001, df=2), and baseline screening rate (χ^2=204.78, p<0.001, df=2). In most cases, the actual difference between the groups was small and the statistically significant difference is likely related to the large sample size. There was no difference in the percentage of immigrant women between the intervention and control groups (χ^2=0.91, p=0.34, df=1).

Table 14 Visible minority, immigration, education, income, and baseline screening rate by study group

Variable	**Intervention group**		**Control group**		***P* value**
	n	%	n	%	
Visible minority status (n=31,006)					
0%	5,660	33.93	4,065	28.38	<0.001
<25%	8,058	48.31	7,560	52.77	
≥25%	2,963	17.76	2,700	18.85	
Immigration status (n=29,543)					
<10%	6,565	42.28	5,927	42.00	0.34
≥10%	8,865	57.45	8,186	58.00	
High school education (n=31,006)					
<50%	1,118	6.07	513	3.58	<0.001
50 to <75%	4,277	25.64	3,997	27.90	
≥75%	11,286	67.66	9,815	68.52	
Average household income (n=31,387)					
<$40,000	4,525	26.58	3,247	22.60	<0.001
$40,000 to <$60,000	6,465	37.98	5,853	40.74	
≥$60,000	6,032	35.44	5,265	36.65	
Baseline screening rate (n=31,452)					
<60%	5,012	29.36	5,307	36.90	<0.001
60% to 69%	7,064	41.39	5,440	37.82	
≥70%	4,992	29.25	3,637	25.29	

8.8.2 Multicollinearity

Before running the multivariable models, the following variables that may have measured related concepts were examined for mulitcollinearity: visible minority status and immigration status, high school education and average household income, and opportunity to be screened and continuity of care. Visible minority status and

immigration status as well as high school education and average household income did not show collinearity. However, opportunity to be screened and continuity of care appeared to be collinear.

Table 15 shows the relationship between opportunity to be screened and continuity of care. Overall, 9,928 women (73.72%) who had continuity of care had six or more visits compared to 4,114 women (22.88%) who did not have continuity of care. Similarly, no women who had continuity of care had any visits because if a woman never visited a doctor, there was no opportunity to change doctors.

Table 15 Relationship between continuity of care and opportunity to be screened

	Continuity of care				***P* value**
	Yes		**No**		
Opportunity to be screened	n	%	n	%	
0 visits	0	0	9,053	50.34	<0.001
1 to 5 visits	3,540	26.28	4,817	26.78	
6 or more visits	9,928	73.72	4,114	22.88	
Total	13,468		17,984		

Therefore, a four-level composite variable called access was created that combined continuity of care and opportunity to be screened. If opportunity to be screened was 0 and continuity of care was no, then access was very low. If opportunity to be screened was one to five visits and continuity of care was no, then access was low. If opportunity to be screened was one to five or more visits and continuity of care was yes, then access was medium. If opportunity to be screened was six or more visits and continuity of care was either yes or no, then access was high.

Table 16 shows the number and percentage of women by access level for each study group. In the intervention group, 4,879 women (28.59%) had very low access, 2,685

women (15.73%) had low access, 1,965 women (11.51%) had medium access, and 7,539 women (44.17%) had high access. In the control group, 4,174 women (29.02%) had very low access, 2,132 women (14.82%) had low access, 1,575 women (10.95%) had medium access, and 6,503 women (45.21%) had high access. There was a significant difference in access between the intervention and control groups (χ^2 =8.81 p=0.03, df=2).

Table 16 Access (opportunity/continuity) by study group

Access (opportunity/ continuity)	**Intervention group (n=17,068)**		**Control group (n=14,384)**		***P* value**
	n	%	n	%	
Very low	4,879	28.59	4,174	29.02	0.03
Low	2,685	15.73	2,132	14.82	
Medium	1,965	11.51	1,575	10.95	
High	7,539	44.17	6,503	45.21	

Because access and RUB represent two different but possibly related ways of defining contact with the health care system, they were also examined for multicollinearity. The relationship between access and RUB was not collinear.

8.8.3 Residuals and influence statistics

Logistic regression diagnostic statistics including standardized deviance residuals and leverage values were examined. No influential observations were observed.

8.8.4 Multivariable models

Five multivariable logistic regression models using a GEE with an exchangeable correlation matrix to account for clustering within the dataset were conducted. Model one examined the impact of the invitation letter on Pap test use adjusted for predisposing factors. Model two adjusted for enabling factors and model three adjusted for need

factors. Models four and five viewed the theoretical framework from the contextual and individual perspective and adjusted for contextual-level and individual-level factors respectively.

The presence of the Pap test clinic in 20 of the intervention group FSAs was not included in the models because this occurred for the intervention group only; therefore, no reference group was available. For all models, the dependent variable was a Pap test within six months, the independent variable was the invitation letter (yes or no), and an ITT analysis was used.

Table 17 shows the ORs, 95% CIs, and type 3 *p* values for the univariable model and model one that included predisposing factors (visible minority status, immigration status, high school education, average household income, age group, and RUB). The 95% CI indicates whether each category in the variable is different than the reference category while the type 3 *p* value indicates whether or not there was a significant effect of the variable on the likelihood of having a Pap test.

After adjusting for predisposing variables, women who were sent an invitation letter were significantly more likely to have had a Pap test in the next six months compared to women who were not sent an invitation letter (OR = 2.05, 95% CI 1.80-2.36, $p<0.001$). There was a significant effect of average household income ($p=0.01$), age group ($p<0.001$), and RUB ($p<0.001$) on the likelihood of having a Pap test. The odds of having a Pap test were higher if a woman lived in an area with an average household income of $40,000 to less than $60,000 (OR=1.32, 95% CI 1.09-1.60) or $60,000 or greater (OR=1.30, 95% CI 1.06-1.61) compared to women who lived in an area with an average household income of less than $40,000. The odds of having a Pap

test were also higher if a woman was 30 to 39 years of age (OR=1.39, 95% CI 1.16-1.61), 40 to 49 years of age (OR=1.68, 95% CI 1.44-1.97), or 50 to 59 years of age (OR=1.27, 95% CI 1.12-1.44) compared to women who were 60 to 69 years of age and if she had no morbidity (OR=1.88, 95% CI 1.57-2.25), low morbidity (OR=2.26, 95% CI 1.92-2.65), moderate morbidity (OR=2.25, 95% CI 1.96-2.59), high morbidity (OR=2.44, 95% CI 1.91-3.11) or very high morbidity (OR=1.92, 95% CI 1.18-3.13) compared to women who had no use.

Table 17 Logistic regression for model one: Predisposing factors

Variable		OR	95% CI	*P* value
Univariable model				
Letter	Yes	2.05	1.78-2.37	<0.001
	No	1.00		
Model 1: Predisposing factors				
Letter	Yes	2.05	1.80-2.36	<0.001
	No	1.00		
Visible minority status	0%	1.03	0.83-1.27	0.66
	<25%	1.07	0.92-1.24	
	≥25%	1.00		
Immigration status	<10%	1.08	0.95-1.24	0.25
	≥10%	1.00		
High school education	<60%	1.08	0.79-1.49	0.68
	60% to <75%	1.05	0.92-1.20	
	≥75%	1.00		
Average household income	≥$60,000	1.30	1.06-1.61	0.01
	$40,000 to <$ 60,000	1.32	1.09-1.60	
	<$40,000	1.00		
Age group	30 to 39	1.39	1.16-1.67	<0.001
	40 to 49	1.68	1.44-1.97	
	50 to 59	1.27	1.12-1.44	
	60 to 69	1.00		
Resource utilization band	Very high morbidity	1.92	1.18-3.13	<0.001
	High morbidity	2.44	1.91-3.11	
	Moderate morbidity	2.25	1.96-2.59	
	Low morbidity	2.26	1.92-2.65	
	Healthy user (no morbidity)	1.88	1.57-2.25	
	No use	1.00		

Note: The type 3 *p* value was used to determine if there was a significant effect of the variable on the likelihood of getting a Pap test. The threshold *p* value was 0.10.

Table 18 shows the results for the univariable model and model two that included enabling factors (area of residence, residential mobility, and access). The enabling factor

Pap test clinic was included in a separate analysis as it was applicable only to women in the intervention group.

After adjusting for enabling variables, women who were sent an invitation letter were significantly more likely to have had a Pap test in the next six months compared to women who were not sent an invitation letter (OR = 1.94, 95% CI 1.70-2.22, $p<0.001$). There was a significant effect of area of residence ($p=0.05$), residential mobility ($p=0.01$) and access ($p<0.001$) on the likelihood of having a Pap test. The odds of having a Pap test were higher if a woman had one or more postal code changes in the previous five years (OR=1.20, 95% CI 1.05-1.36) compared to women who had no postal code changes, if her level of access was low (OR=2.33, 95% CI 2.01-2.72), medium (OR=2.03, 95% CI 1.60-2.57), or high (OR=2.38, 95% CI 2.03-2.78) compared to very low, and if she lived in rural or Northern Manitoba (OR=1.57, 95% CI 1.23-2.00) or in the non-core of Winnipeg (OR=1.36, 95% CI 1.10-1.67) compared to the Winnipeg core.

Table 18 Logistic regression for model two: Enabling factors

Variable		OR	95% CI	*P* value
Univariable model				
Letter	Yes	2.05	1.78-2.37	<0.001
	No	1.00		
Model 2: Enabling factors				
Letter	Yes	1.94	1.70-2.22	<0.001
	No	1.00		
Area of residence	Winnipeg non-core	1.36	1.10-1.67	0.05
	Brandon	1.11	0.84-1.47	
	Rural/Northern	1.57	1.23-2.00	
	Winnipeg-core	1.00		
Residential mobility	1 or more postal code changes	1.20	1.05-1.36	0.01
	0 postal code changes	1.00		
Access (opportunity/continuity)	High	2.38	2.03-2.78	<0.001
	Medium	2.03	1.60-2.57	
	Low	2.33	2.01-2.72	
	Very low	1.00		

Note: The type 3 *p* value was used to determine if there was a significant effect of the variable on the likelihood of getting a Pap test. The threshold *p* value was 0.10.

Table 19 shows the results for the univariable model and model three that included the need factor of FSA baseline screening rate. After adjusting for the FSA baseline screening rate, women who were sent an invitation letter were significantly more likely to have had a Pap test in the next six months compared to women who were not sent an invitation letter (OR = 2.02, 95% CI 1.77-2.31, $p<0.001$). There was a significant effect of baseline screening rate on the likelihood of having a Pap test ($p=0.07$). The odds of having a Pap test were higher if a woman lived in an FSA that had a baseline rate of screening of 60% to less than 70% (OR=1.23, 95% CI 1.02-1.51) compared to less than 60%.

Table 19 Logistic regression for model three: Need factor

Variable		OR	95% CI	*P* value
Univariable model				
Letter	Yes	2.05	1.78-2.37	<0.001
	No	1.00		
Model 3: Need factors				
Letter	Yes	2.02	1.77-2.31	<0.001
	No	1.00		
FSA baseline screening rate	≥70%	1.01	0.85-1.21	0.07
	60% to <70%	1.23	1.02-1.51	
	<60%	1.00		

Note: The type 3 *p* value was used to determine if there was a significant effect of the variable on the likelihood of getting a Pap test. The threshold *p* value was 0.10.

In addition to viewing the theoretical framework in terms of predisposing, enabling, and need factors, the framework for examining the effectiveness of the invitation letters was also examined at the contextual and individual levels. Table 20 shows the results for the univariable model and model four that included contextual-level factors (visible minority status, immigration status, high school education, average household income, and baseline screening rate).

After adjusting for contextual variables, women who were sent an invitation letter were significantly more likely to have had a Pap test in the next six months compared to women who were not sent an invitation letter (OR = 2.04, 95% CI 1.77-2.27, $p<0.001$). There was a significant effect of average household income ($p=0.03$) and baseline screening rate ($p=0.09$) on the likelihood of having a Pap test. The odds of having a Pap test were higher if a woman lived in an area with an average household income of $40,000 to less than $60,000 (OR=1.24, 95% CI 1.03-1.50) or $60,000 or greater

(OR=1.25, 95% CI 1.05-1.49) compared to women who lived in an area with an average household income of less than $40,000 and if a woman lived in an FSA that had a baseline rate of screening of 60% to less than 70% (OR=1.20, 95% CI 1.00-1.43) compared to less than 60%.

Table 20 Logistic regression for model four: Contextual-level factors

Variable		**OR**	**95% CI**	***P* value**
Univariable model				
Letter	Yes	2.05	1.78-2.37	<0.001
	No	1.00		
Model 4: Contextual factors				
Letter	Yes	2.04	1.77-2.27	<0.001
	No	1.00		
Visible minority status	0%	0.98	0.82-1.18	0.69
	<25%	1.04	0.90-1.21	
	≥25%	1.00		
Immigration status	<10%	1.10	0.96-1.26	0.15
	≥10%	1.00		
High school education	<50%	1.27	0.78-2.07	0.49
	50 to <75%	1.08	0.94-1.23	
	≥75%	1.00		
Average household income	≥$60,000	1.25	1.05-1.49	0.03
	$40,000 to <$ 60,000	1.24	1.03-1.50	
	<$40,000	1.00		
FSA baseline rate of screening	≥70%	0.98	0.82-1.18	0.09
	60% to <70%	1.20	1.00-1.43	
	<60%	1.00		

Note: The type 3 *p* value was used to determine if there was a significant effect of the variable on the likelihood of getting a Pap test. The threshold *p* value was 0.10.

Table 21 shows the results for the univariable model and model five that included individual-level factors (age group, RUB, area of residence, residential mobility, and

access). After adjusting for the individual-level variables, women who were sent an invitation letter were significantly more likely to have had a Pap test in the next six months compared to women who were not sent an invitation letter (OR = 1.94, 95% CI 1.70-2.22, $p<0.001$).

There was a significant effect of age group ($p<0.001$), area of residence ($p=0.05$), residential mobility ($p=0.05$), and access ($p=0.0003$) on the likelihood of having a Pap test. The odds of having a Pap test were higher if a woman was 30 to 39 years of age (OR=1.36, 95% CI 1.14-1.62), 40 to 49 years of age (OR=1.62, 95% CI 1.40-1.89), or 50 to 59 years of age (OR=1.27, 95% CI 1.12-1.43) compared to women who were 60 to 69 years of age, if a woman lived in rural or Northern Manitoba (OR=1.59, 95% CI 1.25-2.03) or in the non-core of Winnipeg (OR=1.38, 95% CI 1.13-1.70) compared to the Winnipeg core, if a woman had one or more postal code changes (OR=1.15, 95% CI 1.00-1.30) compared to no postal code change, and if her level of access was low (OR=1.99, 95% CI 1.64-2.41), medium (OR=1.67, 95% CI 1.25-2.24), or high (OR=2.03, 95% CI 1.56-2.64) compared to very low.

Table 21 Logistic regression for model five: Individual-level factors

Variable		OR	95% CI	*P* value
Univariable model				
Letter	Yes	2.05	1.78-2.37	<0.001
	No	1.00		
Model 5: Individual factors				
Letter	Yes	1.94	1.70-2.22	<0.001
	No	1.00		
Age group	30 to 39	1.36	1.14-1.62	<0.001
	40 to 49	1.62	1.40-1.89	
	50 to 59	1.27	1.12-1.43	
	60 to 69	1.00		
Resource utilization band	Very high morbidity	1.28	0.86-1.90	0.22
	High morbidity	1.28	0.95-1.73	
	Moderate morbidity	1.27	1.03-1.58	
	Low morbidity	1.34	1.09-1.63	
	Healthy user (no morbidity)	1.20	0.95-1.52	
	No use	1.00		
Area of residence	Winnipeg non-core	1.38	1.13-1.70	0.05
	Brandon	1.12	0.85-1.48	
	Rural/Northern	1.59	1.25-2.03	
	Winnipeg-core	1.00		
Residential mobility	1 or more postal code changes	1.15	1.00-1.30	0.05
	0 postal code changes	1.00		
Access (opportunity/continuity)	High	2.03	1.56-2.64	0.0003
	Medium	1.67	1.25-2.24	
	Low	1.99	1.64-2.41	
	Very low	1.00		

Note: The type 3 *p* value was used to determine if there was a significant effect of the variable on the likelihood of getting a Pap test. The threshold *p* value was 0.10.

Table 22 compares the results for the univariable and multivariable models. Enabling and individual-level factors adjusted the relationship between the invitation

letter and Pap test use more than predisposing, need, or contextual-level factors. However, the impact of adding these variables to the univariable model was small.

Table 22 Summary of logistic regression analyses of Pap test utilization by model

Model	OR	95% CI
Univariable	2.05	1.78-2.37
Multivariable		
Predisposing	2.05	1.80-2.36
Enabling	1.94	1.70-2.22
Need	2.02	1.77-2.31
Contextual	2.04	1.77-2.27
Individual	1.94	1.70-2.22

8.8.5 Final multivariable model

A final multivariable logistic regression GEE model was conducted that included all variables in the study's theoretical framework (Table 23). After adjusting for all variables, women who were sent an invitation letter were significantly more likely to have had a Pap test in the next six months compared to women who were not sent an invitation letter (OR = 2.60, 95% CI 2.09-3.35, $p<0.001$). There was a significant main effect of age group ($p<0.001$), average household income ($p=0.01$), area of residence ($p=0.01$), residential mobility ($p=0.05$), and access ($p=0.001$). Interactions between the invitation letter and each significant main effect were tested. Only the interaction between the invitation letter and age group remained significant ($p=0.02$).

The main effect of age for women who were not sent an invitation letter was 2.01 (95% CI 1.49-2.69) for women 30 to 39 years of age, 2.17 (95% CI 1.65-2.84) for women 40 to 49 years of age, and 1.64 (95% CI 1.30-2.06) for women 50 to 59 years of age compared to women who were 60 to 69 years of age. The main effect of age for women

who were sent a letter was 1.16 (95% CI 0.95-1.41) for women 30 to 39 years of age, 1.51 (95% CI 1.25-1.81) for women 40 to 49 years of age, and 1.15 (95% CI 1.00-1.32) for women 50 to 59 years of age compared to women who were 60 to 69 years of age.

The odds of having a Pap test were higher if a woman lived in an area with an average household income greater than $60,000 (OR=1.28, 95% CI 1.08-1.52) or an average household income of $40,000 to <$60,000 (OR=1.27, 95% CI 1.05-1.54) compared to less than $40,000, if a woman lived in rural or Northern Manitoba (OR=1.53, 95% CI 1.22-1.93) compared to the Winnipeg core, if she had one or more postal code changes (OR=1.15, 95% CI 1.01-1.21) compared to no postal code changes, and if a woman had high (OR=2.06, 95% CI 1.56-2.72), medium (OR=1.71, 95% CI 1.26-2.32), or low access (OR=1.91, 95% CI 1.53-2.39) compared to very low access.

Overall, the effect of the invitation letter increased with age; the odds of having a Pap test was 1.51 times greater for women 30 to 39 years who were sent a letter compared to those who were not sent a letter (OR=1.51, 95% CI 1.17-1.94), 1.81 times greater than for women 40 to 49 years of age who were sent a letter compared to those who were not sent a letter (OR=1.81, 95% CI 1.44-2.27), 1.83 times greater for women 50 to 59 years of age who were sent an invitation letter compared to those who were not sent a letter (OR=1.83, 95% CI 1.45-2.30), and 2.60 times greater than for women 60 to 69 years of age who were sent a letter compared to women who were not sent a letter (OR=2.60, 95% CI 2.09-3.25).

Table 23 Final logistic regression model that includes all study variables and significant interactions

Variables		**OR**	**95% CI**	***P* value**
Univariable model				
Letter	Yes	2.05	1.78-2.37	<0.001
	No	1.00		
Final multivariable model				
Letter	Yes	2.60	2.09-3.25	<0.001
	No	1.00		
Predisposing factors				
Age group - for women who were not sent a letter	30 to 39	2.01	1.49-2.69	0.001
	40 to 49	2.17	1.65-2.84	
	50 to 59	1.64	1.30-2.06	
	60 to 69	1.00		
Age group - for women who were sent a letter	30 to 39	1.16	0.95-1.41	0.001
	40 to 49	1.51	1.25-1.81	
	50 to 59	1.15	1.00-1.32	
	60 to 69	1.00		
Visible minority status	0%	0.86	0.70-1.06	0.35
	1 to <25%	0.96	0.84-1.10	
	≥25%	1.00		
Immigration status	<10%	1.01	0.89-1.14	0.91
	≥10%	1.00		
High school education	< 50%	1.12	0.72-1.74	0.80
	50-75%	1.03	0.91-1.17	
	≥75%	1.00		
Average household income	≥$60,000	1.28	1.08-1.52	0.01
	$40,000 to <$60,000	1.27	1.05-1.54	
	<$40,000	1.00		
Resource utilization band	Very high morbidity	1.07	0.66-1.74	0.23
	High morbidity	1.38	0.99-1.91	
	Moderate morbidity	1.30	1.02-1.65	
	Low morbidity	1.37	1.08-1.74	
	Healthy user (no morbidity)	1.20	0.93-1.55	
	No use	1.00		
Enabling factors				
Area of residence	Winnipeg-non core	1.17	0.92-1.49	0.01
	Brandon	1.00	0.57-1.34	
	Rural/Northern	1.53	1.22-1.93	
	Winnipeg-core	1.00		
Residential mobility	1 or more postal code	1.15	1.01-1.21	0.05

	changes				
	0 postal code changes		1.00		
Access (opportunity/continuity)	High		2.06	1.56-2.72	0.001
	Medium		1.71	1.26-2.32	
	Low		1.91	1.53-2.39	
	Very low		1.00		
Need factors					
Baseline rate of screening	≥70%		1.11	0.49-1.38	0.30
	60% <70%		1.18	0.97-1.45	
	<60%		1.00		
Interactions					
Letter and age group	30 to 39	Yes	1.51	1.17-1.94	0.02
		No	1.00		
	40 to 49	Yes	1.81	1.44-2.27	
		No	1.00		
	50 to 59	Yes	1.83	1.45-2.30	
		No	1.00		
	60 to 69	Yes	2.60	2.09-3.25	
		No	1.00		

Notes: The type 3 *p* value was used to determine if there was a significant effect of the variable on the likelihood of getting a Pap test. The threshold *p* value was 0.10.

8.9 Pap test clinic

An univariable logistic regression GEE model with an exchangeable correlation matrix was conducted to evaluate the influence of the Pap test clinic on cervical cancer screening participation for women who were sent an invitation letter (intervention group only). The dependent variable was a Pap test within the six-month follow-up period and the independent variable was the presence of a Pap test clinic in the FSA two to three weeks after the invitation letter was mailed. Women who had a Pap test clinic in their FSA were not significantly more likely to have had a Pap test in the next six months compared to women who did not have a Pap test clinic in their FSA (OR = 1.04, 95% CI 0.82-1.32, p=0.76).

8.10 Per-protocol results

A per-protocol multivariable logistic regression GEE model with an exchangeable correlation matrix was conducted by including in the model women who died, had an end of coverage flag from Manitoba Health, or whose invitation letter was returned to the screening program undelivered.

Table 24 shows the number and percentage of women who died, had an end of coverage flag, and/or had their mail returned to the program during the six-month follow-up period by study group. In the intervention group, 78 women (0.46%) died and had an end of coverage flag, seven women (0.04%) died, had an end of coverage flag, and had their mail returned to the program, 101 women (0.59%) had an end of coverage flag and had their mail returned to the program, 451 women (2.64%) had their mail returned to the program, and 158 women (0.92%) had an end of coverage flag only. In the control group, 59 women (0.41%) died and had an end of coverage flag and 239 women (1.67%) had an end of coverage flag only. No women in the control group had their mail returned to the program because they were not sent an invitation letter. There was no difference in women who died and had an end of coverage flag between the intervention and control groups (p=0.53). There was a significant difference in women who had an end of coverage flag only between the intervention and control groups (p<0.001).

Table 24 Number and percentage of women who died, had an end of coverage flag, or had mail returned to the program during the six month follow-up period

Variable	**Intervention group (n=17,068)**		**Control group (n=14,384)**		***P* value**
	n	%	n	%	
Died and end of coverage flag	78	0.46	59	0.41	0.53
Died, end of coverage flag, and mail returned	7	0.04	0	0	NA
End of coverage flag and mail returned	101	0.59	0	0	NA
Mail returned	451	2.64	0	0	NA
End of coverage only	158	0.92	239	1.67	<0.001
Total	795	4.66	298	2.01	<0.001

The per-protocol logistic regression GEE model found that women who were sent an invitation letter were significantly more likely to have had a Pap test in the next six months compared to women who were not sent an invitation letter (OR= 2.65, 95% CI 2.12-3.31, $p<0.001$). The following main effects were significant: age group ($p<0.001$), average household income ($p=0.01$), area of residence ($p=0.01$), residential mobility ($p=0.04$), and access ($p=0.001$). The interaction between the letter and age group remained significant ($p=0.01$). Therefore, the results for the per-protocol model were almost identical to the results for the ITT model (OR= 2.60, 95% CI 2.09-3.25, $p<0.001$).

8.11 Screening outcomes

Table 25 shows the Pap test results for women who had a Pap test in the six-month follow-up period by study group. A total of 67 women (4.62%) had an unsatisfactory result – 43 women (4.26%) in the intervention group and 24 women (5.44%) in the control group. Unsatisfactory results include Pap tests that could not be

processed by the laboratory because of the presence of primarily endocervical cells (10.45%), insufficient epithelial cells (44.78%), obscuring inflammation (11.94%), obscuring blood (7.46%), or for other unstated reasons (25.37%). These women required another Pap test in three months.

A total of 1,328 women (91.5%) had a negative Pap test result – 929 women (91.98%) in the intervention group and 399 women (90.48%) in the control group. In total, 23 women (1.58%) had an ASC-US result and 12 women (0.83%) had an LSIL result. These women required another Pap test in six months. Twenty-one women (1.45%) had a high-grade or more severe Pap test result (AGC, ASC-H, HSIL, carcinoma in situ, or invasive cervical cancer). Women with a high-grade Pap test result were referred for colposcopy.

Table 25 Pap test results by study group

Result	**Intervention group**		**Control group**		**Total**	
	n	%	n	%	n	%
Unsatisfactory	43	4.26	24	5.44	67	4.62
Negative	929	91.98	399	90.48	1,328	91.52
ASC-US	15	1.48	8	1.81	23	1.58
LSIL	(s)	(s)	(s)	(s)	12	0.83
High-grade or more severe*	(s)	(s)	(s)	(s)	21	1.45
Total	1,010		441		1,451	

Note: High-grade or more severe includes AGC, ASC-H, HSIL, carcinoma in situ, and invasive carcinoma. (s) indicates a suppressed rate.

8.12 Cost

The cost of the invitation letter intervention is shown in Table 26. The modification of the screening registry was a one-time cost and therefore will not be required if

invitation letters are sent to Manitoba women in the future. Including the cost of the registry modification, the average cost per woman for the invitation letter was $1.68 and the average cost per woman screened was $28.35. The average cost per high-grade result was $1,909.16. Excluding the cost of the registry modification, the average cost per woman for the invitation letter was $0.86, the average cost per woman screened was $14.56 and the average cost per high-grade results was $980.49.

Table 26 Cost of the invitation letter intervention

Resource	**Unit cost ($)**	**Total cost ($)**	**Average cost per woman (n=17,068) ($)**	**Average cost per woman screened (n=1,010) ($)**	**Average cost per high-grade Pap test (n=15) ($)**
Registry modification		13,930.00			
Postage	0.39	6,656.52			
Letterhead	0.08	1,365.44			
Envelope	0.07	1,194.76			
Brochure	0.18	3,072.24			
Insert	0.08	1,365.44			
Clerical time (13 groups, 3 hours per group)	18.00	702.00			
Programmer time (13 groups, 1 hour per group)	27.00	351.00			
Total cost including registry modification		28,637.40	1.68	28.35	1,909.16
Total cost excluding registry modification		14,707.40	0.86	14.56	980.49

8.13 Chapter Summary

A total of 31,452 unscreened women were randomized by FSA to an intervention group that was sent an invitation letter (n=17,068) or a control group (n=14,384). Six months after the invitation letters were sent, 1,010 women in the intervention group (5.92%) and 441 women in the control group (3.06%) had a Pap test. The difference in the percentage of women who had a Pap test between the two groups was 2.86%.

The percentage of women who had a Pap test in the intervention group was highest at weeks three and four (7.52%). At 20 days, the cumulative Pap test incidence in the intervention or control groups diverged which suggests that women began to have Pap tests three weeks after the invitation letters were mailed. Overall, women who were sent an invitation letter were significantly more likely to have had a Pap test in the next six months compared to women who were not sent an invitation letter (OR = 2.05, 95% CI 1.78-2.37, $p<0.001$). The ICC was very small (0.001) which indicates that the variation due to clustering was negligible.

Five multivariable logistic regression GEE models based on the BMHSU were conducted. Compared to the univariable model, enabling and individual-level factors adjusted the relationship between the invitation letter and Pap test use more than predisposing, need, or contextual-level factors. However, the impact of adding these variables to the univariable model was small.

A final model that adjusted for all variables in the study's theoretical framework found that women who were sent an invitation letter were significantly more likely to have had a Pap test in the next six months compared to women who were not sent an invitation letter (OR = 2.60, 95% CI 2.09-3.35, $p<0.001$). There was a significant main

effect of age group ($p<0.001$), average household income ($p=0.01$), area of residence ($p=0.01$), residential mobility ($p=0.05$), and access ($p=0.001$).

In addition, the interaction between the invitation letter and age group remained significant ($p=0.02$). Overall, the effect of the letter increased with age; the odds of having a Pap test was 1.51 times greater for women 30 to 39 years who were sent a letter compared to those who were not sent a letter (OR=1.51, 95% CI 1.17-1.94), 1.81 times greater than for women 40 to 49 years of age who were sent a letter compared to those who were not sent a letter (OR=1.81, 95% CI 1.44-2.27), 1.83 times greater for women 50 to 59 years of age who were sent an invitation letter compared to those who were not sent a letter (OR=1.83, 95% CI 1.45-2.30), and 2.60 times greater than for women 60 to 69 years of age who were sent a letter compared to women who were not sent a letter (OR=2.60, 95% CI 2.09-3.25).

A univariable logistic regression GEE model with also conducted to evaluate the influence of the Pap test clinic on screening participation for women who were sent an invitation letter. Women who had a Pap test clinic in their FSA were not significantly more likely to have had a Pap test in the next six months compared with women who did not have a Pap test clinic in their FSA (OR = 1.04, 95% CI 0.82-1.32).

For the per-protocol analysis, 1,093 women who had died, had an end of coverage flag, or had their mail returned to the program were included in the model. The results were very similar to the ITT analysis: women who were sent an invitation letter were significantly more likely to have had a Pap test in the next six months compared to women who were not sent an invitation letter (OR= 2.65, 95% CI 2.12-3.31).

Of the 1,451 women who had a Pap test in the six-month follow-up period, 1,328 women (91.52%) had a negative Pap test result, 23 women (1.58%) had an ASC-US result, 12 women had an LSIL result (0.83%), and 21 women had a high-grade or more severe Pap test result (AGC, HSIL, carcinoma in situ, or carcinoma) (1.45%).

Including the cost of the registry modification, the average cost per woman for the invitation letter was $1.68, the average cost per woman screened was $28.35, and the average cost per high-grade result was $1,909.16. Excluding the cost of the registry modification, the average cost per woman for the invitation letter was $0.86, the average cost per woman screened was $14.56, and the average cost per high-grade results was $980.46.

The next chapter summarizes this study's main findings and compares these results to previous cervical cancer screening invitation letter studies. The study's strengths, limitations, generalizability, and unique contribution to the literature are also discussed.

Chapter 9. Summary and Discussion

9.1 Introduction

This chapter summarizes the main study findings and compares these findings to those reported from other cervical cancer screening invitation letter studies. The study's strengths, limitations, and generalizability are discussed. Finally, the unique contributions of this research are highlighted and the research questions outlined in Chapter 2 are answered.

9.2 Summary of study findings

This study evaluated the effectiveness of an invitation letter on the cervical cancer screening participation among unscreened women. A CRT study design was used in which all unscreened, eligible Manitoba women 30 to 69 years of age (n=31,452) were randomly assigned by the FSA of their postal code to an intervention group that was sent an invitation letter (n= 17,068) or a control group that was not sent an invitation letter (n=14,384).

Six months after the invitation letters were mailed, 1,010 women in the intervention group (5.92%) and 441 women in the control group (3.06%) had a Pap test. The difference in participation was between the two groups was 2.86%. Twenty-one women (1.45%) had a high-grade Pap test result. Overall, women who were sent an invitation letter were significantly more likely to have a Pap test in the next six months compared to women who were not sent an invitation letter (OR= 2.05, 95% CI 1.78-2.37, $p<0.001$).

Using the BMHSU as a theoretical framework, ten predisposing, enabling, and need factors at individual and contextual-levels were included as covariables in logistic

regression GEE models that examined the impact of the invitation letter on screening participation. Previous studies have found that these variables can have an important influence on screening participation. Enabling and individual-level variables adjusted the relationship between the invitation letter and Pap test use more than predisposing, contextual-level, or need factors but the impact of adding these variables to the univariable model that included only the invitation letter was small.

A final multivariable model included all variables in the study's theoretical framework. There was a significant main effect of age group ($p<0.001$), average household income ($p=0.01$), area of residence ($p=0.01$), residential mobility ($p=0.05$), and access ($p=0.001$). Women who had a higher average household income were more likely to be screened compared to those with a lower average household income. Women who lived in the north or rural areas of the province were more likely to have a Pap test compared to women who lived in the core area of Winnipeg. Surprisingly, women who lived in Brandon or the non-core areas of Winnipeg were not more likely to be screened compared to women who lived in the Winnipeg core. This may be because Brandon and the non-core areas of Winnipeg have higher baseline screening rates. Therefore, the unscreened women who live in Brandon or more affluent neighbourhoods in Winnipeg have barriers to screening that are less likely to be influenced by an invitation letter and improved access than women in rural or northern areas.

Women who had one or more postal code change were more likely to be screened compared to women who had no postal code change. Although a change in address can lead to a lack of continuity of care with a primary health care provider, in this study a change of address may represent women who have informed Manitoba Health of their

address change and may also be more proactive in other areas including preventive care and screening. Finally, women who had a high, medium, or low level of health care system access as determined by continuity of care and opportunity to be screened were more likely to have a Pap test than women who had a very low level of access.

In addition to the significant main effects, the interaction between the invitation letter and age group remained significant (p=0.02). Therefore, the main effects of the letter and age should be interpreted in relation to the interaction. The main effect for the letter indicates that women who were sent an invitation letter were significantly more likely to have a Pap test than women who were not sent a letter. The main effect for age indicates that women 40 to 49 years of age were more likely to have a Pap test compared to women 60 to 69 years of age. However, when the significant interaction effect is considered, it appears that the effect of the letter increased with age; the odds of having a Pap test was 1.51 times greater for women 30 to 39 years who were sent a letter compared to those who were not sent a letter (OR=1.51, 95% CI 1.17-1.94), 1.81 times greater than for women 40 to 49 years of age who were sent a letter compared to those who were not sent a letter (OR=1.81, 95% CI 1.44-2.27), 1.83 times greater for women 50 to 59 years of age who were sent an invitation letter compared to those who were not sent a letter (OR=1.83, 95% CI 1.45-2.30), and 2.60 times greater than for women 60 to 69 years of age who were sent a letter compared to women who were not sent a letter (OR=2.60, 95% CI 2.09-3.25).

A univariable logistic regression GEE model was also conducted to evaluate the influence of the Pap test clinic on cervical cancer screening participation for women who were sent an invitation letter. Women who had a Pap test clinic in their FSA were not

significantly more likely to have had a Pap test in the next six months compared to women who did not have a Pap test clinic in their FSA (OR = 1.04, 95% CI 0.82-1.32, p=0.76).

The amount of contamination between the intervention and control groups was assessed by comparing the spontaneous screening rate from a cohort of unscreened women prior to the invitation letter intervention with the control group. A total of 1,092 women (3.30%) had a Pap test between December 1, 2009 and June 1, 2010 which is very close to the percentage of women in the control group who had a Pap test (3.06%). Therefore, contamination between the intervention and control groups in this study was unlikely.

A per-protocol analysis that included 1,093 women who had died, had an end of coverage flag, or had their mail returned to the program found that women who were sent an invitation letter were significantly more likely to have had a Pap test in the next six months compared to women who were not sent an invitation letter (OR= 2.65, 95% CI 2.12-3.31, p<0.001).

Including the cost of the registry modification, the average cost per woman for the invitation letter was $1.68, the average cost per woman screened was $28.35, and the average cost per high-grade result was $1,909.16. Excluding the cost of the registry modification, the average cost per woman for the invitation letter was $0.86, the average cost per woman screened was $14.56 and the average cost per high-grade results was $980.49.

9.3 Comparison to previous literature and discussion

Previous studies that have examined the effectiveness of cervical cancer screening invitation letters have found ORs that ranged from 0.85 to 2.4 and differences in participation between the intervention and control groups that ranged from 0% to 17%. Therefore, some studies found that women who were sent an invitation letter were not more likely to have had a Pap compared to women who were not sent a letter while other studies found that the odds of women having a Pap test after being sent an invitation letter was more than doubled. In this study, unscreened women who were sent an invitation letter were significantly more likely to have a Pap test in the next six months compared to women who were not sent a letter. However, differences in populations, methodology, and follow-up periods between previous studies and the current study make the comparison of results difficult.

One important difference between previous studies and the current study is the screening history of women selected to participate in the intervention. Most previous studies included under-screened women (women who had not had a Pap test in the previous one to three years) while the current study included unscreened women (women had never been screened or who had not had a Pap test in at least five years).

Unscreened women include women who are the most difficult to encourage to participate in cervical cancer screening because despite being exposed since 2001 to health promotion campaigns, media coverage, and alternative screening delivery methods such as walk-in Pap test clinics during the annual Pap test week, these Manitoba women remain unscreened. Their attitudes towards cervical cancer screening are most likely

well established. Attitudes to screening are moderately strong predictors of participation and long-held attitudes are more resistant to change (Cooke R & French D, 2008).

In contrast, under-screened women may be more likely to respond to an invitation letter and be "nudged" towards participation because they have experienced screening in the past. Hence, an invitation letter may be less likely to change screening behaviours among unscreened women than among under-screened women. This means that the effectiveness of an invitation letter for under-screened women, who were the focus of most previous studies, might not be generalizeable to unscreened women.

Four previous studies did focus on women who had not had a Pap test in over five years: Johnston et al. (2003) included women who had not had a Pap test in ten years, McDougall et al. (2009) and Pierce et al. (1989) included women who had not had a Pap test in five years, and Stein et al. (2005) included women who had not had a Pap test in 15 years (Johnston GM et al., 2003; McDougall L & Linehan M, 2011; Pierce M et al., 1989; Stein K et al., 2005). Table 27 compares the results of these studies to the current study.

Table 27 Comparison to previous studies that included unscreened women

Study	Design	Population	Follow-up and difference in participation	OR (95% CI)
Current study	CRT	n=31,452 30 to 69 yrs No Pap test, registered for at least 5 years Manitoba	6 months 2.86% (30-69 yrs) 1.79% (30-39 yrs) 3.12% (40-49 yrs) 2.71% (50-59 yrs) 3.42% (60-69 yrs)	2.05 (1.78-2.37)
Johnston GM et al., 2003	Cohort	n=114,426 18+ yrs No Pap test in 10 years Cape Breton, NS	6 months 2.30%	1.64 (1.53-1.74)
McDougall L & Linehan M, 2011	RCT	n=30,738 21 to 69 yrs No Pap test in 5 years Calgary, AB	6 months 1.7% (21-34 yrs) 2.3% (35-49 yrs) 1.6% (50-69 yrs)	NA
Pierce M et al., 1989	RCT	n=274 35 to 62 yrs No Pap test in 5 years UK	One year 17%	2.15 (1.35-3.45)
Stein K et al., 2005	RCT	n=570 39 to 64 yrs No Pap test in 15 years UK	3 months 2.8%	NA

Notes: NA – not available

Both the studies from the UK (Pierce, 1989 and Stein, 2005) were small and did not use a six-month follow-up period. A three-month follow-up period most likely excluded some Pap tests while a one-year follow-up period may have included Pap tests that were not related to the invitation letter.

The two Canadian studies followed-up women for six months after the invitation letters were sent. Johnston et al.'s cohort study (2003) found a 2.3% difference in screening (OR=1.64, 95% CI 1.53-1.74) which is similar to the results of this study (Johnston GM et al., 2003). Like the present study, McDougall et al. (2009) found that

the difference in screening between the intervention and control groups was highest for women 35 to 49 years of age and then decreased for women 50 to 69 years of age (McDougall L & Linehan M, 2011). However, McDougall et al. (2009) did not remove women who had a hysterectomy which may have reduced the response rate to the invitation letter in the older age group nor did they test for an interaction between age and the invitation letter (McDougall L & Linehan M, 2011).

Overall, despite several methodological differences, the results from this study support the findings from previous Canadian studies; unscreened women who were sent an invitation letter were significantly more likely to be screened but the absolute difference in screening participation between the intervention and control groups was small. Invitation letters can improve the screening participation of unscreened women but other interventions may be needed to make a more substantial difference.

This study found that invitation letters were more effective with increasing age. There are several possible reasons to explain this result: older women may pay more attention to information received by mail, they may be more concerned about the possibility of developing cancer, and they may have had a Pap test before the start of the screening registry and therefore were more likely to be prompted by the letter because they were in fact under-screened not unscreened. Since the invitation letter was less effective for younger women, alternative mediums of communication such as facebook, twitter, or blogs may be required.

Previous cervical cancer screening invitation letter studies did not use a theoretical foundation to guide the study. Incorporating predisposing, enabling, and need factors at the individual and contextual-levels based on the BMHSU did not improve the predictive

capabilities of the study models. However, by including these factors, the study found there was no interaction between the invitation letter and visible minority status, immigration status, high school education, average household income, health status, area of residence, residential mobility, or access. It appears that the reasons why unscreened women in Manitoba do not have a Pap test after being sent an invitation letter are less influenced by the predictors of screening participation in the entire population. Previous research has found that age, visible minority status, immigration status, education, income, mobility, health status, area of residence, and access to health care all influence screening participation. This study found that age, average household income, area of residence, residential mobility, and access were predictors of screening but the effectiveness of the invitation letter was only influenced by age. It is possible that the models could not detect an interaction between the covariables and the invitation letter that would have been detected if the entire population of Manitoba women (under-screened and unscreened) were included in the study.

Two weeks after the invitation letters were mailed, a Pap test clinic was held by a health center in 20 of the 27 FSAs that were randomized to the intervention group. The screening program's rationale for providing a Pap test clinic after the invitation letters were mailed was to ensure screening access for women who may not have a regular health care provider that performs Pap tests and to decrease the amount of time to schedule an appointment for a Pap test. However, women who had a Pap test clinic in their FSA were not significantly more likely to have a Pap test in the next six months compared to women who did not have a Pap test clinic in their FSA. Therefore, for unscreened women, access to a health care provider, perhaps at a clinic to which they do

not usually attend and have no continuity of care, is not an important factor in the decision to be screened.

9.4 Strengths, limitations, and generalizability

Strengths

Strengths of this study include the use of a theoretical framework to guide the study design, a CRT study design that included all unscreened women in the population, and reliable information on screening history, cytology outcomes, hysterectomy procedures, gynaecological cancer diagnoses, and address information.

Theoretical framework

The BMHSU was chosen as the theoretical framework for this study because it includes individual and contextual factors associated with screening participation. Previous cervical cancer screening invitation letter studies did not state a theoretical framework that guided the study. In this study, the framework was an important part of organizing and summarizing the literature about the factors that influence screening. The framework provided a guide for operationalizing the factors that were important considerations when modeling the effectiveness of invitation letters on cervical cancer screening participation.

Study design

A population-wide, CRT was chosen as the design for this study. All previous cervical cancer screening invitation letter studies used an RCT design except the Nova Scotia cohort study and the quasi-randomized study from Belgium (de Jonge E et al., 2007; Johnston GM et al., 2003). Although an RCT produces the least biased, internally valid results, an RCT has two limitations when evaluating a community health

intervention: contamination between the intervention and control groups and limited applicability to the operation of a population-based, provincial screening program.

By using a CRT that included all unscreened women in the population and randomizing by cluster instead of individual, this study was able to retain a high level of internal validity while reducing any contamination that may have occurred between the intervention and control groups. To assess the level of contamination, a pre-invitation cohort of unscreened women was identified using the screening registry and followed for six months to determine the percentage of women who had a Pap test. Overall, 3.30% of the women in the pre-invitation cohort had a Pap test compared to 3.06% of women in the study control group. Consequently, there was no evidence of contamination or the amount of contamination present was negligible.

Evidence from RCTs is considered a critical component of evidence-based decision making (Vernon SW, Briss PA, Tiro JA, & Warnecke RB, 2004). However, when evaluating public health interventions, the evidence from RCTs may not be sufficient because RCTs typically have a narrow focus and do not take place in an applied context thus limiting the generalizability of the results to other areas (Victora CG, Habicht J-P, & Bryce J, 2004). This CRT took place throughout an entire province and included a large sample size making it possible to evaluate differences between the intervention and control groups with more power and precision than previous RCTs with small sample sizes or cohort studies that may have not eliminated other possible reasons for the differences in participation rates between the groups. This CRT also used an ITT analysis that did not compromise the original randomization of women and appropriate statistical methods that took into account the clustered nature of the data.

Screening, procedure, and address information

Screening history, gynaecological cancer diagnoses, hysterectomy procedures, vital status, and provincial health insurance registration status information was available which permitted the exclusion of women not eligible to be screened from the study. This was possible because of on-going updates to the screening registry from all cytology laboratories in the province, the Medical Claims database, the MHPR, and the Manitoba Cancer Registry. Many previous studies were unable to exclude women prior to randomization and therefore sent invitation letters to women who were not eligible for screening.

Since this study had access to a comprehensive cytology registry, self-reported Pap test information was not required eliminating any bias in the reporting of screening history and subsequent Pap test use. In addition, Pap test information was abstracted from the screening registry one year after the last invitation letters were mailed (September 2011) in order to take into account any delay between the date the Pap test was performed and the date the Pap test was entered into the screening registry. This ensured as high a Pap test capture rate as possible. Information about the Pap test result was also available which permitted an evaluation of the burden of abnormal cytology and allowed the calculation of the cost of the invitation letter per high-grade Pap test result.

An important limitation of many previous studies was the accuracy of address information. In some cases, the quality of address information was unknown, not current, or was poor (Buehler SK & Parsons WL, 1997; Hunt JM et al., 1998; McDougall L & Linehan M, 2011; Pierce M et al., 1989). In this study, the screening registry was

refreshed with address information from the MHPR immediately prior to mailing the invitation letters and only 2.5% of invitation letters were returned to the program.

Information on factors that may affect screening was also available because of the availability of postal code information and a scrambled PHIN that could be linked to Statistics Canada 2006 census data, the Medical Claims database, and the Hospital Abstracts database. Therefore, this study was able to evaluate the success of the invitation letter among women of different ages, visible minority status, levels of education, area of residence, health status, and access to the health care system.

Limitations

This study has several limitations. Since a completely randomized CRT design was used, no stratification was done prior to randomization. Stratification should occur on variables associated with the outcome. However, only the baseline screening rate compared between the intervention and control. Therefore, it is possible that there were systematic differences between the groups that influenced the study results. These factors were compared between the group after randomization and the practical differences were small. In addition, these factors were included in the logistic regression models.

It was not possible to determine how many invitation letters did not reach the intended recipient other than for those women whose letter was returned to the program. Address information is updated in the screening registry only if changes are reported to Manitoba Health by a woman or a health care facility that she has attended. Therefore, if a woman moved and did not inform Manitoba Health or did not visit a health care facility

in the two years before the start of the study, the invitation letter could have been sent to the wrong address.

This study used DA-level measures of visible minority status, immigration status, high school education, and average household income as proxy measures for individual-level variables. Since these area-level variables are estimates of individual-level variables, some measurement error may have been present which could have reduced the power available to detect a true effect (Mustard CA, Derksen S, Berthelot J-M, & Wolfson M, 1999; Pampalon R, Hamel D, & Gamache P, 2009). Previous research in Canada has found that associations between health (life expectancy and disability-free life expectancy) and socioeconomic characteristics (using a deprivation index that included education, income, employment, marital status, living alone, and being in a lone-parent family) are stronger when the socioeconomic characteristics are measured at an individual-level rather than an area-level (Pampalon R et al., 2009).

In addition, the measurement error may be larger in rural areas because the population in a rural DA is less homogenous than in an urban area; hence, the match between area-level measures and individual-level measures in rural areas is not as accurate (Mustard CA et al., 1999). However, Mustard et al. (1999) found that risk estimates derived from neighbourhood-level measures of income were not reduced relative to estimates obtained from household-level income providing evidence for the use of area-level income measures when an individual-level measure is not available (Mustard CA et al., 1999). There are also several advantages to area-level measures; they include the entire population, they produce estimates that are statistically reliable and

consistent with individual indicators (the direction of the relationship is identical), and they can detect sizable inequalities between groups (Pampalon R et al., 2009).

Literacy is a key factor when providing information about cancer screening and is an inherent limitation of all invitation letter interventions. In Manitoba, the cervical cancer screening invitation letter and brochure were tested for literacy (approximately grade five to six reading level) and the letter was provided in English and French. However, approximately 40% of adult Canadians score below level three (high school completion) on the prose literacy scale (ABC Life Literacy Canada, 2012). Among these individuals, 15% have serious difficulty reading printed materials and an additional 27% can only manage simple reading tasks (ABC Life Literacy Canada, 2012). In addition, 60% of immigrants have low literacy compared to 37% of native-born Canadians (ABC Life Literacy Canada, 2012). In Manitoba, the percentage of women who score below a literacy level three is much higher for urban First Nations or Métis women (68.9% and 51.7% respectively) compared to urban non-Aboriginal women (41.2%) (Bougie, 2008). Hence, if an unscreened woman could not read English or French or did not know someone who could read the letter out loud, the effect of the letter would be negligible.

Generalizability

Although the context may differ somewhat between provinces, the basic organization and delivery of cervical cancer screening is the same across Canada. Pap tests are primarily provided by family physicians on a fee-for-service basis as well as by some nurses, nurse practitioners, and mid-wives. Therefore, despite differences in population characteristics between Canadian provinces/territories such as the proportion of visible minority women, Aboriginal women, or new immigrants, the results of this study can

provide other Canadian cervical cancer screening programs information about the expected change in participation when invitation letters are sent to unscreened women (i.e. invitation letters will increase screening participation for a small proportion of women but many unscreened women will remain unscreened). Because of differences in population characteristics and health care systems, it is unlikely that the results can be generalized to women outside of Canada.

9.5 Unique contributions

This research makes the following unique contributions to the cervical cancer screening literature:

1. This study is the only provincial-wide, randomized evaluation of cervical cancer screening invitation letter effectiveness in Canada. This research has demonstrated that unscreened women who were sent an invitation letter were significantly more likely to have a Pap test in the next six months compared to women who were not sent an invitation letter but the difference in participation between the intervention and control groups was small. However, the effectiveness of the invitation letter increased with age. Women who were sent an invitation letter who had a Pap test clinic in their FSA were not significantly more likely to have had a Pap test in the next six months compared to women who were sent an invitation letter but did not have a Pap test clinic in their FSA.
2. This study took place in a Canadian context in which cervical cancer screening is an insured service and is fairly accessible by women; therefore, the results of this study provide information about the additional effect of an invitation letter in an environment in which screening is well established.

3. The BMHSU was chosen as the theoretical framework for this study. No previous cervical cancer screening invitation letter study stated a theoretical framework that guided the study. This theoretical framework was used to organize and operationalize the individual and contextual-level factors that influence screening participation. This allowed an evaluation of invitation letter effectiveness by age, visible minority status, immigration status, high school education, average household income, health status, area of residence, residential mobility, access to screening, and baseline screening rate.
4. Due to the availability of Pap test outcome information, this study was able to determine the resources required to implement invitation letters and calculate the cost per high-grade lesion detected.

9.6 Research questions

Answers to each of the research questions addressed in this study are summarized as follows:

Research question 1: To what extent does an invitation letter increase the cervical cancer screening participation of unscreened Manitoba women?

Unscreened women who were sent an invitation letter were significantly more likely to have a Pap test in the next six months compared to women who were not sent an invitation letter (OR= 2.05, 95% CI 1.78-2.37, $p<0.001$). In the intervention group, 1,010 women (5.92%) had a Pap test compared to 441 women (3.06%) in the control group. The difference in cervical cancer screening participation between the intervention and control groups was 2.86%. For the intervention group only, women who had a Pap test clinic in their FSA were not significantly more likely to have had a Pap test in the six

month follow-up period compared to women who did not have a Pap test clinic in their FSA (OR = 1.04, 95% CI 0.82-1.32, p=0.76).

Research question 2: Is an invitation letter more effective for some groups of women?

The effectiveness of the invitation letter increased with age. The odds of having a Pap test was 1.51 times greater for women 30 to 39 years of age who were sent a letter (OR=1.51, 95% CI 1.17-1.94), 1.81 times greater than for women 40 to 49 years of age who were sent a letter (OR=1.81, 95% CI 1.44-2.27), 1.83 times greater for women 50 to 59 years of age who were sent a letter, and 2.60 times greater for women 60 to 69 years of age who were sent a letter (OR=2.60, 95% CI 2.09-3.25) compared to women in the same age group who were not sent a letter.

Research question 3: For women who were screened, does an invitation letter result in the identification of a high-grade cervical abnormality which could be treated before progression to invasive cancer?

Ninety percent of the women who were screened had a normal Pap test. Twenty-one women (1.45%) had a high-grade Pap test (ACG, ASC-H, HSIL or more severe cytology outcome). Estimates of progression from a high-grade cervical lesion to invasive cervical cancer range from 26% to 53% (International Agency for Research on Cancer, 2005). Therefore, by diagnosing and treating these cases of high-grade cervical dysplasia, several cases of invasive cervical cancer may have been prevented.

9.7 Chapter Summary

This chapter summarized and discussed the study findings and compared the results to previous cervical cancers screening invitation letter studies. This study found that

women who were sent an invitation letter were significantly more likely to have a Pap test than women who were not sent a letter. The difference in screening participation between the intervention and control groups was 2.86%. This is consistent with previous studies that included unscreened Canadian women. The small difference in screening participation between women who were sent an invitation letter and those who were not may be because unscreened women are the most difficult to encourage to participate in screening.

The study had many strengths including the use of a theoretical framework to guide the study, a CRT that included all unscreened women in the population, the use of appropriate statistical methods that took into account the clustered nature of the data, access to a population-based screening registry that included reliable information on screening history, cytology outcomes, hysterectomy procedures, gynaecological cancer diagnoses, and address information, and the ability to link to other health administrative databases and census data which allowed the inclusion of covariables in the models.

Limitations include the possibility of systematic differences between the intervention and control groups because no stratification was performed, inaccurate address information for women who did not inform Manitoba Health of an address change, measurement error because of the use of area-level measures as proxy measures for some individual-level variables, and literacy issues for women who were sent the letter.

Since the basic organization of cervical cancer screening is similar across Canada, the results of this study can provide other screening programs information about the expected change in participation when invitation letters are sent to unscreened women. This research also provides valuable information that can be used for policy

recommendations and future research questions. These policy recommendations and suggested future research directions are provided in Chapter Ten.

Chapter 10. Policy Recommendations and Future Research Directions

10.1 Introduction

This chapter discusses the policy recommendations that arise from this research. Future research questions that evolved from the results of this study are also outlined.

10.2 Making screening policy decisions

In Manitoba, cervical cancer incidence and mortality rates have decreased significantly since the 1970s (Demers A et al., 2003). This is largely attributed to screening using the Pap test. However, from 2008 to 2011, 63.3% of Manitoba women 20 to 69 years of age had a Pap test (CervixCheck CancerCare Manitoba, 2011). This rate has stabilized in the past 10 years resulting in over 30,000 unscreened women in the province (Martens P et al., 2008). In addition, 178 women in Manitoba were diagnosed with invasive cervical cancer between 2005 and 2008; half of these women had not had a Pap test in the previous five years or had never had a Pap test (Decker KM, McLachlin CM, Kan L, Rose J, Onysko J, Ahmad R, et al., 2011). Therefore, there is a need to continue to develop interventions to educate unscreened women about screening because they are at increased risk of developing invasive cervical cancer.

This study found that an invitation letter can significantly improve cervical cancer screening participation among unscreened women but the difference in participation between women who were sent a letter and women who were not sent a letter was small. These results raise two screening policy questions: should invitation letters continue to be sent to unscreened women by the screening program in Manitoba? As well, is it

recommended that other Canadian cervical cancer screening programs use invitation letters to encourage participation among unscreened women?

In order to answer these questions and make effective policy decisions in screening, three factors must be considered: the evidence, the level of resources required and saved, and the goals, values, and beliefs about screening (Raffle A & Gray M, 2007).

Evidence

Does an invitation letter increase cervical cancer screening participation among unscreened women in Manitoba?

This study found that unscreened women who were sent an invitation letter were significantly more likely to have had a Pap test in the next six months compared to women who were not sent an invitation letter (OR= 2.05, 95% CI 1.78-2.37, $p<0.001$). The effectiveness of the invitation letter increased with age. Overall, 1,010 women (5.92%) who were sent an invitation letter had a Pap test compared to 441 women (3.06%) who were not sent an invitation letter for a difference in participation of 2.86%.

Resources

What resources were required for the invitation letter intervention? What are the potential costs or savings to the health care system?

In order to determine the resources required for the invitation letter and estimate the cost or savings to the health care system, the number of women who still would have had a Pap test in the absence of the invitation letter and the number of women who had a Pap test because of the invitation letter must first be calculated. By applying the screening rate in the control group (3.06%) to the number of women in the intervention group (n=17,068), the number of women that would still have had a Pap test without a letter

was 523 (Table 28). Therefore, 487 women had a Pap test because of the invitation letter (1,010 minus 523).

Table 28 Number of women who had a Pap test because of the invitation letter

	Intervention group (N=17,068)	**Control group (N=14,384)**
Number of women screened	1,010	441
Screening rate	5.92%	3.06%
Number of women who would have had a Pap test without the letter	523	
Number of women who had a Pap test because of the letter	487	

The next step is determining the number of women who had a low or high-grade lesion detected because of the invitation letter (Table 29). Twelve women had a low-grade lesion. The low-grade lesion rate was 0.83%. Therefore, 4.34 low-grade lesions would still have been detected without the invitation letter (0.83%*523) and 4.04 low-grade lesions were detected because of the invitation letter (0.83%*487).

Similarly, 21 women had a high-grade lesion. The high-grade lesion rate in the intervention group was 1.45%. Therefore, 7.58 high-grade lesions would still have been detected without the invitation letter (1.45%*523) and 7.06 high-grade lesions were detected because of the invitation letter (1.45%*487).

Table 29 Number of women who had a low or high-grade lesion detected because of the invitation letter

	Intervention and control groups
Low-grade lesions detected	12
Low-grade lesion rate	0.83%
Number of women who would have had a low-grade lesion without the letter	4.34
Number of women who had a low-grade lesion because of the letter	4.04
High-grade lesions detected	21
High-grade lesion rate	1.45%
Number of women who would have had a high-grade lesion without the letter	7.58
Number of women who had a high-grade lesion because of the letter	7.06

Table 30 shows the incremental cost of the invitation letter (i.e. the cost for the 487 women who had a Pap test because of the invitation letter). In Manitoba, the laboratory cost of processing a Pap test is $14.80 and the reimbursement to a physician or midwife for providing a Pap test is $75.55[6] (Manitoba Health, 2011). The estimated cost of treating a low-grade cervical lesion (ASC-US and LSIL) is $179 and the estimated cost of treating a high-grade cervical lesion (AGC, ASC-H, HSIL) is $984 (BC Cancer Agency, 2006). Therefore, the cost of the invitation letters for the 487 women who had a Pap test

[6] The cost for a complete history and physical examination with a gynaecological examination which includes a Pap test and a full patient history, an inquiry into and an examination of all relevant parts or systems required to make a diagnosis, a review of results of ordered investigations, a Pap test, a comprehensive pelvic examination, a complete written or electronic record, and advice to the patient (Manitoba Health, 2011).

because of the invitation letter was $66,378.05 excluding the cost of the registry modification or $80,308.05 including the cost of the registry modification.

Table 30 Incremental cost of the invitation letter

Description	Cost	Number	Total
Pap test by health care provider	$75.55	487	$36,792.85
Pap test – lab processing	$14.80	487	$7,207.60
Low-grade lesion treatment	$179	4.04	$723.16
High-grade lesion treatment	$984	7.06	$6,947.04
Sub-total			$51,670.65
Total including letter (excluding registry modification)	$14,707.40	1	**$66,378.05**
Total including letter (including registry modification)	$28,637.40	1	**$80,308.05**

The cost of the invitation letter does not take into consideration the cost of treating invasive cervical cancers that may have been prevented by screening. Table 31 shows the cost of treating invasive cervical cancer if some of the 7.06 high-grade lesions that were detected because of the invitation letter had not been detected and had progressed to cancer. Estimates of progression from a high-grade lesion to invasive cervical cancer range from 26% to 53% (International Agency for Research on Cancer, 2005).

The cost of treating an invasive cervical cancer is approximately $11,716 for a local disease (Stage I), $23,749 for regional disease (Stage II), and $35,979 for distant disease (Stages III and IV) (BC Cancer Agency, 2006). In 2008, 46% of invasive cervical cancers diagnosed in Manitoba women were stage I, 14% were stage II, 16% were stage III, 12% were stage IV, and 12% had an unknown stage (Epidemiology and Cancer Registry, CancerCare Manitoba, 2011). The cost for the 12% of cases that had an unknown stage was assumed to be the average treatment cost ($18,695).

If 26% of the 7.06 high-grade lesions had progressed to invasive cervical cancer, 1.83 cancer cases would have occurred. The cost of treating these cancers is approximately $39,072.48. If 53% of the 7.06 high-grade lesions had progressed to invasive cervical cancer, 3.74 cancer cases would have occurred. The cost of treating these cancers is approximately $80,304.36.

Table 31 Cost of treating invasive cervical cancer if high-grade lesions were not detected

Scenario 1 – 26% progression rate			
	Estimated number of cases	Treatment cost	Estimated cost
Stage I (46%)	0.84	$11,716	$9,841.40
Stage II (14%)	0.26	$23,749	$6,174.74
Stage III (16%)	0.29	$35,979	$10,433.91
Stage IV (12%)	0.22	$35,979	$7,915.38
Missing stage (12%)	0.22	$18,695	$4,112.90
Total	1.83		**$38,478.33**
Scenario 2 – 53% progression rate			
Stage I (46%)	1.72	$11,716	$20,151.52
Stage II (14%)	0.52	$23,749	$12,349.48
Stage III (16%)	0.60	$35,979	$21,587.40
Stage IV (12%)	0.45	$35,979	$16,190.55
Missing stage (12%)	0.45	$18,695	$8,412.75
Total	3.74		**$78,691.70**

Lastly, Table 32 combines the incremental cost of the invitation letter with the cost of treating invasive cervical cancers that would have occurred without the invitation letter (i.e. high-grade lesions that progressed to cervical cancer because the woman was not screened) to estimate the cost or savings to the health care system for four scenarios: 1) the cost of the invitation letters with the registry modification and a 26% progression rate; 2) the cost of the invitation letters with the registry modification and a 53% progression rate; 3) the cost of the invitation letters without the registry modification and a 26%

progression rate; and 4) the cost of the invitation letters without the registry modification and a 53% progression rate.

Including the cost of the registry modification, the estimated cost to the health care system due to the invitation letter intervention ranged from $41,829.72 at a 26% progression rate to $1,616.35 at a 53% progression rate. If invitation letters continue to be sent by the program to unscreened women, the registry modification can be excluded as it was a one-time cost. In this case, the estimated cost to the health care system due to the invitation letter will range from $27,899.72 at a 26% progression rate to a savings of $12,313.65 at a 53% progression rate. It is also important to note that these estimates do not include the indirect costs of a cancer diagnosis such as other medical costs, medication, loss of productivity, etc.

Table 32 Estimated health care system cost or savings

Incremental cost of the invitation letter	**Cost**	**Estimated cost (+) or savings (-)**
No registry modification	$66,378.05	
Registry modification	$80,308.05	
Cost of treating invasive cervical cancer		
26% progression rate	$38,478.33	
53% progression rate	$78,691.70	
Four scenarios		
1. Registry modification and 26% progression rate	$80,308.05 minus $38,478.33	(+) $41,829.72
2. Registry modification and 53% progression rate	$80,308.05 minus $78,691.70	(+) $1,616.35
3. No registry modification and 26% progression rate	$66,378.05 minus $38,478.33	(+) $27,899.72
4. No registry modification and 53% progression rate	$66,378.05 minus $78,691.70	(-) $12,313.65

Goals, values and beliefs

What goals, values, and beliefs should be considered when making this policy decision?

The goal of organized screening is to reduce disease incidence and mortality at the population level (Strong K et al., 2005). Reductions in cancer incidence and mortality are possible only if population uptake is adequate and higher participation rates, particularly among unscreened women, are associated with greater population benefits (Barratt AL, 2006). Therefore, high participation is considered one of the most important factors in determining the success of a screening program and is a key goal of organized screening (Barratt A et al., 2002).

However, there has been shift over the past decade from a goal that is focused entirely on high participation to a goal of providing unbiased information that can be used to make an informed decision about screening participation. Informed decision making is based on the belief that a screening program must strive to ensure that women are provided balanced information about screening (Weller DP, Patnick J, McIntosh HM, & Dietrich AJ, 2009). Balanced information includes information about the nature and frequency of the individual benefits and harms of screening as well as the population benefits of screening (Marteau TM, Dormandy E, & Michie S, 2001; Marteau TM et al., 2010). Informed decision making is important since cervical cancer screening can cause harm from false positive Pap test outcomes that result in unnecessary anxiety, further testing, and treatment.

There is a concern that the goal of increased participation conflicts with the goal of informed decision making because providing information about the harms of screening could lead to lower participation rates particularly among lower income and less educated

women (Marteau TM et al., 2010). This is an example of the "inverse care law" which states the availability of health care varies inversely with the need for it in the population (Tudor Hart J, 2000).

Several studies have found that providing balanced information to support informed decision making does not adversely affect participation in diabetes, breast cancer, or colorectal cancer screening (Fox R, 2006; Kellar I, Sutton S, Griffin S, Prevost AT, Kinmonth AL, Marteau TN, 2008; Marteau TM et al., 2010; Mathieu E, Barratt A, Davey HM, McGeechan K, Howard K, Houssami N, 2007; Trevena LJ, Irwig L, Barratt A, 2008). In addition, information can increase knowledge about screening which may result in an individual being better educated about the screening process which in turn may decrease the anxiety that can occur when recalled for further tests (Shaw C, Abrams K, Marteau T, 1999).

However, in 2003, Adab et al. assessed whether providing women with additional information on the benefits and risks of cervical cancer screening affected their intention to be screened (Adab P et al., 2003). They found that after adjusting for variables such as previous Pap test use, socio-economic status, and other preventive health behaviours, women exposed to the intervention brochure expressed a reduced willingness to be screened although the results of the study were not statistically significant.

Screening must also be available to all members of the population so they may equally make an informed decision to participate (Smith SK et al., 2010). Therefore, both increased participation and informed decision making are related to equity. Equity is a central component of organized screening. Equity is the belief that all women should be provided with information about screening and have access to screening. Organized

screening programs that systematically invite all eligible individuals are important means of ensuring equity because without a systematic approach, the highest-risk individuals tend to be the most under-screened (Raffle AE, 2001).

Policy recommendations

This study found that invitation letters can significantly increase cervical cancer screening participation among unscreened Manitoba women 30 to 69 years of age. The estimated cost of invitation letters to the health care system ranges from $1,616.35 to $41,829.72 and may have prevented two to four women from being diagnosed with invasive cervical cancer by diagnosing and treating high-grade lesions before further progression. Finally, an invitation letter initiative is consistent with the goals, values, and beliefs of organized screening – maximizing participation, providing information for informed decision making, and promoting equity of access. Therefore, the following policy recommendations are suggested:

1. Invitation letters should continue to be sent to unscreened Manitoba women 30 to 69 years of age who have not previously been sent a letter to provide information about Pap tests, HPV, and colposcopy, and to encourage cervical cancer screening. It is not necessary to ask health centers to organize a Pap test clinic in conjunction with the mailing of invitation letters.
2. Other provincial screening programs should consider sending invitation letters to unscreened women. This recommendation recognizes that for invitation letters to be effective, a population-based, comprehensive, and accurate cervical cancer screening registry must be implemented and maintained.

10.3 Future research questions

There is a need for additional studies to address the following research questions:

How often should invitation letters be sent to unscreened women?

Previous research on the effectiveness of a second invitation letter has found varied results. Eaker et al. (2004) found that a second invitation letter improved cervical cancer screening participation by 9.2% (Eaker S et al., 2004). Conversely, Byles et al. (1996) found that a second letter had no effect on cervical cancer screening participation (Byles JE & Sanson-Fisher RW, 1996). Therefore, evaluating the effectiveness of a second invitation letter to unscreened Manitoba women and the costs of expanding the intervention would be useful.

How effective is an invitation letter for under-screened women (i.e. no Pap test in the previous three to five years) in Manitoba?

Most previous cervical cancer screening invitation letter studies included under-screened women. Although the effectiveness of an invitation letter is generally better for under-screened women compared to unscreened women, previous studies have shown varied results. The effectiveness of an invitation letter for under-screened Manitoba women is unknown and should be evaluated.

Why was the invitation letter successful for some women and not for others? What additional strategies should be explored and evaluated to further improve screening participation?

Qualitative research studies such as focus groups and surveys are required to understand why some unscreened women decided to be screened after receiving an invitation letter while other women were not screened. Information is required about

cervical cancer risk perception and the level of screening knowledge (risks of developing cervical cancer, familiarity with cervical cancer screening and the provincial screening program, and the need for screening), attitudes about screening (benefits and harms), self-efficacy beliefs (ability to participate), system and structural barriers, and social influences. This information will help the screening program develop additional strategies to improve screening participation.

A few studies have evaluated the effectiveness of an invitation letter from the woman's health care provider or from both the provider and the screening program (McDougall L & Linehan M, 2011). In Manitoba, the screening program could work with primary health care clinics such as those that participate in the Physician Integrated Network (PIN) that have an electronic health record to identify unscreened women and send invitation letters from the health care provider and the program. The PIN initiative began in 2006 and currently includes 130 family physicians from 13 group practice sites in Manitoba (PRA Inc., 2009). One of the goals of the initiative is to improve access to cervical cancer screening. By partnering with these clinics, an organized approach to screening would be maintained while providing women with support from their own health care provider further enhancing continuity of care. This strategy might be most effective for the 42.82% of unscreened Manitoba women who have good continuity of care.

Did the information provided in the invitation letter and brochure improve knowledge? If screening knowledge was improved, was it adequate for making an informed choice about screening?

The invitation letter and brochure were not tested to determine if the information improved knowledge or if this knowledge was sufficient for making an informed choice about screening participation. Currently, there is very little research and evidence in this area but studies in Manitoba would be valuable to address these questions.

How will changes in screening technology influence sending invitation letters?

Future research in cervical cancer screening in Manitoba should consider changes in screening technology such as HPV testing. It has been suggested that HPV testing could adversely affect screening participation because of the connotation of sexual promiscuity attached to a positive HPV test (Everett T et al., 2011). In addition, HPV testing of self-collected vaginal specimens might also be used to improve participation among unscreened women because self-sampling overcomes some of the practical and emotional barriers to screening (Lazcano-Ponce E et al., 2011; Szarewski A et al., 2011). Studies that have examined cervical cancer screening self-sampling participation among unscreened women have found a wide range of uptake rates from 10% in the UK to 39% in the Netherlands (Szarewski A et al., 2011). In Canada, a recent pilot study that included 49 First Nations women from Northern Ontario who had previously had a Pap test found that self-sampling was an acceptable and feasible screening strategy (Zehbe I et al., 2011). Therefore, as new screening tests such as HPV testing become available, research is required about how an invitation letter can be used to support, enhance, and provide information about this new technology.

10.4 Chapter Summary

This chapter discussed the policy recommendations that arise from this study and future research questions. The policy recommendation depends on the evidence available about cervical cancer screening invitation letter effectiveness, the resources required to implement the intervention and the potential savings to the health care system, and the goal, values, and beliefs of an organized screening program and society. Based on this assessment, it is recommended that invitation letters should continue to be sent to unscreened Manitoba women 30 to 69 years of age and that other provincial screening programs consider sending invitation letters to unscreened women.

Further research is needed about how often invitation letters should be sent to unscreened women, if under-screened women should be included in the intervention, why the invitation letter was most successful for some women such as older women, what additional participation strategies should be explored and evaluated, whether or not the invitation letter and brochure provided enough information to make an informed decision and improve the woman's level of knowledge, and how an invitation letter can support future changes in screening technology.

Appendices

Appendix A Similarities and differences between organized and opportunistic screening

Aspect of screening	Organized screening	Opportunistic screening
Philosophy	Collectivistic	Individualistic
Goal	Reduce cancer incidence and mortality at the population level	Reduce cancer incidence and mortality at the individual level
Screening method	Fixed: chosen by government/health department	Variable: chosen by health care provider and individual
Sensitivity	Sensitivity is balanced with specificity. Sensitivity targets are established and monitored to improve test performance.	The most sensitive test is usually chosen. Sensitivity at the health care provider or program level is not generally monitored.
Specificity	High specificity is important for reducing adverse effects and costs due to false positive results.	High specificity is less important at the individual level.
Screening interval	Fixed: chosen to maximize population benefit at a reasonable cost.	Variable: chosen to maximize an individual's protection against cancer incidence and mortality. Often does not consider the harms of over screening. Usually more frequent than in organized program.
Available financial resources	Limited at the population level in relation to all health policies and other aspects of health care.	Limited at the individual level and health plan level. Depends primarily on the finances and insurance status of the individual.
Health technology	Must be confirmed to yield more benefit than	Efficacy does not necessarily have to

assessment	harm.	be demonstrated.
Quality assurance	Targets are monitored and have to be met. Targets are continually reviewed to ensure that screening is of the highest quality possible.	Targets may or may not be set or monitored.
Targeted uptake rates	Specified and monitored. Lower rates result in organized efforts for improvement.	May or may not be specified or monitored. There are few opportunities for systematic application of population-based improvement.
Individuals invited	Fixed: all individuals within a specified age range.	Variable: individuals who have contact with health care providers who recommend screening; individuals exposed to marketing of screening tests.
Invitation strategy	Active: everyone in the eligible population is invited.	Passive: no consistent strategy.
Equality of access	Equality of access built into the organization of the program.	Equality of access is desired but lack of data, organization, and resources limit the potential of outreach efforts.
Relation between individuals invited and cancer risk	Individuals invited represent the age group most likely to receive the greatest benefit from screening.	Individuals screened are not necessarily those at highest risk which may lead to over screening of low-risk individuals and under screening of high-risk individuals.
Benefits	Maximized for the population within available resources.	Maximized for the individual.
Harms	Minimized for the population within available resources.	Not necessarily minimized.

Source: Adapted from Miles A et al., 2004. Used with permission from John Wiley and Sons.

Appendix B Cervical cancer screening policies across the world

Country	Policy	Age range	Interval	Lifetime no of tests	Coverage
Austria	S	20+	1	50+	60% (lifetime)
Belgium	S	25-64	3	14	59%
Denmark	O	23-59	3	13	75%
Finland	O	30-60	5	6	93% (5 yr)
France	S	25-65	3	14	54% (3 yr)
Germany	S	20+	1	50+	42-47% (1 yr)
Greece	S	25-64 (pilot)	3 after 2 negative	15	NA
Hungary	O	25-65	3 after 2 negative	15	NA
Iceland	O	20-69	2-3	16-24	83% (3 yr)
Ireland	O	25-60	3 for 25-44, 5 for 45-60	8	62%
Italy	S	25-64	3	14	50% (3 yr)
Luxembourg	S	15+	1	55+	39%
Netherlands	O	30-60	5	6	80% (2 yr)
Norway	S	25-69	3	15	71% (3 yr)
Portugal	S	20-64	3 after 2 negative	17	NA
Romania	S	25-65	3	14	NA
Slovenia	O	20-64	3 after 2 negative	17	NA
Spain	S	25-65	5 after 2 negative	14	44% (3 yr)
Sweden	O	23-59	3	14	50-70% (5 yr)
United Kingdom	O	25-64	3 for 25-49, 5 for 50-64	16-10	85% (5 yr)
Australia	O	20-69	2	24	74% (3 yr), 86% (5 yr)
New Zealand	O	20-69	3	16	73% (3 yr)
United States	S	21-65 or 70	2 for 21-29, 3 for 30-70	17	65%
Korea	O	30+	NA	NA	74%
Japan	O	20+	2	24	23%

Notes: S – opportunistic; PO – partially organized; O – organized; NA – not available.

Data sources: Antilla A et al., 2004; Antilla A, Ronco G, & Working group on the registration and monitoring of cervical cancer screening programmes in the EU, 2009; Australian Institute of Health and Welfare, 2009; International Agency for Research on Cancer, 2005; National Cervical Cancer Screening Programme, 2005; Schenck U & von Karsa L, 2000; The American College of Obstetricians and Gynecologists, 2009.

Appendix C Summary of studies that have used invitation letters to increase cervical cancer screening

Author, publication year	**Setting, population**	**Design, intervention, number of participants, follow-up**	**Results**	**Limitations**
Canadian Studies				
Johnston GM et al., 2003	Canada (Cape Breton Island, NS) 18 years of age and older. Population-based. Unscreened (no Pap test in 10 years). Under-screened (no Pap test in 3 years).	Cohort Exposed (letter) (n=22,601) Not exposed (n=91,825) Follow-up 6 months.	OR = 1.64 (95% CI 1.53-1.74) 4.6% screening among not exposed vs. 6.9% screening among exposed (2.3% difference).	No randomization. Excluded some women who had a hysterectomy after the invitation letters were mailed. No upper age limit so many elderly women were sent a letter who may not have required screening. Excluded women who were mistakenly sent a letter from the analysis.
McDougall L & Linehan M, 2011 Unpublished data	Canada (Calgary, AB) 21 to 69 years of age. No Pap test in 5 years.	RCT Stratified by age group (21-34, 35-49, 50-69) Cases (n=19,426)	Age 21 to 34 – 13.7% cases (all three letter groups) vs. 12% control (1.7% difference p=0.01). Age 35 to 49 – 11.2% cases vs. 8.9% control	Did not exclude women who had a hysterectomy. Did not include entire province. Quality of address information unknown.

		standard letter (n=6,650), loss-framed letter (n=6,616), gain-framed letter (n=6,260) Control (n=11,312) Follow-up 6 months	(2.3% difference *p*=0.001). Age 50 to 69 – 6.6% cases vs. 5.0% control (1.6% difference *p*=0.001). No difference between the three difference letter groups.	
Buehler SK & Parsons WL, 1997	Canada (St. John's, NF) Two family medicine clinics. 18 to 69 years of age. No Pap test in 3 years. No hysterectomy.	RCT Two letters (initial and reminder 4 weeks later) (n=221) Control (n=220) Follow-up 6 months.	10.7% letter vs. 6.2% control. 4% difference NS). OR=1.71 (95% CI 0.87-3.36)	Small sample size (which may be why the results were not significant). Addresses not current. 61% of sample less than 40 years of age. Did not use ITT analysis – removed women after randomization and before the analysis.
McDowell I et al., 1989	Canada (Ottawa, ON) Six family medicine clinics. 18 to 35 years of age.	RCT Physician reminder (n=332) Letter reminder (n=367) Telephone reminder	16.1% physician reminder vs. 13.7% control (2.4% difference). 20% telephone vs. 13.7% control (6.3%	Small sample size. Did not assess eligibility of women before randomization. Follow-up based on family

	No Pap test in previous year.	(n=337) Control (n=330) Follow-up one year.	difference $p<0.05$). 25.9% letter reminder vs. 13.7% control (12.2% difference $p<0.05$). OR=1.89 (95% CI 1.13-3.18)	medicine clinic administrative records. Exclusion criteria not stated.
Australian Studies				
Morrell S et al., 2005	Australia. 20 to 69 years of age. Population-based. No Pap test in 4 years.	RCT Letter (n=60,189) Control (n=30,058) Follow-up 90 days.	4.44% letter group vs. 2.90% control group (1.54% difference) HR=1.54 (95% CI 1.43-1.67).	Letter was in English only. Rural areas had substantially lower non-English speaking population than urban areas. Exclusion criteria not stated.
Del Mar C et al., 1998	Australia 18 to 67 years of age. Vietnamese women identified by last name from the electoral roll. No Pap test in 2 years.	RCT Letter (n=359) Control (n=330) Follow-up not stated.	0% difference (letter group vs. control) RR=0.85 (95% CI 0.55-1.30)	Moderate sample size. Mass media campaign occurred at the same time. Women were from one community so there is the possibility of contamination. Exclusion criteria were not stated.

Hunt JM et al., 1998	Australia (Darwin). Aboriginal women's health clinic. 18 to 70 years of age. No Pap test in 3 years or no Pap test in 1 year after an abnormal test.	RCT Letter (n=125) Personal approach (n=119) Control (n=122) Follow-up 3 months.	2.4% letter vs. 0% control. 6.7% personal approach vs. 0% control. 3 women in the letter group had a Pap test; 0 women in the control group had a Pap test.	Small sample size. Only 22 women in the personal approach group were contacted. 30% of letters in the letter group were undelivered or returned to the clinic. Women may have had a Pap test at another clinic and therefore were not included in the participation rates. Exclusion criteria were not stated. Follow-up was based on clinic administrative records.
Bowman J et al., 1995	Australia. Family medicine clinic. 18 to 70 years of age. No Pap test in 3 years. No hysterectomy.	RCT 5,706 women identified by a random household survey consented to be surveyed. 913 eligible to participate. 878 agreed to participate. Final sample 658.	36.9% physician letter vs. 24.5% control (12.4% difference) 22.6% health clinic letter vs. 24.5% control (-1.9% difference) OR=1.81 (95% CI 1.13-2.91)	Small sample size. Used a mailed survey to select subjects which could have alerted them to the need for screening. Women excluded after randomization. Follow-up based on administrative records and self-reported data.

		Pamphlet (n=162) Health clinic letter (n=164) Physician letter (n=178) Control (n=155) Follow-up 6 months.		
Pritchard DA et al., 1995	Australia (Perth). Family medicine clinic. 36 to 69 years of age. No Pap test in 2 years.	RCT Tagged physician notes (n=198) Letter (n=206) Letter and appointment (n=168) Control (n=185) Follow-up 12 months.	21.2% tagged notes vs. 16.8% control (4.4% difference) 25.7% letter vs. 16.8% control (8.9% difference $p<0.05$). OR=1.67 (95% CI 1.01-2.77) 30.4% letter and appointment vs. 16.8% control (13.6% difference) OR=2.13 (95% CI 1.34-3.57).	Small sample size. Follow-up was 1 year and recommended screening interval was 2 years so some women may have been screened after study but within recommended interval. Did not exclude women who had a hysterectomy. Women who did have a hysterectomy were retained in the analysis. Follow-up was based on administrative records and a patient questionnaire.
European Studies				
de Jonge E et al., 2007	Belgium. Population-based.	Quasi-randomized design – letters were mailed for 16 age-	671 women had a Pap test for a difference of 6.4% (95% CI 5.9-	Quasi-randomized not RCT. No Pap test outcome data collected.

	25 to 64 years of age. No Pap test in 30 months.	specific units. Letter (n=43,523) Control (n=44,131) Follow-up 12 months.	6.9)	
Stein K et al., 2005	UK. 39 to 64 years of age. No Pap test in the previous 15 years. No hysterectomy.	RCT Telephone call (n=285) Letter from celebrity (n=285) Letter from screening program (n=285) Control (n=285) Follow-up 3 months.	Participation rates: Telephone – 1.4% (95% CI 0.38-3.6) Celebrity letter – 1.8% (95% CI 0.57-4.0) Program letter – 4.6% (95% CI 2.5-7.7) Control – 1.8% (95% CI 0.57-4.0) 2.8% difference (letter compared vs. control *p*=0.09).	Women were excluded after randomization by their family physician. The groups were compared after exclusions were made.
Eaker S et al., 2004	Sweden. Population-based. 25 to 59 years of age. No Pap test 3 years.	RCT Modified invitation letter (n=6,100) Standard invitation letter (n=6,140) Invitation and reminder letter (n=4,476) Invitation and no	27% modified vs. 25.7% standard (1.3% difference, NS) 15.5% invitation and reminder vs. 6.6% invitation and no reminder (9.2% difference).	Did not exclude women who had moved which may underestimate the absolute effects. Did not include a control group.

		reminder (n=4,477) Follow-up 6 months.		
Pierce M et al., 1989	UK Family medicine clinic. 35 to 62 years of age. No Pap test in 5 years. No hysterectomy. Large proportion of study population was lower SES.	RCT Letter (n=140) Physician notes (n=142) Control (n=134) Follow-up one year.	32% letter vs. 15% control (17% difference $p<0.05$). 27% tagged vs. 15% control (12% difference) OR=2.15 (95% CI 1.35-3.45)	Small sample size. Inaccurate address information - only 73% of women received the intervention. Follow-up was based on clinic administrative records. Pap tests obtained outside the clinic were not included.
American Studies				
Vogt TM et al., 2003	USA (Portland, Oregon) HMO 18 to 70 years of age. No Pap test in 3	RCT Letter then second letter (n=300) Letter and phone call (n=300) Two phone calls (n=300) Control (n=300)	18% letter vs. 16% control (2% difference NS). 32% letter and phone call vs. 16% control (16% difference $p<0.05$).	Moderate sample size. Did not have complete hysterectomy information. Follow-up based on HMO administrative records. Pap tests obtained outside the

	years. No hysterectomy.	Follow-up 12 weeks.	27% phone calls vs. 16% control (11% difference $p<0.05$).	HMO were not included.
Burack RC et al., 1998	USA (Detroit, Michigan) 3 HMO sites. 18 to 40 years of age. Inner-city, minority women. Previous abnormal or no Pap test in last year.	RCT Patient letter (n=964) Physician reminder (n=960) Patient letter and physician reminder (n=960) Control (n=964) Follow-up 12 months.	Control – 28% Patient letter – 29% Physician reminder – 29% Patient letter and physician reminder – 32% Patient letter OR=1.07 (95% CI 0.88-1.30). Physician reminder OR=1.05 (95% CI 0.86-1.28). Both OR=1.23 (95% CI 1.01-1.50). 1% difference (patient letter group vs. control, NS).	Women excluded after randomization. Did not exclude women who had a hysterectomy. The HMO recommended annual screening but some physicians disagreed and may have carried out biennial screening. Follow-up based on HMO administrative records. Pap tests obtained outside the HMO were not included.
Binstock MA et al., 1997	USA (Southern California) HMO. 25 to 49 years of age. No Pap test in 3 years.	RCT Letter (n=1526) Phone call (n=1526) Memo to physician (n=1526) Chart reminder (n=1526) Control (n=1526)	35.1% phone call vs. 16.3% control (18.8% difference $p<0.05$), 26.4% letter vs. 16.3% control (10.1% difference $p<0.05$), 25.5% memo vs. 16.3% control (9.2% difference), 23.9% chart reminder vs. 16.3%	Moderate sample size. Had to be enrolled in the HMO for at least 3 years and likely to seek care at the HMO. Follow-up based on HMO administrative records. Pap tests obtained outside the

		Follow-up 12 months.	control (7.6% difference) OR=1.84 (95% CI 1.54-2.19)	HMO were not included.
Somkin C et al., 1997	USA (California). HMO. 20 to 64 years of age. No Pap test in 3 years.	RCT Letter (n=1188) Letter and chart reminder (n=1188) Control (n=1188) Follow-up 6 months.	19.4% letter vs. 9.1% control (10.3% difference $p<0.001$) 22.6% letter and chart reminder vs. 9.1% control (13.5% difference $p=0.04$). OR=2.40 (95% CI 1.89-3.05)	Women had to be continuously enrolled in the HMO for the previous 3 years and residents of the ZIP codes served by the HMO to be eligible. Exclusion criteria not stated. Follow-up based on HMO administrative records. Pap tests obtained outside the HMO were not included.

Appendix D Summary of studies included in cervical cancer screening invitation letter meta-analyses

Study	Tseng DS et al., 2001	Baron RC et al., 2008 (Task Force on Community Preventive Services)	Everett T et al., 2011 (Cochrane Review)
McDowell I et al., 1989	✓	✓	✓
Pierce M et al., 1989	✓	✓	✓
Lancaster G & Elton P, 1992			✓
Bowman J et al., 1995	✓		✓
Lantz PM et al., 1995		✓	
Pritchard DA et al., 1995	✓	✓	
Binstock MA et al., 1997	✓	✓	✓
Buehler SK & Parsons WL, 1997	✓	✓	✓
Somkin C et al., 1997	✓	✓	
Burack RC et al., 1998	✓	✓	✓
Del Mar C et al., 1998			✓
Hunt JM et al., 1998			✓
Hogg, 1998	✓	✓	
Kvale, 1999	✓		
Vogt TM et al., 2003		✓	
Johnston GM et al., 2003			
Morrell S et al., 2005			✓
Stein K et al., 2005			✓
de Jonge E et al., 2007			
Meta-analyses outcomes	OR=1.64 (1.49-1.80) n=22,722	Median 9.8% increase n=not stated	RR=1.44 (1.24-1.67) n=99,651

Notes: Lancaster (1992) used cervical and breast cancer screening as the outcome measure. Hogg (1998) used preventive procedures for the entire family as the outcome. Kvale (1999) is unpublished data.

Appendix E Invitation letter and brochure

Susan Jones
1234 Main St.
Winnipeg, MB, R5W 2B3

August 12, 2010

Dear Susan Jones:

This letter is to tell you about screening for cervical cancer. The Manitoba Cervical Cancer Screening Program operates a confidential Registry of all Pap tests and follow-up test results in Manitoba. We work with doctors and nurses who take Pap tests, as well as the laboratories that read Pap tests.
Our records show that you have not had a Pap test in at least five years. Most cervical cancers can be prevented by having regular Pap tests and treatment for follow-up of abnormal results. We encourage you to have a Pap test. Contact your doctor or nurse to make an appointment.
Our program can be reached at (204) 788-8626 or toll free at (866) 616-8805.
Pour recevoir cette letter en français, veuillez appeler au 788-8626 (à Winnipeg) ou au (866) 616-8805 (sans frais).

Sincerely,

Ms. K. Templeton
Program Manager

Dr. R. Lotocki
Medical Director

Invitation letter and brochure used with permission from CervixCheck, 2012.

Pap tests help prevent cervical cancer. All women who have ever been sexually active should have a Pap test at least every two years. Book your appointment today.

Le test de Pap contribue à prévenir le cancer du col utérin. Toutes les femmes qui ont déjà été actives sexuellement doivent subir un test de Pap au moins tous les deux ans. Prenez rendez-vous aujourd'hui même.

Ang pap test ay makakatulong upang maiwasan ang cancer sa bungad ng matris (cervical cancer). Ang lahat ng mga babae na mayroong karanasan sa pakikipagtalik ay dapat magpa-pap test kahit minsan lang sa dalawang taon. Makipag-appointment na ngayon.

팹 테스트(자궁경부 세포진 검사)는 자궁경부암을 예방해줍니다. 성관계를 가진 적이 있는 여성은 누구나 적어도 2년마다 팹 테스트를 받아야 합니다. 오늘 검진 예약을 하십시오.

Durch regelmäßige Abstrichtests (Papanicolaou-Tests) kann Gebärmutterhalskrebs verhindert werden. Alle Frauen, die je sexuell aktiv waren, sollten sich mindestens alle zwei Jahre einem Abstrichtest unterziehen. Lassen Sie sich noch heute einen Arzttermin geben.

पैप जाहच पैप (गर्भाशय ग्रीवा) कैंसर की रोकथाम में सहायक होती है। सभी महिलायें जो कि लैंगिक रूप से सक्रिय हैं उन्हें दो वर्षों में कम से कम एक बार पैप जाहच करवानी चाहिये। अपनी नियोजित भेंट आज ही निश्चित करें।

Baaritaanka Pap test waxa uu caawimo ka geystaa sidii looga hortegi lahaa Kansarka ku dhaca makaanka afkiisa. Dhamaan haweenka mar uun galmo soo sameeyay waa in ay isku sameeyaan baaritaanka Pap test ugu yaraan labadii sanoba mar. Maanta balan samayso.

تست پاپ اسمیر به زنان در پیشگیری از ابتلاء به سرطان دهانه رحم کمک می کند. تمام زنانی که در هر مقطع زمانی مقاربت جنسی فعال داشته اند، بهتر است که تست پاپ اسمیر را هر دو سال یکبار حتما انجام دهند.

إن فحص عنق الرحم يمنع الإصابة بسرطان عنق الرحم. يجب أن تخضع كل النساء اللواتي أن قد مارسن الجنس لفحص عنق الرحم مرة على الأقل كل سنتين. احجزي موعدك الآن.

Pap tests ezhinikaadegin andone'igaade amogowin ikwewining. Ikwewag gii-waawiipengewaad ji-andawaabamaawaapan mashkikiiwininiwan endaso-niizhwaaki. Noongom izhichigen ji-waabamad.

Kā natawāpānikawiyan ōma ēkā ta akosiyan ita kā oci ocawāsimisiyan. Ōkik iskwēwak kākīpē nōcitōhitocik ōma kākīpē nīso askiwak tākī natawāpamācik maskikīwininiwa. Sēmāk anoc kākīsikāk isicikē ta wāpamikawiyan ēkwēniw oci.

ᑲ ᓇᑕᐋᐸᒥᑲᐏᔭᐣ ᐆᒪ ᐁᑳ ᑕ ᐊᑯᓯᔭᐣ ᐃᑕ ᑲ ᐅᒋ ᐅᒐᐚᓯᒥᓯᔭᐣ. ᐆᑭᐠ ᐃᐢᑵᐘᐠ ᑳᑮᐯ ᓅᒋᑑᐦᐃᑐᒋᐠ ᐆᒪ ᑳᑮᐯ ᓃᓱ ᐊᐢᑭᐘᐠ ᑖᑮ ᓇᑕᐚᐸᒫᒋᐠ ᒪᐢᑭᑮᐏᓂᓂᐘ. ᓭᒫᐠ ᐊᓄᐨ ᑳᑮᓯᑳᐠ ᐃᓯᒋᑫ ᑕ ᐚᐸᒥᑲᐏᔭᐣ ᐁᑵᓂᐤ ᐅᒋ.

Uchunguzi wa shingo la mfuko wa uzazi huzuia saratani la shingo la mfuko wa Uzazi. Wanawake wote ambao wamefanya ngono wanahitaji uchunguzi wa mfuko wa uzazi kila miaka miwili. Agiza uteuzi wako leo.

Quick Facts

- 75% of men and women will be infected with HPV during their lifetime.
- HPV can cause abnormal changes on the cervix and cervical cancer.
- 1 in 4 women will have an abnormal Pap test in her lifetime.
- About 45 women are diagnosed with cervical cancer each year in Manitoba.
- Regular Pap tests can prevent up to 80% of cervical cancer.

CancerCare MANITOBA
Action Cancer Manitoba

Manitoba Cervical Cancer Screening Program
Programme Manitobain de dépistage du cancer du col utérin

Tell her how much you care.

Tell her to get a Pap test.

Say it with our new TellEveryWoman Greeting Cards:

- Happy Birthday
- Thinking of You
- Happy Anniversary
- Thank You
- Happy Mother's Day

For more information please contact:

Manitoba Cervical Cancer Screening Program
#5-25 Sherbrook St.
Winnipeg, MB R3C 2B1

Telephone: (204) 788-8626
Toll Free: 1-866-616-8805
mccsp@cancercare.mb.ca
www.TellEveryWoman.ca

Pour recevoir cette brochure en français veuillez:

appeler au 788-8626 (à Winnipeg)
ou au 1-866-616-8805 (sans frais)
mccsp@cancercare.mb.ca
www.TellEveryWoman.ca

Pap Tests:

What you need to know

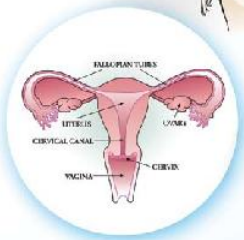
Manitoba Cervical Cancer Screening Program
Programme Manitobain de dépistage du cancer du col utérin

What is a Pap test?

A Pap test is a test that can find changes on your cervix. During a Pap test, cells are taken from your cervix, placed on a slide and sent to a lab for assessment. In most cases, the cells are normal.

What is the cervix and where is it located?

The uterus (womb) is made up of two parts. The upper part is where a baby grows. The cervix is the lower part of the uterus. It joins the womb to the vagina. Abnormal changes (cervical dysplasia) may develop at this opening to the womb.



What causes abnormal changes?

Human Papillomavirus, or HPV, is a very common sexually transmitted virus that can cause abnormal changes on your cervix. Eight percent of women will have an abnormal Pap test each year in Manitoba.

Why should I have Pap tests?

Sometimes abnormal changes caused by HPV can become cancerous. A Pap test can find these abnormal changes before they turn into cancer. Regular Pap tests with follow-up for abnormal changes can prevent most cancer of the cervix.

What should I do before the test?

- Schedule your Pap test after your period (menstruation) has stopped completely,
- Schedule your Pap test two weeks after treatment for any cervical or vaginal infection,
- Do not use tampons, douches, creams and/or foams for 48 hours before your Pap test, and
- Try not to have sexual intercourse for 24 hours before the test.

If you need a repeat Pap test, you should wait at least three months in order to allow cells on the cervix to grow back.

Am I at risk for HPV?

If you have ever had sex or experienced intimate touching, you are at risk for HPV.

HPV is very common. Three out of four people will have at least one HPV infection in their lifetime. You can get HPV easily from oral, genital or rectal sex or intimate touching. Most infections will disappear on their own. When they do not disappear, these changes can be found with a Pap test and treated with follow-up procedures.

All women who have ever been sexually active (sexual intercourse and intimate touching) should have regular Pap tests.

What is the HPV Vaccine?

Two HPV vaccines, Gardasil and Cervarix, have been approved for use in Canada. Gardasil provides protection against HPV 16, 18, 6 and 11. Cervarix provides protection against HPV 16 and 18. HPV 16 and 18 cause over 70% of all cervical cancers. HPV 6 and 11 cause 90% of all genital warts. Gardasil is given in three doses over six months and cannot be used to treat existing HPV infections.

Gardasil is approved for males and females between the ages of 9 and 26 and is free for grade six girls through the Manitoba HPV Immunization Program. Ask your doctor where you can get the vaccine outside the immunization program.

How effective is the vaccine?

The vaccine is most effective when given to females before they start having sexual contact. If you receive Gardasil before exposure to HPV 16, 18, 6 and 11, it will be almost 100% effective in preventing infections from these four types. If you have previously been infected with one of these four types, the vaccine will still protect you against the remaining three types.

Do I still need Pap tests if I have had the vaccine?

Yes. You will still need to have regular Pap tests as the vaccine does not protect you against all types of HPV that can cause cervical cancer.

Where can I go for a Pap test?

Ask your doctor or nurse, or contact your local health centre for a Pap test. To find out where you may be able to have a Pap test in your community, call the Manitoba Cervical Cancer Screening Program or visit our website at TellEveryWoman.ca.

How often should I have a Pap test?

You should start having Pap tests three years after you become sexually active. Most women need a Pap test at least every two years. Talk to your doctor or nurse about what is best for you.

If my Pap test is abnormal, does it mean I have cancer?

No, it does not. In most cases, cancer is not the reason for an abnormal Pap test. Most of the time, abnormal changes will disappear on their own without any treatment. You may need a repeat Pap test, or in some cases, you may need colposcopy. Most women who have abnormal Pap test results and who have follow-up tests and/or treatment will never get cancer of the cervix.

What if I need a colposcopy?

A colposcopy (COL-POS-COPY) refers to an examination of the cervix and vagina using a low-powered magnifying instrument known as a colposcope.

It is done to assess any abnormalities on your cervix and to determine if any treatment is necessary. A gynecologist who is specially trained as a colposcopist does this examination.

Keep all appointments after an abnormal Pap test. Most cervical cancers can be prevented if women have regular Pap tests with follow-up for abnormal changes. Regular screening with Pap tests can prevent up to 80% of cervical cancer.

When can I stop having Pap tests?

If you are 70 years or older and have had three or more normal Pap tests in the previous 10 years with no change in sexual partner, you may be able to stop having Pap tests. Talk to your doctor or nurse about what is best for you.

What is the Manitoba Cervical Cancer Screening Program?

The Manitoba Cervical Cancer Screening Program operates a confidential Registry of Pap test and follow-up test results for all Manitoba women. This is to make sure that anyone who has an abnormal Pap test gets the follow-up they need. The program will also notify women when they are overdue for a Pap test. You can contact us:

- for information about your results, Pap tests and cervical cancer, or
- to find out where you can go for a Pap test.

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