CHANGING CERVICAL CANCER SCREENING GUIDELINES: PATIENT ATTITUDES AND CLINICAL PRACTICE

By
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Abstract:

Objectives:

Cervical cancer screening guidelines have been revised, and now emphasize evidence-based medicine, resulting in recommendations for less frequent screening; however, these changes have been met with concern by both patients and providers. Understanding the patterns of acceptance versus reticence to accept these guidelines by health systems, providers, and patients is critical to developing successful strategies for translating policy change into routine practice. Here we fill some of these knowledge gaps by incorporating both actual cervical cancer screening practice data and patient perspectives towards HPV testing and screening interval changes through the following specific aims: 1a) describe the uptake of co-testing and examine the correlates of receiving an HPV co-test, 1b) estimate the length of time until the next screening test following either a negative Pap smear alone or a dual negative co-test, and 2) investigate the correlates of reluctance to adhere to revised guidelines, which recommend the addition of HPV testing along with less frequent cervical cancer screening.

Methods:

Using cervical cancer screening records from the Pathology Data Systems (PDS) at Johns Hopkins Hospital, we estimate temporal trends in choice of screening strategy (cytology alone or with HPV DNA testing) and the interval between successive screening tests in routine clinical practice. We then incorporate the patient perspective by using data collected in the HPV in Perimenopause (HIP) natural history study of women age 35-60 years, we will compare women who indicate willingness versus reluctance to accept

alternative screening strategies such as HPV testing and a longer interval between cervical cancer screening tests.

Results:

In clinical practice, we saw a significant increase in use of HPV co-testing over the last 10 years, reaching almost 80% of screening tests. We also saw a significant increase in time between screening tests following a dual-negative co-test to almost 3 years, but essentially no change in time to next screening test following a normal Pap smear, remaining near 1.5 years. Among patients, we found a majority of study participants indicated a willingness to adopt a cervical cancer screening strategy of cytology alone or Pap-HPV co-testing every 3 years if recommended by their physician, but remain concerned about primary HPV testing and co-testing with 5-year screening intervals.

Conclusion:

HPV testing was incorporated into screening with an assumption of less frequent screening due to its greater sensitivity and negative predictive value. While intervals have increased following a co-test, more time will be needed to see whether they reach 5 years as recommended. We also found evidence of continued reticence to accepting newer HPV-based screening algorithms among routinely screened women over age 35, highlighting a need for more patient education regarding the use and meaning of HPV testing.

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Chapter 1: Introduction

Introduction:

Professional medical associations in the United States base screening guidelines and recommendations on systematic reviews of the evidence. Recently, evidence-based review standards have begun to pay particular attention to the relative harms as well as benefits to screening. This has led to a reduction in the overall recommended screening frequency for several cancer prevention strategies including breast, prostate, and cervical cancer screening. In 2012, several organizations issued updated cervical cancer screening recommendations, emphasizing the need for less frequent screening and specifically advocating against the use of annual Pap smears (1-3). These policy changes have been met with anxiety among both patients and providers. Understanding the patterns of acceptance versus reticence to accept evidence-based guidelines by health systems, providers, and patients will be critical to development of successful strategies for translation of policy change into routine practice so that we can continue to prevent cervical cancer while minimizing the harms associated with screening.

Here we attempt to fill some of these critical knowledge gaps by incorporating both actual cervical cancer screening practice data and patient perspectives towards HPV testing and screening interval changes. To do so, we used data from the Johns Hopkins Department of Pathology, Pathology Data Systems (PDS), and an ongoing cohort of women aged 35-60 years in routine gynecological screening who were enrolled in the HPV In Perimenopause (HIP) Study, to address the following questions: What are the current cervical cancer screening practices at Johns Hopkins and are they in line with contemporaneous evidence-based guidelines? What is the knowledge of and attitude

towards changes in cervical cancer screening methods and frequency among women currently participating in routine cervical cancer screening?

Background

HPV and cervical cancer: Infection with the human papillomavirus (HPV) is the primary cause of cervical cancer (4, 5). HPV is a double-stranded DNA virus in the papillomavirus family. There are well over 100 known types of HPV, and they can be divided into two categories: oncogenic (high-risk) and non-oncogenic (low-risk). Oncogenic HPV types have been attributed to a range of cancers including cervical, vaginal, anal, and oral, while non-oncogenic types may cause a variety of warts. The vast majority of HPV infections, however, are subclinical (6).

HPV epidemiology: Approximately 40 of the HPV types are transmitted through sexual contact and can establish infection in the epithelial cells of the oral and anogenital tract (7, 8). Approximately fourteen of these types are considered high-risk—able to be isolated from just about every cervical cancer. Persistent infection with high-risk HPV strains may lead to the development of precancerous lesions and potentially invasive cancer, while some of the low-risk types can cause genital warts, though most do not cause detectable disease (5, 6, 9). Two of the high-risk types, 16 and 18, cause approximately 70% of all cancers (10).

Estimates suggest HPV is the most prevalent sexually transmitted infection among women in the United States (11), with high rates of infection following the onset of

sexual activity. In a cohort of university women aged 18-20 years, cumulative incidence of HPV infection was over 40% within 3 years of sexual debut (12, 13). Prevalence is highest in young women and then decreases though middle age, although a second peak in prevalence is seen around the age of menopause in many countries (14). It is estimated that over 80% of women will be exposed to HPV in their lifetime (15, 16). The majority of HPV infections are self-limiting, with over 80% of infections becoming undetectable within one to two years (6). Persistently detectable HPV infections can lead to the development of high-grade lesions and invasive cancer if left untreated (6).

Cervical cancer epidemiology: HPV is a necessary, but not sufficient cause of cervical cancer (4, 5). The progression from infection to invasive cancer is slow, usually taking ten to fifteen years (17). Nonetheless, because of the very high prevalence of high risk HPV in the population, cervical cancer is the 4th most common cancer diagnosis and the 2nd leading cause of cancer mortality in women worldwide, with an estimated 528,000 new cases and 260,000 deaths each year, over 85% of which are in the developing world (18).

In countries with effective screening programs, invasive cervical cancer (ICC) rates are much lower. Estimates suggest that there will be almost 12,400 new cases of cervical cancer and a little over 4,000 cervical cancer deaths in the United States in 2014. In the US, the age-adjusted incidence rate is 7.8 per 100,000 women per year (up to 18.6 per 100,000 after hysterectomy adjustment (19)) and the mortality rate is 2.4 per 100,000

women per year. These rates have been on the decline for over 40 years largely due to successful, widespread implementation of routine screening (20).

Cervical cancer prevention: Unlike many other cancers, cervical cancer is entirely preventable as there are highly effective primary and secondary prevention strategies available. Two vaccines have been licensed for the prevention of HPV infection, both of which prevent infection of the two HPV strains (types 16 and 18) that cause 70% of cervical cancer cases. Merck's quadrivalent Gardasil vaccine protects against low-risk HPV types 6 and 11, which cause genital warts, in addition to the high-risk strains 16 and 18, and was first licensed by the FDA in 2006 (21). GlaxoSmithKline's bivalent Cervarix vaccine prevents against HPV types 16 and 18, and was licensed by the FDA in 2009 (22). Gardasil is approved for use in males and females ages 9-26 years, while Cervarix is approved for use in females ages 9-25 years. Both vaccines have shown over 90% efficacy in protecting against their intended strains (23, 24).

However, the vaccines are only effective at preventing infection in HPV-naïve (unexposed to the vaccine strains), which is why vaccination is recommended prior to sexual debut. Since vaccines were only introduced starting in 2006, and showed slow uptake (<35% coverage of eligible females in the first 5 year), many women remain unvaccinated and therefore need to continue routine cervical cancer screening (25). Women vaccinated shortly after vaccine approval but after sexual debut may have already been exposed to high-risk strains, and so they also need to continue screening. Lastly, even among those vaccinated early, these vaccines only protect against the 2

strains that cause 70% of cervical cancer cases, so women remain at risk for developing cervical cancer from the other high-risk strains. Newer HPV vaccines are also under development, which aim to prevent against 9 of the high-risk strains, and so would offer greater protection as well. However, continued secondary prevention of cervical cancer through routine screening programs will remain important at least until screening populations are fully vaccinated. As both primary and secondary prevention options improve, cervical cancer rates will continue to fall, and thus the efficiency of screening becomes even higher priority.

Evolution of cervical cancer screening: Since its development in the 1940s, screening for cervical cancer has been based primarily on morphologic examination of cervical cytology specimens, or Pap smears (26). However, recognition that HPV is the necessary cause of cervical cancer has led to the development of newer screening technologies based on detection of biological markers of HPV infection. As our understanding of HPV and cervical cancer evolves, so do our screening options, requiring frequent updating of our tools and the guidelines for their use.

Pap smears: The Pap smear is a screening test used to detect cervical cancer and its precursors, and was first described by Dr. George Papanicolaou in the 1920s, but didn't gain widespread use until the 1940s. Dr. Papanicolaou discovered that he could detect abnormal cells on a vaginal smear, thus providing a relatively cheap and less invasive way to screen for cancer on a large population than performing biopsies (26, 27).

As a result, Pap smears, also referred to as cervical cytology, have been in wide use in the United States for over 50 years and is the most frequently used cancer screening test. Pap smears are credited with over a 50% reduction in cervical cancer over the past 30 years (20). In 2012, 78% of women over age 18 in the US reported having a Pap smear in the last three years (28).

The test is performed by a trained health care provider during a speculum examination. The physician or nurse collects exfoliated cervical cells using a small brush or other collection device. The sample is then placed on a glass slide and preserved with a fixative so it can be sent to a laboratory to be evaluated. Results will indicate whether or not abnormal cells were detected, and if so, the type or degree of abnormality detected (29). Cytology has a sensitivity in the range of 50-80% for high-grade disease and around 50% for low-grade disease, and specificity of 85-100% (30-32).

Since its initial discovery, the method has evolved from conventional cytology to liquid based cytology (LBC), a more automated process. For LBC, the sample is placed into a container with a preservative fluid instead of smeared on a slide. Once in the laboratory, a machine transfers a layer of cells onto a slide for analysis (29). This method is comparable in terms of sensitivity and specificity, but is an improvement over conventional Pap smears in that it reduces the number of inadequate or unsatisfactory results (33, 34). The residual fluid can also be used for HPV DNA testing, without requiring an additional sample. In the US, LBC is now the primary method of cervical cancer screening in use.

HPV DNA testing: The discovery that HPV is the necessary cause of cervical cancer has led to the development of newer screening methods that can identify an HPV infection by detecting the presence of HPV DNA or other molecular markers of HPV infection in a sample of cells from the cervix. The first HPV DNA test was approved for clinical use in the United States in 2003. This Hybrid Capture 2 (hc2) test can detect the presence of any of 13 high-risk and 5 low-risk HPV types, but is not type specific and does not distinguish which of the genotypes are present (35). More recently, the US FDA approved the first HPV test for an indication of primary HPV only screening (36).

Approval of new screening tests meant that they needed to be evaluated for evidence-based application in cervical cancer screening programs. Multiple uses of HPV tests have been evaluated and approved by the FDA, including ASCUS triage, HPV alone as a primary screen, and co-testing in conjunction with Pap tests. ASCUS triage with HPV testing means that only those Pap results that come back as ASCUS will be followed up with testing to look for the presence of HR-HPV. This method has a sensitivity and specificity of approximately 91% and 62% for CIN2+ and 95% and 60% for CIN3+. As a primary screening test, HPV testing had high sensitivity (90% or higher), but specificity varied by setting from 50-100% for high-grade disease (37). Co-testing involves the use of an HPV test along with a Pap smear, increasing both the sensitivity and negative predictive value of the screening result, thus safely allowing for longer intervals between screening in dual negative women. Co-testing is only recommended for women 30 years of age and older, as the test is less specific for precancerous lesions due to the higher

prevalence of HPV in younger women. Reflex testing of ASCUS Pap results is recommended in all women.

Potential harms of screening: While the benefits of cervical cancer screening are obvious, the potential harms are less so, but are important nonetheless. The slow growing nature and long detectable precancerous period of cervical cancer provide ample opportunity for early detection (38-40). Since many HPV infections and precancerous lesions resolve on their own, screening too frequently will lead to detection of transient abnormalities, causing the potential for psychological trauma and overtreatment of regressive lesions (38, 41-44). Continued follow-up and treatment of these abnormal results is costly in terms of both time to the patient and for the procedures being done. In addition to more frequent follow-up appointments, over-screening can lead to false positives resulting in colposcopies and either excisional (ie: loop electrosurgical excision procedure (LEEP)) or ablative (ie: laser, cryotherapy) treatment. Furthermore, these procedures carry risks of their own, such as infection, as well as other long-term consequences such as adverse pregnancy outcomes including increased risk of pre-term delivery. Thus when performed for an abnormal result that would otherwise clear on its own, the harm outweighs the benefit (45-47). It was the need to balance these harms with the benefits of screening, combined with newer knowledge about HPV natural history and study data indicating comparable benefits with less frequent screening, that has led to the need to revise screening interval guidelines (1, 2).

Changes to cervical cancer screening guidelines: While annual screening with Pap smears remained the norm in the United States for decades following its introduction, over the last decade or so, professional medical and public health organizations have been revising their cervical cancer screening guidelines, with little consensus until the recent 2012 guidelines.

Table 1.1: Summary of routine screening guidelines for women age 30-65 by organization since 2002 *(see next page)*

Updated screening recommendations: In 2012, the US Preventive Service Task Force (USPTF), American Cancer Association (ACS), American Society for Colposcopy and Cervical Cytology (ASCCP), and American Society for Clinical Pathology (ASCP) updated their joint guidelines for cervical cancer screening, specifically recommending *against* annual screening using any strategy. Cytology alone at 3-year screening intervals and HPV co-testing with cytology at 5-year intervals were both considered acceptable strategies for women aged 30-65 years (1, 2). These recommendations were made following a thorough review of available data and concluded that the harm from unnecessary follow-up of regressive disease outweighs the benefit (45, 46), when comparing annual to every 3 year screening (1, 2). The American College of Obstetricians and Gynecologists (ACOG) updated their guidelines shortly thereafter, recommending Pap-HPV co-testing over age 30 at a 5-year interval as the preferred method, but cytology every 3 years as acceptable (3). While primary screening with

Table 1.1: Summary of cervical cancer screening guidelines for women age 30-65 by organization over time

	ACS	ACOG	ASCCP**	USPSTF
Pre-2003	Yearly Pap test, but after 3 consecutive normal exams, less frequently at the discretion of the doctor (48)	Yearly Pap test (49)	Annual or Bienniel Pap smears (50)	Pap test at least every 3 years, but no benefit to annual Paps (51)
2003-2009	Age 30+: after 3 normal Paps in a row- can move to every 2-3 years; OR screen every 3 years with Pap/HPV co-test (48, 52)	Age 30+: after 3 normal Paps in a row- can move to every 2-3 years; OR screen every 3 years with Pap/HPV co-test (53)	2004: Okay to co-test every 3 years (54)	Pap test at least every 3 years, but no benefit to annual Paps, insufficient evidence to recommend co-testing (55)
2009-2012	No change	Age 30+: Pap every 2 years; OR after 3 consecutive negative Paps can be screened once every 3 years (56)	No change	No change
2012-present	Age 30-65: Pap test every 3 years or Pap/HPV co-test every 5 years* (1, 48)	Age 30-65: Pap test every 3 years or Pap/HPV co-test every 5 years* (3)	Age 30-65: Pap test every 3 years or Pap/HPV co-test every 5 years* (1)	Age 30-65: Pap test every 3 years or Pap/HPV co-test every 5 years (2)

*Cytology only acceptable, Co-test preferred method
**guidelines primarily for abnormal cytology until 2012

HPV testing was not recommended in the 2012 guidelines, in April 2014 the US Food and Drug Administration (FDA) approved the Roche cobas® HPV test for a primary screening indication (36), and interim guidelines for use of an HPV only strategy are anticipated.

Current screening practices: Given the different cervical cancer screening guidelines that have been issued over the last 10-15 years, it is not immediately clear which of the alternative screening methods are being used and whether they are being employed as recommended (52, 56). There is no mandate for providers to adhere to evidence-based guidelines, and there is ample evidence to suggest a general lack of adherence to the published guidelines. Both focus groups and nationally representative surveys of physicians have shown that doctors frequently recommend cervical cancer screening more often than indicated by the guidelines (57-59). In addition to frequent reports of not extending screening intervals where appropriate, physician report of non-evidence based screening practices such as low-risk HPV DNA testing, HPV testing in women under 30, and HPV testing after an ASC-H or HSIL Pap result have been commonly documented (60-64). Clearly there is wide variation in screening recommendations and practices at the provider level.

Most studies about physician knowledge and adherence to guidelines have been based on self-report or response to vignettes and not on actual practice (57-60, 62-64). While data showing physician intentions for screening recommendations are important, we must also consider what is actually being done in practice. Two recent studies of a large academic

medical center showed slow uptake of new screening practices, with rates of co-testing plateauing around 15% for women over 30 from 2006 through 2008 before increasing to about 40% between 2008 and 2010. Within this single institution, rates of co-testing varied greatly by clinic. There was also indication of non-evidence based practices including HPV testing in women under 30 and repeat testing within 3 years of a dual-negative (65, 66). Similar trends were seen in data from other reference laboratories and academic primary care settings (67, 68), with one study showing that 66% of women who were eligible for extended screening intervals had unnecessary screening tests performed between 2008 and 2009 (69).

Now that consistent screening guidelines are in place, it is important to evaluate whether these new consensus recommendations are being adopted. Although the recommendations are based on strong evidence from randomized controlled trials comparing cytology alone to HPV co-testing, providers faced with choosing between these options are calling for more direct "real-world" evidence of the harms and benefits of alternative screening strategies. As the newest evidence suggests HPV tests are the superior screening method, eventual displacement of Pap by HPV testing as a primary screening method is possible. Thus, it is important to evaluate whether HPV testing is being incorporated into routine practice, screening intervals are simultaneously being extended, and if there is population variability in HPV test utilization. Increases in co-testing frequency without interval lengthening may result in increasing, rather than decreasing, costs to patients and the health care system.

Table 1.2: Summary of publications examining physician recommendations and clinical practices *(see next page)*

Patient attitudes towards new recommendations: Adherence to evidence-based screening is influenced not just by provider practice. If the nuanced message explaining the reasoning behind less frequent screening is not conveyed clearly to the public, it is unlikely that this policy will be effectively translated into practice. People may see it as unsafe or a means to 'ration care' rather than an evidence-based decision (70, 71), as was the case with the breast cancer screening guideline changes in 2009 (72, 73). Additionally, patient anxiety and expectation of having a screening test has been shown to influence a provider's screening recommendation (74). As a result, it is important to more fully understand how news of these updated guidelines is received by women and whether that influences their (and their provider's) decisions about screening frequency (71, 74, 75).

Evidence suggests that the public is resistant to being screened less frequently (70, 76, 77), and the preference for annual screening compared to less frequent screening has been demonstrated repeatedly (62, 70, 71, 78). For example, Australian women reported a preference for annual Pap smears despite a national policy of biennial screening, citing early detection and peace of mind as the primary motivation behind their preference (79). Similarly, a survey of racially and ethnically diverse women in San Francisco reported that a third of women between the ages of 50 and 65 wanted annual Pap testing after dual-negative co-testing, and almost half of women over age 65 indicated the same (78).

Table 1.2: Summary of publications examining physician recommendations and clinical practices

Author	Year		Study Design	Study Population or Data Source	Findings
Phelan	2011	(65)	Pap and HPV pathology clinical screening results	178,510 Johns Hopkins Hospital Pathology records between 2001-2007	High uptake of reflex by 2007, co-test uptake remained low around 15% in 2008
Tatsas	2012	(66)	Pap and HPV pathology clinical screening results	Johns Hopkins Hospital Pathology records 2008-2010	Co-tests reached 40% by 2010, large differences in co-test rates by clinic
Cooper	2005	(57)	13 qualitative telephone focus groups asking about guideline knowledge and screening practices (self-report)	69 physicians in 17 states and DC	In 2002/2003, no physicians were familiar with NBCCEDP's (National Breast and Cervical Cancer Early Detection Program) trienniel Pap policy and none routinely extended intervals, even though policy had been in place for over a year at the time of study
Berkowitz	2010	(58)	Cross-sectional nationally representative survey using clinical vignettes for a 35 year old woman (self-report)	Nationally representative sample of 950 physicians	Most physicians (87.8%) did not adhere to guideline recommendations for mildly abnormal results or discordant results (45.7%), recommending more screening than necessary
Holland-Barkis	2005	(80)	Cross-sectional mailed survey to assess guideline knowledge and clinical vignettes to assess practice preferences (self-report)	136 physicians in a large university affiliated practice associated with an HMO in Central Texas	Based on vignette response, 57.4% of physicians were found to adhere to published guidelines, but wide variations exist; physicians were uncomfortable lengthening the interval

					in low-risk patients with negative screening history
Mathias	2012	(69)	Electronic health records of Pap tests and colposcopies	Non high-risk women 30-65 years with a normal Pap during 2007 at the Northwestern Medical Faculty Foundation Clinic	65.7% of women receive a Pap smear soon than recommended following a history of normal results in 2008 or 2009, with 25.3% receiving them in both years (instead of every 3)
Roland	2011	(62)	Cross-sectional nationally representative survey of self-reported screening practices and response to clinical vignettes	Nationally representative sample of 376 physicians	<15% of providers who ordered an HPV test recommended the next screen in 3 years, recommending 1 year instead in 3 clinical vignettes
Saraiya	2010	(63)	Mailed survey to a nationally representative sample of physicians	Representative sample of 950 primary care physicians	Fewer providers recommended extending intervals to 3 with an HPV co-test (19%) than with a Pap test alone (32%)
Meissner	2010	(59)	Nationally representative survey of physicians using a clinical vignette	Nationally representative sample of 1114 primary care physicians who perform Pap smears	32% of physicans had adopted a 3-year interval, factors associated with less frequent screening included serving a higher proportion of Medicaid patients
Lee	2011	(60)	Cross-sectional survey of a nationally representative sample of Pap test providers	376 office-based healthcare providers and 216 outpatient clinics	Of the providers who offer HPV testing (75%), 29% also used low-risk tests; Most providers performed co-testing in women under 30 and also performed HPV reflex after ASC-H and HSIL

Moriarty	2008	(61)	Used data from the College of American Pathologists Supplementary Questionnaire in 2006	679 laboratories	45% of labs offered low-risk HPV testing despite lack of clinicial signficance; many clinics used HR-HPV reflex testing used in non-recommended situations (ASC-H: 48%, LSIL: 28%, HSIL: 22%, AGC: 20%); Co-testing in women over 30: 25%
Yabroff	2009	(64)	Cross-sectional nationally representative survey assessing knowledge, attitudes, and practices related to cervical cancer screening using mailed questionnaire with clinical vignettes	Nationally representative sampler of 1212 primary care physicians	On a composite measure (combining all4 vignettes) ~20% had guideline consistent recommendations for screening frequency; large range by physician specialty and vignette-range: 25%-65% individual vignettes for women over 30
Shirts	2010	(67)	Retroactive analysis of laboratory test ordering patterns	454,532 HPV tests ordered between Sept 2003 and Oct 2009 from 110 laboratories	Decrease in non-recommended HPV testing among women under 30; only 6% of repeat HPV tests in women over 30 followed a 3-year interval
Thrall	2010	(68)	Computerized laboratory records for University of Rochester Medical Center were reviewed from Jan 1, 2006, to Dec 31, 2006	All (N=2719) Pap tests performed during 2006 at URMC with NILM results and HPV co-testing	Almost half of dual-negative women received another screen within 18 months, which is not consistent with guidelines (too frequent)

A nationally representative survey of women in the US in 2005 found that almost 80% thought a woman should have a Pap smear every year, but almost two-thirds were willing to extend screening to every three years if their provider recommended it (59).

Table 1.3: Summary of publications examining patient attitudes toward changes in cervical cancer screening *(see next page)*

Table 1.3: Summary of publications examining patient attitudes toward changes in cervical cancer screening

Author	Year		Study Design	Study Population or Data Source	Findings
Sirovich	2005	(70)	Random digit dialing telephone survey in 2002 about acceptance of less intense screening	Nationally representative sample of women age 40+ with no cancer history	75% of women preferred to be screened annually; less than half had heard about recommendations for less frequent screening; 69% would try to be screened annually even if heir doctor recommended less frequent screening
Dieng	2011	(79)	Structured telephone interview about testing preferences, information and decision making needs	Random sample of 1279 Australian women between 18 and 70 years	50%of women preferred having Pap smears at least annually, 38% every 2 years; 85% wanted concurrent HPV testing
Ashok	2012	(81)	Data from 2007 Health Information National Trends Survey (HINTS)	2915 female respondents between age 18-64	65% had been screened within 1 year; 81% of women expected to be screened again within a year
Huang	2008	(78)	Telephone and in-person interviews about awareness of HPV, preferences for HPV testing	865 diverse women between 50 and 80 years	60% wanted to be tested for HPV and another 15% would be tested if recommended by their physician; of those willing to be tested- 55% would accept 3 year intervals, 12% more would if recommended by doctor, remaining 33% would still want annual screening

Smith	2003	(71)	8 focus groups with semi-structured interviews to explore attitudes, beliefs and barriers to cervical cancer screening	58 diverse women over 18 years old	Women were not open to the idea of reducing Pap screening frequency because they perceive annual screening to be an effective screening method
Rolnick	1999	(75)	Mailed survey to random sample of women within a large health maintenance organization about Pap smear history and perceptions of the new guideline (trienniel screening)	673 women between ages 20-69	63% had no recollection of being informed about the guideline change, 14% responded positively to the change while 50% responded negatively
Sirovich	2004	(77)	Data from the National Health Interview Survey (NHIS), a cross-sectional population-based telephone survey	16467 women age 21 or older with no history of cancer	93% had at least 1 Pap smear, 55% were screened annually, 17% every 2 years, 16% every 3 years, 11% not regularly screened, (>70% screened more frequently than recommended)
Meissner	2010	(59)	Data from the 2005 Health Information Trends Survey (HINTS) a bienniel telephone survey	Nationally representative sample of 2206 women eligible for Pap screening	Women were more willing to follow a 3-year interval if the were older, less willing if they had personal/family cancer experience or followed an annual Pap test schedule
Cooper	2011	(82)	15 focus groups in 4 major US cities to understand their awareness and knowledge of screening and risk factors for gynecologic cancers	132 women aged 40-60	Some misunderstood about what a Pap test screens for and thought it was all-inclusive for other cancers, STDs, etc; strong emphasis on the benefit of early detection; Very few were aware of extended intervals, and when mentioned, many reacted negatively

Specific Aims

United States cancer screening guidelines are based on systematic reviews of the evidence conducted at the behest of professional medical and public health associations. Recently, evidence-based review standards have begun to give a proportionate weight to evaluation of the harms relative to benefits of a given cancer screening strategy. In this context**, screening guidelines have been revised for several cancers, including breast, prostate, and cervical cancer, often recommending *less* screening compared with previous guidelines**. Such evidence-based recommendations can be misinterpreted by the public as a means to ration care rather than to provide the safest and most effective screening strategy. Such **misperceptions by the targeted screening population regarding the policy change are significant barriers to rapid and effective translation of evidence-based guidelines to clinical practice.**

For cervical cancer, the most recent guidelines recommend routine screening every 3-5 years, which is at odds with the common practice of annual Pap smears. **In our study of perimenopausal women attending routine gynecological care in the US between 2008 and 2012, 80% believed cervical cancer screening should be performed at least once per year, and 50% were not willing to reduce the frequency of screening even if recommended by her physician.** We hypothesize that this reluctance to accept evidence-based guidelines will delay compliance with the revised cervical cancer screening guidelines, and that women expressing reluctance to accept extended screening intervals can be differentiated from women accepting revised guidelines according to the

following characteristics: a) more likely to have a higher perceived cervical cancer risk and 2) report a higher compliance with other prevention services (e.g., the worried well).

To address these hypotheses and to gain further insight into the attitudes and behaviors of patients which limit their compliance with screening guidelines, we propose the following specific aims:

SPECIFIC AIM 1: To examine trends in cervical cancer screening practices from 2001-2013 in a large academic medical center.

Using data from the Pathology Data Systems at Johns Hopkins Hospital, we will estimate temporal trends in choice of screening strategy (cytology alone or in combination with HPV DNA testing) and frequency of screening.

SPECIFIC AIM 2: To investigate the correlates of reluctance to adhere to revised guidelines, which recommend less frequent cervical cancer screening.

Using data collected in the HPV in Perimenopause (HIP) natural history study of women age 35-60 years, we will compare women who indicate willingness versus reluctance to accept a longer interval between cervical cancer screening tests by the following factors: demographics, age, health status, cervical cancer screening history, sexual history, perceived HPV and cervical cancer risk, and participation in preventive health programs. This cohort offers a unique opportunity to address this aim by allowing simultaneous evaluation of women's self-reported perceived risk

and their actual risk of cervical cancer based on intensive measurement of HPV and cervical cancer risk markers over a 2-year period.

Evidence-based recommendations are valuable only if broadly implemented in routine clinical and public health practice. However, **key components to effective translation, including the perceptions and acceptance of screening recommendations, are often absent from the evidence. This proposal is designed to address this gap by using mixed methods to provide a comprehensive assessment of the uptake of recommendations in a large academic medical center and identify potential patient-specific characteristics which may affect efficient translation.** We will provide much needed data on psychosocial impact of changes in screening guidelines, which are critical to patient-centered outcomes evaluation.

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Chapter 2: HPV test utilization increasing in routine screening of women over age 30 years: results from surveillance in a large academic medical system

Abstract:

Objective: HPV DNA tests have been approved for routine use for over a decade, and their use will likely continue to increase. As the newest evidence suggests they are the superior screening method, eventual displacement of Pap by HPV testing as a primary screening method is possible. Thus, it is important to evaluate not just patterns of use, but also whether there is population variability in HPV test utilization. In this analysis, we describe the uptake of co-testing in Johns Hopkins Hospital System affiliated clinics between 2006 and 2013 as well the correlates of receiving an HPV co-test during this period.

Methods: This analysis included 55,575 Pap and HPV test records from 27,035 women screened through from the Johns Hopkins Hospital (JHH) Pathology Data System (PDS) between 2006 and 2013. Using this data, we estimated co-test uptake by year and by clinic. Prevalence ratios for co-testing by age and race by insurance categories were calculated by time period using adjusted multivariate log-binomial models with robust standard errors. To account for the clustering of observations within clinics, these same models were run with the addition of a random-effect variable for clinic.

Results: Co-test rates increased from below 10% in 2006 to a mid-year peak of 78% in 2013. Despite high rates of co-testing in recent years, the distribution of co-test uptake among clinics and subgroups varied across the entire period. Co-testing proportions were highest among younger women, black women, and women with Medicaid. Furthermore, rates of co-testing were consistently higher among black women for all insurance types

other than Tricare. Once the model was further adjusted for the difference in clinic-level practices using a cluster term, we no longer saw an effect of age, race, or insurance on co-test prevalence. The initial differences seem to be largely explained by demographic differences among clinics with higher co-test frequencies than those with lower frequencies.

Conclusion: In the earlier time periods, a greater proportion of the predominantly black clinics had high rates of co-testing, indicating that these clinics may be earlier adopters of co-testing as compared to the predominantly white clinics. This difference by race and insurance type clustered within clinics, and demographic differences between clinics with higher versus lower co-test frequency appear to be a potential explanation for these differences. These clinic level differences attenuated significantly over time, suggesting that clinics with underserved minority and government insured populations were the earliest adopters of co-testing.

Introduction

Rates of cervical cancer in the United States have dropped by over 50% in the last 30 years due to a high proportion (>80%) of women participating in routine Pap smear screening programs (1, 2). As scientific knowledge regarding the natural history of cervical cancer, and its necessary cause- the human papillomavirus (HPV) have evolved, guidelines for these screening programs have changed to incorporate the new science. The first HPV DNA test was approved by the FDA in 2003 for use in routine cervical cancer screening for women over age 30, and was incorporated into select screening recommendations soon after (3-6).

Previous studies have shown that uptake of HPV testing as a reflex for mildly abnormal Pap smears occurred rather quickly, with almost complete adoption in some locations within 5 years (7-9). However, following the FDA approval of the Digene hc2 test for co-testing women over 30 years of age, the addition of HPV testing to Pap smear screening visits occurred much more slowly, with reports of less than 40% uptake in 2010 (9-11). In 2012, several professional screening organizations revised their screening guidelines to emphasize both HPV testing and the need for less frequent screening. In their joint guidelines, the American Cancer Association (ACS), American Society for Colposcopy and Cervical Cytology (ASCCP), and American Society for Clinical Pathology (ASCP) as well as the American College of Obstetricians and Gynecologists (ACOG) all recommended Pap/HPV co-testing with a 5-year screening interval as the preferred screening method (12, 13). Likewise, in 2012, the US Preventive Services Task Force (USPSTF) also issued revised screening guidelines that

recommended cytology every three years or co-testing every 5 years for woman who want a longer screening interval (14). More recently, the FDA approved the Roche Cobas HPV test for an additional indication of primary, stand-alone cervical cancer screening (15).

Now that HPV DNA tests have been approved for routine use for over a decade, their use will likely continue to increase. As the newest evidence suggests they are the superior screening method, eventual displacement of Pap by HPV testing as a primary screening method is possible. Thus, it is important to evaluate not just patterns of use, but also whether there is population variability in HPV test utilization. In this analysis, we describe the uptake of co-testing in Johns Hopkins Hospital System affiliated clinics between 2006 and 2013 as well the correlates of receiving an HPV co-test during this period.

Methods

Data source and data collection

This analysis used data obtained from the Johns Hopkins Hospital (JHH) Pathology Data System (PDS), and included all Pap smear and HPV tests processed by the Pathology Department between January 1, 2001 and May 28, 2013. PDS is an in-house clinical database routinely used by the Pathology Department to collect and store test results. It contains results of any sample processed by the Hopkins Pathology Department, which receives samples from over 200 clinics in and around the Baltimore area. Records were

obtained through a data use agreement with Johns Hopkins Hospital Systems, and a limited dataset was created to replace medical record numbers with a unique patient identifier. The dataset included a patient identifier, patient age, race, insurance type, date of sample collection, date of test, test result, diagnosis, ordering physician and clinic where the patient was seen. All study procedures were approved by the Johns Hopkins Bloomberg School of Public Health Institutional Review Board.

Pap smear and HPV test results were extracted from the free text diagnosis variable by searching for expressions or strings of words. For this analysis, all Pap smear results were coded as normal (or no intraepithelial lesion or malignancy, NILM), atypical squamous cells of undetermined significance (ASCUS), low-grade squamous intraepithelial lesion (LSIL), atypical squamous cells- cannot rule out high grade lesion (ASC-H), high-grade squamous intraepithelial lesion (HSIL), carcinoma (cancer), or atypical glandular cells (AGUS) based on the most severe diagnosis in the text field. HPV testing was performed using the Digene hc2 test according to manufacturer's instructions (Qiagen, Gaithersburg, MD) and results coded as negative (relative light unit (RLU) <0.85), equivocal (RLU 0.85-3.0), or positive (RLU >3.0).

Statistical Analysis

We received all Pap smear and HPV test results in PDS processed between January 1, 2001 and mid-2013 (N=306,722 records), and then applied several restrictions to the data as described in Figure 2.1. For the initial data cleaning step, we eliminated records with male or unknown sex, samples collected prior to January 1, 2001, duplicate records, and

records without a Pap smear result. We then restricted our dataset to include only samples collected from clinics likely to be performing routine screening (excluding specialty locations such as colposcopy and HIV clinics). Given our aim of estimating HPV co-test uptake, we performed our analysis only among women of routine screening age who were eligible for HPV co-testing (ages 30-65), starting in 2006 when co-test prevalence first began to increase.

Insurance was characterized by type of provider: private (including HMOs, PPOs, Blue Cross), Medicare, Medicaid, and Tricare (military), and any records without an insurance code or with an insurance code that could not be verified were excluded. To eliminate any HPV testing as a follow-up to a prior abnormal result and not as part of routine screening, we restricted our analyses to routine screening tests, which were defined as a test performed at least 300 days after a prior screen. This restriction necessarily meant that only women with at least 2 records were included in this analysis. Additionally, because there was no consistent code to indicate whether a co-test was ordered, we restricted the analysis to normal Pap results where there would be no other indication for HPV testing other than as a co-test, and thus co-tests were defined as any visit with a negative Pap smear that included an HPV test, and 92.6% of screening records fell into this category.

The percent of all screening visits that included a co-test were calculated by year, age, race, and insurance category, and were stratified by time period. Percent co-testing and percent black race at each clinic were calculated and graphed by time period, with scaling

of circle size according to the number of screening tests performed at each clinic. Prevalence ratios for co-testing by age and race by insurance categories were calculated by time period using adjusted multivariate log-binomial models with robust standard errors. To account for the clustering of observations within clinics, additional models were run including a random-effect variable for clinic. All analyses were performed in Stata 13.1 (College Station, TX).

Results

Population Characteristics

The restricted dataset for this analysis included 55,575 records from 27,035 women of routine screening age who were eligible for HPV co-testing (30 to 65 years of age) between 2006 and mid-2013 (Table 1). These women had a median age of 47 years (interquartile range (IQR): 38-55). Overall, this group was 51% white, 36% black, and 13% other races. Seventy percent had private insurance, 8% had Medicare, 13% Medicaid, and 10% had Tricare (military) insurance.

Uptake of Pap/HPV co-testing instead of cytology alone

Following the approval of HPV co-testing for use in routine screening, initial uptake of co-testing in the Johns Hopkins System was low (below 5% through 2005), but it has significantly increased since that time (Figure 2.2). Co-testing increased almost 9-fold, from 8.85% in 2006 to 78.35% in mid-2013. The overall proportion of co-testing during

this time was about 35%, but the distribution of co-test uptake among subgroups varied across the entire period. Co-testing proportions were highest among younger women, black women, and women with Medicaid. Furthermore, rates of co-testing were consistently higher among black women for all insurance types other than Tricare.

To account for the significant effect of time on co-test uptake, we stratified our data into 3 time periods based on the recommendations in place at that time: 2006-2008 was when co-testing was first incorporated into guidelines and so co-test use was low (5-25%), 2009-2011 was when guidelines continued to add co-testing to their recommendations and co-test use was moderate (25-50%), and 2012-2013 when the new consensus guidelines were put in place and co-testing rates increased (>50%). While differences in the distribution of co-testing among sub-groups remained through each time period, the magnitude of those differences diminished with time as co-testing became more prevalent overall (Table 2.1). The average percent of co-test samples during the 3 time periods were 12.61%, 42.18%, and 61.25%, respectively.

Despite this overall trend of increasing rates of co-testing in this system, tremendous variability existed on a clinic-by-clinic basis (Figure 2.3). There were clinics in the earliest years with rates over 50% and clinics in the most recent years with rates of co-testing remaining below 10% in some clinics, while reaching almost 100% in others. We explored whether these differences in clinic practices could account for the differences seen among sub-groups by examining the distribution of race by clinic (Figure 2.3). In addition to showing the general trends of increasing co-test uptake, they also demonstrate

that uptake differed by racial make-up of the clinics. In all three time periods, a greater proportion of the predominantly black clinics had high rates of co-testing, indicating that these clinics may be earlier adopters of co-testing as compared to the predominantly white clinics.

Prior to accounting for clinic-level differences, co-test prevalence decreased significantly by age, even after mutually adjusting for the effects of race and insurance, with older women less likely to be co-tested than younger women. However, the differences by age decreased over time (Table 2.2). Once the model was further adjusted for the difference in clinic-level practices using a cluster term, we no longer saw an effect of age on co-test usage. Similar findings were seen for the insurance by race categories—while significant differences were seen among many of these categories, most notably in the earliest time period, those differences diminished over time, and seem to be largely explained by demographic differences among clinics with higher co-test frequencies than those with lower frequencies.

Discussion

Cervical cancer screening recommendations have had to evolve over the last fifteen years to keep pace with scientific knowledge and technologic advancements. First, there was the addition of ViraPap to conventional cytology, then the transition to liquid-based cytology and more recently the incorporation of HPV DNA testing, as either a reflex or co-test (and soon as a primary test) (3, 4, 6, 16). While screening guidelines are an important driver of clinical practice, they are not a mandate. Despite the fact that the

recommendations in the cervical cancer screening guidelines are based on strong evidence from randomized controlled trials comparing cytology alone to HPV co-testing(9, 10) , providers faced with choosing between these options are calling for more direct "real-world" evidence of the harms and benefits of alternative screening strategies (17, 18). To meet this demand, it is critical to first estimate the proportion of screening by each strategy and eventually the harms and benefits which result from them in actual practice. We have been tracking the uptake of co-testing with the Johns Hopkins Hospital Pathology Data Systems since 2001. Our prior analysis showed a rapid increase in co-test frequencies in women 30 years and older in 2009, reaching a plateau at approximately 40% by mid-2010. The current analysis, which extends to May 2013, demonstrates a second wave of co-test increase beginning in 2012, to a mid-year peak of 78% in 2013. Here, we expand upon these analyses and examined correlates of co-test use by key demographic and clinic characteristics. In time periods with less than 25% co-testing, a significantly higher frequency of co-testing was observed in women of black race and women with non-private medical insurance. This difference by race and insurance type clustered within clinics, and demographic differences between clinics with higher versus lower co-test frequency appear to be a potential explanation for these differences. Those clinic level differences attenuated significantly over time, suggesting that clinics with underserved minority and government-insured populations were the earliest adopters of co-testing.

The overall increasing trend in co-testing frequency, however, masks substantial heterogeneity in practices between clinics within this single system. Even in 2013, when

on average 78% of all tests included a co-test, some clinics still had rates below 10%. Furthermore, rates of co-testing by clinic did not increase universally. While the majority of the clinics showed trends of increased co-testing, 4 of the 24 clinics with data in all three time periods did not. These clinics only performed a small number of screening tests, however, and so we are uncertain of the significance of the observed decline in co-testing over time. Nonetheless, the stark contrast in co-test rates among clinics in this hospital system strongly illustrates the importance of clinic-wide policies in driving routine clinical practice. Over the three time periods examined, the proportion of clinics that co-tested over 75% of patients increased from under 10% to almost 50%, while the proportion of clinics co-testing <25% of patients decreased from over 60% to about 20%. This finding is promising as providing a potentially impactful method to change medical practice on a larger scale than targeting individual patients or providers. Like those of Tatsas et al., our results support the effectiveness of a top-down approach to making a policy change for the entire clinic, such that in the clinic where a decision to implement co-testing was decidedly put in place, rates appeared to quickly increase to almost complete compliance (10).

Understanding the uptake of new technologies and changes to screening recommendations into routine clinical practice is an important step in streamlining implementation for future changes and ensuring that preventive healthcare is delivered as appropriately and effectively as possible. Although we lacked a clear indication of which screening tests were ordered, by restricting our analysis to normal Pap results, we ensured that all HPV tests included would have been ordered as a co-test and not as a reflex test.

Furthermore, by defining a screening test as at least 300 days from a prior test, we aimed to eliminate most follow-up visits of a prior abnormal result, and could therefore more clearly look at co-test use in routine screening. Importantly, this study utilized clinical practice data from a large medical system that includes a diversity of clinics and patients, providing direct evidence about how screening is occurring in a real world setting, not relying on self-report or vignette data as is frequently the case (10, 19-25).

Our results suggest that while co-test prevalence has increased significantly over the last several years, these decisions appear to cluster at the practice-level not the system-level, and so tremendous variability exists on a clinic-by-clinic basis. While this analysis is an important first step in assessing adoption of screening technologies, it only focused on those patients for whom co-testing is recommended—those aged 30-65 years. However, studies have shown inappropriate use of screening and HPV tests in woman younger than 30, women older than 65, and women with hysterectomies (8, 10, 19-21, 25, 26). Furthermore, the addition of HPV testing is only part of the screening recommendation, meant to go alongside a corresponding reduction in screening frequency because of the greater negative predictive value of using both tests. As co-testing has now become the norm in many clinics, an important next step will be to explore whether screening intervals are simultaneously being extended, since increases in co-testing frequency without corresponding interval lengthening may result in increasing, rather than decreasing, costs to patients and the health care system.

Figure 2.1: Sample size flowchart

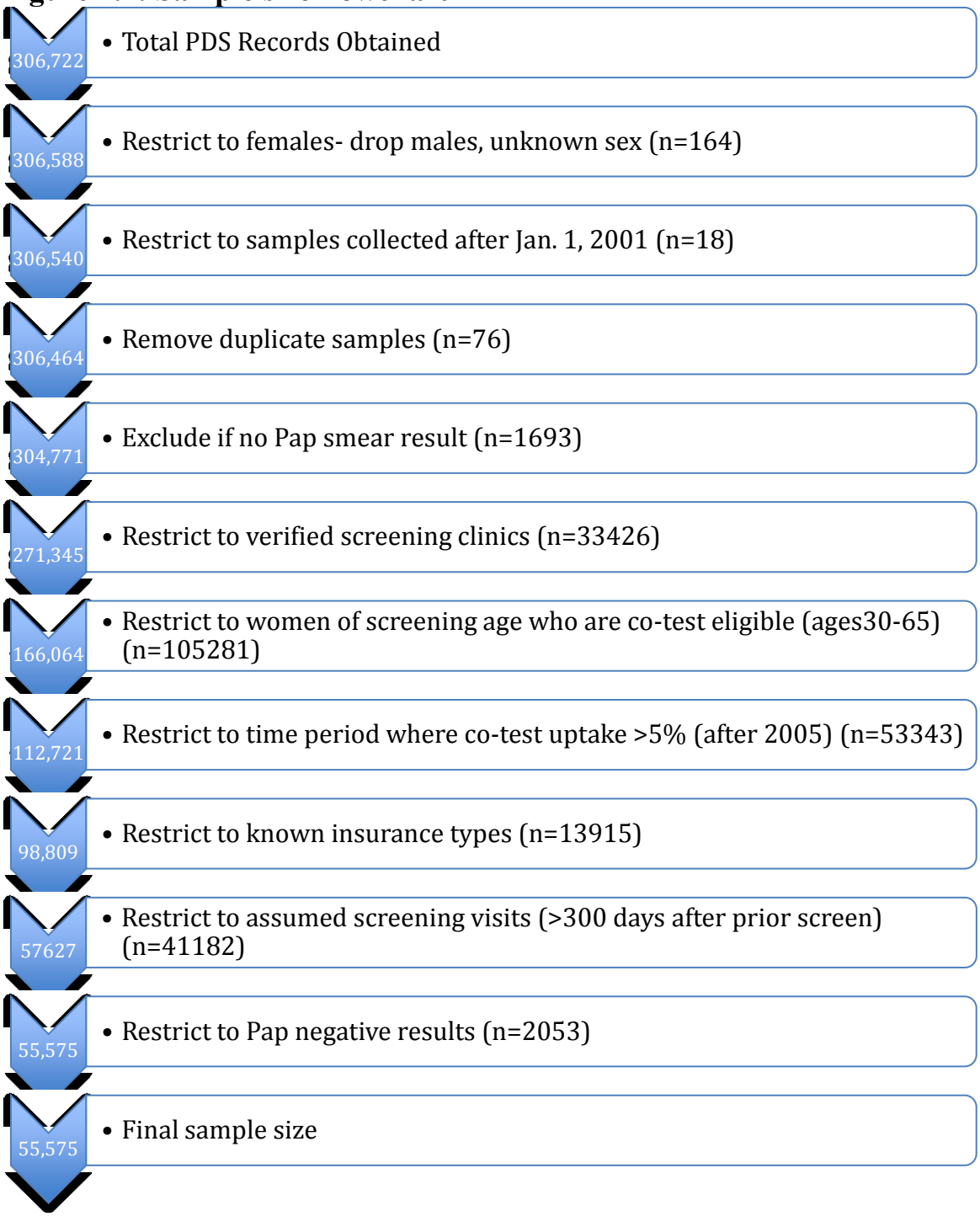


Figure 2.2: Co-test uptake by year

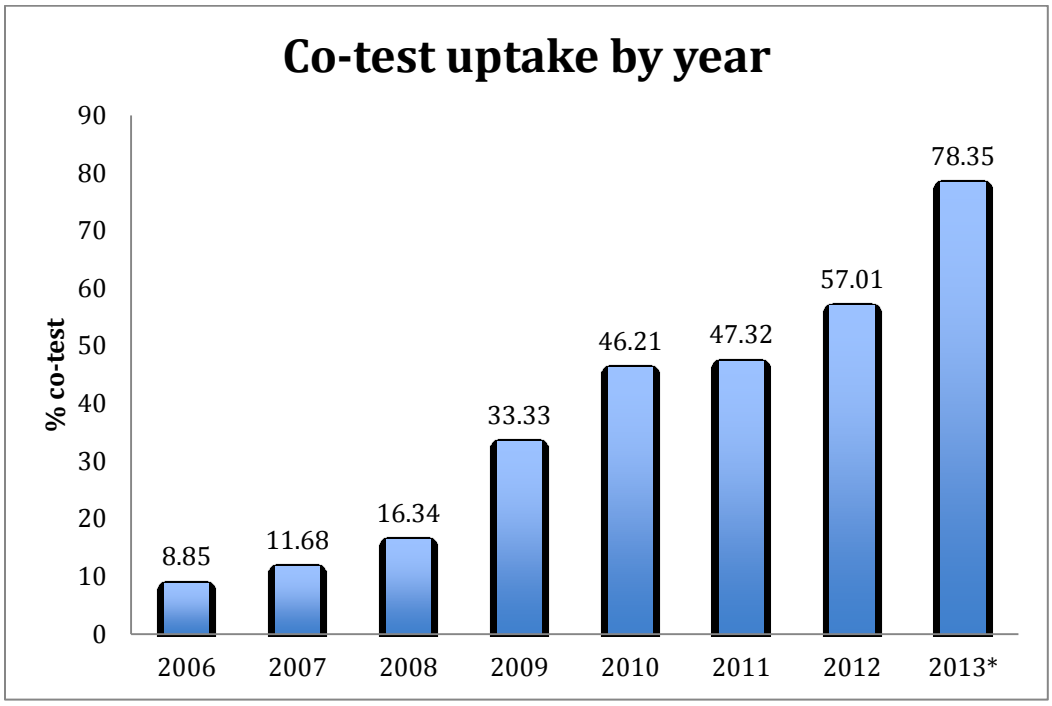


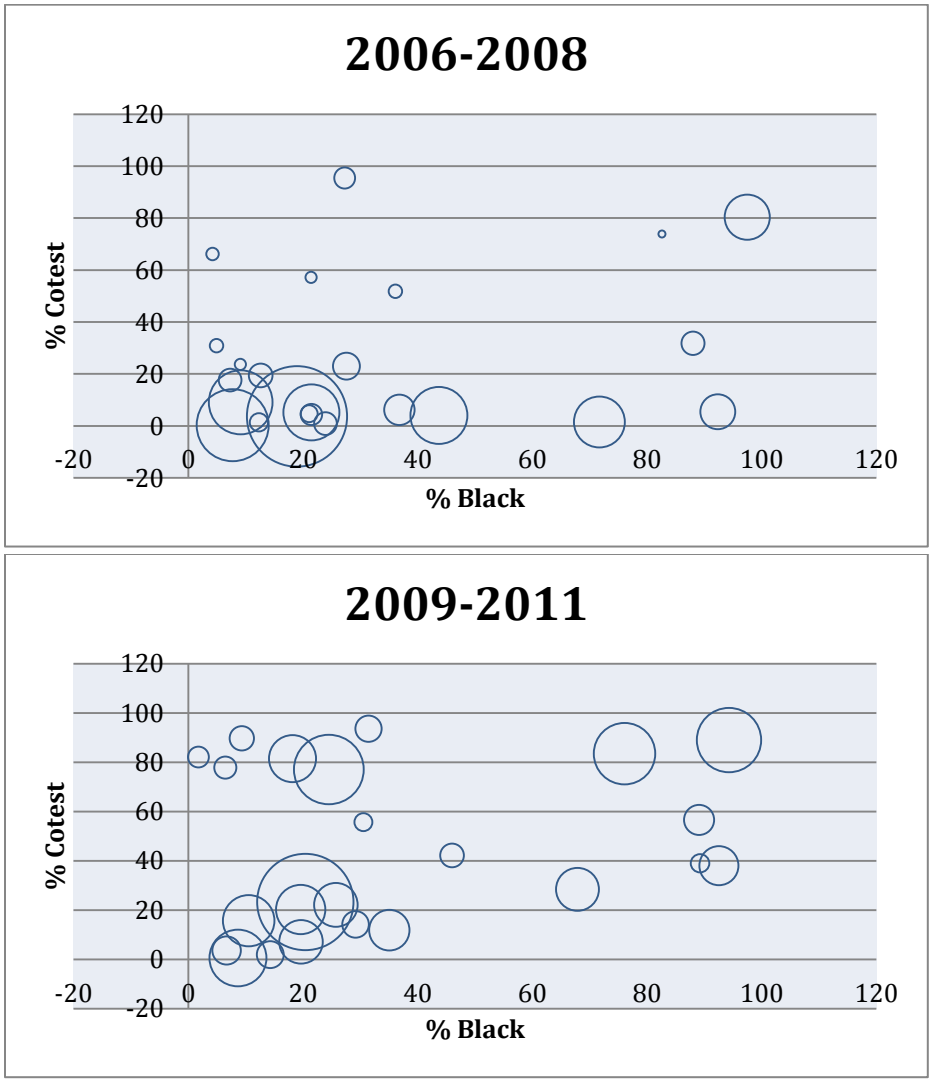
Table 2.1: Demographics and distribution of co-testing (N=55575)

	Total Population		Population Co-tested		2006-2008		2009-2011		2012-2013	
	N	%	N cotested	% cotested	N cotested	% cotested	N cotested	% cotested	N cotested	% cotested
Age										
30-39	16527	29.74	6458	39.08	5459	15.19	7654	45.96	3414	61.83
40-49	15831	28.49	6045	38.18	5728	14.8	7295	46.91	2808	63.21
50-59	15302	27.53	4711	30.79	6015	10.36	6821	38.09	2466	60.42
60-65	7915	14.24	2031	25.66	3327	8.69	3458	31.93	1130	56.46
Race										
White	28324	50.97	7442	26.27	11638	7.61	12417	33.11	4269	57.27
Black	20063	36.1	9461	47.16	6855	22.7	9143	56.52	4065	67.33
Other	71888	12.93	2342	32.58	2036	7.22	3668	37.16	1484	56.06
Insurance										
Private	38644	69.53	12241	31.68	14747	9.32	16955	38.61	6942	62.24
Medicare	4334	7.8	1219	28.13	2253	13.05	1581	39.78	500	59.2
Medicaid	7128	12.83	3783	53.07	1863	32.27	3509	57.74	1756	62.64
Tricare (Military)	5469	9.84	2002	36.61	1666	15.85	3183	45.27	620	47.9
Insurance by Race										
Private- White	21928	39.46	5576	25.43	9021	6.34	9384	31.02	3523	59.41
Private- Black	11706	21.06	5027	42.94	4193	17.2	5194	52.81	2319	67.4
Private- Other	5010	9.01	1638	32.69	1533	5.28	2377	37.53	1100	60.45
Medicare- White	2308	4.15	379	16.42	1343	6.33	764	24.87	201	51.74
Medicare- Black	1825	3.28	795	43.56	818	25.06	734	56.4	273	64.47

Medicare- Other	201	0.36	45	22.39	92	4.35	83	30.12	26	61.54
Medicaid- White	930	1.67	318	34.19	247	15.38	473	39.75	210	43.81
Medicaid- Black	5651	10.17	3318	58.72	1525	39.8	2736	64.22	1390	68.63
Medicaid- Other	547	0.98	147	26.87	91	13.19	300	27	156	34.62
Tricare- White	3158	5.68	1169	37.02	1027	18.6	1796	45.77	335	46.57
Tricare- Black	881	1.59	321	36.44	319	7.21	479	53.03	83	53.01
Tricare- Other	1430	2.57	512	35.8	320	15.62	908	40.2	202	48.02

*2013 includes visits through May 28, 2013

Figure 2.3: Distribution of % co-test and % black race by clinic size over time



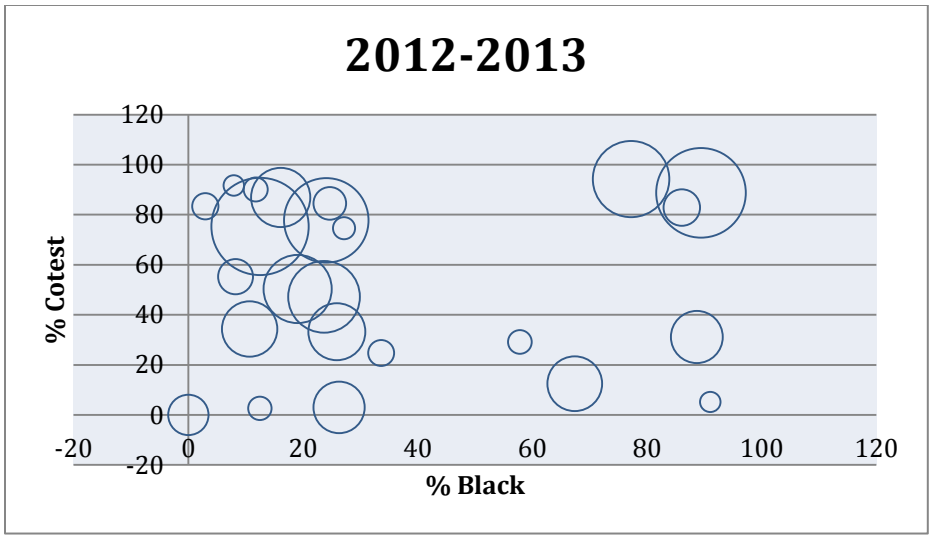

2012-2013
120
100
80
60
40
20
0
-20
% Cotest
-20
0
20
40
60
80
100
120
% Black

Table 2.2: Correlates of co-testing by demographics with and without clinic adjustment

	2006-2008		2009-2011		2012-2013	
	aPR1 (95% CI)	aPR2 (95% CI)	aPR1 (95% CI)	aPR2 (95% CI)	aPR1 (95% CI)	aPR2 (95% CI)
Age						
30-39	1	1	1	1	1	1
40-49	1.05 (0.97-1.14)	1.04 (0.97-1.10)	1.04 (1.01-1.08)	1.02 (0.99-1.04)	1.03 (0.99-1.07)	0.99 (0.96-1.03)
50-59	0.88 (0.80-0.97)	1.01 (0.95-1.09)	0.92 (0.88-0.95)	1.01 (0.98-1.03)	0.99 (0.95-1.04)	0.98 (0.94-1.03)
60-65	0.72 (0.63-0.84)	1.03 (0.94-1.14)	0.83 (0.78-0.88)	1.00 (0.95-1.04)	0.94 (0.89-1.00)	0.96 (0.89-1.04)
Insurance by Race						
Private- White	1	1	1	1	1	1
Private- Black	1.23 (0.96-1.56)	1.18 (0.76-1.81)	0.87 (0.77-1.00)	0.94 (0.88-1.01)	0.89 (0.78-1.02)	1.03 (0.93-1.14)
Private- Other	2.34 (1.73-3.17)	1.00 (0.86-1.17)	1.24 (1.10-1.39)	1.05 (0.97-1.15)	0.73 (0.63-0.85)	1.00 (0.93-1.08)
Medicare- White	3.02 (2.60-3.51)	1.09 (0.99-1.19)	1.46 (1.38-1.55)	1.01 (0.97-1.06)	0.78 (0.70-0.88)	0.77 (0.59-1.00)
Medicare- Black	2.62 (3.60-2.90)	0.91 (0.82-1.01)	1.65 (1.58-1.72)	1.06 (1.02-1.11)	1.13 (1.08-1.17)	1.10 (1.06-1.14)
Medicare- Other	4.31 (3.71-5.00)	0.89 (0.79-1.00)	1.84 (1.72-1.98)	1.07 (1.00-1.15)	1.09 (0.99-1.19)	1.12 (1.04-1.22)
Medicaid- White	5.94 (5.36-6.58)	0.92 (0.83-1.01)	1.98 (1.89-2.07)	1.11 (1.05-1.18)	1.14 (1.09-1.20)	1.13 (1.07-1.20)
Medicaid- Black	1.15 (0.77-1.72)	0.79 (0.54-1.15)	1.67 (1.53-1.83)	0.99 (0.93-1.05)	0.89 (0.72-1.09)	0.91 (0.69-1.17)
Medicaid- Other	0.81 (0.64-1.01)	0.89 (0.75-1.06)	1.17 (1.10-1.25)	1.00 (0.96-1.04)	1.01 (0.96-1.07)	1.05 (1.00-1.09)
Tricare- White	0.82 (0.31-2.15)	0.65 (0.29-1.44)	1.05 (0.76-1.46)	0.99 (0.81-1.21)	1.05 (0.77-1.42)	1.16 (0.97-1.38)
Tricare- Black	1.96 (1.15-3.45)	1.89 (1.07-3.35)	0.83 (0.69-1.00)	1.16 (1.02-1.32)	0.58 (0.47-0.72)	1.04 (0.90-1.19)
Tricare- Other	2.40 (1.84-3.14)	1.13 (0.91-1.38)	1.27 (1.16-1.38)	1.01 (0.96-1.07)	0.80 (0.69-0.93)	0.90 (0.81-1.00)

*aPR1 includes age, race insurance adjustment
aPR2 – also includes clinic level adjustment

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Chapter 3: Cervical cancer screening intervals following cytology and Pap/HPV co-testing in women over age 30 years: results from surveillance in a large academic medical system

Abstract:

Objective: Cervical cancer screening guidelines have been revised several times over the last decade, and now emphasize evidence-based medicine, resulting in recommendations for less frequent screening for both cytology alone and Pap/HPV co-testing. Following these changes, few studies have reported the time to next screening test following a normal result over time. Here we estimate the length of time from a baseline screening test with normal results conducted between 2006 – 2010 to the next screening test. In addition, we compare the interval between screens following a normal baseline test by age, race, and insurance to evaluate the predictors of use of extended screening intervals in clinical practice over time.

Methods: This analysis included 31,701 Pap and HPV records from 18,048 women screened through from the Johns Hopkins Hospital (JHH) Pathology Data System (PDS) between 2006 and 2010. Median time to next visit along with corresponding 95% confidence intervals for were calculated by cytology alone vs co-test, year of screening, age, race, and insurance. Hazard ratios and 95% confidence intervals for time to next screening test by cytology alone and co-testing were estimated using Cox proportional hazards models. To account for the clustering of observations these same models were run with the addition of a random effects term for clinic.

Results: Little change was seen over time in screening interval following cytology screening alone—the median time to next screening test remained between 1.4 and 1.5

years from 2006-2010. However, we found an increase in the median time to next screening visit following a normal co-test result, with intervals increasing from about 1.5 years in 2006/2007 when broader co-test uptake began to just over 2.5 years in 2010 when 45% of screens included an HPV test. These changes were not uniform as several differences in the median times to next screen were found among some of the age, race, and insurance subgroups.

Conclusion: No increases were seen in time to next screening test following a normal Pap smear, remaining at half the length of the recommended interval. Following a co-test, there was a steady increase in screening interval length over time, approaching 3 years, which was the recommendation since at least 2003. However, more time will be needed before we will be able to assess whether the most recent recommendation of 5-year intervals after a dual negative co-test issued in 2012 is being followed. Additionally, reasons for the differences we found by age, race and insurance, must be understood and corrected rapidly to prevent a widening of the disparities already seen in cervical cancer screening, diagnosis, and treatment outcomes.

INTRODUCTION

Routine Pap smear screening programs in the United States have reduced rates of cervical cancer by over 50% in the last 30 years due to the high proportion (>80%) of women screened (1, 2). Recently, professional medical and public health organizations have begun to undertake evidence-based reviews of cancer screening guidelines, evaluating the harms relative to the benefits for each strategy. These reviews led to revised guidelines for several cancers, often recommending less screening compared with previous guidelines. In the past, there had been a lack of uniformity in the cervical cancer screening guidelines issued by different professional organizations. However, in 2012, the US Preventive Service Task Force (USPTF), American Cancer Association (ACS), American Society for Colposcopy and Cervical Cytology (ASCCP), and American Society for Clinical Pathology (ASCP) issued updated consensus guidelines for cervical cancer screening. These guidelines reemphasized the need for less frequent screening after a normal result, recommending screening either once every 3 years for cytology alone or once every five years after Pap/HPV co-testing (3, 4). In their joint guidelines, the ACS, ASCCP, and ASCP specifically recommend against routine annual screening (3).

As screening recommendations have evolved several times over the last decade, it is not immediately clear what guidelines are currently being followed (3, 5). There is no mandate for providers to adhere to evidence-based guidelines, and there is ample evidence to suggest a lack of adherence to the published guidelines. Both focus groups and nationally representative surveys of physicians have shown that doctors frequently

recommend cervical cancer screening more often than indicated by the guidelines (6-8). Most of the previous studies about physician knowledge and adherence to guidelines have been based on self-report or response to vignettes and not on actual clinical practice (6-12).

Two recent studies of a large academic medical center showed slow uptake of new screening practices, and within this single institution, rates of co-testing varied greatly by clinic (Chapter 2, 13, 14). Similar trends were seen in data from other reference laboratories and academic primary care settings (15, 16), with one study showing that 66% of women who were eligible for extended screening intervals had unnecessary screening tests performed between 2008 and 2009 (17). However, few studies have reported the time to next screening test following a normal result over time. In this study, we estimate the length of time from a normal baseline screening test conducted between 2006 – 2010 until the next screen (screening interval). We also compare the screening interval by age, race, and insurance in order to evaluate the predictors of adherence to extended screening intervals in clinical practice over time.

Methods

Data source and data collection

This analysis used data obtained from the Johns Hopkins Hospital (JHH) Pathology Data System (PDS), and included all Pap smear and HPV tests processed by the Pathology Department. PDS is an in-house clinical database routinely used by the Pathology

Department to record and store test results. It contains the results from any sample processed by the Hopkins Pathology Department, which receives samples from over 200 clinics in and around the Baltimore area. Records were obtained through a data use agreement with Johns Hopkins Hospital Systems, and a limited dataset was created to replace medical record numbers with a unique patient identifier. The dataset included a patient identifier, patient age, race, zip code, insurance type, date of sample collection, date of test, test result, diagnosis, ordering physician and clinic where the patient was seen. All study procedures were approved by the Johns Hopkins Bloomberg School of Public Health Institutional Review Board.

Pap smear and HPV test results were extracted from the free text diagnosis variable by searching for expressions or strings of words. For this analysis, all Pap smear results were coded as normal (or no intraepithelial lesion or malignancy, NILM), atypical squamous cells of undetermined significance (ASCUS), low-grade squamous intraepithelial lesion (LSIL), atypical squamous cells- cannot rule out high grade lesion (ASC-H), high-grade squamous intraepithelial lesion (HSIL), carcinoma (cancer), or atypical glandular cells (AGUS) based on the most severe diagnosis in the text field. HPV testing was performed using the Digene hc2 test according to manufacturer's instructions (Qiagen, Gaithersburg, MD) and results coded as negative (relative light unit (RLU) <0.85), equivocal (RLU 0.85-3.0), or positive (RLU >3.0).

Statistical Analysis

We received all Pap smear and HPV test results in PDS processed between January 1, 2001 and May 28, 2013, which was a total of 306,722 records, and then applied several restrictions to the data (Figure 3.1). In brief, for the initial data cleaning step, we eliminated records with male or unknown sex, samples collected prior to January 1, 2001, duplicate records, and records without a Pap smear result. We then restricted our dataset to include only samples collected from clinics likely to be performing routine screening (i.e., excluding specialty locations such as colposcopy and HIV clinics). We performed our analysis only among women of routine screening age who were eligible for HPV co-testing (ages 30-65), between January 1, 2006 when co-test prevalence first begins to increase and May 1, 2010 to allow for at least three years of follow-up. This resulted in a final sample size of 31,701 records from 18,048 women.

Insurance was characterized by type of provider: private (including HMOs, PPOs, Blue Cross), Medicare, Medicaid, and Tricare (military), and any records without an insurance code or with an insurance code that could not be verified were excluded. To eliminate any HPV testing as a follow-up to a prior abnormal result and not as part of routine screening, we restricted our analyses to tests performed at least 300 days after a prior screen. This restriction necessarily meant that only women with at least 2 records were included in this analysis. Additionally, because there was no consistent code to indicate whether a co-test was ordered, we restricted the analysis to normal Pap results where there would be no other indication for HPV testing other than as a co-test. Thus, co-tests were defined as any visit with a negative Pap smear that included an HPV test, and 92.6% of screening records fell into this category.

Median times to next routine screening visit, along with corresponding 95% confidence intervals were calculated and graphed by cytology alone vs co-test, year of screening, age, race, and insurance. Hazard ratios and 95% confidence intervals for time to next screening test for cytology alone and co-testing were estimated using Cox proportional hazards models. To account for the clustering of observations within clinics, these models were also run with the addition of a random effect term for clinic. All analyses were performed in Stata 13.1 (College Station, TX).

RESULTS

Population Characteristics

The women included in this analysis had a median age of 48 years (interquartile range (IQR): 39-56). Overall, this group was 55% white, 34% black, and 11% other races. Seventy percent had private insurance, 10% had Medicare, 10% Medicaid, and 10% had Tricare (military) insurance.

Temporal changes in screening intervals

Little change was seen over time in screening intervals following cytology screening alone—the median time to next screening test remained between 1.4 and 1.5 years from 2006-2010 (Figure 3.2). During this time, the proportion of screening tests that were co-tests increased from 10% in 2006 to almost 50% by 2010. We observed an increase in

the time to next screening test concomitant with temporal increases in co-test usage. Screening intervals following dual negative co-tests increased from around 1.5 years in 2006 to 2.5 years in 2010 (Figure 3.2).

Age-specific screening intervals

Overall, only small differences (<3 months) were seen between age groups following cytology alone (Figure 3.3a). Additionally, little change was seen in intervals across all age groups over time following a negative Pap smear, with medians staying between 1.2 and 1.7 years throughout this time period. Following cytology alone, the longest interval was seen among the oldest women, but only reached 1.6 years in 2010, only half as long as the currently recommended interval. On the other hand, increases in median intervals were seen among all age groups receiving co-tests between 2006 and 2010, increasing from just under 1.5 years to 2.5 years for the youngest women and larger increases from 1.75 years to 3.2 years for the oldest women (Figure 3.3b). Younger women (age 30-39) had consistently shorter median intervals than older women following a dual negative co-test, with this difference reaching a whole year at some points. All ages saw an increase in intervals to at least every 2 years after co-testing, with the oldest women actually meeting at least a 3-year interval.

Race and insurance-specific screening intervals

Here we focused only on the differences between black and white race as the other race category was small and too heterogeneous to draw meaningful conclusions

(Supplementary Table S3.1). White women returned slightly sooner than black women following cytology alone (Figure 3.4a), with medians remaining generally remaining under 1.5 years for both races. Conversely, following a co-test, black women returned sooner than white women (Figure 3.4b), with white women seeing a larger increase over this time period with intervals reaching almost 3 years (2.84, 95% CI: 2.66-3.02), while black women saw a much smaller increase, only reaching 2 years by 2009 (2.03, 95% CI: 1.88-2.18).

Differences were also seen by insurance type, such that women on Medicaid had the longest interval following cytology alone, but the shortest following a co-test (Figure 3.5a and 3.5b). Among women screened by cytology alone, no change in interval was seen for private insurance (average of 1.4 years) or Medicaid (average of 1.8 years). However, increases following negative cytology alone were seen for both Tricare and Medicare, each changing from 1.4 years in 2006 to about 2 years in 2010 (Figure 3.5a). Unlike the cytology results, little change was seen among co-tested patients for Medicaid intervals (remaining just under 2 years- 1.84, 95% CI: 1.52-2.16), while private insurance and Tricare intervals increased to 3 years each. Medicare intervals also increased to 3 years through 2009, but showed some decline in 2010 (Figure 3.5b).

We also examined race and insurance as a combined variable of mutually exclusive categories. When median times to next screen are compared by race within each insurance type, several patterns emerge. Women with private insurance have almost identical median screening intervals following cytology in 2010--1.25 years for white

women (95% CI: 1.17-1.33) and 1.32 years (95% CI: 1.21-1.43) for black women, but after co-testing black women return almost a year earlier than white women (Figure 3.6a). Among women with Medicare, black women initially had a longer median time for cytology but a shorter time for co-testing, though these differences attenuate with time so that in 2010, the median interval was 2 years for both races and screening methodologies (Figure 3.6b). There was not enough data to estimate median intervals for white women being co-tested on Medicaid, but for all other women, the median fluctuates between 1.5 and 2 years with no real trend over time for both cytology and co-testing (Figure 3.6c). On the other hand, trends for median time differed by screening method, but not race, for all women with Tricare. Intervals increased from 1.2 years to 3 years between 2006 and 2010 after co-testing but only increased slightly in that time period for cytology (Figure 3.6d).

Hazard Ratios for time to next screening visit

To estimate the hazard ratios of age and race/insurance groups for time to next screen, we used data from the most recent time period (2009 to mid-2010) to capture the most current clinical scenario, and stratified by screening method (cytology alone or co-testing) (Table 3.1). Following cytology alone, older women had a shorter interval than younger women, and white women with private insurance had shorter screening intervals than all other race and insurance categories. Conversely, following a dual-negative co-test, older women had a longer interval than younger women, and white women with private insurance had a longer interval than the other race and insurance categories.

To account for the differences in clinic-level screening practices we have previously described, models were also run with a random effect term for clinic to account for clustering at that level. With this additional adjustment, many results attenuated towards the null for both age and race/insurance categories and across both screening methods, though several significant differences remained. Among those screened by cytology alone, both white and black women with Medicare had statistically significantly longer median intervals (HR: 0.87, 95% CI: 0.75-0.99; HR: 0.81, 95% CI: 0.66-0.99, respectively). Differences also remained for co-testing after accounting for clinic-level differences—black women with private insurance (HR: 1.20, 95% CI: 1.05-1.37) and black women with Medicaid (HR: 1.30, 95% CI: 1.10-1.54) both had statistically significantly shorter screening intervals. Older women also had much longer median intervals than younger women following co-testing (50-59 years HR: 0.85, 95% CI: 0.76-0.96; 60-65 years HR: 0.63, 95% CI: 0.53-0.74).

DISCUSSION

We have previously shown differential uptake of co-testing on a clinic-level (Chapter 2, 13, 18). Here, we were able to build upon these earlier studies and show that along with an increase in the proportion of women being co-tested, there was also an increase in the median time before the next screening visit following a normal co-test result, but not following cytology alone. Co-test intervals increased from about 1.5 years in 2006/2007 when broader co-test uptake began to just over 2.5 years in 2010 when 45% of screens included an HPV test. If the steady increase in screening interval length continues with time, the screening interval may reach three years, which was the recommendation since

at least 2003. However, more time will be needed before we will be able to tell whether the most recent 2012 recommendation of a 5 year interval after a dual negative co-test is being followed. These guidelines also stated that annual Pap smears were unnecessary and specifically recommended against them. Instead, the guidelines emphasized that if screening was done by cytology alone, return screening should be every three years. In this setting, we saw very little evidence of a lengthening interval among who were screened by cytology alone over the last several years in this population, remaining steadily around 1.5 years, suggesting a pattern of continued over-screening.

Unlike the overall appearance of a lack of change in median cytology intervals over time, when stratified, several differences by race and insurance appear. When comparing black and white women, the trends for each race are the same, though black women have a consistently longer interval of about 2-3 months. This difference between black and white women becomes more striking with co-testing, though in the opposite direction—black women are re-screened almost a year sooner than white women despite having the same test result. Reasons for these differences in co-test screening intervals by race should be explored, as overuse of co-testing can actually increase the harms of screening, since the likelihood of false positives results and their sequelae increases with more frequent testing.

Within an insurance type, the large difference in time to next screening by race following a co-test remained among women with private insurance, but essentially disappeared in the most recent years for women with government provided health insurance (Medicare,

Medicaid, Tricare). It is not very surprising to see more uniformity amongst the government-insured recipients, as those are run by a single body with a single set of policies and reimbursement patterns, while there is more heterogeneity among the different private insurers. Pap screening intervals remained shortest for those with private insurance, possibly because private insurance continues to reimburse for annual Pap smears, while Medicare/Medicaid has moved to reimburse for Pap smears only once every two years and Tricare only once every three years. This difference illustrates the power of financial considerations in guiding clinical practice. Surprisingly, this pattern of longer intervals for non-private insurance did not hold for co-testing; instead, we found little evidence for extending intervals beyond two years for Medicare/Medicaid recipients, while both private insurance and Tricare intervals consistently increased through 2010. While this again may be due in part to higher risk populations using Medicare and Medicaid, continued research is needed to better understand why we see these opposing trends across test methods within an insurance type.

Some of these race and insurance differences appear to result from clinic-level differences in screening practice. While almost all race/insurance categories differed significantly in hazard of returning for the next screening visit, many of those differences attenuated or completely disappeared once we accounted for the clustering of women within clinics and any clinic-level differences in practice. It is interesting to note that the remaining differences are primarily among government-insured women. Whether this is due to truly different risk histories or simply due to practice-level differences remains to be seen. Further investigation into how screening policy decisions are made and

implemented at a clinic level could provide important implementation experience for clinics wishing to standardize their practice.

Current screening guidelines state Pap smears should be performed no more often than once every three years, but the time to next screening visit following negative cytology continues to be at least a year shorter than recommended across all races and insurance types. Often, screening is being performed at half the recommended interval, so those women are being screened twice as frequently as recommended. Similarly, co-testing is only supposed to be done once every five years, or else any comparative benefit is lost, and yet all race and insurance sub-groups were screened at least once every three years. However, the 5-year interval is part of the newest recommendations and not enough time has elapsed yet to determine whether they are being adopted. Considering the slow uptake of co-testing initially, it is promising to the see the relatively rapid pace with which 3-year intervals are now being achieved. The continued upward trajectories of those intervals is a promising trend that will need to be followed closely. Notably, black women are still only being screened approximately every 2 years after co-testing by both private insurance and Medicare/Medicaid, which is a year sooner than white women and is less than half the recommended interval. This more frequent use of testing greatly increases the likelihood of false positives and negates the high negative predictive value that makes co-testing beneficial. There is no immediately obvious explanation for this difference in intervals by race, as this comparison was among women with normal screening results, and so further exploration into this disparity is warranted.

This analysis shows the initial adoption of newer screening algorithms with evidence of increasing time between tests, into routine clinical practice with co-testing, but not traditional Pap smear screening. The recency of the newest guidelines precludes us from examining the long-term uptake until at least five years have passed, and so follow-up of these changes will be necessary. Importantly, this study utilized clinical practice data from a large medical system that includes a diversity of clinics and patients, providing direct evidence about how screening is occurring in a real world setting. However, with this clinical dataset, our analysis was limited to visits when patients are seen in an affiliated clinic and have a Pap smear and/or HPV test taken. As a result, we lack a true population denominator, and do not know who is coming in and out of this cohort, and whether women are being screened elsewhere. We also lack information on each women's screening history prior to the data included, and so cannot rule out that some of the differences seen are due to true risk differences among the women where different follow-up algorithms may have been appropriate. This is where comprehensive, population-based datasets created through the increasing use of electronic medical records and large screening registries such as the New Mexico Pap/HPV Registry (19) can supplement clinical data. As more and more women are co-tested, the potential for increasing rather than decreasing costs to patients and the health care system grow. Reasons for the differences we found by age, race and insurance, must be understood and corrected rapidly to prevent a widening of the disparities already seen in cervical cancer screening, diagnosis, and treatment outcomes.

Figure 3.1: Sample size flow chart

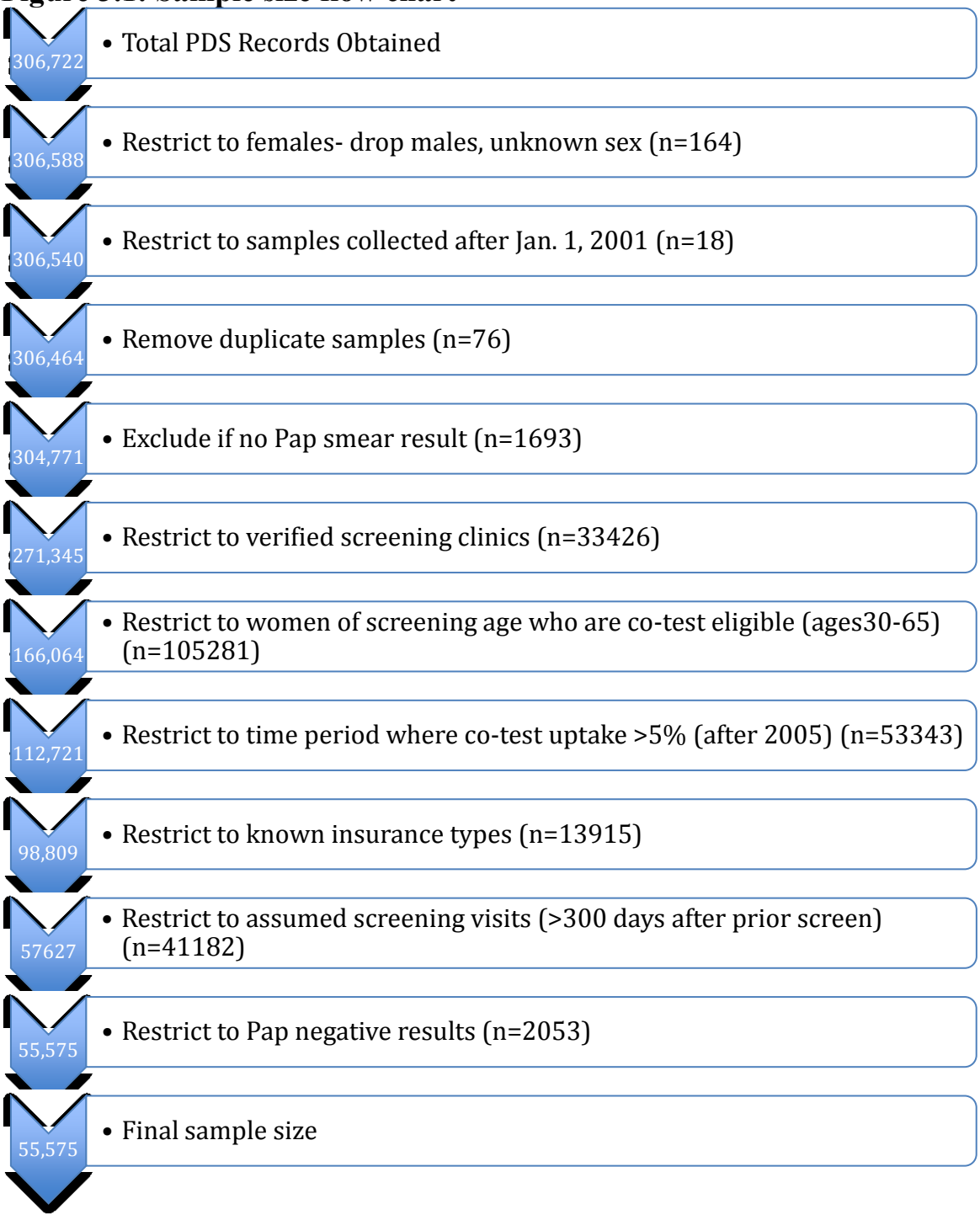


Figure 3.2: Time to next screen by year

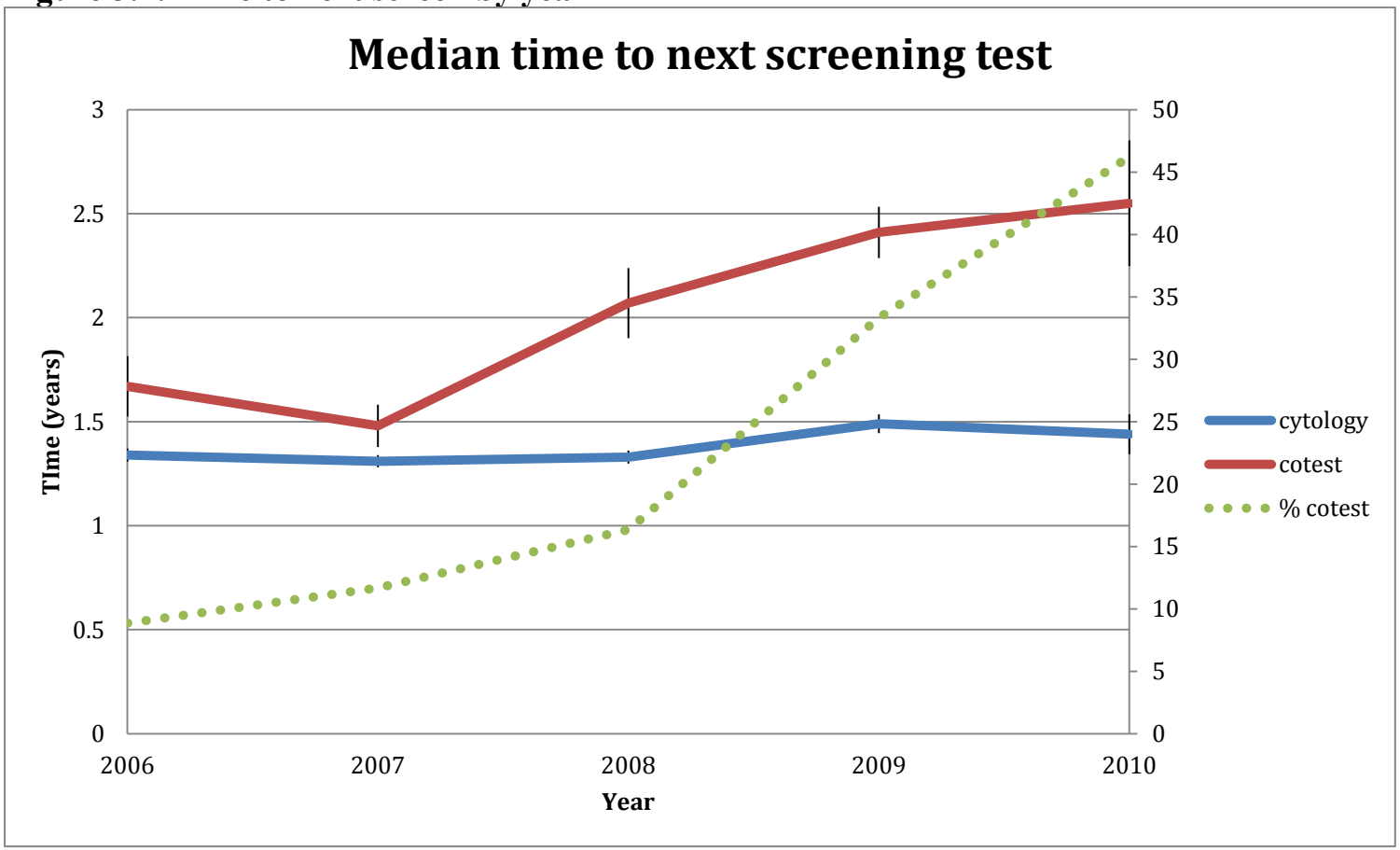
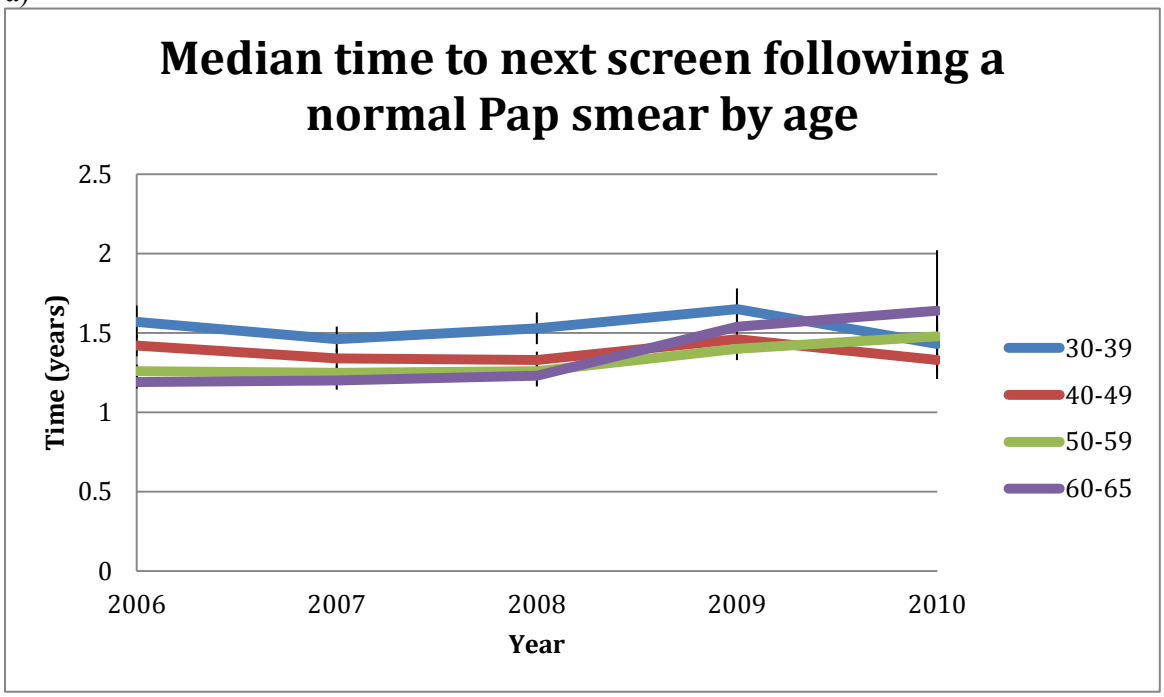


Figure 3.3: Time to next screen by age

a)



b)

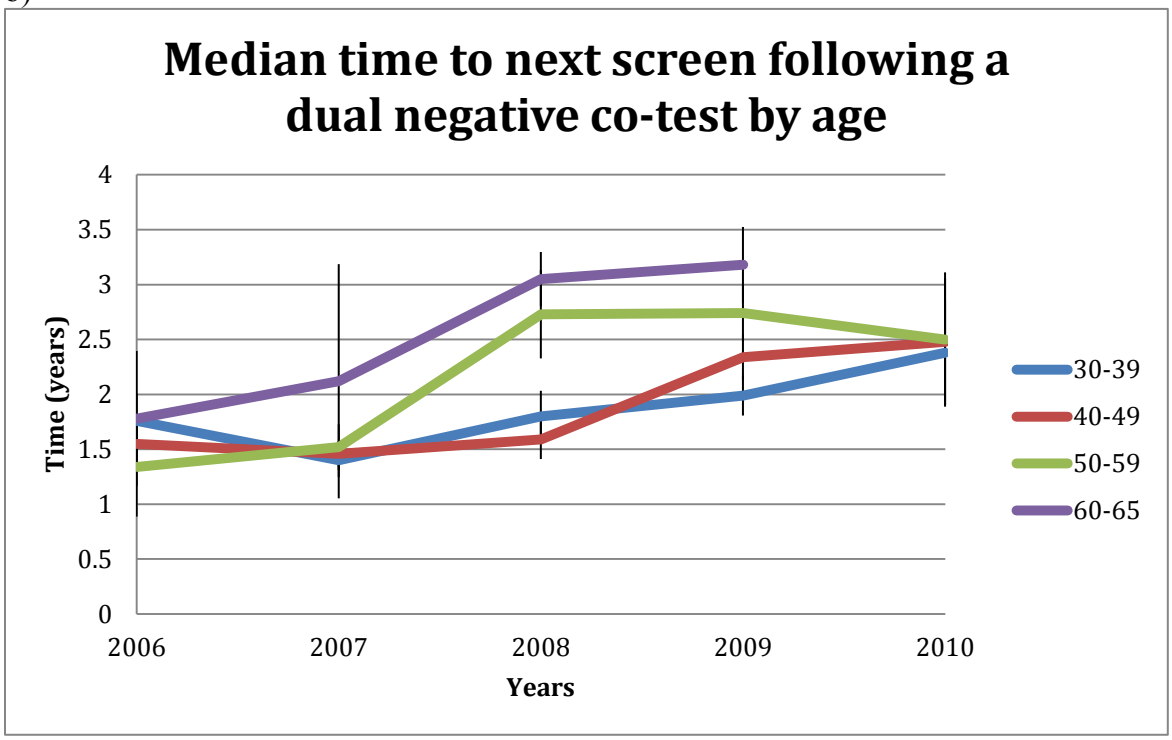
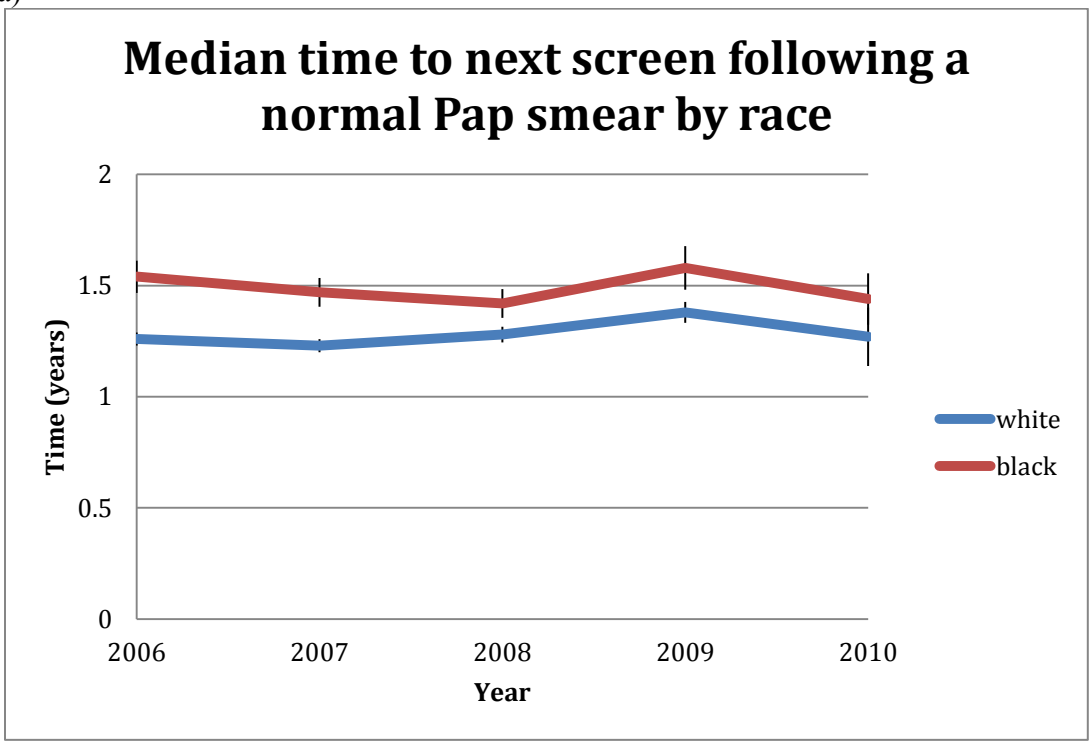
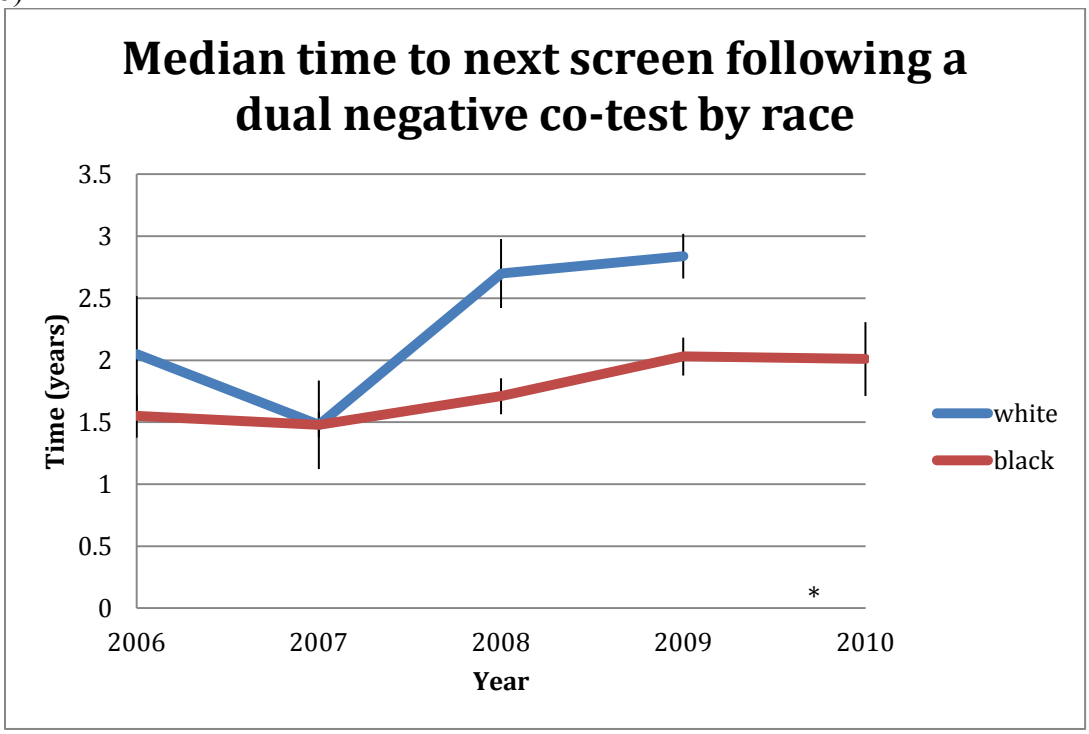


Figure 3.4: Time to next screen by race

a)



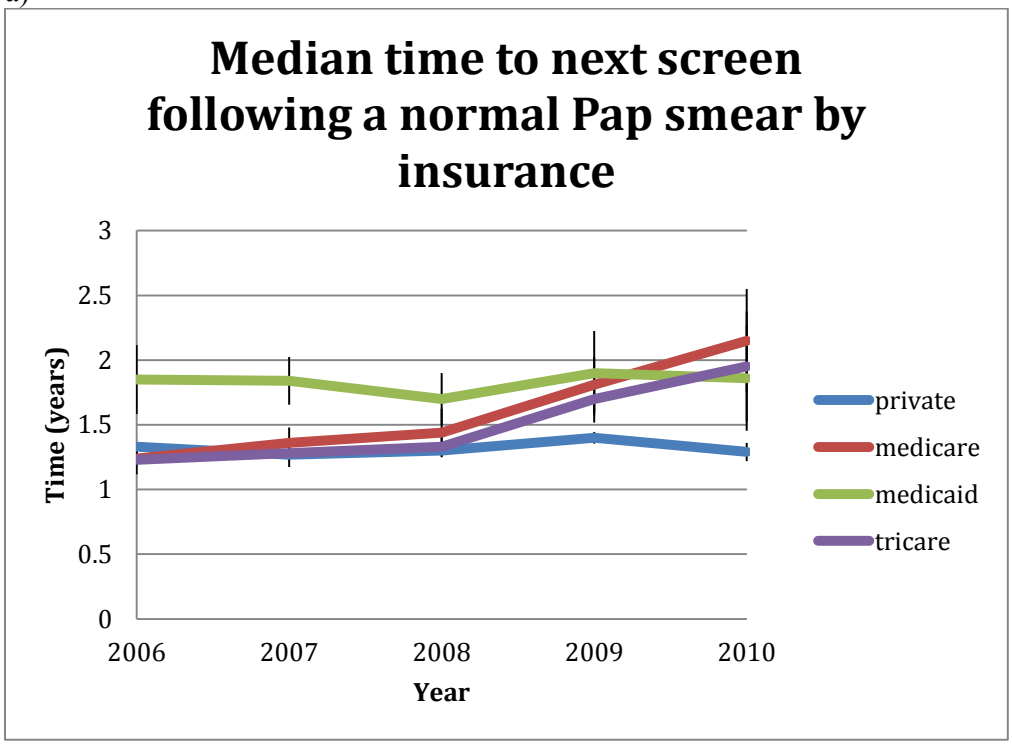
b)



*no median for white women in 2010 because <50% had returned for their next visit as of that date

Figure 3.5: Time to next screen by insurance

a)



b)

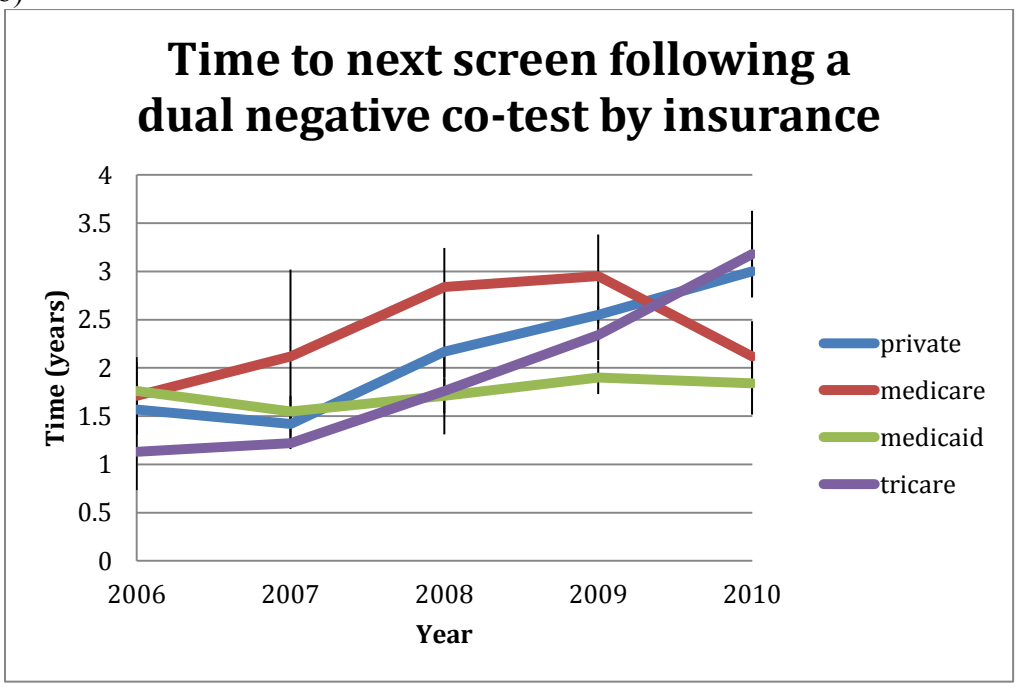
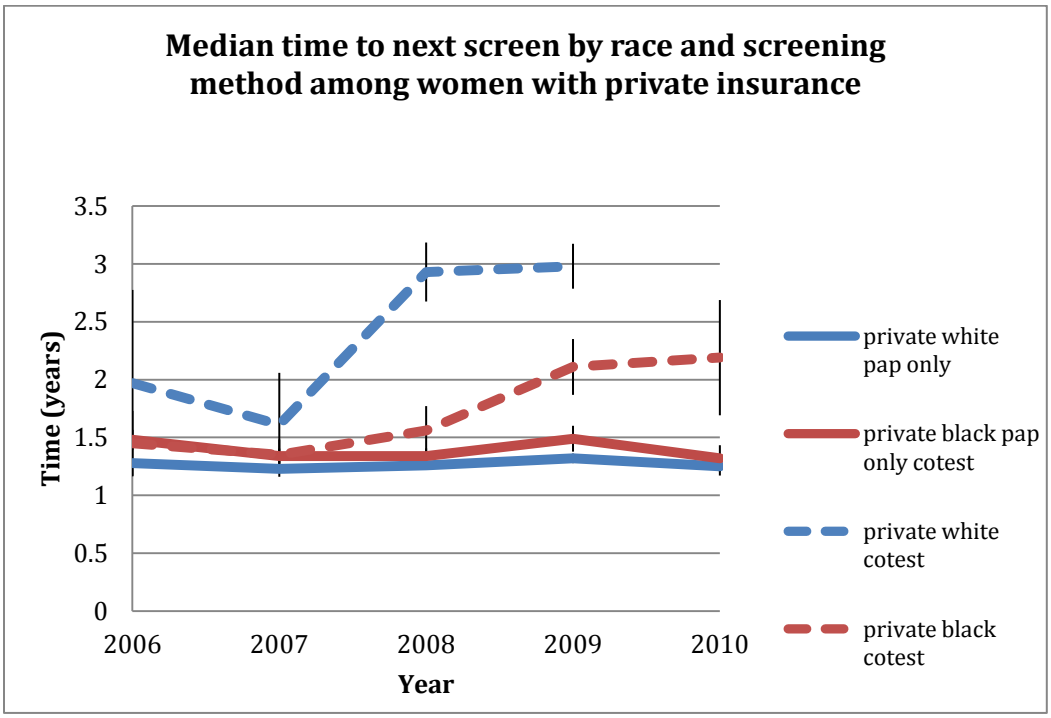
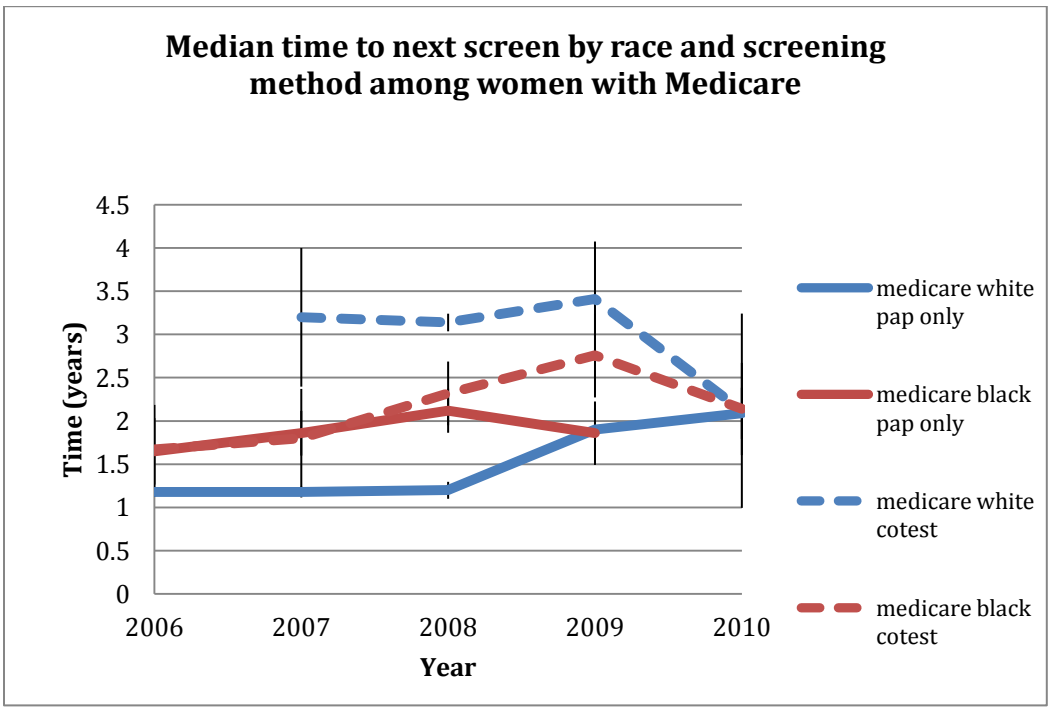


Figure 3.6: Median time to next screen by race and insurance

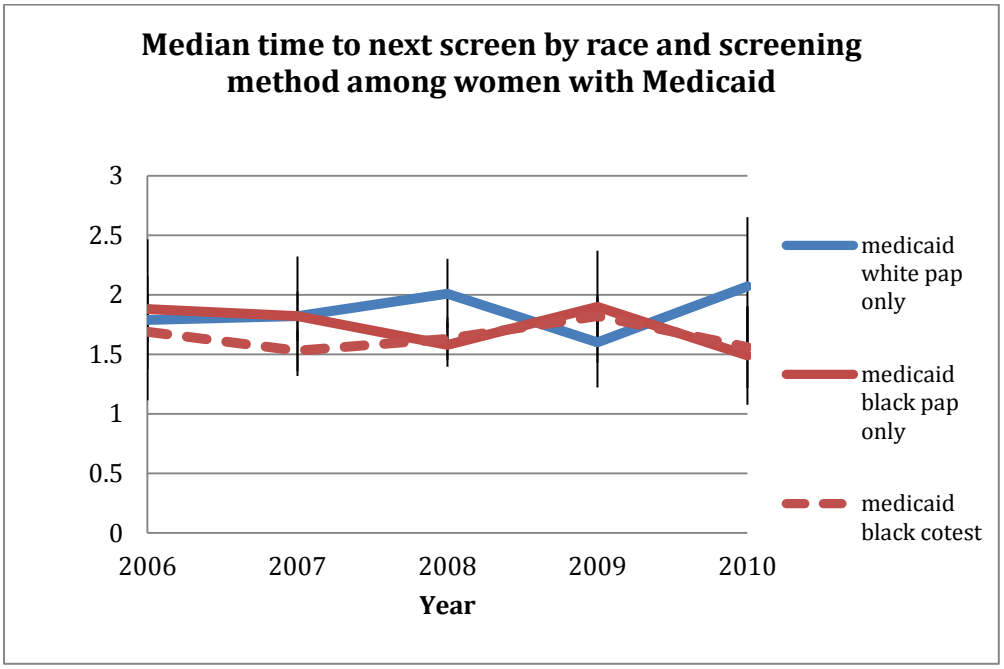
a)



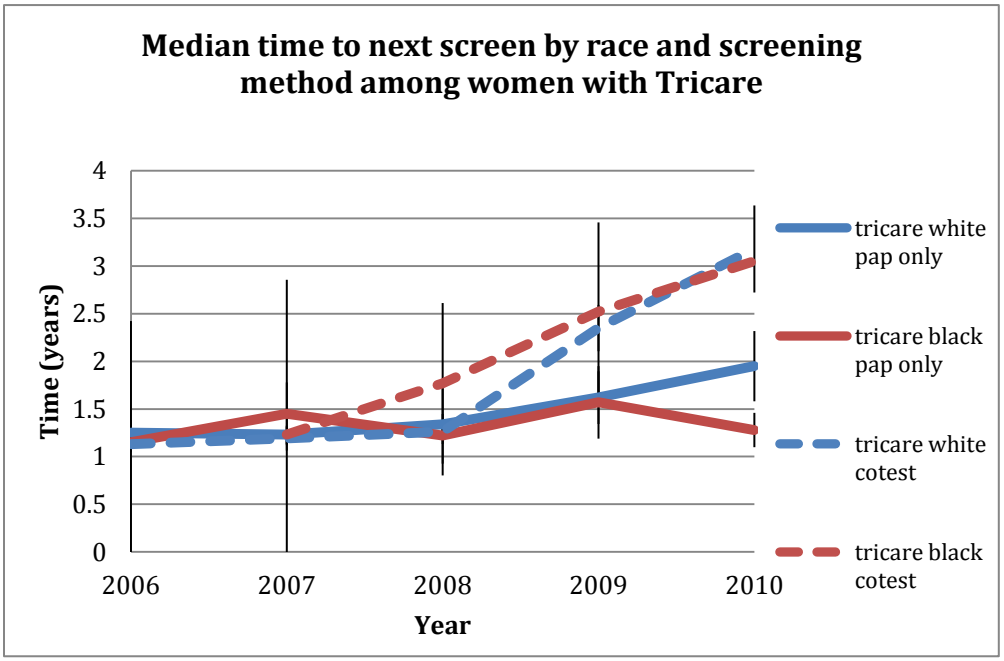
b)



c)



d)



note: not enough data to estimate medicaid white cotest

Table 3.1: Hazard Ratio for time to next screen (2009-mid 2010)

	Cytology alone		Co-testing	
	aHR1 (95% CI)	aHR2 (95% CI)	aHR1 (95% CI)	aHR2 (95% CI)
Age (in years)				
30-39	1	1	1	1
40-49	1.19 (1.09-1.29)	1.12 (1.03-1.22)	0.99 (0.89-1.10)	0.97 (0.88-1.07)
50-59	1.14 (1.06-1.24)	1.05 (0.96-1.14)	0.88 (0.79-0.99)	0.85 (0.76-0.96)
60-65	1.09 (0.99-1.21)	0.94 (0.85-1.05)	0.68 (0.58-0.80)	0.63 (0.53-0.74)
Insurance Type by Race				
White Private	1	1	1	1
White Medicare	0.82 (0.72-0.95)	0.87 (0.75-0.99)	1.02 (0.76-1.37)	1.01 (0.74-1.36)
White Medicaid	0.77 (0.61-0.97)	0.94 (0.73-1.22)	0.88 (0.61-1.27)	0.90 (0.61-1.31)
White Tricare	0.79 (0.71-0.88)	0.92 (0.80-1.05)	1.24 (1.06-1.45)	1.15 (0.98-1.37)
Black Private	0.92 (0.85-0.99)	0.98 (0.90-1.06)	1.34 (1.20-1.49)	1.20 (1.05-1.37)
Black Medicare	0.71 (0.58-0.86)	0.81 (0.66-0.99)	1.21 (0.99-1.48)	1.05 (0.84-1.31)
Black Medicaid	0.80 (0.71-0.91)	0.95 (0.80-1.13)	1.50 (1.33-1.70)	1.30 (1.10-1.54)
Black Tricare	0.93 (0.76-1.14)	0.99 (0.80-1.23)	1.13 (0.86-1.48)	1.05 (0.80-1.39)

*aHR1 includes age, race insurance adjustment
aHR2 – also includes clinic level adjustment

Supplemental Table S3.1: Breakdown of 'other' race category

Race	N	% of analytic population
Asian	1,016	3.2
Hispanic	362	1.14
Indian	36	0.11
Mixed	10	0.03
Other	804	2.54
Unknown	1227	3.87
Missing	120	0.38

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Chapter 4: Women express concern about HPV testing and 5-year intervals in routine cervical cancer screening

Women express concern about HPV testing and 5-year intervals in routine cervical cancer screening

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Short Title: Concern about changes in cervical cancer screening

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HPV in Perimenopause study participants and study staff

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Abstract

Objective: To explore attitudes towards new cervical cancer screening options and understand factors associated with those beliefs among women in routine gynecologic care.

Methods: Interviewer-administered survey of 551 women aged 36-62 enrolled in the HPV in Perimenopause Study. Poisson regression with robust error variance was used to estimate prevalence ratios and 95% confidence intervals to compare women's preferences for cervical cancer screening methods and frequency.

Results: A majority of women (55.6%, 95%CI: 51.4-59.8%) were aware that screening recommendations had changed, yet 77.9% (95%CI: 74.3-81.3%) still believed women should be screened annually. If recommended by their doctor, 68.4% (95% CI: 64.4-72.2%) were willing to extend screening to every three years, but only 25.4% (95%CI: 21.9-29.2%) would extend screening to five years. Most women (60.7%, 95%CI: 56.5-64.7%) expressed a strong preference for Pap testing, and 41.4% (95%CI: 37.4-45.6%) expressed at least moderate concern over having an HPV test without a Pap test. A desire for more frequent care, higher degree of worry and perceived risk, and abnormal screening history were all associated with reduced willingness to accept HPV testing and longer screening intervals.

Conclusion: A majority of routinely screened women indicated a willingness to adopt a cervical cancer screening strategy of cytology alone or Pap-HPV co-testing every 3 years

if recommended by their physician. However, they remain concerned about HPV testing and extension of screening intervals to once every 5 years. Our results suggest continued reticence to accepting newer HPV-based screening algorithms among routinely screened women over age 35.

Introduction

In 2012, the US Preventive Services Task Force, American Cancer Society, American Society for Colposcopy and Cervical Cytology, and American Society for Clinical Pathology updated their joint guidelines for cervical cancer screening, specifically recommending *against* annual screening using any strategy (1). Cytology alone at 3-year intervals and HPV co-testing with cytology at 5-year intervals were both considered acceptable strategies for women aged 30-65 years. While primary screening with HPV testing was not in the 2012 guidelines, in April 2014 the US Food and Drug Administration approved the Roche Cobas® HPV test for primary screening, and interim guidelines for a primary HPV screening strategy are anticipated.

HPV co-testing with a 3-year screening interval has been an acceptable option since 2003, yet uptake of co-testing in clinical practice has been slow (2, 3). Studies have shown that despite these guidelines, physicians continue to screen more frequently than recommended (4-9), and surveys have indicated that patient anxiety and expectation of annual screening influence a provider's screening recommendation (10, 11). Because recommendations strive to achieve a balance between benefits and both physical and psychological harms of screening, it is important to assess patient preferences and attitudes towards each alternative cervical cancer screening strategy.

We assessed the attitudes towards HPV testing strategies and patient-specific factors associated with willingness to lengthen screening intervals to 3- or 5-years in a cohort of

routinely screened women ages 36-62 years participating in a natural history study of HPV infection during the menopausal transition.

Methods

A survey to assess knowledge of the cervical cancer screening guideline changes, current screening practices, preferred screening method and frequency, willingness to extend the screening interval, and perceived risk of HPV and cervical cancer was offered to all women completing the HPV in Perimenopause Study final study visit. Five-hundred sixty-six of 885 women enrolled into the HPV in Perimenopause Study (64.0%) completed the final study visit, and 551/566 (97.3%) completed the screening-focused survey. Women who completed the full two years of follow-up did not differ significantly on any of the demographic or baseline risk factor variables from the total 885 women enrolled (Table 4.1).

Details of the HPV in Perimenopause Study have been reported elsewhere (12, 13). In brief, women receiving routine gynecological care were recruited to participate from Johns Hopkins Hospital affiliated outpatient OB/GYN clinics in Baltimore, MD from March, 2008 to March, 2011. Women were eligible to participate in the study if they were between 35 and 60 years, had an intact cervix, and were willing to provide informed consent. Women were not eligible for enrollment into the study if they were pregnant, had plans to become pregnant, had a history of organ transplantation or were known to be HIV-positive.

During this 2-year prospective natural history study of HPV infection in the menopausal transition, consenting women provided information on socio-demographic characteristics, lifetime sexual history and current sexual behavior, cervical cancer screening history, menstrual and reproductive histories, medication, and alcohol and tobacco use via a telephone-administered questionnaire. All women underwent a speculum-assisted pelvic examination, with swab and secretion samples collected for research purposes. A HIPAA waiver was signed allowing the study to abstract all cervical cytology and HPV test results obtained clinically during their study participation from their medical records. Several patient-specific factors evaluated in this study (including screening history, sexual behavior, and clinical Pap/HPV results) were derived from these data sources. The questions asked to participants in the screening study are included in the appendix (Supplementary Table S4.1). All study procedures were approved by the Johns Hopkins Bloomberg School of Public Health Institutional Review Board.

Descriptive statistics including frequencies and proportions and their corresponding confidence intervals were estimated to summarize survey responses. Poisson regression with robust error variance was used to estimate unadjusted prevalence ratios (PRs) and corresponding 95% confidence intervals (95% CI) comparing women willing to be screened every three years (by Pap only or by Pap/HPV co-testing) to women unwilling to extend screening intervals beyond one year. Women willing to extend screening to every five years following a dual negative co-test were also compared to women only willing to extend to three years. Women preferring Pap testing only were compared to

women preferring HPV testing only or who didn't express a preference. All analyses were carried out in Stata version 13.1.

Results

The women in this analysis were between 36 and 62 years of age with a median age of 50 (IQR: 44-55) at the time of the screening survey administration. The majority of women were white (76.2%), married (64.7%) and currently non-smokers (91.8%) (Table 4.1). Many women (60.9%) reported having five or more lifetime sex partners and at the time of the final visit, 70.0% reported sex with a steady partner, 25.5% were not sexually active, and 4.6% reported having a new sex partner in the prior six months. Most participants had some education beyond high school (85.0%), with 64.6% completing college and/or a post-graduate degree and 80.1% reported household incomes of $40,000 or higher. Consistent with our planned recruitment from women attending routine OB/GYN visits, all women reported having had a prior Pap smear, 47.2% reported having an abnormal Pap smear prior to study enrollment, and 99% reported a having a Pap smear within the past three years. In addition to OB/GYN care, participants were actively engaged in other medical care—less than 1% of women reported that their OB/GYN was their primary care physician and 97.6% had a check-up or physical in the past 5 years (Table 4.2). Additionally, 92.2% of women reported cholesterol tests, 75.1% reported diabetes screens, and 88.4% mammograms in the past 5 years.

A majority of participants (55.6%, 95%CI: 51.4-59.8) were aware that current cervical cancer screening guidelines recommended against annual screening (Table 4.2).

However, when asked how often they thought women their age should have a Pap smear, 3.8% (95%CI: 2.5-5.8) reported more than once a year, 74.1% (95%CI: 70.3-77.7) reported yearly, 13.4% (95%CI: 10.8-16.6) reported every other year, and 6.4% (95%CI: 4.6-8.7) reported every three years or longer. Despite a majority believing that screening should occur annually, over two-thirds of participants (68.4%, 95% CI: 64.4-72.2) were willing to extend their screening to once every three years by either Pap only or Pap-HPV co-testing following a normal result if a doctor recommended it; however, among those women willing to be screened every three years, only 39.5% (95%CI: 34.5-44.7), which was 25.2%, (95%CI: 21.8-29.0,) of women overall, were willing to extend screening to 5 years. Over two-thirds of participants (69.7%, 95%CI: 65.7-73.4) indicated that they would continue annual OB/GYN well-woman visits even if Pap screening was not performed. This proportion remained unchanged when restricted to the women willing to be screened every three years or longer. Primary reasons cited for continuing annual visits included a desire for routine check-up/ physical exam, other gynecologic concerns, breast exams, to maintain relationships with their doctor, and reassurance that everything is okay.

When asked about screening test preference, 60.7% (95%CI: 56.5-65.7) of women preferred Pap smears only, 31.5% (95%CI: 27,7-35.5) did not have a preference and were willing to be screened by either Pap or HPV testing, and only 7.8% (95%CI: 5.9-10.4) preferred HPV testing alone (Table 4.2). Furthermore, 30.1% (95%CI: 26.4-34.1) of women reported they would experience moderate anxiety and 11.3% (95%CI: 8.9-14.3) reported severe anxiety if they were screened with an HPV test alone. When asked which

test result they found more concerning, 26.6% (95%CI: 23.0-30.4) said an abnormal Pap result and 9.3% (95%CI: 7.1-12.0) reported an HPV positive result, with the majority reporting them to be equally concerning. To understand factors associated with screening assay preference, univariate analyses compared women who preferred Pap testing alone to the women who didn't have a preference or preferred HPV testing (Table 4.3). Women with a higher household income (PR: 0.56, 95% CI: 0.35-0.90), women recruited from the clinic that routinely co-tests (PR: 0.80, 95% CI: 0.69-0.93), women who were more concerned about an HPV positive test (PR: 0.45, 95% CI: 0.31-0.66) or equally concerned about an abnormal Pap/HPV result (PR: 0.73, 95% CI: 0.65-0.83), or thought they had a moderate or high risk of HPV (PR: 0.67, 95% CI: 0.49-0.92) were more likely to not have a test preference or to prefer HPV only compared with preferring Pap testing alone. Women with moderate (PR: 1.54, 95% CI: 1.25-1.90) or severe (PR: 1.39, 95% CI: 1.07-1.80) concern about HPV only testing preferred Pap only testing compared with women with low/no concern about HPV only testing.

In univariate analyses, we saw little to no difference in willingness to be screened every three years versus annually by age, race, marital status, education, and menopausal status (Table 4.4). Women with household income below $40,000 were 30% more likely (PR: 1.3, 95% CI: 1.1-1.5) to agree to extended screening intervals than women with higher income. Women seen at clinic B (which instituted a clinic-wide co-test policy in 2009) were more likely to agree to extended intervals (PR: 1.2, 95% CI: 1.1-1.4) compared with women recruited from clinic A which did not have a consensus co-testing policy. Participants' knowledge and attitudes towards cervical cancer screening, as well as self-

reported screening history, were among the strongest predictors of whether a woman was willing to be screened every three years. Both women who had last been screened longer than a year ago (PR: 1.3, 95% CI: 1.2-1.5) and women who didn't expect to have their next Pap smear screening for at least one year (PR 1.4, 95% CI: 1.2-1.5 next screen within 2 years; PR 1.4, 95% CI: 1.1-1.7 next screen within 5 years) were 30-40% more likely to agree to a 3-year screening interval. Women who believed Pap smears should be done every other year (PR: 1.3 95% CI: 1.2-1.5) or every 3-5 years (PR 1.5, 95% CI: 1.4-1.7) were also significantly more likely to state they would accept extended screening intervals than those who thought screening should be yearly or more often. Prior knowledge of the change in screening guideline was not associated with an increased willingness to follow the new guidelines. Women with a history of an abnormal Pap smear in the last 5 years were at least 30% less likely to agree to extended intervals (PR: 0.7, 95%CI: 0.5-0.9 extend to 3 years; PR: 0.5, 95% CI: 0.2-1.0 extend to 5 years). Women who reported a moderate to high perceived risk of developing cervical cancer in the future were 30% less willing to extend screening intervals to 3 years (PR: 0.7, 95% CI: 0.6-0.9), but no association was seen with perceived risk of HPV infection or genital warts. Risk factors for HPV infection and cervical cancer such as lifetime number of sex partners, recent new sex partners, HPV serology status, and HPV DNA status were also not associated with a woman's willingness to follow the 3-year screening recommendation.

Only 39.5% (95%CI: 34.5-44.7) of women willing to be screened every three years (25.2%, 95%CI: 21.8-29.0 of all women) were willing to be screened every 5 years

(Table 4.4). Women with a BMI over 30 were 50% more likely to accept a 5-year interval (PR: 1.5, 95% CI: 1.1-2.0). Many of the same determinants of willingness to extend to 3-year intervals were associated with willingness to extend to 5-year intervals though these associations did not reach statistical significance in this smaller sample. No significant associations were seen with risk factors of lifetime number of sex partners, new sex partners, HPV serology status, and HPV DNA status.

Discussion

Cervical cancer screening has evolved significantly in the past 10-15 years. However, the preference of women regarding alternative screening strategies is an understudied aspect of changing screening guidelines. In our survey of routinely screened women 36-62 years, we found that almost half were aware that screening recommendations had changed, and the majority still believed women should be screened every year. Despite this, two-thirds stated they would be willing to extend screening to every three years if their doctor recommended it, but only a quarter were willing to extend the interval to five years following a dual negative co-test, the preferred recommendation in the newest guidelines. Women also expressed a clear preference for Pap testing over HPV testing, and many expressed concern over having an HPV test alone without a Pap test. A desire for more frequent care, higher anxiety, and higher perceived risk were all associated with being less willing to accept alternatives to annual Pap smears.

Resistance to less frequent screening has been reported previously (14-21), and this reticence appears to persist over time. For example, the results from a nationally

representative survey of women in the US in 2005 were strikingly similar to our survey results collected almost a decade later (15). Our results suggest a continued preference for cytology testing compared with HPV testing. This observation is especially relevant in light of the recent FDA approval of one HPV test (Roche Cobas) for an indication of primary cervical cancer screening (22). Future US guideline revisions are likely to consider recommendations for primary screening using HPV testing, especially given the transition to primary HPV screening by other large national screening programs such as those in Australia (23) and the United Kingdom (24).

Interestingly, despite the preference for Pap over HPV testing, women in our study were more concerned about an abnormal Pap test compared to a positive HPV test. Data from a large study of women routinely screened with an HPV co-test algorithm showed 35% of CIN3/AIS and 29% of total cancers were in women with HPV positive and cytology negative co-test results (25). Taken together, these results suggest that educational interventions to communicate risks associated with alternative screening test results are needed in order for women to make understand alternative screening choices.

Women with a lower household income were more likely to accept longer screening intervals, which may be related to the cost saving aspect of reducing unnecessary tests or other barriers such as difficulty scheduling time off work for preventative health care needs. In addition, women with high levels of worry and/or high perceived risk, as well as women who indicated a preference for more care and contact with their provider were less likely to agree to extended screening intervals, as previously shown (14, 26). These

women may represent a combination of those with historically high risk, who should be screened more frequently (27), as well as a subset of 'worried well' in whom frequent screening appears to be the result of a desire for continual reassurance.

Surveys of physicians have indicated that concern about losing the well-woman annual clinical encounters as a result of less frequent screening was a common barrier to use of co-testing strategies, which are cost-effective only when performed at the recommended extended intervals (8, 28). It is important to understand whether a lack of willingness to extend the cervical cancer screening interval reflects a concern among the patients about missing other opportunities for care. We found that nearly 70% of women reported that they would continue annual well-women visits even if a Pap smear was not taken at each visit. However, our questions did not explicitly ask about willingness to extend screening intervals in the context of continued annual gynecologic exams, and thus it is possible that acceptance would be higher if women are reassured that less frequent screening would not result in less frequent general gynecologic care.

A unique strength of our analysis was the ability to nest responses into a larger and more comprehensive evaluation of the natural history of HPV infection. For example, women in this study were primarily recruited from two GYN practices, which had distinctly different screening policies. We observed that women recruited from the clinic with a practice-wide policy of routine co-testing in women over 30 since 2009 were slightly more likely to accept extended intervals than those being screened in the other clinics with less frequent use of co-testing. However, having had one or more HPV tests or

being in the clinic with a policy of routine co-testing was not associated with a woman being more comfortable with HPV only testing, again highlighting a need for more patient education regarding the use and meaning of HPV testing.

A limitation of this cohort is that it is not representative of the general population. Our study participants are older, of higher socio-economic status, and are in routine screening. Despite this, we believe that the responses from this population are particularly relevant when the aim is to examine the attitudes towards changes in routine screening guidelines, since it is the well-screened women who would be most affected by extension of screening intervals. Moving forward, it will be important to assess whether more diverse or representative populations also express similar attitudes towards screening strategies. We also acknowledge that screening involves a dialog between patient and provider, and we have only provided the patient perspectives. Future studies incorporating both patient and provider perspectives will be essential for a complete evaluation of the dynamics of this shared decision-making. In addition, many of the questions were phrased as screening intentions and future behaviors, and it is thus unclear whether these intentions will directly translate to practice. All of the information collected in our questionnaire are self-reported and so are subject to inaccuracies in recall and reporting. Despite these limitations, these data contribute to a significant gap in the evidence regarding patient perceptions of benefits and harms of screening, which have been historically underrepresented in cervical cancer screening guideline development.

Table 4.1: Comparison of Total Enrollment Population with Women Completing Study

	Completed study		Enrollment Population	
	N	%	N	%
Demographics				
Age (years)				
35-39	95	17.2	162	18.3
40-44	112	20.3	187	21.1
45-49	143	26.0	223	25.2
50-54	120	21.8	181	20.5
55-60	81	14.7	132	14.9
Race				
White	420	76.2	653	73.8
Black	91	16.5	167	18.9
Other	40	7.3	65	7.3
BMI				
Normal	351	39.7	222	40.5
Overweight	263	29.8	177	32.3
Obese	270	30.5	149	27.2
Income ($)				
<40,000	35	6.4	66	7.5
40-80,000	125	22.7	212	24.0
80-120,000	133	24.2	195	22.0
120,000+	183	33.3	261	29.5
Unknown	74	13.5	150	16.9
Clinic				
Clinic A (no co-test policy)	293	53.3	449	50.7
Clinic B (co-test policy)	224	40.7	385	43.5
Clinic C (no co-test policy)	33	6.0	51	5.8
Married				
Never	84	15.3	164	18.6
Divorced/ Widowed/ Separated	110	20.0	165	18.7
Married	356	64.7	555	62.8
Education				
High school or less	82	15.0	153	17.3
Some post high school	112	20.4	208	23.5
College graduate	171	31.2	257	29.0
Post graduate	183	33.4	267	30.2
Smoking				

Never	393	71.9	608	68.7
Former	109	19.9	176	19.9
Current	45	8.2	101	11.4
Menopausal Status (BL)				
Premenopausal	224	40.7	373	42.2
Perimenopausal	165	30.0	260	29.4
Postmenopausal	149	27.0	233	26.3
Not Classified	13	2.4	19	2.2
Screening History				
Time Since Last Abnormal Pap (BL)				
Never abnormal	291	52.8	465	52.5
0-5 years	62	11.3	114	12.9
6+ years	182	33.0	286	32.3
Unknown	16	2.9	20	2.3
Ever Had Colposcopy (BL)				
No	417	76.1	694	78.4
Yes	131	23.9	191	21.6
Risk Factors				
Lifetime Number of Sex Partners at Enrollment				
<5	214	39.1	335	38.0
5+	333	60.9	547	62.0
Recent Sex				
No Sex	140	25.5	199	22.6
Yes, no new partner	385	70.0	655	74.5
Yes, new partners	25	4.6	25	2.8
HPV Serology at BL				
Negative	190	40.9	273	37.9
Positive	275	59.1	448	62.1
Research HPV Testing (during study)				
Always negative	448	81.3	735	83.1
Ever positive	103	18.7	150	16.9
Clinical Pap Abnormality (during study)				
No	507	93.2	811	93.1
Yes	37	6.8	60	6.9
Clinical HPV Test (during study)				
Always negative	318	58.4	476	54.6
Ever positive	26	4.8	42	4.8
Not tested	201	36.9	354	40.6

* p>.05 for all comparisons between visits (no significant differences)

Abbreviations: N= number, %= percent, BL=baseline, indicates data only collected at time of study enrollment, Recent Sex= within the last 6 months

Missing data: N=3 for smoking, education, ever had colposcopy; N=1 for recent sex; N=10 for Pap result during study; N=6 for clinical HPV test; N=86 for

Table 4.2: Knowledge, Attitudes, and Preferences towards Cervical Cancer Screening & Guidelines

serology (unable to get blood sample)

	N	%	95% CI
How often should women have a Pap smear?			
Yearly	408	74.1	70.3-77.7
Every other year	74	13.4	10.8-16.6
Every 3 or longer	35	6.4	4.6-8.7
More than once a year	21	3.8	2.5-5.8
Don't know	13	2.4	1.2-3.8
Aware of the guideline change?			
No	240	43.6	39.5-47.8
Yes	306	55.6	51.4-59.8
Don't Know	5	0.9	0.3-1.9
Willing to have an annual without a Pap			
No	132	24.1	20.7-27.9
Yes	382	69.7	65.7-73.4
Don't Know	34	6.2	4.5-8.6
Screening Test preference			
Pap Only	333	60.7	56.5-65.7
HPV Only	43	7.8	5.9-10.4
Either	173	31.5	27.7-35.5
Which is more concerning			
Abnormal Pap	146	26.6	23.0-30.4
HPV Positive	51	9.3	7.1-12.0
Equally concerning	353	64.2	60.1-68.1
If HPV test only, how much concern about not having a Pap smear			
None	120	21.9	18.6-25.6
Slight	201	36.7	32.7-40.8
Moderate	165	30.1	26.4-34.1
Severe	62	11.3	8.9-14.3
Perceived Risk of Warts			
None/Low	518	95.1	92.9-96.6
Moderate/High	27	5.0	3.4-7.1
Perceived Risk of HPV			
None/Low	492	89.6	86.8-91.9
Moderate/High	57	10.4	8.1-13.2
Perceived Risk of Cervical Cancer			

None/Low	475	86.5	83.4-89.1
Moderate/High	74	13.5	10.9-16.6
Willing to be screened every 3 years by either Pap only or co-testing			
No	174	31.6	27.8-35.6
Yes	377	68.4	64.4-72.2
If willing to be screened every 3 years, willing to extend to 5 years			
No	213	60.5	55.3-65.5
Yes	139	39.5	34.5-44.7
Have pap every 5 years if Pap & HPV tests normal			
No	412	74.8	71.0-78.2
Yes	139	25.2	21.8-29.0
Other Health Behaviors			
Primary care provider?			
Internist/ Family Practitioner	476	86.4	83.3-89.0
Physician's Assistant	18	3.3	2.1-5.1
Nurse Practitioner	14	2.5	1.5-4.3
Gynecologist	5	0.9	0.4-2.2
Other Medical Specialist	7	1.3	0.6-2.6
Don't know/ can't remember	3	0.5	0.2-1.7
No primary care provider	28	5.1	3.5-7.3
In the last 5 years had a …			
General health check-up or physical	538	97.6	96.0-98.6
Cholesterol test	508	92.2	89.6-94.2
Diabetes screen or blood glucose test	417	75.7	71.9-79.1
Dental Exam	527	95.6	93.6-97.1
Clinical breast exam	534	96.9	95.1-98.1
Mammogram	487	88.4	85.4-90.8

* Abbreviations: N=number, %=percent;

Missing data: N=3 for annual w/o Pap, HPV only; N=2 test preference; N=1 concern

Table 4.3: Correlates of Preference of Pap Only Screening (compared to HPV only or either)

	N (%)	PR	CI
Demographics			
Age			
35-39	59 (62.1)	1	
40-44	61 (54.5)	0.88	.70-1.11
45-49	85 (59.4)	0.96	.78-1.18
50-54	81 (68.1)	1.10	.90-1.34
55-60	47 (58.8)	0.95	.74-1.20
Race			
White	256 (61.0)	1	
Black	53 (58.9)	0.97	.80-1.17
Other	24 (61.5)	1.01	.78-1.31
BMI			
Normal	140 (63.4)	1	
Overweight	108 (61.4)	0.97	.83-1.13
Obese	84 (56.4)	0.89	.75-1.06
Income ($)			
<40,000	268 (60.9)	1	
40,000+	**12 (34.3)**	**0.56**	**.35-.90**
Unknown	53 (71.6)	1.16	1.0-1.38
Clinic			
Clinic A (no co-test policy)	195 (66.8)	1	
Clinic B (co-test policy)	**120 (53.6)**	**0.80**	**.69-.93**
Clinic C (no co-test policy)	18 (54.6)	0.88	.59-1.13
Married			
Never	50 (59.5)	1	
Divorced/ Widowed/ Separated	66 (60.0)	1.01	.80-1.27
Married	216 (61.0)	1.03	.84-1.25
Education			
High school or less	44 (53.7)	1	
Some post high school	70 (62.5)	1.16	.91-1.49
College graduate	104 (60.8)	1.13	.90-1.43
Post graduate	114 (63.0)	1.17	.93-1.48
Smoking			
Never	241 (61.6)	1	
Former	64 (58.7)	0.95	.80-1.14
Current	27 (58.7)	0.95	.74-1.23

Menopausal Status			
Premenopausal	134 (59.8)	1	
Perimenopausal	103 (62.4)	1.04	.89-1.22
Postmenopausal	90 (61.2)	1.02	.87-1.21
Not classified	6 (46.2)	0.77	.42-1.40
Screening History			
Time Since Last Abnormal Pap (BL)			
No abnormal Pap ever	176 (60.7)	1	
0-5 years	38 (61.3)	1.01	.81-1.26
6+ years	112 (61.9)	1.02	.88-1.18
Unknown	7 (43.8)	0.72	.41-1.27
Ever Colposcopy (BL)			
No	255 (61.3)	1	
Yes	77 (59.2)	0.97	.82-1.14
When was last Pap			
Within last year	266 (61.9)	1	
1-5 years ago	65 (56.5)	0.91	.77-1.09
Don't Know	1 (33.3)	0.54	.11-2.68
Next Expected Pap			
Within a year	273 (62.1)	1	
Within 2 years	49 (61.3)	0.99	.82-1.19
Within 5 years	5 (33.3)	0.54	.26-1.10
Don't Know	6 (42.9)	0.69	.38-1.27
Risk Factors			
Lifetime Number of Sex Partners (BL)			
<5	128 (60.4)	1	
5+	204 (61.3)	1.01	.88-1.17
Recent Sex*			
No sex	84 (60.0)	1	
Yes, no new partner	235 (61.4)	1.02	.87-1.20
Yes, new partners	14 (56.0)	0.93	.65-1.36
HPV Serology at BL			
Negative	120 (63.5)	1	
Positive	162 (59.1)	0.93	.80-1.08
Research HPV Status (during study)			
Always negative	277 (62.0)	1	
Ever positive	56 (54.9)	0.89	.73-1.07
Clinical Pap Abnormality (during study)			
No	311 (61.6)	1	
Yes	19 (51.4)	0.83	.60-1.15
Clinical HPV Testing (during study)			
Negative	182 (57.6)	1	
Positive	10 (38.46)	0.67	.41-1.10

Not Tested	**138 (68.7)**	**1.19**	**1.04-1.36**
Knowledge and Attitudes towards Cervical Cancer Screening & Guidelines			
How often should women have Pap smear?			
Yearly	262 (64.5)	1	
Every other year	40 (54.1)	0.84	.67-1.05
Every 3-5 years	16 (45.7)	0.71	.49-1.02
More than once a year	12 (57.1)	0.89	.61-1.29
Don't know	2 (16.7)	0.26	.07-.92
Aware of the guideline change?			
No	143 (59.6)	1	
Yes	186 (61.2)	1.03	.89-1.18
Don't Know	3 (75.0)	1.26	.71-2.24
Willing to have annual without Pap			
No	78 (59.1)	1	
Yes	231 (60.6)	1.03	.87-1.21
Don't Know	23 (67.7)	1.14	.87-1.50
Which is more concerning			
Abnormal Pap	114 (78.1)	1	
HPV Positive	**18 (35.3)**	**0.45**	**.31-.66**
Equally concerning	**201 (57.1)**	**0.73**	**.65-.83**
If HPV test only, how much concern about not having a Pap smear			
None	57 (47.5)	1	
Slight	114 (56.7)	1.19	.95-1.49
Moderate	**120 (73.2)**	**1.54**	**1.25-1.90**
Severe	**41 (66.1)**	**1.39**	**1.07-1.80**
Perceived Risk of Warts			
None/Low	316 (61.2)	1	
Moderate/High	13 (48.2)	0.79	.53-1.17
Perceived Risk of HPV			
None/Low	307 (62.7)	1	
Moderate/High	**24 (42.1)**	**0.67**	**.49-.92**
Perceived Risk of Cervical Cancer			
None/Low	290 (61.3)	1	
Moderate/High	42 (56.8)	0.93	.75-1.14

* Abbreviations: N=number, %=percent, BL=baseline, **bold** = $p<0.05$

Table 4.4: Correlates of willingness to extend cervical cancer screening intervals

	Extend to 3 years only			Extend from 3 to 5 years		
	N (%)	PR	CI	N (%)	PR	CI
Demographics						
Age (years)						
35-39	67 (70.5)	1		28 (43.1)	1	
40-44	65 (58.0)	0.8	0.7-1.0	34 (54.0)	1.3	0.9-1.8
45-49	102 (71.3)	1.0	0.9-1.2	29 (31.2)	0.7	0.5-1.1
50-54	82 (68.3)	1.0	0.8-1.2	25 (33.8)	0.8	0.5-1.2
55-60	61 (75.3)	1.1	0.9-1.3	23 (40.4)	0.9	0.6-1.4
Race						
White	298 (80.0)	1		108 (38.9)	1	
Black	55 (60.4)	0.9	0.7-1.0	20 (40.0)	1.0	0.7-1.5
Other	24 (60.0)	0.9	0.7-1.1	11 (45.8)	1.2	0.7-1.9
BMI						
Normal	152 (68.5)	1		49 (34.0)	1	
Overweight	126 (71.2)	1.0	0.9-1.2	45 (38.8)	1.1	0.8-1.6
Obese	97 (25.9)	1.0	0.8-1.1	**45 (50.0)**	**1.5**	**1.1-2.0**
Income ($)						
<40,000	**30 (85.7)**	**1.3**	**1.1-1.5**	15 (55.6)	1.5	1.0-2.2
40,000+	301 (68.3)	1		106 (37.2)	1	
Unknown	46 (61.3)	0.9	0.7-1.1	18 (45.0)	1.2	0.8-1.8
Clinic						
Clinic A (no co-test policy)	183 (62.5)	1		62 (36.1)	1	
Clinic B (co-test policy)	**172 (76.4)**	**1.2**	**1.1-1.4**	67 (41.9)	1.2	0.9-1.5
Clinic C (no co-test policy)	22 (66.7)	1.1	0.8-1.4	10 (50.0)	1.4	0.9-2.3
Married						
Never	57 (67.9)	1		21 (39.6)	1	
Divorced/ Widowed /Separated	74 (67.3)	1.0	0.8-1.2	29 (42.0)	1.1	0.7-1.7
Married	245 (68.8)	1.0	0.9-1.2	89 (38.9)	1.0	0.7-1.5
Education						
High school or less	61 (74.4)	1		18 (32.7)	1	
Some post high school	77 (68.8)	0.9	0.8-1.1	34 (48.6)	1.5	1.0-2.3
College graduate	113 (66.1)	0.9	0.8-1.1	37 (35.2)	1.1	0.7-1.7
Post graduate	124 (67.8)	0.9	0.8-1.1	50 (51.7)	1.3	0.8-2.0
Smoking						
Never	266 (67.7)	1		96 (38.9)	1	
Former	74 (67.3)	1.0	0.9-1.2	27 (38.0)	1.0	0.7-1.4

Current	35 (76.1)	1.1	0.9-1.3	16 (50.0)	1.3	0.9-1.9
Menopausal Status						
Premenopausal	151 (67.4)	1		60 (41.1)	1	
Perimenopausal	109 (66.1)	1.0	0.9-1.1	42 (41.6)	1.0	0.8-1.4
Postmenopausal	106 (71.1)	1.1	0.9-1.2	35 (36.8)	0.9	0.7-1.2
Not classified	11 (84.6)	1.3	1.0-1.6	2 (20.0)	0.5	0.1-1.7
Screening History						
Time Since Last Abnormal Pap (BL)						
Never abnormal	214 (73.5)	1		90 (44.8)	1	
0-5 years	**31 (50.0)**	**0.7**	**0.5-0.9**	6 (21.4)	0.5	0.2-1.0
6+ years	121 (66.5)	0.9	0.8-1.0	41 (36.3)	0.8	0.6-1.1
Unknown	11 (68.8)	0.9	0.7-1.3	2 (20.0)	0.5	0.1-1.6
Ever Colposcopy (BL)						
No	299 (71.7)	1		114 (41.0)	1	
Yes	76 (58.0)	0.8	0.7-1.0	25 (34.7)	0.9	0.6-1.2
When was last Pap						
W/in last year	277 (64.1)	1		97 (37.5)	1	
1-5 years ago	**96 (83.5)**	**1.3**	**1.2-1.5**	40 (44.9)	1.2	0.9-1.6
Don't Know	**3 (100)**	**1.6**	**1.5-1.7**	1 (33.3)	1.3	0.5-3.6
Next Expected Pap						
Within a year	280 (63.4)	1		96 (36.2)	1	
Within 2 years	**70 (87.5)**	**1.4**	**1.2-1.5**	27 (43.6)	1.2	0.9-1.7
Within 5 years	**13 (86.7)**	**1.4**	**1.1-1.7**	**11 (84.6)**	**2.3**	**1.8-3.1**
Don't Know	**14 (100)**	**1.6**	**1.5-1.7**	5 (41.7)	1.2	0.6-2.3
Risk Factors						
Lifetime Number of Sex Partners (BL)						
<5	146 (68.2)	1		58 (41.7)	1	
5+	229 (68.8)	1.0	0.9-1.1	81 (38.4)	0.9	0.7-1.2
Recent Sex*						
No sex	106 (75.7)	1		40 (40.8)	1	
Yes, no new partner	256 (66.5)	0.9	0.8-1.0	93 (38.9)	1.0	0.7-1.3
Yes, new partners	15 (60.0)	0.8	0.6-1.1	6 (40.0)	1.0	0.5-1.9
HPV Serology at BL						
Negative	135 (71.1)	1		49 (39.5)	1	
Positive	183 (66.6)	0.9	0.8-1.1	68 (39.5)	1.0	0.8-1.3
Research HPV Testing (during study)						
Always negative	310 (69.2)	1		109 (37.7)	1	
Ever positive	67 (65.1)	0.9	0.8-1.1	30 (47.6)	1.3	0.9-1.7
Clinical HPV Testing (during study)						
Always negative	225 (70.6)	1		87 (41.2)	1	
Ever positive	20 (76.9)	1.1	0.9-1.4	9 (47.4)	1.1	0.7-1.9
Not Tested	128 (63.7)	0.9	0.8-1.0	42 (35.6)	0.8	0.6-1.1
Pap Abnormality (BL)						

No	348 (69.1)	1		131 (40.6)	1	
Yes	22 (59.5)	0.9	0.7-1.1	7 (31.8)	0.8	0.4-1.5
Knowledge and Attitudes towards Cervical Cancer Screening & Guidelines						
How often should women have Pap smears?						
Yearly	260 (63.7)	1		86 (35.0)	1	
Every other year	**62 (83.8)**	**1.3**	**1.2-1.5**	23 (39.7)	1.1	0.8-1.6
Every 3-5 years	**34 (97.1)**	**1.5**	**1.4-1.7**	**19 (61.3)**	**1.8**	**1.3-2.4**
More than once a year	9 (42.9)	0.7	0.4-1.1	5 (71.4)	2.0	1.2-3.4
Don't know	12 (100)	1.5	1.2-1.7	6 (60.0)	1.7	1.0-2.9
Aware of the guideline change?						
No	157 (65.4)	1		60 (40.5)	1	
Yes	217 (70.9)	1.1	1.0-1.2	77 (38.3)	0.9	0.7-1.2
Don't Know	2 (50.0)	0.9	0.5-1.9	1 (50.0)	1.6	0.7-3.8
Have annual w/o pap						
No	105 (79.6)	1		43 (43.4)	1	
Yes	245 (64.1)	0.8	0.7-0.9	82 (36.0)	0.8	0.6-1.1
Don't Know	25 (73.5)	0.9	0.7-1.2	14 (60.9)	1.4	0.9-2.1
Test preference						
Pap Only	211 (63.4)	1		64 (33.0)	1	
HPV Only	27 (62.8)	1.0	0.8-1.3	10 (38.5)	1.2	0.7-2.0
Either	**138 (79.8)**	**1.3**	**1.1-1.4**	**64 (48.9)**	**1.5**	**1.1-1.9**
Which is more concerning						
Abnormal Pap	99 (67.8)	1		35 (37.6)	1	
HPV Positive	40 (78.4)	1.2	1.0-1.4	14 (38.9)	1.0	0.6-1.7
Equally concerning	238 (67.4)	1.0	0.9-1.1	90 (40.4)	1.1	0.8-1.5
If HPV test only, how much concern about not having a Pap smear						
None	103 (85.8)	1		48 (49.5)	1	
Slight	147 (73.1)	0.9	0.8-1.0	52 (38.0)	0.8	0.6-1.0
Moderate	**90 (54.6)**	**0.6**	**0.5-0.7**	29 (34.5)	0.7	0.5-1.0
Severe	**35 (56.5)**	**0.7**	**0.5-0.8**	10 (31.3)	0.6	0.4-1.1
Perceived Risk of Warts						
None/Low	357 (68.9)	1		132 (39.4)	1	
Moderate/High	17 (63.0)	0.9	0.7-1.2	5 (35.7)	0.9	0.4-1.9
Perceived Risk of HPV						
None/Low	339 (68.9)	1		122 (38.4)	1	
Moderate/High	38 (66.7)	1.0	0.8-1.2	17 (50.0)	1.3	0.9-1.9
Perceived Risk of Cervical Cancer						
None/Low	338 (71.2)	1		119 (37.7)	1	
Moderate/High	**39 (68.7)**	**0.7**	**0.6-0.9**	20 (55.6)	1.5	1.1-2.0

* Abbreviations: N=number, %=percent, BL=baseline, **bold** = $p<0.05$

Supplemental Table S4.1: Screening Survey Questions

Is your primary care provider a(n):
- Internist/ Family Practitioner
- Physician's Assistant (PA)
- Nurse Practitioner
- Gynecologist
- Other Medical Specialist
- No primary care provider
- Don't know/ can't remember

To the best of your knowledge, in the last 5 years have you had a(n)…? (Check all that apply)
- General health check-up or physical exam
- Cholesterol test
- Diabetes screen or blood glucose test
- Dental exam
- Clinical breast exam
- Mammogram

When did you have your last Pap smear?
- Within the last year
- Within the last 3 years
- Within the last 5 years
- Within the last 10 years
- More than 10 years ago
- Don't know/ can't remember

When do you expect to have your next Pap smear?
- Within a year
- Within 2 years
- Within 5 years
- More than 5 years from now
- Am not planning to have another
- When doctor/ healthcare provider recommends it
- If I have symptoms
- Don't know

How often do you think a woman your age should have a Pap smear?
- More than once a year
- Every other year
- Every 3-5 years
- Every 5-10 years
- Every 10 years or longer
- Don't know

The American College of Obstetricians and Gynecologies (ACOG) recently changed Pap smear recommendations for screening to every 3 years for healthy woman over age 30 with a history of 3 consecutive normal Pap smears. Have you heard about this change in guidelines?

- No
- Yes
- Don't know

Would you have a Pap smear every three years (instead of yearly) if your healthcare provider recommended it?

- No
- Yes
- Don't know

Why would you have Pap smears yearly instead of every 3 years? (select all that apply)

- Early detection
- Family history
- Prior history of abnormal Paps
- Concern for new exposure (partner change)
- Fear/ anxiety
- Other, specify _____

Studies show that the risk of a pre-cancerous lesion within 5 years of a normal Pap result and a negative high-risk HPV test result is nearly 0%. Would you get screened once every 5 years if both your Pap and HPV results were normal?

- No
- Yes
- Don't know

If you were getting a Pap and/or HPV test once every 3-5 years, would you still continue to see your gynecologist every year for an annual exam even if you were not due for a Pap smear?

- No
- Yes
- Don't know

What would be your primary reason for seeing the GYN if you did not need a Pap test?

If you could choose to be screened only with a Pap smear or only with an HPV test, which would you choose?

- Pap smear only
- HPV test only
- No difference/ either one

Which would cause you more concern and/or anxiety, an abnormal Pap smear or a positive HPV result?

- Abnormal Pap smear
- Positive HPV result
- Equally concerning

If guidelines changed and HPV screening was recommended as the primary screen for cervical cancer over Pap testing, how much concern or anxiety would you feel about not having a Pap test?
No concern or anxiety
Slight concern or anxiety
Moderate concern or anxiety
Severe concern or anxiety
What do you think is the chance that you will get an HPV infection in the future?
No chance/ low chance
Moderate/ high chance
What do you think is the chance that you will get genital warts in the future?
No chance/ low chance
Moderate/ high chance
What do you think is the chance that you will get cervical cancer in the future?
No chance/ low chance
Moderate/ high chance

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Chapter 5: Conclusion and Future Directions

Summary of Results:

This dissertation aimed to examine the impact of revised cervical cancer screening guidelines on both patients and health care systems. Updated several times over the last decade, newer guidelines continue to emphasize evidence-based medicine and the balance between benefits and harms. As a result, these updates have included recommendations for the addition of HPV testing and extending the time between screening tests following a normal result. However, these policy changes have been met with anxiety and concern among both patients and providers. Understanding the patterns of acceptance versus reticence to accept evidence-based guidelines by health systems, providers, and patients is critical to developing successful strategies for translation into routine practice so that we can continue to prevent cervical cancer while minimizing the harms associated with screening.

Here we fill some of these knowledge gaps by incorporating both actual cervical cancer screening practice data and patient perspectives towards HPV testing and screening interval changes through several specific aims: 1) To examine trends in cervical cancer screening practices from 2001-2013 in a large academic medical center by a) describing the uptake of co-testing in this medical system between and examining the correlates of receiving an HPV co-test during this period and b) estimating the length of time until the next screening test following either a negative Pap smear alone or a dual negative co-test and comparing these times by age, race, and insurance; 2) investigating the correlates of reluctance to adhere to revised guidelines, which recommend the addition of HPV testing along with less frequent cervical cancer screening.

In chapter 2, we used data from the Pathology Data System (PDS) at Johns Hopkins Hospital to examine the incorporation of HPV testing into routine cervical cancer screening. We found a steady increase in the proportion of screening tests in women aged 30 years and older that included an HPV co-test, from under 10% in 2006 to almost 80% in mid-2013. In the earlier years we also saw differences in the percent of women being co-tested by age, race, and insurance type; however these differences narrowed with time as co-testing became more common overall. In addition to differences in who received co-tests, we found large heterogeneity amongst the clinics in this single medical system—some clinics performed essentially no co-testing, while in others co-testing approached 90%. We also saw that clinics with a majority black population seemed to have earlier uptake of co-testing. To determine whether these clinic-level differences and the clustering of patients within clinics affected our prevalence estimates, we used adjusted multivariate log-binomial models with robust standard errors, and then to account for the clustering of observations within clinics, ran the same models with the addition of a random-effect variable for clinic. With the addition of this clinic adjustment, almost all significant associations attenuate greatly, with many becoming non-significant, showing that the differences by race and insurance were determined at the clinic level, not the individual level.

Over the three time periods examined, the proportion of clinics that co-tested over 75% of patients increased from under 10% to almost 50%, while the proportion of clinics co-testing <25% of patients decreased from over 60% to about 20%. These findings suggest

that clinic-wide policies may be important determinants driving clinical practice. This finding is promising as it suggests that a top-down clinic-level intervention may be as effective as a more broad target of individual provider behavior change.. (1)

In chapter 3, we used the same PDS data to explore the uptake of newer screening guidelines beyond just the addition of HPV testing—we examined the time between screening tests for both cytology alone and Pap/HPV co-testing followed the recommendation to extend the interval between tests. Overall, we saw a coinciding increase in screening intervals with increasing rates of co-testing, but almost no change in screening intervals following cytology alone. Larger differences in time to next screen were seen by age, race and insurance following co-testing than following cytology. When median times to next screening test were stratified by both race and ethnicity, a somewhat different pattern emerged. The only significant difference between races for co-testing was among women with private insurance. Initial differences by race were also seen among Medicare recipients; however, those racial differences diminished over time. There was also very little difference by race in interval length among women with either Medicaid or Tricare insurance with either testing method. The steepest increase in interval length was seen among black and white women with Tricare, increasing by almost 2 years during the study period.

Given the effects we saw by age, race, and insurance in co-test uptake (chapter 2), we also ran adjusted multivariate cox proportional hazards models determine whether there were also differences in screening intervals by age, race, and insurance. We saw

essentially opposite trends for cytology and co-testing. For cytology, older women had a higher hazard of returning compared to younger women and compared to white women with private insurance, all other race and insurance groups had a lower hazard of returning. At the same time though, for co-testing, older women had a lower hazard compared to younger women, and almost all race and insurance categories had higher hazards than white women with private insurance. However, considering the clinic-level effects demonstrated in co-test uptake (chapter 2), we also ran the screening interval models with the addition of a shared frailty term for clinic, so that records from the same clinic are assumed to have the same frailty, which accounts for the clustering of women within a clinic. With this adjustment, we found many of the significant differences disappeared, though a few remained. Both black and white women with Medicare continued to have a lower hazard ratio following cytology, while black women with private insurance or Medicaid continued to have higher hazards.

Overall, these analyses demonstrated that along with an increase in co-testing, there was an increase in the median time before the next screening visit following a normal co-test result, with intervals increasing from 2006 when broader co-test uptake began through mid-2010. The steady increase in this trajectory suggests that given more follow-up time the screening interval may reach three years, which was the recommendation since at least 2003. More time will be needed to see whether the most recent 2012 recommendation of 5 year intervals after a dual negative co-test is being followed. These guidelines also stated that annual Pap smears were unnecessary and specifically recommended against them, and stated that if screening was done by cytology alone,

return screening should be every three years. We saw very little evidence of a lengthening interval among who were screened by cytology alone over the last ten years in this population, remaining steadily around 1.5 years, suggesting a pattern of continued over-screening. The time to next screening visit following negative cytology is almost a year shorter than the recommended 3-years across all races and insurance types. Similarly, co-testing is only recommended once every five years, or else any comparative benefit is lost, and yet no race or insurance group was screened less often than once every three years. Notably, black women are only being screened approximately every 2 years after co-testing by both private insurance and Medicare/Medicaid, which is less than half the recommended interval. This greatly increases the likelihood of false positives and negates the high negative predictive value that makes co-testing beneficial.

In chapter 4, we incorporated the patient's perspective about changing cervical cancer screening recommendations using data collected in the HPV in Perimenopause (HIP) natural history study of women age 35-60 years. We compared women who indicated willingness versus reluctance to accept primary HPV-only testing or a longer interval between cervical cancer screening tests by the following factors: demographics, age, health status, cervical cancer screening history, sexual history, perceived HPV and cervical cancer risk, and participation in preventive health programs. This cohort provided a unique opportunity to simultaneously evaluate a women's self-reported perceived risk and their actual risk of cervical cancer based on intensive measurement of HPV and cervical cancer risk markers over a 2-year period. In this analysis, we found a majority of women were aware that screening recommendations had changed, yet most

still believed women should be screened annually. If recommended by their doctor about two-thirds were willing to extend screening to every three years, but only a quarter would extend screening to five years. Most women also expressed a strong preference for Pap testing, and many expressed at least moderate concern over having an HPV test without a Pap test. A desire for more frequent care, higher degree of worry and perceived risk, and abnormal screening history were all associated with reduced willingness to accept HPV testing and longer screening intervals.

Overall we found a majority of study participants indicate a willingness to adopt a cervical cancer screening strategy of cytology alone or Pap-HPV co-testing every 3 years if recommended by their physician, but remain concerned about primary HPV testing and co-testing with 5-year screening intervals. Our results suggest continued reticence to accepting newer HPV-based screening algorithms among routinely screened women over age 35. This observation is especially relevant in light of the recent FDA approval of one HPV test for an indication of primary cervical cancer screening (2) and that future US guideline revisions are likely to consider recommendations for primary screening using HPV testing, especially given the transition to primary HPV screening by other large national screening programs such as those in Australia (3) and the United Kingdom (4). These results suggest that educational interventions to communicate risks associated with alternative screening test results are needed in order for women to understand alternative screening choices, and contribute to a significant gap in the evidence regarding patient perceptions of benefits and harms of screening, which have been underrepresented in cervical cancer screening guideline development

Public Health Implications:

The findings of this dissertation highlight several important considerations when translating updated evidence-based cervical cancer screening guidelines into routine practice. Themes of communication, education, and the need for large-scale policies re-appeared throughout this research.

Through our work on this study, we had heard anecdotally from both patients and providers about some of these issues. Clinicians mentioned that they weren't extending screening intervals because their patients wouldn't accept them, while many patients said they were unaware that screening recommendations had even changed from annual Pap smears. If patients and clinicians aren't communicating about the changes, it will be hard to break this cycle, though first the guidelines must be effectively communicated from those who make them to those for whom they are intended. It is important that both patients and providers are clearly educated about why the guidelines changed, how they were determined, and what the clinical implications are, so that both parties can feel comfortable with the changes. This research also demonstrates the importance of buy-in from all parties affected by screening guidelines. Going forward, we believe that assessing patient and provider attitudes and concerns and refining recommendations prior to publicizing changes would be a critical step in easing the transition to such changes.

Another important finding resulting from this research was the potential influence of clinic-level practices in determining what screening guidelines would be followed by

individual physicians. Within a single academic medical system, we found tremendous variability in rates of co-testing and screening intervals by clinic. In one instance for example, we did find that a clinic that adopted a clinic-wide policy had relatively quick and complete uptake of HPV co-testing (1), (Chapter 3). Additionally, women in this clinic with a uniform co-testing policy were slightly more likely to accept extended intervals (Chapter 2). Taken together, these results support the idea that a top-down approach to determining routine practice—both at the clinic-level and perhaps even a system-wide level – may be more effective than targeting behavioral interventions to individual physicians. This would, however, still require sufficient education of patients and providers with information that specifically addresses their concerns about changing screening practice. The greater and more rapid adoption of extended screening interval guidelines by government-funded insurance types, which have changed some of their policies to only reimburse screening every two years, also suggests that system-level changes in reimbursement coverage are also effective in translation of evidence based guidelines to clinical practice.

While this research focused on cervical cancer in particular, many of these findings can be applied to future screening guideline revisions for other cancers or health conditions as the emphasis towards evidence-based medicine grows. Recently, there have been changes to breast cancer, prostate cancer, and lung cancer screening, and it will be important to carefully examine their implementation, uptake, and effectiveness based on what we have learned from cervical cancer screening.

Future Directions:

Although this dissertation addressed several knowledge gaps in the implementation of evidence-based screening guidelines, it also uncovered several new questions, some of which can only be answered with more time. For example, we were only able to look at data regarding the time between routine negative screens through mid-2010 in order to leave at least 3 years for follow-up (the longest recommended interval at that time). While we do see evidence of longer time until next screen following a dual negative co-test, we were unable to look at the effects of the most recent guidelines changes from 2012. It will take several more years of follow-up to determine whether Pap intervals are being extended to 3 years and co-test intervals to 5 years. Given the lack of willingness to wait 5 years for screening among women in the HIP study, this will be particularly important moving forward.

Extending follow-up of the HIP Cohort (or a similar cohort with detailed information on attitudes and intentions), with linkage to their medical records, will enable us to determine to what extent a woman's stated intentions match her actual practice. As women were enrolled into our study for 2 years of follow-up, it was not a long enough time to accurately assess their screening intervals. Additionally, our questionnaire asked whether woman would be willing to extend intervals or would they feel concerned about HPV testing, and while this is important information on it's own, being able to correlate those with a woman's screening tests and intervals going forward would provide additional value. In addition, incorporating qualitative research into this process will provide greater insight into a woman's response. Knowing their concerns is an important

first step, but in order to address them it is crucial to understand what is motivating their beliefs—whether it's a lack of information, fear, or misunderstanding will help determine what type of education or other intervention would be most effective.

An additional piece of information that we were unable to obtain directly was the provider's knowledge of the guidelines and what information they discuss with and recommend to their patients. We used actual screening practice from laboratory records as a proxy for clinical practice as it shows the outcome of the interaction between patient and provider. However, this does not capture the entire interaction, and so surveys, interviews with physicians, or direct observation of patient-provider discussions would provide more detail about what information is conveyed and what questions patients express. This provides an additional opportunity to include a mixed methods approach by incorporating a qualitative assessment of a physician's reaction to and comfort with the changing recommendations.

It will also be important to verify our findings using a more representative dataset than just women in Baltimore, MD. For example, a population-based cervical cancer registry, such as the New Mexico HPV Pap Registry (NMHPVPR), which has data for all cervical cancer screening, diagnosis, and treatment in the state will be a valuable resource to determine whether our findings replicate on a larger scale (5). Another important next step is to replicate this analysis using comprehensive electronic medical record data, not just laboratory record data as we had access to for this study. This type of record would provide us with much greater information, including all visits a patient had, regardless of

whether screening took place, so we could verify women were still in active follow-up. Furthermore, these records would contain a woman's screening history, which would provide a denominator for the number of women eligible for extended intervals, and demonstrate which high-risk women or women with an abnormal screening history should actually be under more frequent follow-up.

As more and more young women are receiving the HPV vaccine, new challenges arise in determining the most appropriate way to screen vaccinated women. While the introduction of a primary prevention tool for cervical cancer has been a critical development in the fight against cervical cancer, it also raises several new questions and concerns about screening in the post-vaccine era. As intended, the rates of cervical cancer will continue to decrease with both vaccination and continued screening; however, this reduction in prevalence also reduces the positive predictive value of our screening methods, leading to more false positives and all of the follow-ups and procedures that may result. As a result newer screening strategies with alternative testing and triage algorithms are being evaluated, and the efficiency of screening becomes an even higher priority.

Conclusion:

Evidence-based recommendations are valuable only if broadly implemented in routine clinical and public health practice. However, key components to effective translation, including perceptions and acceptance of screening recommendations by the target population, are often absent from the evidence. We addressed this gap by providing a

comprehensive assessment of the uptake of recommendations in a large academic medical center and identifying potential patient-specific characteristics, which may affect efficient translation. Understanding uptake of new technologies and screening recommendations into routine practice is important for streamlining implementation of future changes and ensuring healthcare is delivered appropriately and effectively. Importantly, these findings are likely applicable across conditions as evidence-based medicine and cost-effectiveness grows in importance.

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2. FDA. FDA approves first human papillomavirus test for primary cervical cancer screening. In; 2014.

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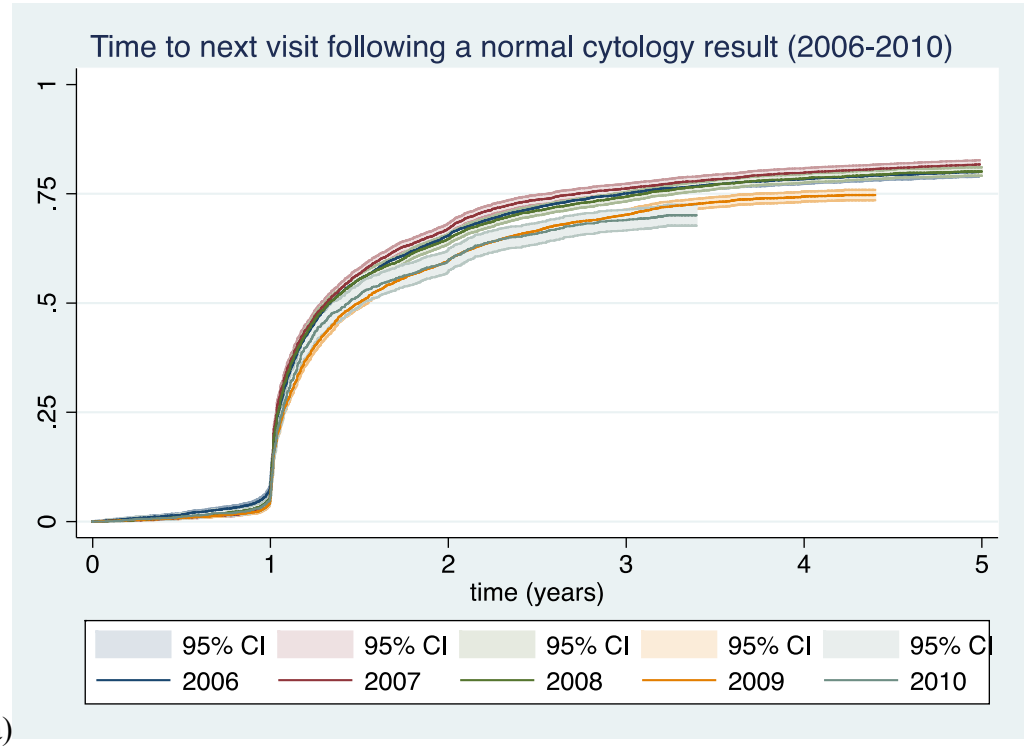
5. Cuzick J, Myers O, Hunt WC, Robertson M, Joste NE, Castle PE, et al. A Population-Based Evaluation of Cervical Screening in the United States: 2008–2011. Cancer Epidemiology Biomarkers & Prevention 2014;23(5):765-773.

Appendix 1: Kaplan-Meier curves for distribution of screening interval lengths

Methods

Time to next screening visit (screening interval) was summarized using Kaplan-Meier curves, and stratified by several variables, including cytology alone versus co-test, year of screening, age, race, and insurance.

Figure A1.1: Time to next screening test by year and test method



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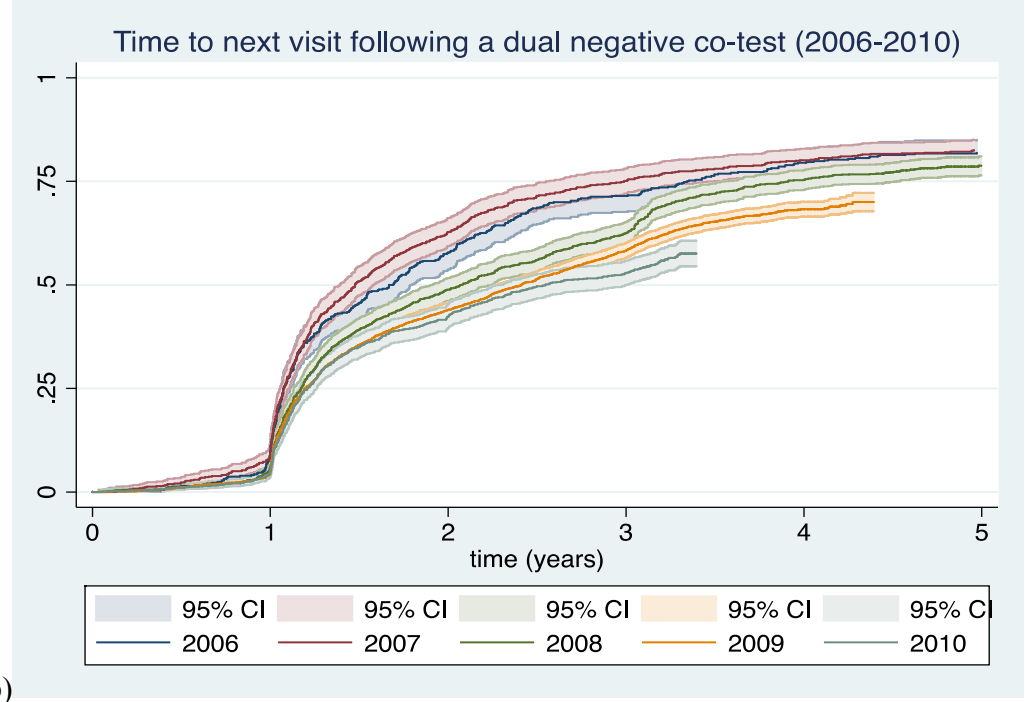

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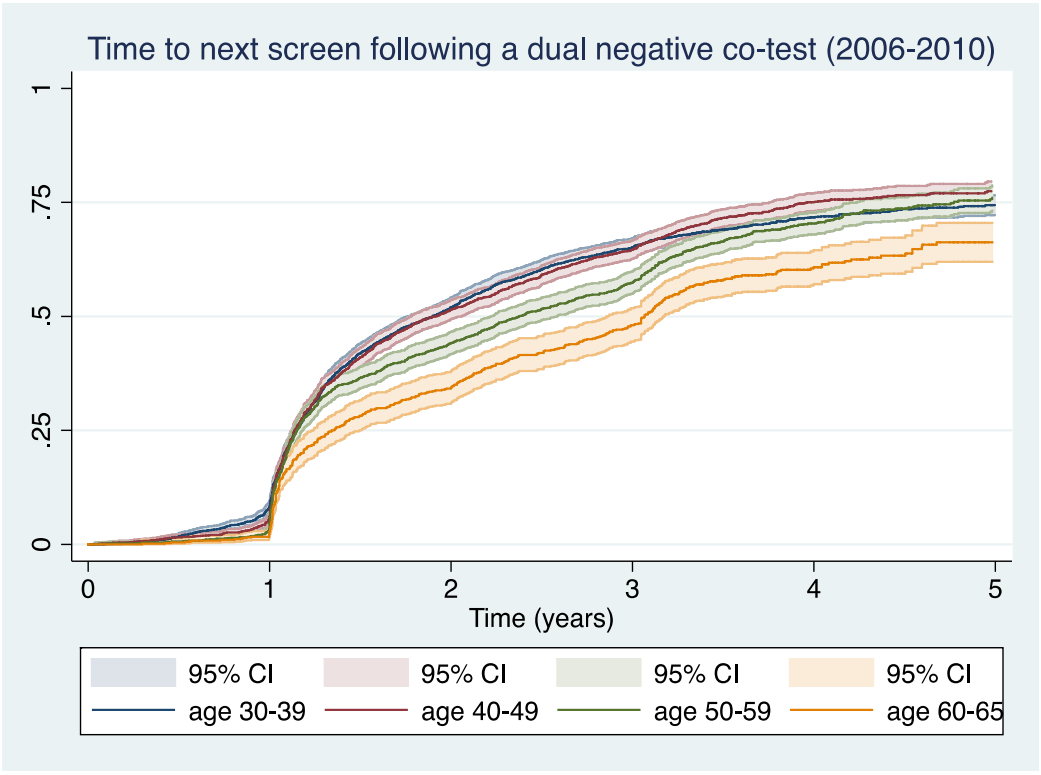
Figure A1.2: Time to next screening test by age and test method



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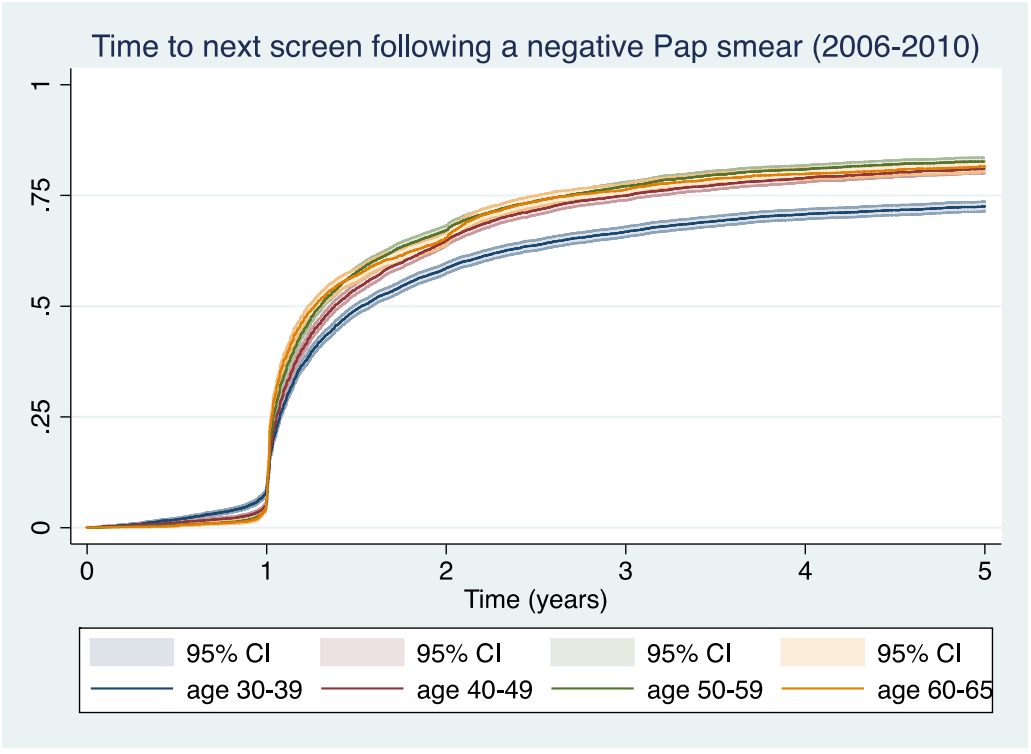
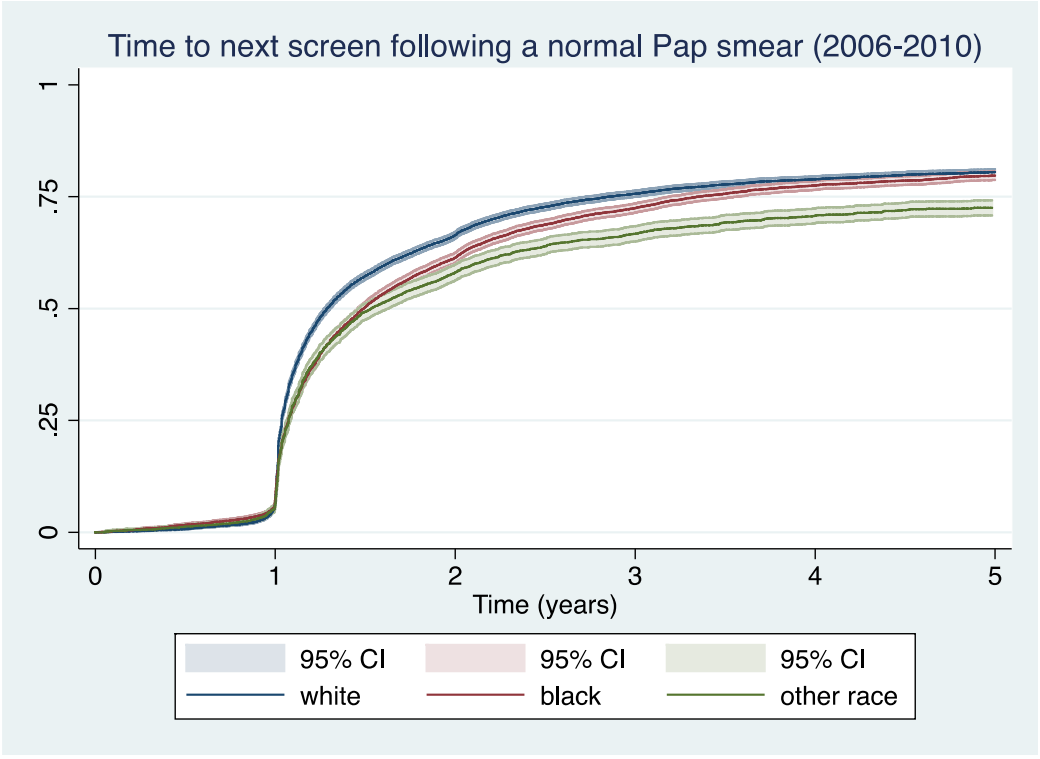


b)

Figure A1.3: Time to next screening test by race and test method

a)



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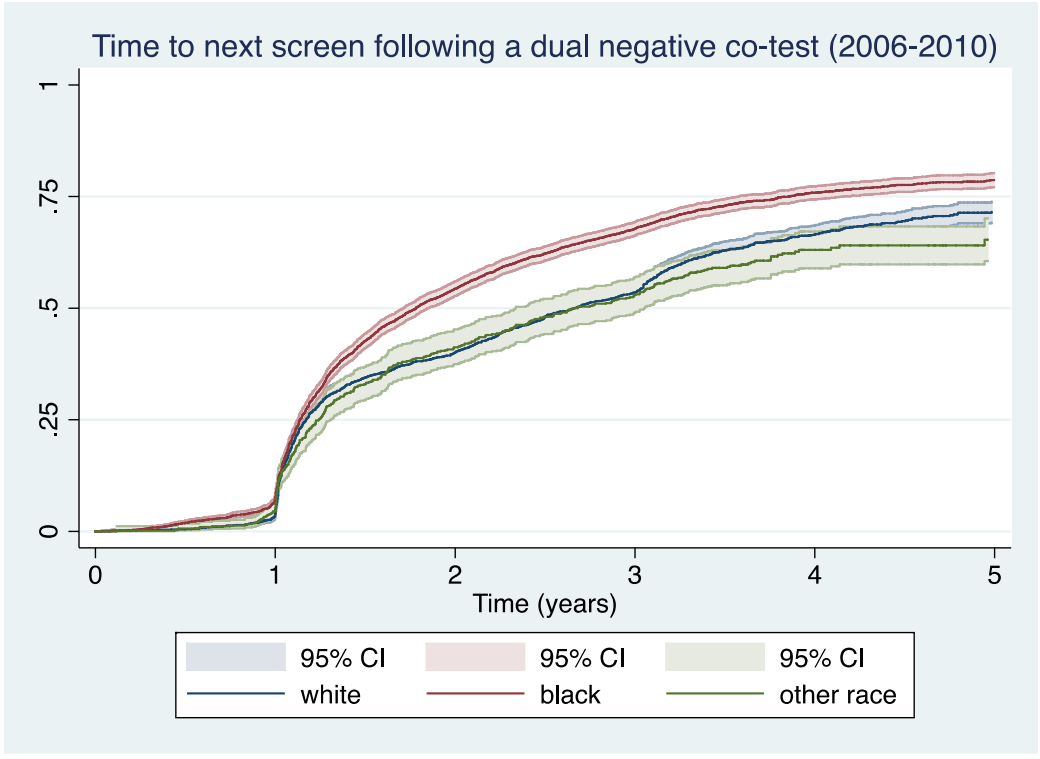
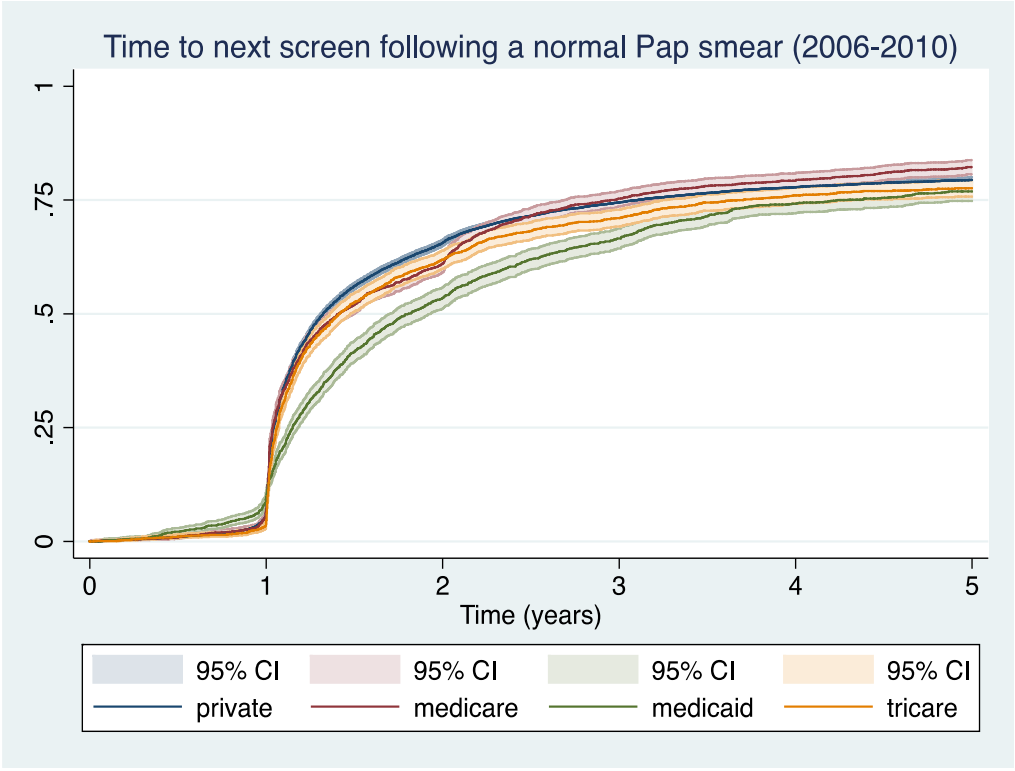


Figure A1.4: Time to next screening test by insurance and test method



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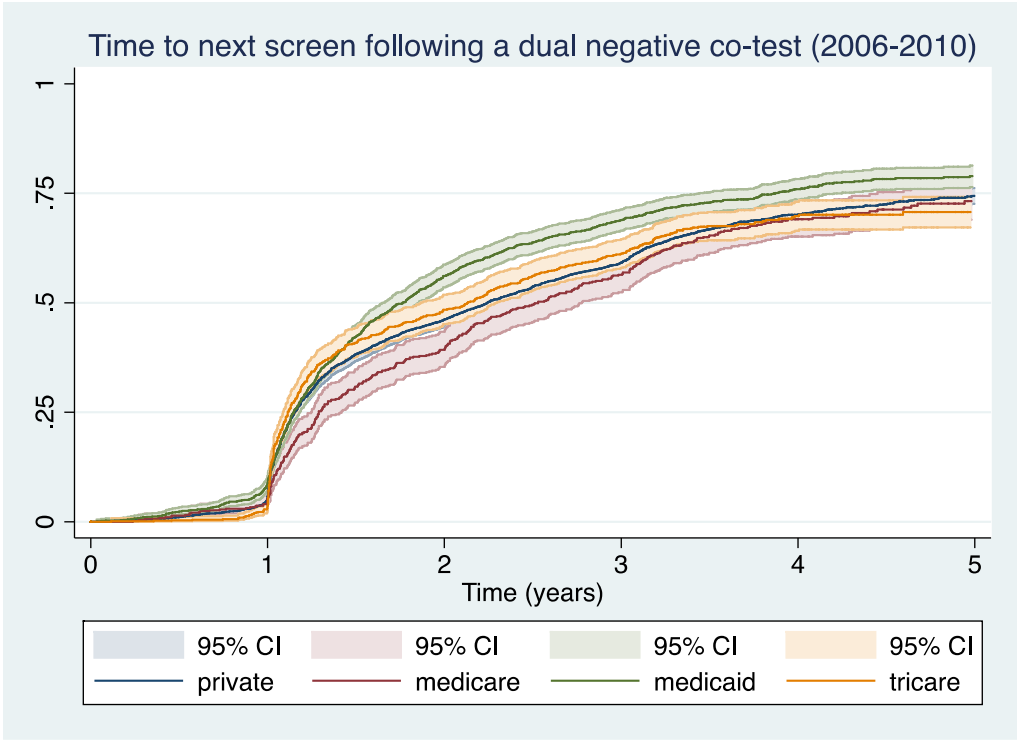

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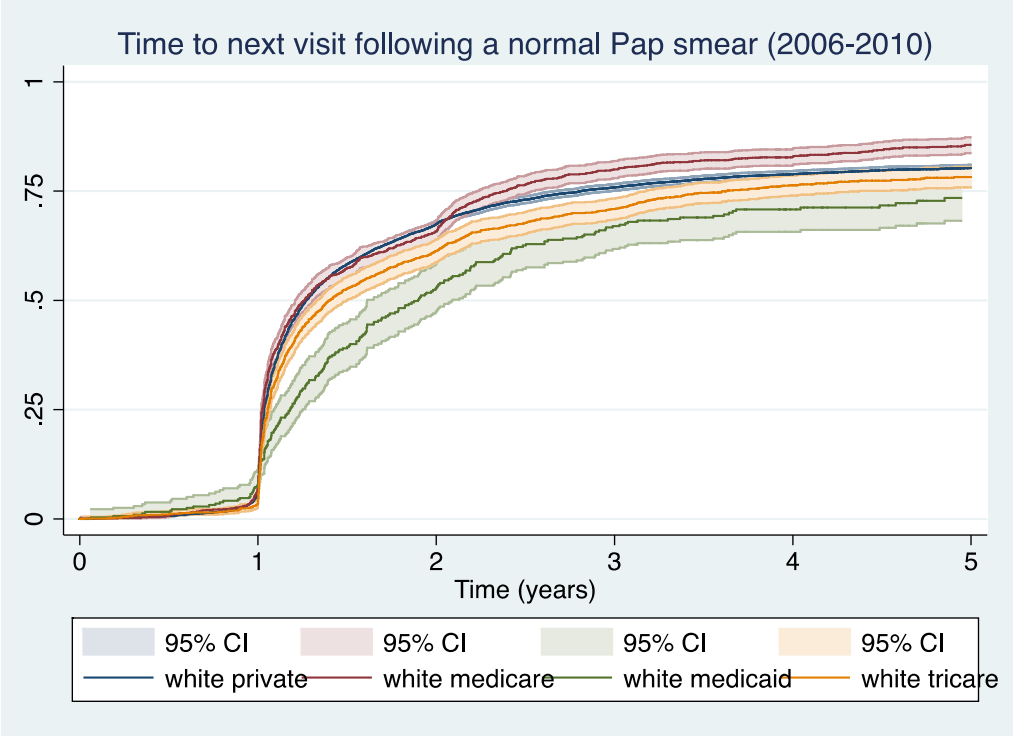
Figure A1.5: Time to next screening test by race/ insurance and test method

a)



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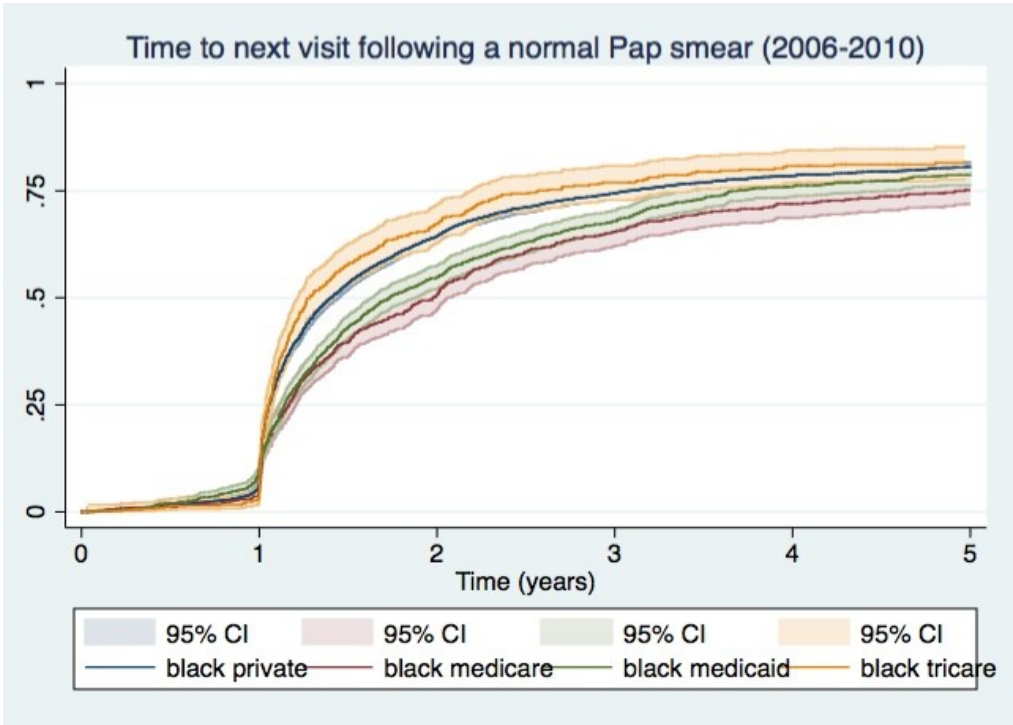

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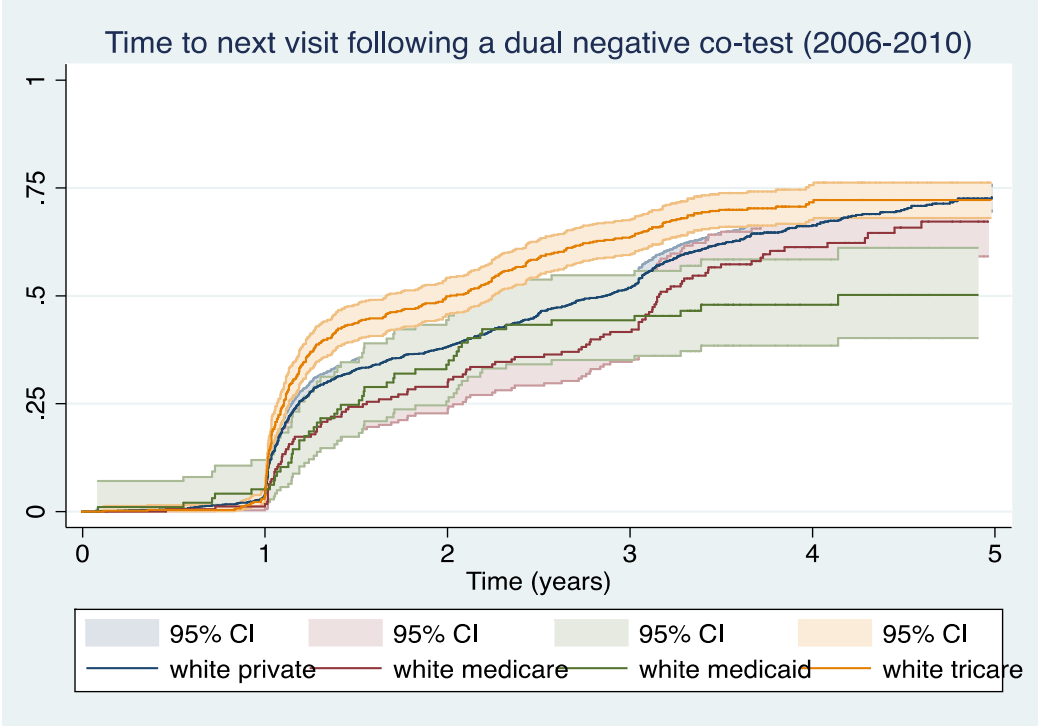
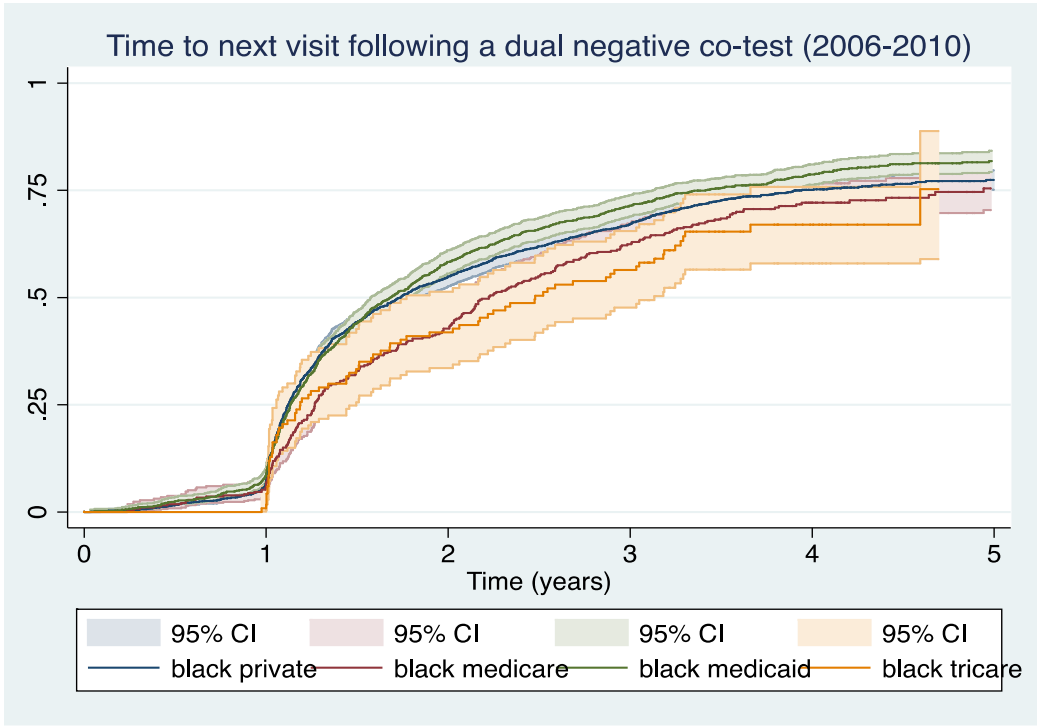

Time to next visit following a dual negative co-test (2006-2010)
0
.25
.5
.75
1
0
1
2
3
4
5
Time (years)
95% CI
95% CI
95% CI
95% CI
white private
white medicare
white medicaid
white tricare

d)


Time to next visit following a dual negative co-test (2006-2010)
0
.25
.5
.75
1
0
1
2
3
4
5
Time (years)
95% CI
95% CI
95% CI
95% CI
black private
black medicare
black medicaid
black tricare

Appendix 2: Classification and Regression Tree Analysis (CART) for the HIP Study

Methods

As an alternative to traditional regression analyses, we also explored the use of Classification and Regression Tree (CART) analysis (non-parametric binary recursive partitioning) to determine the variables able to separate our population into distinct subgroups of women based on their willingness to extend to five years, three years, or not willing to extend at all. CART analysis provides an alternative way to understand how characteristics clustered and predicted willingness than a traditional multivariable regression model. The Gini impurity index was used as the decision criterion for node splits in order to minimize misclassification. After fitting, the tree was pruned using cross-validation. Poisson regression with robust error variance was then used to assess correlates of the variables selected by the CART analysis. Regression analyses were carried out in Stata version 13.1 and CART analysis was carried using RStudio version 0.98.501 and R version 3.1.0.

Classifying women into groups of willingness (CART)

Classification and regression tree (CART) analyses were used to identify subgroups of participants within our study and the shared characteristics or beliefs that influence their attitudes toward adopting extended intervals for cervical cancer screening. The final pruned classification tree (Figure 1) identified seven variables that best split the study population into three groups (those willing to extend to five years, those willing to extend to three years only, and those not willing to extend at all). Three of those variables are fixed characteristics (recent sexual activity, age, marital status) and four were based on

attitudes and beliefs (concern about not having a Pap smear, expected time until next Pap smear, whether a women would still have an annual exam if she wasn't having a Pap smear, and perceived risk of cervical cancer). The strongest factor predicting whether a woman would extend screening to at least three year intervals was if she said not having a Pap smear would give her none or only slight anxiety, while those reporting moderate to severe anxiety were likely to prefer to continue with annual screening. Women who expected to have their next Pap smear in a year and those who perceived themselves to be at a moderate or high risk of developing cervical cancer in the future were also unlikely to agree to extended screening intervals. Younger women and women who had never been married were most likely to accept five year screening intervals.

Correlates of Attitude and Belief Variables Selected in CART

We then explored the determinates of the four attitude and belief variables identified as determining a woman's willingness to extend screening, as these could offer insight into the development of future education or intervention (Table 1). Women seemed to have a good sense of their personal risk of cervical cancer—former and current smokers were more likely to report a moderate or high perceived risk of developing cervical cancer in the future compared to women who never smoked (PR: 1.79, 95% CI: 1.10-2.94, PR: 2.76, 95% CI: 1.60-4.77, respectively), as were obese women (PR: 1.73, 95% CI: 1.03-2.90), and women with a prior history of abnormal Pap smears (PR: 2.06, 95% CI: 1.31-3.24) or colposcopies (PR: 1.55, 95% CI: 0.99-2.43). Likewise, woman with 5 or more lifetime sex partners (PR: 1.76, 95% CI: 1.09-2.86) and women who had an abnormal

Pap smear during the two years of follow-up (PR: 1.94, 95% CI: 1.05-3.58) reported higher perceived risks of cervical cancer.

Those women most concerned about having a primary HPV test instead of a Pap test were those with moderate or high perceived risk of cervical cancer (PR: 1.46, 95% CI: 1.16-1.84), recent abnormal Pap smears (PR: 1.40, 95% CI 1.07-1.82), current smokers (PR: 1.68, 95% CI: 1.30-2.17), and those who believed women should have more frequent screening (PR: 1.68, 95% CI: 1.29-2.18). Post-graduate education (PR: 0.70, 95% CI: 0.52-0.93) and believing that women should have Pap smears less often than every year was associated with less concern switching from Pap to HPV testing (every other year PR: 0.51, 95% CI: 0.33-0.78, every 3-5 year testing PR: 0.38, 95% CI: 0.18-0.79). Women who preferred HPV testing (PR: 0.29, 95% CI: 0.14-0.61) or who didn't have a test preference (PR: 0.71, 95% CI: 0.56-0.89) were less likely to be concerned about a change to HPV testing.

Women aged 55-60 were more likely to report an interval of greater than one year before they expected to have their next Pap smear (PR: 1.72, 95% CI: 1.00-2.96). Women who were currently or formerly married were more than twice as likely to wait more than a year for their next Pap smear than women who had never been married (PR: 2.66, 95% CI 1.27-5.60, PR: 2.65, 95% CI: 1.20-5.86). Women who were aware of the change in guidelines at the time of the questionnaire and women seen in the practice that implemented routine Pap/HPV co-testing were also twice as likely to wait more than a year before their next screen. Women with a history of abnormal Pap smears (PR: 0.64,

95% CI: 0.44-0.91), colposcopies (PR: 0.55, 95% CI: 0.34-0.91) and those who tested HPV positive by hc2 (PR 0.30, 95% CI: 0.08-1.15) or did not have a clinical HPV test (0.48, 95% CI: 0.31-0.72) during the study were more likely to expect their next Pap smear within a year.

Non-white women were more likely to state that they would continue to see their doctor for annual exams regardless of whether they were having a Pap smear that year (Black PR: 1.14, 95% CI: 1.03-1.28, Other races PR: 1.23, 95% CI: 1.09-1.39). Similarly, women who reported having any concern about changing to primary HPV testing were more likely to continue annual exams even without screening. Current smokers were nearly 20% less likely to continue annual exams without screening (PR: 0.78, 95% CI: 0.62-0.99).

Figure A2.1: Classification and Regression Tree (CART)

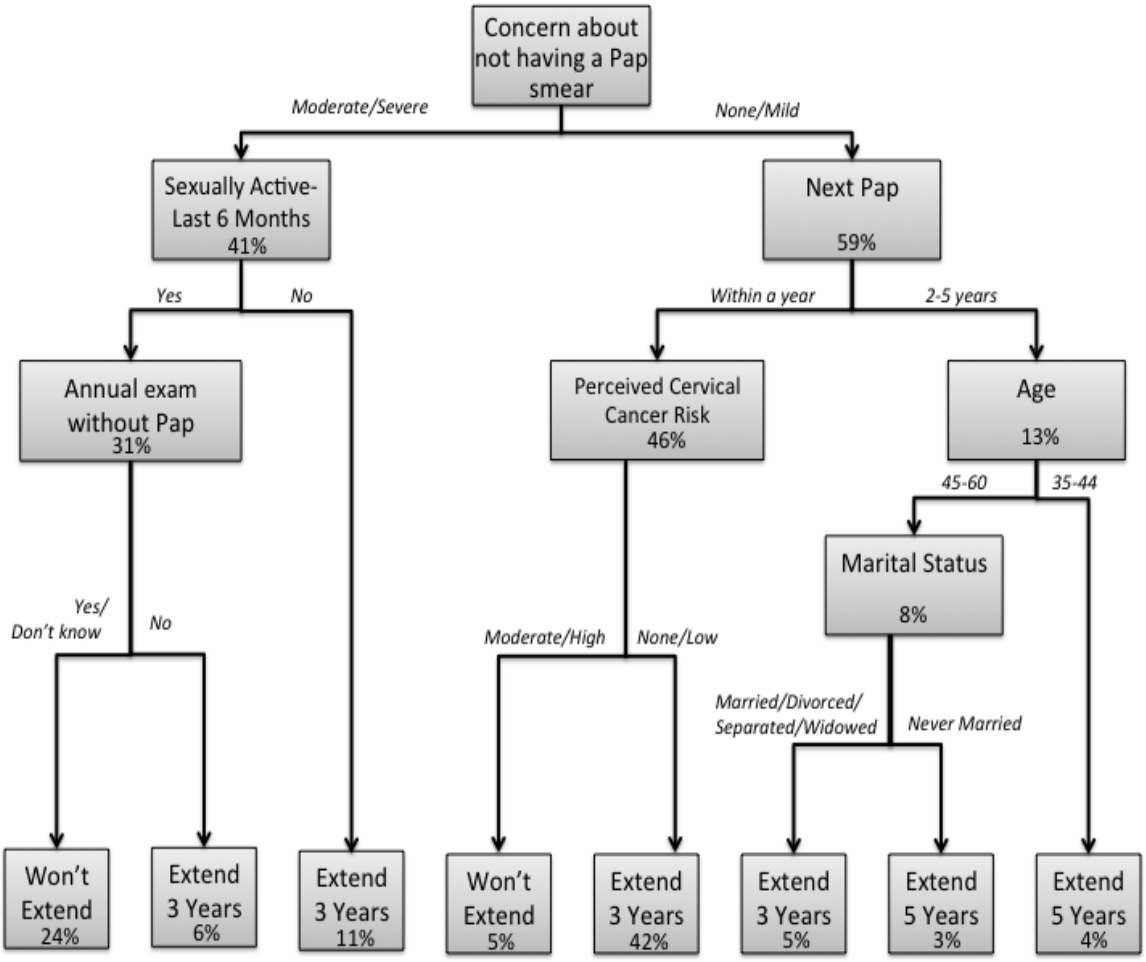


Table A2.1: Correlates of Attitude and Belief Variables Selected in CART

		Perceived risk cervical cancer		Concern about no Pap smear		Next expected pap		Annual without Pap	
		PR	CI	PR	CI	PR	CI	PR	CI
Demographics									
Age	35-39	1		1		1		1	
	40-44	0.92	0.47-1.80	1.51	1.09-2.10	1.06	0.59-1.89	1.02	0.88-1.20
	45-49	0.67	0.33-1.34	1.14	81-1.60	1.17	0.69-2.00	1.1	0.96-1.27
	50-54	1.36	0.74-2.48	1.2	0.85-1.70	0.74	0.39-1.38	0.94	0.79-1.11
	55-60	0.59	0.25-1.38	0.97	0.64-1.47	1.72	1.00-2.96	0.99	0.83-1.18
Race									
	White	1		1		1		1	
	Black	1.21	0.72-2.04	1.34	1.06-1.69	0.67	0.39-1.15	1.14	1.03-1.28
	Other	0.38	0.10-1.49	1.26	0.90-1.78	0.83	0.41-1.66	1.23	1.09-1.39
Income									
	<40	1.57	0.77-3.19	1.12	0.77-1.64	0.86	0.40-1.82	0.98	0.80-1.19
	40+	1		1		1		1	
	Unknown	1.17	0.64-2.12	1.08	0.82-1.43	1	0.61-1.64	0.99	0.86-1.14
BMI									
	Normal	1		1		1		1	
	Overweight	1.24	0.72-2.14	1.14	0.90-1.46	1.16	0.78-1.73	0.98	0.88-1.10
	Obese	1.73	1.03-2.90	1.26	0.99-1.61	1.15	0.76-1.76	1.04	0.93-1.16
Clinic									
	GSS	1		1		1		1	
	WM	1.49	0.97-2.30	1.17	0.95-1.44	2.02	1.42-2.85	1.05	0.95-1.16
	BV/GCRC/JHOC	0.8	0.26-2.47	1.19	0.79-1.7	0.42	0.11-1.67	1.06	0.88-1.29
Married									

	Never	1		1		1		1	
	Div/Wid/Sep	1.39	0.64-2.98	0.92	0.66-1.30	2.65	1.20-5.86	1.03	0.87-1.22
	Married	1.3	0.67-2.55	0.99	0.75-1.31	2.66	1.27-5.60	1.05	0.92-1.21
Education									
	High school or less	1		1		1		1	
	Some post HS	0.83	0.43-1.60	0.89	0.66-1.20	0.69	0.36-1.31	1.01	0.86-1.18
	College graduate	0.58	0.30-1.11	0.86	0.65-1.13	1.35	0.81-2.24	1	0.87-1.16
	Post graduate	0.83	0.46-1.50	0.7	0.52-0.93	0.9	0.52-1.54	0.96	0.83-1.11
Smoking									
	Never	1		1		1		1	
	Former	1.79	1.10-2.94	1.26	0.99-1.59	1.09	0.72-1.65	0.97	0.86-1.09
	Current	2.76	1.60-4.77	1.68	1.30-2.17	1.01	0.54-1.88	0.78	0.62-0.99
Menopausal Status									
	Pre	1		1		1		1	
	Peri	1.12	0.68-1.85	0.79	0.62-1.01	1.07	0.71-1.61	0.93	0.83-1.04
	Post	1.04	0.61-1.77	0.9	0.71-1.14	1.15	0.76-1.73	0.9	0.80-1.01
	Not Classified	0.59	0.09-1.02	0.5	0.18-1.36	0.82	0.22-3.03	0.77	0.50-1.18
Screening History									
Ever Abnormal Pap (BL)									
	No	1		1		1		1	
	Yes	2.07	1.32-3.24	1.11	0.91-1.36	0.64	0.44-0.91	0.98	0.89-1.08
Time Since Last Abn (BL)									
	No Abn	1		1		1		1	
	0-5 years	2.02	1.05-3.86	1.4	1.07-1.82	0.34	0.14-0.81	1.01	0.87-1.17
	6+ years	2.1	1.31-3.38	1.03	0.82-1.30	0.76	0.53-1.11	0.97	0.87-1.08
	Don't know	2.1	0.71-6.21	0.95	0.50-1.83	0.53	0.14-1.96	1.06	0.83-1.35

Ever Colpo (BL)								
No	1		1		1		1	
Yes	1.55	0.99-2.43	1.21	0.98-1.50	0.55	0.34-0.91	0.88	0.78-1.00
When was last pap								
W/in last year	1		1		1		1	
1-5 years ago	1.01	0.79-1.28	0.81	0.46-1.42	1.55	1.08-2.24	0.92	0.81-1.05
Don't Know	0.8	0.16-4.00	--	--	3.84	1.68-8.78	0.86	0.39-1.93
Next Expected Pap								
Within a year	1		1				1	
W/in 2 years	1.12	0.63-1.99	0.88	0.65-1.19			1.01	0.88-1.15
W/in 5 years	--		0.47	0.17-1.29			1.06	0.82-1.37
Don't Know	1.6	0.57-4.48	1	0.54-1.85			1.14	0.91-1.42
Knowledge and Attitudes towards Cervical Cancer Screening & Guidelines								
How often should women have a Pap smear								
Yearly	1		1		1		1	
Every other year	0.53	0.24-1.18	0.51	0.33-0.78	2.51	1.70-3.72	0.96	0.83-1.11
Every 3-5 years	0.37	0.09-1.45	0.38	0.18-0.79	3.69	2.46-5.51	0.93	0.74-1.16
More than once a year	0.65	0.17-2.46	1.68	1.29-2.18	0.68	0.18-2.61	1.25	1.12-1.40
Don't know	0.54	0.08-3.58	0.55	0.21-1.48	3.58	1.93-6.62	0.91	0.63-1.31
Aware of the guideline change?								
No	1		1		1		1	
Yes	0.76	0.50-1.17	0.93	0.76-1.38	2.16	1.46-3.20	1.08	0.98-1.19
Don't Know	1.61	0.29-9.06	1.17	0.43-3.14	--	--	0.55	0.19-1.61
Have annual w/o pap								
No	1		1		1			

Yes	1.41	0.82-2.45	1.23	0.96-1.58	1.2	0.79-1.80		
Don't Know	0.83	0.25-2.73	0.56	0.30-1.13	0.16	0.02-1.16		
Test preference								
Pap Only	1		1		1		1	
HPV Only	0.55	0.18-1.70	0.29	0.14-0.61	1.16	0.62-2.17	0.9	0.73-1.11
Either	1.33	0.86-2.06	0.71	0.56-0.89	1.28	0.90-1.83	1	0.90-1.10
Which is more concerning								
Abn Pap	1		1		1		1	
HPV Pos	1.15	0.47-2.79	0.46	0.24-0.86	1.33	0.75-2.36	0.9	0.71-1.13
Equally concerning	1.5	0.86-2.52	1.19	0.94-1.51	1	0.68-1.49	1.12	0.99-1.25
If HPV test only, how much concern								
None	1				1		1	
Slight	4.18	1.50-11.63			1.14	0.74-1.78	1.17	1.01-1.35
Moderate	5.09	1.83-14.14			0.91	0.56-1.48	1.14	0.98-1.33
Severe	7	2.41-20.37			0.73	0.36-1.47	1.28	1.08-1.50
Perceived Risk of Warts								
None/Low	1		1		1		1	
Moderate/High	3.89	2.39-6.33	0.81	0.47-1.39	0.73	0.29-1.84	1.13	0.96-1.33
Perceived Risk of HPV								
None/Low	1		1		1		1	
Moderate/High	3.41	2.23-5.22	0.98	0.70-1.36	0.59	0.29-1.21	1.05	0.91-1.21
Perceived Risk of Cervical Cancer								
None/Low			1		1		1	
Moderate/High			1.46	1.16-1.84	1.02	0.63-1.67	1.08	0.96-1.22
Risk Factors								
Lifetime Sex Partners								

	<5	1		1		1		1	
	5+	1.76	1.09-2.86	1.21	0.98-1.50	0.92	0.66-1.30	0.91	0.83-1.00
Recent Sex									
	No Sex	1		1		1		1	
	Yes, no new partner	1.09	0.65-1.82	0.98	0.78-1.24	1.03	0.69-1.52	1.04	0.93-1.17
	Yes, new partners	1.3	0.48-3.54	1.16	0.74-1.83	0.61	0.20-1.87	1.14	0.94-1.40
HPV Serology at BL									
	Neg	1		1		1		1	
	Pos	1.3	0.81-2.09	1.04	0.84-1.30	0.87	0.61-1.25	0.99	0.90-1.10
HPV Status (during study)									
	Neg	1		1		1		1	
	Pos	1.51	0.94-2.44	1.02	0.79-1.32	0.8	0.50-1.29	1.03	0.91-1.15
Observed Pap Abnormality									
	No	1		1		1		1	
	Yes	1.94	1.05-3.58	1.18	0.84-1.67	0.13	0.02-0.89	0.92	0.74-1.14
Clinical HPV Testing									
	Negative	1		1		1		1	
	Positive	1.15	0.45-2.96	0.51	0.25-1.04	0.3	0.08-1.15	0.74	0.54-1.03
	Not Tested	0.98	0.63-1.55	0.84	0.68-1.04	0.48	0.31-0.72	0.87	0.78-0.96

Curriculum Vitae

CURRICULUM VITAE

MICHELLE SILVER, PhD, ScM

PERSONAL DATA

Johns Hopkins School of Public Health
Department of Epidemiology
615 N. Wolfe St., Rm. E6139
Baltimore, MD 21205
(516) 972-5117
msilver@jhsph.edu

EDUCATION AND TRAINING

2011- 2014: PhD, Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD
Dissertation: When Less is More: Understanding Factors Influencing Patient and Provider Attitudes and Behavior When Cervical Cancer Screening Guidelines Recommend Less Frequent Screening

2009: Masters of Science (ScM) in Epidemiology, Concentration: Infectious Disease, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD
Thesis: Association between latent herpesviruses and acetowhitening in cervical cancer screening

2007: Bachelor of Arts (BA) in Human Biology, Concentration in Immunology, Infectious Disease, & Public Health, Stanford University, Stanford, CA

PROFESSIONAL EXPERIENCE

07/09- present: Senior Research Assistant & Data Manager, HIP (HPV in Perimenopause) Study, Department of Epidemiology, Johns Hopkins School of Public Health, Baltimore, MD
• Create and manage databases, including data checking and data cleaning
• Develop study documentation (protocols, forms, questionnaires)
• Conduct interviews with study participants
• Prepare and analyze data
• Contribute to writing manuscripts

11/11-present: Research Assistant, Project SEARCH: Research to Prevention (R2P)-Concurrency Validity Study, South Africa, Department of Epidemiology, Johns Hopkins School of Public Health, Baltimore, MD
• Data entry and data management
• Data analysis and preparation of manuscripts

5/13-7/13: Research Assistant, myHPV: Malaysian HPV Prevalence Study, Johns Hopkins School of Public Health & Perdana University, Kuala Lumpur, Malaysia
• Prepare IRB and Ethics approval applications
• Develop study materials including protocols, consents, questionnaires, and data collection and management systems
• Site development and preparation for study, including staff training and piloting of interviews, sample collection

06/12-08/12: Research Assistant, MP3 Combination HIV Prevention for MSM in Southern Africa**,** Center for Global Health, Johns Hopkins School of Public Health, Port Elizabeth, South Africa
Global Health Established Field Placement Award
• Site development and preparation for study, including staff training and development of recruitment and retention plans
• Community engagement and establishment of a community advisory board

03/08- 05/09: Research Assistant, Gravitt Lab, Department of Epidemiology, Johns Hopkins School of Public Health, Baltimore, MD
• Performed Hybrid Capture and Real Time PCR assays to test for HPV and other viral infections
• Performed manual DNA extractions and gel electrophoresis
• Data entry and data analysis using ACCESS & STATA

06/05-08/05, 06/06-08/06: Intern, Health Research Training Program- Department of Health, New York City, NY
Office of Intergovernmental Affairs ('05)
• Reviewed and tracked City and State legislation and served as liaison between Dept. of Health and local elected officials
• Assisted on West Nile Virus Steering Committee
• Trained to assist in outbreak investigations of communicable diseases
Bureau of STD Control ('06): Study titled "Knowledge, Attitudes, and Practices of College Students: Sex, Drugs, and Alcohol"
• Designed survey questionnaire and authored literature review, background, methods and procedures
• Drafted IRB and grant applications
• Selected to present study methodology and procedures to all interns and preceptors

HONORS AND AWARDS

2014: Carol Eliasberg Martin Scholarship in Cancer Prevention, Johns Hopkins School of Public Health

2014: Charlotte Silver Award, Department of Epidemiology, Johns Hopkins School of Pubic Health

2013: Meyerhoff Fellowship in Cancer Prevention Award, Department of Epidemiology, Johns Hopkins School of Public Health

2012-2013: Dissertation Research Fund Award, Department of Epidemiology, Johns Hopkins School of Public Health

2012: Student Assembly Conference Fund Award, Johns Hopkins School of Public Health

2012: National Cancer Institute Conference Travel Award, 28th Annual Papillomavirus Society, San Juan, Puerto Rico

2012: Global Health Established Field Placement Award- South Africa, Center for Global Health, Johns Hopkins School of Public Health

2012: Carol Eliasberg Martin Scholarship in Cancer Prevention, Johns Hopkins School of Public Health

2012: Meyerhoff Fellowship in Cancer Prevention Award, Department of Epidemiology, Johns Hopkins School of Public Health

2011-2014: Departmental Tuition Support, Department of Epidemiology, Johns Hopkins School of Public Health

2008: Partial Tuition Scholarship Awarded to Top Students in the Masters Class, Department of Epidemiology, Johns Hopkins School of Public Health

PUBLICATIONS

1. **Silver, MI,** Rositch AF, Burke AE, Chang K, Viscidi R, Gravit PE. Women express concern about HPV testing and 5-year intervals in routine cervical cancer screening. Obestrics and Gynecology. In press Nov. 2014.

2. Low HC, **Silver MI**, Brown BJ, Leng CY, Blas MM, Gravitt PE, Woo YL. Comparison of Hybribio GenoArray and Roche human papillomavirus (HPV) Linear Array for HPV genotyping in anal swab samples. J Clin Microbiol. Dec 2014.

3. Rositch AF**, Silver MI**, Gravitt PE. Cervical cancer screening in older women: new evidence and knowledge gaps. *PLoS Medicine*. Jan 2014;11(1).

4. Brotman RM, Shardell MD, Gajer P, Fadrosh D, Chang K, **Silver M**, Viscidi RP, Burke AE, Ravel J, Gravitt PE. Association between the vaginal microbiota, menopause status and signs of vulvovaginal atrophy. *Menopause*. Oct 2013.

5. Liu SH, Rositch AF, Viscidi RP, **Silver MI**, Burke A, Gravitt PE. Obesity and HPV Infection in Peri-menopausal Women. *JID*. Oct. 2013;208(7):1071-1080.

6. Gravitt PE, Rositch AF, **Silver MI**, Marks M, Chang K, Burke AE, Viscidi RP. A cohort effect of the sexual revolution may be masking an increase in HPV detection at menopause in the U.S. *JID*. Jan 2013;207(2)272-80.

7. Rositch AF, Burke AE, Viscidi RP, **Silver MI**, Chang K, Gravitt PE. Contributions of recent and past sexual partnerships on incident human papillomavirus detection: acquisition and reactivation in older women. *Cancer Res*. Dec 2012;72(23):6183-90.

8. Rositch AF, **Silver MI**, Burke A, Viscidi R, Chang K, Duke CM, Shen W, Gravitt PE. The correlation between HPV and abnormal cervical cytology differs by age among mid-adult women. *J Low Genit Tract Dis*. Jan 2013;17(1):38-47.

9. Marks M, Viscidi R, Chang K, **Silver M**, Burke AE, Howard L, Gravitt P. Differences in the concentration and correlation of cervical immune markers among HPV positive and negative perimenopausal women. *Cytokine*. Dec 2011 56(3):798-803.

10. **Silver MI**, Paul P, Sowjanya P, Ramakrishna G, Vedantham H, Basany, K, Shah KV, Gravitt PE. Shedding of Epstein-Barr virus and cytomegalovirus from the genital tract of women in a peri-urban community in Andhra Pradesh, India. *J Clin Microbiol*. July 2011 49(7):2435-9.

11. Vedantham H, **Silver MI**, Kalpana B, Rekha C, Karuna BP, Vidyadhari K, Mrudula S, Ronnett BM, Vijayaraghavan K, Ramakrishna G, Sowjanya P, Laxmi S, Shah KV, Gravitt PE; CATCH Study Team. Determinants of VIA (Visual Inspection of the Cervix After Acetic Acid Application) Positivity in Cervical Cancer Screening of Women in a Peri-Urban Area in Andhra Pradesh, India. *Cancer Epidemiol Biomarkers Prev.* May 2010 19(5):1373-1380.

CURRICULUM VITAE

MICHELLE SILVER, ScM

PART II

TEACHING

09/13-10/13, 09/14-10/14: ***Teaching Assistant: Practical Skills in Conducting Research in Clinical Epidemiology and Investigation,*** Department of Epidemiology, Johns Hopkins School of Public Health, Baltimore, MD

01/12-03/12, 01/13-03/13: ***Teaching Assistant: Professional Epidemiology Methods I,*** Department of Epidemiology, Johns Hopkins School of Public Health, Baltimore, MD

09/08-10/08: ***Teaching Assistant: Statistical Methods in Public Health I,*** Department of Biostatistics, Johns Hopkins School of Public Health, Baltimore, MD

7/08-08/08: ***Teaching Assistant: Principles of Epidemiology,*** Department of Epidemiology, Johns Hopkins School of Public Health, Baltimore, MD

RESEARCH GRANT PARTICIPATION

2013-2014: R36 Dissertation Research Award (Principal Investigator)
Agency for Healthcare Research and Quality (AHRQ)- R36 HS022199-01A1
"When Less is More: Changing Cervical Cancer Screening Guidelines"

ACADEMIC SERVICE

2012- present: Member, Surveillance and Outbreak Response Team (SORT), Department of Epidemiology & Baltimore City Department of Health

09/2012-present: Member, Optimizing Cancer Screening working group, Sidney Kimmel Comprehensive Cancer Center

09/11-09/2013: Student Representative, Department of Epidemiology Curriculum Committee

PRESENTATIONS

1. **Silver MI**, Rositch AF, Phelan-Emrick D, Gravitt PE. Cervical cancer screening patterns in the Johns Hopkins Hospital system. Poster presented at the International Papillomavirus Society Conference, Seattle, WA, August 2014.

2. Silver MI, Rositch AF, Burke AE, Viscidi RP, Chang K, Gravitt PE. Patient attitudes towards extending cervical cancer screening intervals. Poster presented at the Society for Epidemiologic Research Conference, Seattle, WA, June 2014.

3. Silver MI, Phelan-Emrick D, Gravitt PE. Cervical cancer screening patterns in the Johns Hopkins Hospital system. Poster presented at the Society for Epidemiologic Research Conference, Seattle, WA, June 2014.

4. Silver MI, Rositch AF, Burke AE, Viscidi RP, Chang K, Gravitt PE. Patient attitudes towards extending cervical cancer screening intervals. Poster presented at the JHSPH Cancer Epidemiology Prevention and Control Trainee Symposium, Baltimore, MD, May 2014.

5. Zelaya CE, **Silver MI**, Go VF, Robertson G, Davis W, Gray G, Celentano DD. Improving the validity of the measurement of self-reported sexual concurrency in South Africa. Poster presented at the International AIDS Society Conference, Kuala Lumpur, Malaysia, July 2013.

6. Silver MI, Rositch AF, Burke AE, Viscidi RP, Chang K, Gravitt PE. When less is more: understanding factors influencing patient attitudes and behavior when cervical cancer screening guidelines recommend less screening. Poster presented at the JHSPH Cancer Epidemiology Prevention and Control Trainee Symposium, Baltimore, MD, May 2013.

7. **Silver MI**, Rositch AF, Burke AE, Viscidi RP, Chang K, Gravitt PE. When less is more: understanding factors influencing patient attitudes and behavior when cervical cancer screening guidelines recommend less screening. Poster presented at the International Papillomavirus Conference, San Juan, Puerto Rico, December 2012.

8. Rositch AF, Burke AE, Viscidi RP, **Silver MI**, Chang K, Gravitt PE. The contribution of recent and past sexual partnerships on incident HPV detection: acquisition and reactivation in older women. Poster presented at the International Papillomavirus Conference, San Juan, Puerto Rico, December 2012.

9. Soong TR, Burke AE, Viscidi R, **Silver MI**, Chang K, Gravitt PE. Evaluating the association between hormonal contraceptive use with HPV detection in pre- and perimenopausal women in the US. Poster presented at the International Papillomavirus Conference, San Juan, Puerto Rico, December 2012.

10. Fakhry C, Viscidi R, Chang K, **Silver M**, Burke A, Gravitt P. Racial differences in the serologic response to HPV. Poster presented at the International Papillomavirus Conference, San Juan, Puerto Rico, December 2012.

11. Rositch AF, **Silver MI**, Burke AE, Viscidi RP, Chang K, Duke CM, Shen W, Gravitt PE. The correlation between HPV positivity and abnormal cervical cytology differs

by age among perimenopausal women. Presented at NAMS Annual Meeting, Orlando, FL, Oct 2012.

12. Rositch AF, Burke AE, Viscidi RP, **Silver MI**, Chang K, Gravitt PE. Contributions of recent and past sexual partnerships on incident human papillomavirus detection: acquisition and reactivation in older women. Presented at NAMS Annual Meeting, Orlando, FL, Oct 2012.

13. Silver MI. When less is more: understanding factors influencing patient and provider attitudes and behavior when guidelines recommend less frequent cervical cancer screening. Poster presented at the JHSPH Cancer Epidemiology Prevention and Control Trainee Symposium, Baltimore, MD, May 2012.

14. Marks M, Burke A, Chang K, **Silver M**, Howard L, Viscidi R, Gravitt P. Distinct cervical immune marker patterns in older HPV positive women. Poster presented at the International Papillomavirus Conference, Berlin, Germany, September 2011.

15. Gravitt PE, **Silver M**, Rositch AF, Chang K, Marks M, Howard R, Eby Y, Burke A, Viscidi R. Cohort effects, sexual behaviors, and HPV prevalence in perimenopausal women. Presented at the International Papillomavirus Conference, Berlin, Germany, September 2011.

16. Fakhry C, **Silver M**, Gravitt P, Viscidi R, Burke A, Chang K, Hackett L, Seay E. Associations between race, sexual behaviors, and HPV serostatus. Presented at the International Papillomavirus Conference, Berlin, Germany, September 2011.

17. Duke CM, Shen W, Chang K, **Silver M**, Viscidi R, Burke A, Gravitt PE. There is a Sustained Decrease in Pap Smear and HPV Concordance with Increasing Age: When Should we Stop Screening the Low Risk Perimenopausal Patient? Presented at NAMS Annual Meeting, Washington, DC, September 2011.

18. Gravitt PE, Chang K, Shen W, **Silver M,** Viscidi R, Howard R, Burke A. New sex partners and menopausal stage are predictors of prevalent HR-HPV in women aged 35-60 years. Poster presented at the International Papillomavirus Conference, Montreal, Canada, July 2010.

19. Gravitt PE, Vakkalanka P, Chang K, Burke A, **Silver M,** Silver B, Shen W, Viscidi R. High HPV seroprevalence in perimenopausal women attending routine GYN care in Baltimore, MD. Poster presented at the International Papillomavirus Conference, Montreal, Canada, July 2010.

COMMUNITY SERVICE

10/11-present: Alumni Interviewer, STANFORD UNIVERSITY
• Interview applicants to Stanford University

09/07- present: CAMP KESEM NATIONAL
Camp Kesem is a student-run overnight camp for children whose parents have or had cancer. It provides a safe camp environment for kids to relax, have fun, and deal with grief and other emotional issues with a supportive staff and other children going through similar situations.

Alumni Leadership Board, Camp Kesem National ('14-present)
Advisory Board Member, Camp Kesem Johns Hopkins *('11-present)*
Camp Director- Michigan, UCLA, George Washington University, Berkeley, Johns Hopkins University ('07-'12)
• Drive organization's future through participation in monthly leadership calls
• Liaison between campuses and alumni to provide support in programming, fundraising, community outreach, and other camp issues
• Create reference manual to provide guidance and advice for students as they plan camp
• Assist in execution of large-scale fundraising efforts
• Mentor and serve as a resource for student leadership during the year and at camp
• Oversee all counselors and campers during the week of camp
• Execute crisis management best practices to ensure the safety of campers and staff
• Serve as subject matter expert to resolve critical staff and camper issues (behavioral, health, etc.)

06/05- 06/07: CAMP KESEM**,** Stanford University, Stanford, CA
Administration & Programming Coordinator *(2006-2007)*
• Planned and coordinated all programming for 60 counselors and 105 campers for the week of camp, including camp structure, scheduling, designing special activities, and documents for insurance and emergency procedures
• Created and maintained camp budget of $125,000 and assisted on fundraising efforts for this budget