PRECISION CANCER SCREENING IN HIGH-RISK POPULATIONS: APPLICATIONS IN CERVICAL, ANAL, AND LUNG CANCERS

by

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Abstract

Cancer screening can prevent mortality and morbidity from cancer, but it also causes harms. Recently, precision (i.e. risk-based, personalized) screening approaches have emerged as a way to better balance these benefits and harms. The purpose of this dissertation was to identify opportunities for precision screening among two U.S. populations at high risk for cancer: people living with HIV and people with a history of heavy smoking.

The first aim (Chapter 2) analyzed data from the Women's Interagency HIV Study to compare cervical precancer risks between women living with HIV (WLHIV) and general population women. We used a risk benchmarking framework to draw conclusions regarding appropriate cervical cancer screening and management strategies for WLHIV. We show that current guidelines are largely appropriate, but that in some instances, considering CD4 cell count (immunosuppression status) could inform risk-tailored strategies.

The second aim (Chapter 3) analyzed data from the Multicenter AIDS Cohort Study (MACS) to describe patterns of repeated anal cytology testing among HIV-positive and HIV-negative men who have sex with men (MSM). We show that approximately one-third of HIV-positive MSM have consistently negative anal cytology over 3 years, which may identify men for whom high-resolution anoscopy is unlikely to be beneficial. Following abnormal anal cytology, the next cytology is commonly negative in HIV-negative or immunocompetent HIV-positive MSM, while persistent cytological abnormality is more likely among immunosuppressed HIV-positive MSM.

Finally, the third aim (Chapter 4) develops a risk model to describe how individual lung cancer risk evolved based on screening CT findings during the National Lung Screening Trial. We show that those with a negative CT screen and no emphysema or consolidation maintained reduced lung cancer risk at the next annual screen and thus might be candidates for longer screening intervals. In contrast,

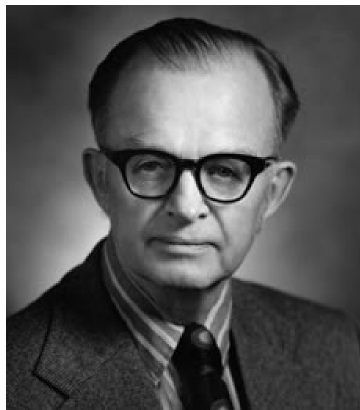
most false-positives experienced substantially increased lung cancer detection at the next screen, which could be stratified by accounting for specific features of lung nodules.

In sum, this dissertation describes three settings in which precision cancer screening could achieve a better balance of benefits and harms for two high-risk populations. Success in implementing these approaches will require interdisciplinary efforts that engage clinicians, patients, and researchers.

Dedication

This dissertation is dedicated to my great-uncle Dr. Lewis C. Robbins. During a long and remarkable career in preventive medicine, "Uncle Louie" served as the first chief of cancer control programs in the U.S. Public Health Service (1957-1965). He helped write the surgeon general's first warning on tobacco, which was published in *JAMA* under Leroy R. Burney's signature in 1959. Louie pioneered the concept of "prospective medicine," which statistically assessed patients' behavioral health risks and offered tailored advice to improve health and increase life expectancy. These individualized "health hazard appraisals" might be considered one of the early examples of precision medicine.

Uncle Louie earned his MPH at Johns Hopkins and is listed as one of the "Heroes of Public Health" on the Johns Hopkins Bloomberg School of Public Health webpage. Much of his writings and records are now kept in the Lewis C. Robbins collection at the JHU Alan Mason Chesney Medical Archives. I did not have the chance to meet him, as he died shortly after I was born, but I continue to be inspired by his work and ideas.



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List of Abbreviations

AIDS: acquired immunodeficiency syndrome

ASC-H: atypical squamous cell of undetermined significance, cannot exclude HSIL

ASC-US: atypical squamous cell of undetermined significance

$_b$HSIL+: biopsy-confirmed high-grade squamous intraepithelial lesion or worse

CDC: Centers for Disease Control and Prevention

CIN: cervical intraepithelial neoplasia

eART: effective antiretroviral therapy

HIV: human immunodeficiency virus

HPV: human papillomavirus

HRA: high-resolution anoscopy

HSIL: high-grade squamous intraepithelial lesion

JHSPH: Johns Hopkins Bloomberg School of Public Health

LCDRAT: Lung Cancer Death Risk Assessment Tool

LCRAT: Lung Cancer Risk Assessment Tool

(LD)CT: (low-dose) computed tomography

LSIL: low-grade squamous intraepithelial lesion

MACS: Multicenter AIDS Cohort Study

MSM: men who have sex with men

NCI: National Cancer Institute

NLST: National Lung Screening Trial

oncHPV: oncogenic human papillomavirus

PLHIV: people living with HIV

WIHS: Women's Interagency HIV Study

WLHIV: women living with HIV

Chapter 1: Introduction

1.1 Cancer in High-Risk Populations: HIV and Smoking

Cancer is "a group of diseases characterized by the uncontrolled growth and spread of abnormal cells."[1] While the cause of some cancers remains unknown, lifestyle-related risk factors cause many cancers in the United States; these factors include tobacco use (particularly cigarette smoking), excess body weight, low physical activity, excess alcohol consumption, and poor nutrition. Infectious agents are also an important cause of cancer, including helicobacter pylori (gastric cancer), hepatitis B virus (liver cancer), hepatitis C virus (liver cancer and non-Hodgkin lymphomas), human papillomavirus (HPV) (multiple oral and anogenital cancers), Epstein-Barr virus (Hodgkin's lymphoma, Burkitt's lymphoma, and nasopharyngeal cancer), human herpesvirus 8 (Kaposi's sarcoma), and human T-cell lymphotropic virus (leukemia and lymphoma).[2]

Taken together, infectious agents were estimated to cause 15.4% of the 2.2 million cancer cases worldwide in 2012.[2] Among these, helicobacter pylori caused 35.4%, followed closely by HPV at 29.5%. The proportion of cancers attributable to infections varies strongly by geographical region, ranging from a maximum of 31.3% in sub-Saharan Africa to 4.0% in North America. However, in certain sub-populations, the relative contribution of infections as a cause of cancer is much higher regardless of geographical region. In particular, people living with human immunodeficiency virus (HIV) infection (PLHIV) have strongly increased risk for infection-related cancers; this is due largely to the immunosuppressive effects of HIV, which allow viruses to establish infection and persist over time. In the United States during 1991-1995, prior to the introduction of effective antiretroviral therapy (eART), the rate of Kaposi sarcoma was increased 2800-fold in PLHIV, non-Hodgkin lymphoma 10-fold, and cervical cancer 3-fold.[3] These three cancers were considered to define the onset of acquired immunodeficiency syndrome (AIDS), but increased risk in PLHIV spans the spectrum of infection-related cancers, with notable increases continuing to persist for anal cancer,

Hodgkin lymphoma, oral cavity/oropharyngeal cancer, and liver cancer.[4,5] Due partly to increased smoking prevalence, the incidence of lung cancer is also increased 2-fold in PLHIV.[4,6]

Since the introduction of eART in 1996, the epidemiology of cancer among PLHIV has shifted in multiple ways. PLHIV now live much longer lives, which has lead to substantial growth in the size of the HIV population as well as a shift toward older ages.[7] Concurrently, since HIV treatment allows more effective immunologic control of viruses, the number of AIDS-defining cancers (all caused by viruses) have decreased over time while the number of non-AIDS-defining cancers has grown substantially.[7] In 2010, an estimated 7,760 cancers occurred among PLHIV in the U.S., of which 3,920 were in addition to those that would be expected if PLHIV had the same cancer rates as the general U.S. population (i.e., excess cancers).[5] The most common types of excess cancer were non-Hodgkin lymphoma, Kaposi sarcoma, lung cancer, and anal cancer, and the majority of excess cancers occurred among men who have sex with men (MSM).

In the U.S. general population, individuals who are former or current tobacco smokers (i.e., ever-smokers) represent another important population at high risk for cancer. The Centers for Disease Control and Prevention (CDC) estimates that 17% of adult men and 14% of adult women currently smoke cigarettes, with prevalence higher among those with lower educational attainment, living in poverty, and living in certain states (notably West Virginia, Kentucky, and Arkansas).[8] Cigarette smoking is by far the most important cause of lung cancer, accounting for 80% of cases.[1] As a result, lung cancer has been the most common cause of cancer death in the U.S. since the 1950s (for men) and 1980s (for women), and in 2017, lung cancer caused 27% of cancer deaths in males and 25% in females. Encouragingly, U.S. lung cancer death rates have declined substantially since their peak in the 1990s (men) and 2000s (women) due to reductions in smoking. The 5-year relative survival for lung cancer is low, ranging from 55% for localized-stage cases to 28% for regional-stage cases to only 4% for distant-stage cases.[9] Since 57% of cases are diagnosed at distant stage, 22% at regional stage, and only 16% at localized stage, improving methods for early detection (i.e.,

identifying lung cancer at earlier stages when survival is higher) is a promising approach for decreasing lung cancer death rates.[1,9]

1.2 Cancer Screening as a Tool to Reduce Cancer Burden

The term "screening" is often used synonymously with the term "early detection." Put simply, the goal of cancer screening is to identify cancer, or pre-cancerous lesions, at earlier stages when they can be more easily treated. Identifying cancer before it causes symptoms can reduce morbidity due to cancer or its treatment and prevent ultimate death from cancer. For some types of cancer, the goal of screening is largely to identify and remove pre-cancerous lesions, thus preventing cancer from occurring altogether. Such screening scenarios include cytology screening for cervical cancer (which identifies cervical intraepithelial neoplasia [CIN] precancerous lesions) and colonoscopy screening for colorectal cancer, which identifies precancerous adenomas. A relatively new screening setting that identifies pre-cancers is cytology screening for anal cancer, which is analogous to cervical cancer screening but occurs at the anus and is usually considered only for men who have sex with men (MSM). Other screening scenarios do not detect pre-cancerous lesions but aim to detect early-stage invasive cancer. These include mammography screening for breast cancer and low-dose computed tomography (CT) screening for lung cancer.

The ongoing development of more sensitive technologies for early detection presents both opportunities and challenges for modern-day cancer screening. For example, using HPV testing for cervical cancer screening gives a very sensitive test, but required the development of appropriate management algorithms for women who are HPV-positive but still at low risk of cervical cancer.[10] CT screening has recently emerged as a sensitive tool for identifying lung cancer at earlier stages among heavy smokers, but because CT screening detects many lung nodules that are not malignant, reducing the rate of false-positive screens and the burden of associated follow-up is a persistent challenge.[11–13]

1.3 Precision Medicine and Cancer Screening

In his State of the Union Address on January 20, 2015, President Barack Obama announced a research initiative to "accelerate progress toward a new era of precision medicine."[14] Precision medicine was defined broadly as "prevention and treatment strategies that take individual variability into account." While the canonical example of precision medicine is the tailoring of cancer treatments based on particular tumor mutations, researchers have increasingly applied concepts of precision or personalization more broadly, including in the setting of cancer prevention and control.[15–17]

Cancer screening has important benefits, namely the prevention of morbidity and mortality due to cancer and its treatment. However, screening also causes harms including overtreatment, false findings, psychological distress, and financial costs. Recently, the application of ideas and approaches within the realm of precision medicine has emerged as a way to find the appropriate balance of these benefits and harms.[16,18,19] In particular, risk-tailored methods use an individual's predicted cancer risk to determine whether, at what ages, and how often individuals should be screened; these methods are particularly relevant in cervical and lung cancer screening.[10,20,21] Underlying risk-tailored approaches is the principle of "equal management of equal risks," which posits that two groups at approximately equal cancer/precancer risk should be screened and managed in the same way.[10] Precision approaches in the setting of cancer screening continue to gain traction: they were the subject of a 2015 National Cancer Institute (NCI) symposium[22] and are now considered a key tool for reducing cancer overdiagnosis and overtreatment.[23]

1.4 HPV as a Cause of Cancer in People Living With HIV

Human papillomaviruses (HPVs) are DNA viruses that infect squamous epithelia.[24] Though there are over 100 distinct sub-types of HPV, only thirteen are classified as carcinogenic ("high-risk"), most notably HPV16.[25] HPV causes multiple anogenital cancers, including virtually all cervical

cancers and most anal cancers, as well as a subset of oropharyngeal cancers.[2] Oncoproteins encoded by high-risk HPVs, namely E6 and E7, enable cancer development by promoting virus replication and immortalization of the human cell: E6 binds to and inactivates the tumor suppressor protein p53, while E7 binds to the tumor suppressor protein Rb.[24] In essence, E6 disrupts cell cycle control, and then E7 allows the cell to replicate despite damaged DNA. Earlier in this process, the integration of HPV into the host DNA is thought to be a key step in carcinogenesis.

Cancers caused by HPV are of particular concern in immunosuppressed individuals, particularly PLHIV. In the era of eART, as PLHIV are living longer and growing in number,[26,27] cancer is an increasing problem.[7,28,29] Higher risks for all infection-related cancers in PLHIV, including HPV-related cancers, result from immunosuppression that allows oncogenic viruses to establish infection, persist, and cause cancer.[30] HPV causes a substantial fraction of cancers among PLHIV in the U.S., which are primarily cervical and anal cancers (Table 1.1).[31] In recent years, cervical cancer rates have declined but anal cancer is increasing,[4] such that defining appropriate prevention strategies is challenging.[29,31,32] Routine screening for these cancers will continue to be necessary for the foreseeable future, as HPV vaccination uptake has been gradual and its population effects will take many years to manifest.[33] For males in particular, low vaccine uptake means that anal cancer rates will not decrease for many years.[34]

A conceptual framework applying to Aims 1 and 2 of this dissertation is shown in Figure 1.1. In this framework, HPV-related cancers progress from normal tissue to HPV infection to precancer to cancer. Each transition can be affected by many risk factors, which include HIV-related immunosuppression and HPV genotype. Removal of precancers can prevent cancers from occurring. The results of a cytology screen at the cervix or anus can be used, along with additional risk factor information, to estimate an individual's precancer/cancer risk. For those at high risk, referral to colposcopy (cervix) or anoscopy (anus) should be considered to detect and remove precancers. For those at low risk, the interval before returning to re-screening should be optimized (risk-tailored). For

those at intermediate or unclear risk, more information should be considered, such as a repeat cytology screen or HPV test.

1.5 Cervical Cancer Screening in Women Living with HIV

Cervical cancer risk among WLHIV was strongly elevated early in the U.S. HIV epidemic,[35] but has substantially declined[4] and is now similar to the general population.[36] I recently led a study showing that only 50 excess cervical cancers occurred in WLHIV in the U.S. in 2010,[5] contradicting the notion that large numbers of excess cases continue to support aggressive screening for WLHIV (Table 1.1).

Screening with pap cytology, combined with colposcopy to diagnose and remove precancers, has dramatically reduced cervical cancer.[37] However, cytology screening also causes harms including vaginal bleeding, pain, infection, and psychological distress.[38] Based largely on a risk benchmarking analysis,[10] updated general population guidelines now suggest a 3-year interval after normal cytology before a woman should return for re-screening.[38] Even though their risk has declined, WLHIV are still recommended for annual screening,[39] with some guidelines lengthening the interval after multiple normal screens.[40] Guidelines for managing atypical squamous cell of unknown significance (ASC-US, i.e., borderline) cytology in WLHIV are inconsistent: some recommend direct referral to colposcopy, while others include WLHIV in general population guidelines (HPV test triage or 6-12 month return for re-screening).[39–41]

One reason for screening uncertainties in WLHIV is that most studies compare precancer risk among WLHIV to women who are HIV-negative but still at high HPV risk.[42–44] Since guidelines are based on the level of risk in the general population, such comparisons are difficult to translate into practice. Therefore, my first dissertation aim analyzed data from the Women's Interagency HIV Study (WIHS) to determine whether WLHIV have similar risks of cervical precancer after normal and ASC-US cytology compared to published risks in general population women, which would support longer screening intervals and less aggressive management. We hypothesized that, after

normal cytology, WLHIV with high CD4 cell counts have similar 3-year cervical precancer risk to general population women, while WLHIV with low CD4 cell counts have higher risk. After ASC-US cytology, we hypothesized that WLHIV regardless of CD4 count have similar 3-year precancer risk to general population women.

1.6 Anal Cancer Screening in Men Who Have Sex With Men

Anal cancer is relatively rare in the United States general population (1.8 per 100,000),[45,46] though rates are increasing.[47] Incidence among HIV-MSM is extremely high (131 per 100,000)[48] because of HPV exposure during anal sex combined with immunosuppression. In 2010, approximately 740 excess anal cancers occurred among PLHIV in the U.S. (Table 1), the vast majority in HIV-MSM.[5] This number is growing due to increasing anal cancer incidence[4] and HIV population size.[7] Anal cancer is also a concern for HIV-uninfected MSM.[49,50]

Due to this disease burden, there is urgent demand for effective anal cancer screening for HIV-MSM.[32,51,52] The leading strategy is anal cytology with referral to high-resolution anoscopy (HRA). This strategy is analogous to cervical cytology and colposcopy, but is severely under-researched.[51,53,54] Thus, despite frequent mention that anal cytology should be considered for HIV-MSM, no national or international guidelines exist,[50] and some recommend that all HIV-MSM should simply have annual HRA.[55]

However, exploiting the utility of cytology alone is extremely important. While cytology has high acceptability among MSM,[56,57] HRA is painful, burdensome, and has a shortage of providers. Avoiding unnecessary treatment of anal precancer is critical, because (1) treatment of anal precancer has harmful sequelae, (2) anal precancer appears less likely than cervical precancer to progress,[58] and (3) evidence does not yet convincingly show that treating anal precancer is effective in preventing cancer.[59–62]

One challenge facing anal cytology is that its repeatability is not described. At the cervix, repeat cytology is used in screening algorithms,[40,63] but the repeatability of anal cytology has not been

assessed or associated with precancer risk. Therefore, my second aim analyzed data from the Multicenter AIDS Cohort Study (MACS) to quantify the proportions of HIV-positive MSM who have a pattern of consistently negative annual anal cytology or a pattern of consistently abnormal cytology over 3 years, and described demographic, clinical, and behavioral characteristics associated with these patterns. We hypothesized that more than 30% of HIV-positive MSM have a pattern of consistently normal anal cytology and that less than 15% have a pattern of consistently abnormal cytology, and that men with consistently abnormal cytology are more likely to have low CD4 counts and more sexual partners compared to men with consistently normal cytology. Among HIV-negative men, among whom only 2 cytology results are typically available, we also quantified transition probabilities between one cytology result (e.g., negative) to another (e.g., abnormal) and compared these to those observed among HIV-positive MSM.

1.7 Lung Cancer Screening in Heavy Smokers

Another important population at high risk for cancer in the U.S. – and one much larger than the HIV-infected population – is individuals with a current or past history of heavy smoking. Cigarette smoking causes lung cancer by exposing the smoker to multiple carcinogenic chemicals, by increasing the frequency of DNA adducts with these carcinogens via metabolic activation or other pathways, by promoting the expression of tumor suppressor genes, and by activating signal transduction pathways that allow the survival of damaged epithelial cells.[64] Excess lung cancer risk declines after cessation of smoking, but does not disappear,[65] and achieving widespread success in smoking cessation remains an unrealized goal.[66–69]

Recently, lung cancer screening has emerged as a new tool to reduce lung cancer mortality among current or former heavy smokers. The National Lung Screening Trial (NLST) primary results were published in 2011, demonstrating a 20% reduction in lung cancer mortality with annual screening by low-dose CT as compared to chest radiography (which has been shown to have no effect on lung cancer mortality).[11,70] Based on the NLST results, the U.S. Preventive Services Task

Force now recommends annual CT screening for adults aged 55 to 80 years who have a 30 pack-year smoking history and either currently smoke or have quit within the past 15 years.[71] However, subsequent analyses of NLST data have demonstrated that the benefit of CT screening was concentrated in those at highest predicted risk of lung cancer,[72] and that selecting individuals for screening based on this individual risk (calculated using detailed risk models) might improve the effectiveness, efficiency, and cost-effectiveness of screening programs.[21,73,74]

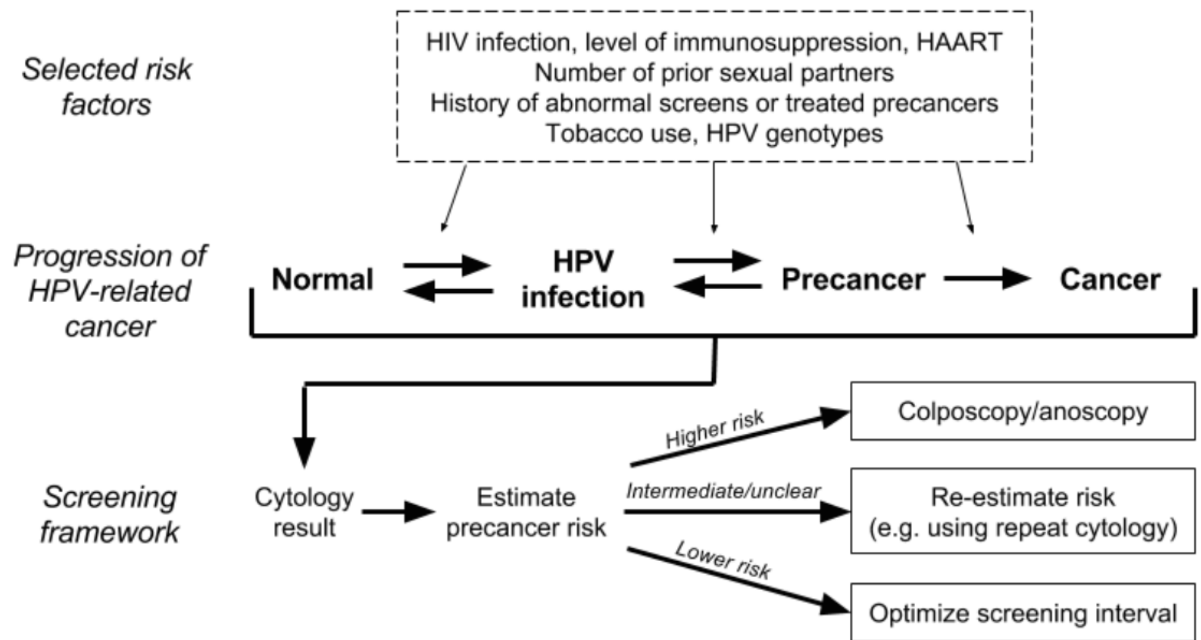
A major challenge facing CT screening programs is high rates of false-positive screens and a large burden of associated diagnostic workup. Thus, there is substantial interest in identifying individuals who can safely lengthen screening intervals beyond 1 year, which could reduce the number of false-positive screens in a screening program.[75–78] Such an approach would require that individual lung cancer risk, which can currently be calculated prior to screening using one of multiple validated risk models, be updated once CT screening results are known. Therefore, my third aim developed a model that calculates how individual lung cancer risk evolved during annual CT screening in the NLST. This model a) quantifies the effect of CT findings on future lung cancer risk and b) identifies individuals who might be candidates for extending screening intervals beyond 1 year. We hypothesized that risk of lung cancer within a CT screening program continues to depend on pre-screening (i.e., smoking-related) risk factors, but is also modified by CT findings. In addition, we hypothesized that those with a false-positive CT screening result have higher future lung cancer risk than those with a negative result, and that this risk can be further stratified by incorporating detailed features identified on CT.

1.8 Tables and Figures

Table 1.1: Descriptive epidemiology of cervical and anal cancers among people living with HIV in the United States

Cancer type	High-risk group	Incidence increase	Incidence trend	Excess cases, 2010 (N)
Cervix	HIV+ women	4-fold[4]	Decreasing[4]	50[5]
Anus	HIV+ MSM	80-fold[48]	Increasing[4]	~700[5]

Figure 1.1: Conceptual framework for applying risk-tailored methods in cervical and anal cancer screening



Chapter 2: Cervical Cancer Screening Intervals and Management for Women Living with HIV: A Risk Benchmarking Approach

2.1 Abstract

Objective: We suggested cervical cancer screening strategies for women living with HIV (WLHIV) by comparing their precancer risks to general population women, and then compared our suggestions to current CDC guidelines.

Design: We compared risks of biopsy-confirmed cervical high-grade squamous intraepithelial neoplasia or worse ($_{b}$HSIL+), calculated among WLHIV in the Women's Interagency HIV Study, to "risk benchmarks" for specific management strategies in the general population.

Methods: We applied parametric survival models among 2,423 WLHIV with negative or ASC-US cytology during 2000-2015. Separately, we synthesized published general population $_{b}$HSIL+ risks to generate 3-year risk benchmarks for a 3-year return (after negative cytology, i.e., "re-screening threshold"), 6-12-month return (ASC-US), and immediate colposcopy (LSIL).

Results: Average 3-year $_{b}$HSIL+ risks among general population women ("risk benchmarks") were 0.69% for a 3-year return (after negative cytology), 8.8% for a 6-12-month return (after ASC-US), and 14.4% for colposcopy (after LSIL). Most CDC guidelines for WLHIV were supported by comparing risks in WLHIV to these benchmarks, including: a 3-year return after three negative cytology tests or a negative cytology/oncHPV co-test with CD4≥500 (all 3y-risks≤1.3%); a 1-year return after negative cytology with either positive oncHPV co-test (1y-risk=1.0%) or CD4<500 (1y-risk=1.1%); and a 6-12-month return after ASC-US (3y-risk=8.2% if CD4≥500; 10.4% if CD4=350-499). Other suggestions differed modestly from current guidelines, including colposcopy (vs. 6-12mo

return) for WLHIV with ASC-US and CD4<350 (3y-risk=16.4%) and a lengthened 2-year (vs. 1-year) interval for WLHIV with CD4≥500 after negative cytology (2y-risk=0.98%).

Conclusions: Current cervical cancer screening guidelines for WLHIV are largely appropriate. CD4 count may inform risk-tailored strategies.

2.2 Introduction

Women living with human immunodeficiency virus (WLHIV) are at elevated risk of cervical cancer and precancer.[5,79,80] This risk has declined in recent years, possibly due to improvements in effective antiretroviral therapy (eART) or cervical cancer screening.[4,36,81] Cervical cancer/precancer risks increase with diminishing immune status among WLHIV, even when comparing women with the same result from a cytology or oncogenic human papillomavirus (oncHPV) test.[43,79,80,63,82–84]

To prevent cervical cancer in the general population, the U.S. Preventive Services Task Force (USPSTF) and the American Cancer Society (ACS) recommend screening by cytology alone or, in women ages 30 years and above, screening either by cytology alone or with oncHPV co-testing.[38,85] For WLHIV, the Centers for Disease Control and Prevention (CDC) issues screening and management guidelines that employ the same modalities in the same age groups, but reflect that WLHIV are at higher cervical cancer risk.[40] For example, after a negative co-test (i.e., a concurrent cytologic diagnosis within normal limits [negative cytology] and negative oncHPV test), the USPSTF and ACS recommendation for HIV-uninfected women is a 5-year return, while the CDC recommends that WLHIV return for re-screening after 3 years.[38,40,85] After negative cytology alone, suggested intervals are 3 years for HIV-uninfected women compared to 1 year for WLHIV.

The CDC guidelines were influenced by data from the Women's Interagency HIV Study (WIHS).[36,42,43,80,63,84,86–89] In WIHS studies, WLHIV have been compared to a parallel group of HIV-uninfected women who are at high risk of acquiring HIV.[44] While these women are an appropriate reference for exploring causal effects of HIV, their cervical precancer risks may be higher than risks

in the general population, since HIV and cervical HPV have shared risk factors. Thus, from these studies, it is difficult to determine whether screening strategies for the general population can be applied to WLHIV.

In this study, we aimed to describe the cervical cancer screening strategies suggested for WLHIV by an explicit comparison of their cervical precancer risks to true general population risks to which USPSTF and ACS guidelines are applied. To draw these comparisons, we used the framework of risk benchmarking, which was adopted during a 2012 conference to establish consensus management guidelines for abnormal cervical cancer screening tests in the general population.[10,20,41] In addition, because immunosuppression is strongly associated with cervical cancer/precancer risk in WLHIV,[43,79,80,63,82–84] we considered CD4 count as a stratifying factor to explore potential opportunities for risk-tailored screening strategies.

2.3 Methods

Overall Approach

Risk benchmarking is used to ensure consistent management of individuals who are at similar risk of disease.[10,20] In brief, a management strategy for a particular test result is chosen by calculating disease risk among patients with the test result, then comparing this to risks following other test results with well-established management guidelines ("risk benchmarks"). Then, the guideline associated with a similar risk is applied to the test result in question. For cervical cancer screening, guidelines in the general population are well established, based on large clinical trials and extensive observational or clinical cohort data. Appropriate data are less available in WLHIV, with the WIHS being one of few cohorts with adequate sample size and follow-up. Therefore, we first estimated risk benchmarks of biopsy-confirmed cervical high-grade squamous intraepithelial neoplasia or worse ($_b$HSIL+) in the general population, and then assessed risks in the WIHS.

Consistent with the approach used to incorporate oncHPV testing into current guidelines, we generated benchmarks for the levels of risk that have historically triggered each of the following

management strategies in the general population: a 3-year return for re-screening (this is the recommendation after negative cytology), a 6-12-month return (after atypical squamous cell of undetermined significance [ASC-US]), and immediate colposcopy (after low-grade squamous intraepithelial lesion [LSIL]).[10,41] Then, for each result defined by cytology alone or cytology/oncHPV co-testing, we applied the strategy whose corresponding benchmark closely approximated the risk among WLHIV.

To address questions regarding the interval between negative screens, we extended the existing framework of risk benchmarking. Specifically, since USPSTF and ACS guidelines recommend a 3-year return following negative cytology, we reasoned that the risk accumulated at 3 years after negative cytology in the general population represents the threshold that triggers re-screening. Therefore, we estimated risk benchmarks at 3 years, and defined the 3y-return benchmark as the re-screening threshold. Then, to identify the suggested return interval for WLHIV following a negative screen, we chose the annual time-point at which risk very closely approximated, or first exceeded, the 3y-return benchmark. For consistency, we also estimated risk benchmarks at 3 years for a 6-12mo return (after ASC-US) or immediate colposcopy (LSIL).

Study Population

We calculated risks among WLHIV in the WIHS, an observational cohort of women with and at risk for HIV (https://statepi.jhsph.edu/wihs/wordpress/). Enrollment occurred during 1994-95, 2001-02, 2011-12, and 2013-15 at 11 study sites across the United States.[44,90,91] Participants are screened every 6 months with cytology and are referred to colposcopy for ASC-US cytology or worse. HPV DNA testing of cervicovaginal lavage samples is also available at many visits from a previous HPV sub-study.[42,43] Conventional single-slide testing[92] and noncommercial type-specific HPV DNA L1 degenerate primer MY09/MY11/HMB01 polymerase chain reaction assays[42] are used for cytology and HPV testing, respectively. We defined oncHPV positivity as the presence of any of the 13 oncogenic HPV types included in the Hybrid Capture II assay, which is commonly used in cervical cancer screening.[93]

This analysis was restricted to the years 2000-2015 (to represent the current HIV treatment era) and to WLHIV aged 21-65 years old (ages when screening is recommended). We analyzed all participants from the different enrollment waves collectively, although ${}_{b}$HSIL+ risk decreases with time in study.[80] We excluded women with a history of hysterectomy prior to entry. We made no exclusions based on history of cervical precancer or its treatment, as we aimed to mimic a clinical care setting representing all WLHIV. Our study updates previous WIHS analyses[36,42,43,80,63,84,86–89] by including new sites in the southern United States. The WIHS protocol was approved by institutional review boards at participating study sites.

Calculation of Benchmarks and Risks

To generate risk benchmarks, we identified large published studies describing risks of ${}_{b}$HSIL+ after negative, ASC-US, or LSIL cytology among general population women in usual care in the United States, and also included risks among WIHS HIV-uninfected women. We synthesized estimates across studies using unweighted linear regression models with random (study-specific) intercepts. For each cytology result, we calculated the corresponding risk benchmark by using the overall mean intercept and slope to predict risk at 3 years (further details in Supplementary Methods).

Among WLHIV in the WIHS, we first analyzed ${}_{b}$HSIL+ risk following a single cytology result, disregarding oncHPV results. We identified each eligible woman's first cytology in 2000 onward, then restricted to women with a negative or ASC-US result. We did not consider results of LSIL or worse. We identified each woman's first occurrence of ${}_{b}$HSIL+ following her entry cytology, then calculated follow-up time from cytology to the earliest of ${}_{b}$HSIL+, age 66, or last screening follow-up (cytology or colposcopy). We used parametric survival models to estimate annual cumulative incidence of ${}_{b}$HSIL+ from 1 to 5 years. We truncated follow-up at 5 years to improve the fit of parametric models to nonparametric estimates (further details in Supplementary Methods).

For risk following combined cytology and oncHPV (co-testing) results, after restricting to women with a concurrent oncHPV test result, we also restricted to WLHIV aged 30-65 years to maintain consistency with age guidelines for co-testing.[38,40,85] Where possible, for women without a

concurrent oncHPV result, we analyzed the next visit with both cytology and oncHPV results available (N=93).

We also analyzed risk following multiple consecutive negative cytology results, which by design were obtained every 6 months. Among women with negative cytology, we further restricted to women whose second, and then third, cytology was negative. We did not consider pre-2000 results. In each case, we calculated follow-up from the final cytology, excluding women with a gap of 4 or more years between consecutive results (N=8 and N=6 after 2 and 3 negative results, respectively).

We used biopsy-confirmed cervical intraepithelial neoplasia grade 2 or higher (CIN2+)[94] as our primary $_{b}$HSIL+ endpoint, given the more limited number of CIN grade 3 or higher (CIN3+). However, we repeated all analyses using CIN3+, as this is a more specific precancer endpoint. For analyses with larger numbers of women, and thus better power to evaluate the effect of CD4 cell count (analyses based on cytology only [disregarding oncHPV], and women with a cytology-negative/oncHPV-negative co-test), we stratified by CD4 cell count at the time of cytology using a standard threshold that was near the median (≥500 or <500 cells/μL). Consistent with other benchmarking studies, we considered risk benchmarks to be measured without error,[10,95,96] but estimated 95% confidence intervals [CIs] for relevant $_{b}$HSIL+ risks among WLHIV. We calculated two-sided Wald p-values for selected statistical comparisons.

2.4 Results

The 3-year $_{b}$HSIL+ (CIN2+) risk benchmark for a suggested 3-year return to screening was 0.69% (Figure 2.1, Table 2.1) based on 4 estimates of risk after negative cytology among general population women[10,97,98] and HIV-uninfected WIHS women. The benchmarks warranting a 6-12mo return and immediate colposcopy were 8.8% (based on 4 studies of risk after ASC-US) and 14.4% (based on 2 studies of risk after LSIL), respectively.

For the cytology-only analysis, we analyzed 2,423 WLHIV in the WIHS, including 2,049 with negative cytology and 374 with ASC-US cytology (Table 2.2). Most women with negative cytology

were non-Hispanic Black (61%), had taken ART (80%), and were aged 30-49 years (74%) at the time of cytology. Approximately half (51%) of women with negative cytology had a CD4≥500 at the time of cytology, compared to only 29% of women with ASC-US cytology (p<0.001). Most women contributed at least 5 years of follow-up. For risk following co-test results, we analyzed 1,439 WLHIV including: 1,070 cytology-negative/oncHPV-negative, 124 cytology-negative/oncHPV-positive, 163 ASC-US/oncHPV-negative, and 82 ASC-US/oncHPV-positive.

<u>Negative cytology, with or without oncHPV testing</u>

We compared $_b$HSIL+ risk among WLHIV with negative cytology to the general population benchmarks. After a single negative cytology result (Figure 2.1A), WLHIV with CD4≥500 (measured concurrently with cytology) first exceeded the 3y-return benchmark (0.69%) at 2 years (2-year risk=0.98% [95%CI 0.44-1.5%]). The 3-year risk among these women (1.5%) was statistically significantly higher than the benchmark (p=0.019). Among WLHIV with a CD4<500, risk first exceeded the benchmark at 1 year (1-year risk=1.1% [95%CI 0.51-1.6%]), and the 2-year risk (2.0%) was statistically significantly higher than the benchmark (p<0.001). This suggests that after a single negative cytology, WLHIV with CD4≥500 may be able to safely return for re-screening in 2 years, whereas risk among women with CD4<500 warrants a 1-year return.

Risks were lower among women with a concurrent negative cytology and oncHPV test (negative co-test, Figure 2.1B). For WLHIV with CD4≥500, risk first exceeded the 0.69% 3y-return benchmark at 3 years (3-year risk=0.94 [95%CI 0.21-1.7%]). Among WLHIV with CD4<500, 1- and 2-year risks were 0.66% (95%CI 0.08-1.2%) and 1.3% (95% CI 0.47-2.1%), respectively, with 3-year risk (1.9% [95%CI 0.87-2.9%]) remaining substantially below the threshold for a 6-12 month return (8.8%). In further analysis, we identified that risk was strongly elevated among the small group of WLHIV with CD4<200 (1-year risk=1.6%), but more moderate among the larger group with CD4 200-499 (1- and 2-year risks=0.33% and 0.90%, respectively). These data thus suggest that risk is low following a negative co-test, consistent with a suggested 3-year return in WLHIV with CD4>500 and possibly a 2-year return in WLHIV with CD4<500.

Finally, when negative cytology was combined with a positive oncHPV co-test (Figure 2.2C), risk among all WLHIV exceeded the 3y-return benchmark at 1 year (1-year risk=1.0% [95%CI 0-2.4%]), suggesting a 1-year return.

ASC-US cytology, with or without oncHPV testing

After ASC-US cytology (Figure 2.3A), the 3-year ${}_{b}$HSIL+ risk among WLHIV with CD4≥500 was 8.2% (95%CI 3.3-13.2%), approximating the 6-12mo return benchmark of 8.8%. Women with CD4<500 appeared to have a higher 3-year risk of 14.2% (95%CI 10.2-18.2%), approximating the colposcopy benchmark of 14.4%, but this was driven by high risk among WLHIV with CD4<350 (3-year risk=16.4% [95%CI 11.1-21.7%], Figure 2.4). This suggests that appropriate management strategies for women with ASC-US and unknown oncHPV status are repeat cytology in 6-12mo for women with current CD4≥350, as currently recommended. For WLHIV with CD4<350, it may be appropriate to consider immediate colposcopy.

Following ASC-US cytology combined with a negative oncHPV test (Figure 2.3B), 3-year risk among all WLHIV was 6.5% (95%CI 2.9-10.1%). Although this is below the 8.8% benchmark for a 6-12mo return, the 1-year risk was much higher than the 3y-return benchmark (1-year risk=4.3% [95%CI 1.6-6.9%] vs. 0.69% benchmark). When ASC-US cytology occurred instead with a positive oncHPV test (Figure 2.3C), the 3-year risk among all WLHIV was 14.6% (95%CI 7.4-21.8%), approximating the benchmark for colposcopy (14.4%). Taken together, this supports a 6-12mo return following an ASC-US/oncHPV-negative co-test, but immediate colposcopy following an ASC-US/oncHPV-positive co-test.

Consecutive negative cytology results

When oncHPV testing is not employed, guidelines have used consecutive negative cytology results to identify women at low risk.[40] Therefore, we compared ${}_{b}$HSIL+ risk after multiple negative cytology results (spaced by approximately 6 months) to the 3y-return risk benchmark. After 3 consecutive negative cytology results, for WLHIV with CD4≥500 (measured at the third cytology), the 3y-return benchmark (0.69%) was first exceeded at 3 years (3y risk=0.96% [95%CI 0.31-1.6%],

Figure 2.5A). For WLHIV with CD4<500, risk appeared slightly higher, matching the benchmark at 2 years (2y risk=0.68% [95%CI 0.12-1.2%], Figure 2.5B); however, confidence intervals were wide and also included the benchmark at 3 years. This suggests that risk after 3 consecutive negative cytology results is low for all women, consistent with a suggested return after 3 years in women with CD4≥500. For women with CD4<500, a return after 2 years might be considered. Of note, among women with CD4≥500, each additional negative cytology result suggested reduced risk (Figure 2.5A), while among women with CD4<500, risks after 2 and 3 negative results were equivalent (Figure 2.5B).

Results based on outcome of CIN3+

We assessed the sensitivity of our results to our definition of $_{b}$HSIL+ by repeating our analysis using CIN3+ instead of CIN2+ (Figure 2.6, Figure 2.7, Figure 2.8, Figure 2.9, Table 2.4). The risk benchmarks for CIN3+ included the same studies as for CIN2+ (Table 2.1) and were 0.36% (3y return), 3.4% (6-12mo return), and 4.7% (colposcopy) (Figure 2.6). Confidence intervals around CIN3+ risk estimates were very wide, and we disregarded them to identify suggested strategies. One analysis had modestly different inferences (concurrent negative cytology and oncHPV co-test), where benchmarks were reached more quickly using CIN3+ (Table 2.3, Table 2.4). Apart from this, strategies suggested by CIN3+ were the same as for CIN2+.

2.5 Discussion

In this study, we explored the cervical cancer screening strategies suggested by an explicit comparison of precancer risks between WLHIV and general population women. Although our approach differed from prior studies in multiple ways, including restriction to the current era of HIV treatment (2000 or later), our results largely supported existing cervical cancer screening guidelines for WLHIV[40] (Table 2.3). We also explored the utility of CD4 cell count for stratifying $_{b}$HSIL+ risks among WLHIV. Although we could not always estimate risks with sufficient precision to rule out

alternative strategies, we identified some scenarios in which CD4 count could be further explored for tailoring screening intervals or management strategies.

Our analysis identified that some WLHIV have low $_{b}$HSIL+ risks. For WLHIV with negative cytology, a negative oncHPV co-test, and a CD4≥500, as well as for WLHIV with 3 consecutive negative cytology results and a CD4≥500, risks of precancer were low (<1% at 3 years). While these risks were still modestly above the benchmark for a 3-year return (0.69%), their confidence intervals included this benchmark while definitively excluding the 6-12mo return benchmark of 8.8% (upper bounds≤1.7%). A previous study of co-test-negative WLHIV in the WIHS did not identify any cases of $_{b}$HSIL+ over 5 years, but did suggest higher risk of low-grade SIL among WLHIV with lower CD4 counts.[42] Our study, which includes larger numbers of WLHIV, suggests that some portion of these low-grade SIL will progress to high-grade SIL.

Further, our results suggested that WLHIV with lower CD4 counts may benefit from more frequent screening than those with higher CD4 counts. Even when co-testing is used, our approach suggested WLHIV with a CD4<500 may have higher $_{b}$HSIL risk than WLHIV with CD4≥500. The small group of WLHIV with CD4<200 had particularly high risk, but it is unlikely that frequent screening would be beneficial in these women, who may have multiple medical problems and/or short life expectancy. When negative cytology was found concurrently with oncHPV, we found that a 1-year return is appropriate, consistent with current guidelines.[40] A previous WIHS study supports the additional guideline for colposcopy if HPV16 or HPV18 is present;[43] however, we did not have sufficient post-2000 data to confirm this strategy. Following ASC-US cytology, which is common among WLHIV,[99] guidelines currently recommend colposcopy only if oncHPV is concurrently detected. Our analysis suggested that when oncHPV is unknown, a CD4<350 indicates similarly high risk, whereas women with higher CD4 counts can safely return for repeated screening within 1 year.

In the United States and other high-resource settings, the proportion of women with low CD4 counts has decreased as more WLHIV are on eART.[100] However, in low-resource settings, any recommendation for more aggressive screening among WLHIV with low CD4 counts could affect a

large proportion of WLHIV.[101,102] It is unclear whether eART itself (independent of its effect on CD4 count) directly impacts ${}_{b}$HSIL+ incidence,[40,89,103] and our study did not stratify by eART status. However, our findings do support guidelines recommending that all WLHIV be offered eART,[104] which increases CD4 counts and thus may reduce ${}_{b}$HSIL+ risks.[89] As in the general population, HPV vaccination will also continue to influence the balance of benefits and harms for cervical cancer screening in WLHIV.[33]

WLHIV constitute a special population that is at elevated risk for cervical cancer, but is also subject to a high burden of medical screening and tests. We explored screening strategies for WLHIV using an approach based on risk benchmarking, which provides a framework for ensuring that similar management is applied to similar risks. We used the best available data from a large and established cohort study to evaluate risks among WLHIV, and applied parametric survival models so that risk estimates did not change sharply when outcomes were sparse. Though many studies have examined cervical cancer screening in the WIHS, our study complements prior work by including additional data from new WIHS cohorts, restricting to the current eART era, and employing benchmarks that reflect true general population risks. Our selection of CD4 cell count as an *a priori* factor for stratification of ${}_{b}$HSIL+ risks is supported by extensive research in the WIHS and other studies.[43,79,80,63,82–84]

Our approach required that we apply risk benchmarking in two novel ways. First, we compared risks across populations (the WIHS and general population studies) that differ with regard to frequency of screening, ${}_{b}$HSIL+ outcome ascertainment, data quality, and statistical methods. Second, the time-to-benchmark approach that we used to suggest screening intervals is a novel application that was not previously established. Consistent with other benchmarking studies, we considered risk benchmarks to be measured without error,[10,95,96] and we set screening intervals according to when these benchmarks were met or exceeded. However, with the first benchmark at 0.69% (3-year return), it could be argued that a higher threshold should be used before shortening the screening interval from 3 years, as the second benchmark was much higher (8.8% for 6-12mo

return) – a matter for guideline committees to consider. Our risk benchmark estimates may be sensitive to the inclusion or exclusion of studies (e.g., non-U.S. studies were excluded). However, we believe that our approach of synthesizing risks from robust studies yielded the best available benchmarks to reflect the risk levels associated with general population screening guidelines in the United States. Finally, while we have identified some opportunities for tailoring screening by CD4 count at the time of cytology/HPV testing, there are other potential stratification factors that we did not consider. For example, ${}_{b}$HSIL+ risk is likely affected by a woman's cumulative history of immunosuppression (including the nadir CD4 value and duration of immunosuppression), and women with a previous history of ${}_{b}$HSIL+ (with or without treatment) may have higher risks and thus require more individualized management. Further, risk may also vary by age, particularly in unscreened women.

Considerable research has evaluated cervical HPV infection and abnormalities among WLHIV, but few studies have explicitly compared risks between WLHIV and general population women within a systematic framework oriented toward screening guidelines. Despite major differences from prior work, our analysis largely supported existing screening guidelines for WLHIV. We additionally found that CD4 cell count, measured at the time of a cervical cancer screening test, may have utility to inform some decisions about screening intervals and management. The impetus to include additional strata to refine screening practices, though, must be balanced against the goal to simplify and harmonize clinical guidelines. As HIV therapies and cervical cancer screening continue to evolve, optimal management will require ongoing evaluation of appropriate screening strategies in this population. The novel benchmarking approach used in this study could be a helpful new tool in this process.

2.6 Supplementary Methods

Generation of Risk Benchmarks

Our goal was to estimate risk benchmarks that summarize the range of $_b$HSIL+ risks to which guidelines are applied in the general population, thus allowing $_b$HSIL+ risks among women living with HIV (WLHIV) to be placed in the context of general population risks. Therefore, we reviewed the literature for published studies describing risks of CIN2+ and/or CIN3+ after negative, ASC-US, or LSIL cytology among general population women in the United States. We included large studies taking place in a usual care setting that presented numerical risk percentages between 1 and 5 years following cytology. We required that data analyzed in these studies extend beyond the year 2000, to ensure overlap with our data for WLHIV. We also included risks generated using data from HIV-uninfected women in the Women's Interagency HIV Study (WIHS), except for the LSIL (colposcopy) benchmarks, where we did not have sufficient data.

We synthesized estimates across studies using mixed-effects linear regression models with random intercepts (for study) and fixed slopes, as random-slope models did not converge due to small numbers of clusters (studies). Although the change in risk over time is not precisely linear, this approach allowed us to adequately capture variation in risk within and between studies (Supplemental Figures 1 and 3). We did not weight the studies based on sample size, as we did not want the benchmarks to heavily reflect the largest studies. Instead, by using unweighted models, we aimed to reflect the variability in risks due to more substantive differences in study populations (e.g., demographic differences, screening programs) and analytical methods.

We expect that the magnitude of our risk benchmarks might be sensitive to the inclusion or exclusion of different studies. For example, the risk benchmarks might differ if we included studies from other countries, particularly those with screening programs different than the United States. By themselves, some of the studies that we included would yield risks too low to compare to the WLHIV in WIHS (for example, risks are notably low in the Kaiser Permanente Northern California data [10]), while others would yield risks too high (for example, the HIV-uninfected women in WIHS, because they are at elevated risk for HIV and therefore HPV). We believed it was important to include risks among HIV-uninfected women in the WIHS so that any unique aspects of the WIHS

screening program (e.g., frequent screening and a low threshold for colposcopy referral) were represented. By synthesizing a diverse set of risks, we aimed to summarize the risks to which general population screening guidelines are applied in the United States.

Calculation of $_b$HSIL+ Risks in WLHIV

To calculate $_b$HSIL+ risks among WLHIV in the WIHS, we used parametric survival models. These models smooth over the sharp changes in risk that can result from non-parametric (e.g., Kaplan-Meier) approaches. Among each group of women defined by cytology result, HPV result, and CD4 cell count, we fit separate models based on the Weibull and log-normal distributions. We then chose one model for each group based on visual fit to Kaplan-Meier estimates and the Akaike information criterion (AIC), and used the resulting model to predict risk (i.e. cumulative incidence, or 1 – S(t)) at 1, 2, 3, 4, and 5 years. We generated the figures by smoothly connecting these annual risk estimates.

2.7 Acknowledgments

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2.8 Tables and Figures

Table 2.1 General population studies analyzed to generate risk benchmarks of cervical intraepithelial neoplasia (CIN) for comparison to risks in women living with HIV.

Characteristic	Study			
	Katki et al., J Low Genit Tract Dis 2013[10]	Gage et al., Cancer Epidemiol Biomark Prev 2016[98]	Castle et al., J Clin Oncol 2012*[97]	Women's Interagency HIV Study (WIHS)†
Cytology results included in analysis	Negative, ASC-US, LSIL	Negative, ASC-US, LSIL	Negative, ASC-US	Negative, ASC-US
Data type	Usual care (HMO)	Usual care (registry)	Usual care (HMO)	Cohort
Sample size	965,360	452,045	19,512	1,018
Timch e period	2003-2010	2007-2013	1989-2006	2000-2015
Location	Northern California	New Mexico	Portland, Oregon	11 study sites in the United States
Age range, years	30-64	21-64	16-94	21-64
Age distribution, years	Not reported	27% age 21-29 23% age 30-39 23% age 40-49 27% age 50-64	Mean 35.8 Median 34.0	25% age 20-29 32% age 30-39 29% age 40-49 13% age ≥50
Race/ethnicity distribution	62% White‡ 12% Hispanic 12% Asian/PI 8% African-American	Not reported	Not reported	65% African-American 21% Hispanic 10% White 4% Other
Cytology distribution	96% Negative 3% ASC-US 1% LSIL <1% HSIL/other	93% Negative 4% ASC-US 2% LSIL	95% Negative 3% ASC-US 2% LSIL <1% HSIL	91% Negative 9% ASC-US
Treatment of hysterectomy	Not mentioned	Basis for both exclusion and censoring	Basis for exclusion	Basis for exclusion

HMO, health maintenance organization; PI, Pacific Islander. Percentages may not sum exactly to 100% due to rounding.
*Exact numerical risk estimates are not displayed in the figures in this study, but were provided by the publisher.
†We analyzed data from HIV-uninfected women in the WIHS using the same methods described in this manuscript (see Methods). Women who seroconverted (became HIV-infected) during follow-up were censored at the time of seroconversion.
‡Demographic characteristics listed from Katki et al., Lancet Oncol 2011.[105] Estimates provided for race/ethnicity are based on a survey to which 49% of the population responded.

Table 2.2 Descriptive characteristics of 2,423 women living with HIV in the Women's Interagency HIV Study with negative or ASC-US cytology at their first visit in 2000 or later.

Characteristic	Negative cytology N (%)	ASC-US cytology N (%)	p-value
Total	2,049 (100)	374 (100)	
oncHPV status			<0.001
Negative	1,247 (60.9)	191 (51.1)	
Positive	159 (7.8)	103 (27.5)	
Unknown	643 (31.4)	80 (21.4)	
Age, years			0.046
20-29	243 (11.9)	62 (16.6)	
30-39	773 (37.7)	145 (38.8)	
40-49	744 (36.3)	123 (32.9)	
50 or older	289 (14.1)	44 (11.8)	
Race/ethnicity			0.66
Non-Hispanic Black	1,254 (61.2)	238 (63.6)	
Non-Hispanic White	259 (12.6)	39 (10.4)	
Hispanic	467 (22.8)	85 (22.7)	
Other	69 (3.4)	12 (3.2)	
WIHS enrollment cohort			<0.001
1994-95	932 (45.5)	189 (50.5)	
2001-02	509 (24.8)	116 (31.0)	
2011-12	215 (10.5)	34 (9.1)	
2013-15	393 (19.2)	35 (9.4)	
Current CD4 count (cells/μL)*			<0.001
≥500	1,042 (50.9)	108 (28.9)	
350-499	423 (20.6)	90 (24.1)	
200-349	359 (17.5)	88 (23.5)	
<200	203 (9.9)	87 (23.3)	
Missing	22 (1.1)	1 (0.3)	
Smoking status†			0.07
Current smoker	1,118 (54.6)	184 (49.3)	
Not a current smoker	930 (45.4)	189 (50.7)	
Ever ART			0.16
No	409 (20.0)	63 (16.8)	
Yes	1,640 (80.0)	311 (83.2)	
Length of follow-up, years (median, IQR)	6.9 (1.6-12.9)	5.0 (1.6-12.8)	0.12

ART, antiretroviral therapy; IQR, interquartile range. Percentages may not sum exactly to 100 due to rounding.
*If CD4 count was missing, we used the most recent CD4 count measured prior to the time of cytology (N=36, 1.5%), allowing a gap of up to 2 years.
†Missing for one woman.

Table 2.3 Summary of bHSIL+ (CIN2+) risks among women living with HIV and the cervical cancer screening strategies suggested by this risk benchmarking approach.

Cytology	HPV	CD4	Observed bHSIL+ (CIN2+) risk, % (95% CI) at:			Risk-based	CDC
			1 year	2 years	3 years	strategy	guideline
3 Negative	Unknown	≥500	0.11 (0-0.30)	0.45 (0.02-0.89)	0.96 (0.31-1.6)	3y return	3y return
		<500	0.19 (0-0.46)	0.68 (0.12-1.2)	1.3 (0.52-2.1)	2-3y return	
Negative	Negative	≥500	0.20 (0-0.51)	0.53 (0-1.1)	0.94 (0.21-1.7)	3y return	3y return
		<500	0.66 (0.08-1.2)	1.3 (0.47-2.1)	1.9 (0.87-2.9)	2y return*	
	Unknown	≥500	0.46 (0.10-0.81)	0.98 (0.44-1.5)	1.5 (0.83-2.3)	2y return	1y return
		<500	1.1 (0.51-1.6)	2.0 (1.2-2.8)	2.9 (1.9-3.9)	1y return	
	Positive	Any	1.0 (0-2.4)	3.0 (0.40-5.5)	5.1 (1.7-8.6)	1y return	1y return.†
ASC-US	Negative	Any	4.3 (1.6-6.9)	5.6 (2.4-8.8)	6.5 (2.9-10.1)	6-12mo return	(Not stated)
	Unknown	≥500	3.7 (0.62-6.7)	6.2 (2.2-10.2)	8.2 (3.3-13.2)	6-12mo return	6-12mo return
		350-499	6.9 (2.4-11.4)	9.0 (3.4-14.4)	10.4 (4.3-16.5)	6-12mo return	
		<350	8.9 (5.3-12.6)	13.1 (8.6-17.7)	16.4 (11.1-21.7)	Colposcopy	
	Positive	Any	8.3 (3.2-13.3)	12.0 (5.7-18.2)	14.6 (7.4-21.8)	Colposcopy	Colposcopy

Three-year risk benchmarks based on general population risks were 0.69% (3y return), 8.8% (6-12mo return), and 14.4% (colposcopy). Risks after combined cytology/HPV testing (co-testing) were calculated only among women aged 30 years and older, consistent with U.S. Preventive Services Task Force, American Cancer Society, and Centers for Disease Control and Prevention (CDC) guidelines. CD4 count was measured at the time of cytology/HPV testing.
bHSIL+, biopsy-confirmed high grade squamous intraepithelial lesion or worse; CIN2+, cervical intraepithelial neoplasia grade 2 or higher; WLHIV, women living with HIV; CDC, Centers for Disease Control and Prevention.
*We found that a 2-year return was more appropriate than a 1-year return for most women in this group (see Results).
† Colposcopy if HPV16+ or HPV16/18+. We did not have sufficient data to evaluate this guideline.

Table 2.4 Summary of $_b$HSIL+ (CIN3+) risks among women living with HIV and the cervical cancer screening strategies suggested by this risk benchmarking approach.

Cytology	HPV	CD4*	Observed $_b$HSIL+ (CIN3+) risk, % (95% CI) at: 1 year	2 years	3 years	Risk-based strategy	CDC guideline
3 Negative	Unknown	≥500	0.04 (0-0.15)	0.15 (0-0.41)	0.32 (0-0.70)	3y return	3y return
		<500	0.15 (0-0.40)	0.39 (0-0.81)	0.65 (0.08-1.2)	2y return	
Negative	Negative	≥500	0.15 (0-0.43)	0.32 (0-0.74)	0.49 (0-1.03)	2y return	3y return
		<500	0.32 (0-0.72)	0.80 (0.16-1.4)	1.3 (0.46-2.1)	1y return	
	Unknown	≥500	0.23 (0-0.48)	0.44 (0.08-0.81)	0.65 (0.18-1.12)	2y return	1y return
		<500	0.40 (0.06-0.74)	0.84 (0.34-1.3)	1.3 (0.60-1.9)	1y return	
	Positive	Any	0.17 (0-0.69)	0.67 (0-1.9)	1.5 (0-3.3)	1y return	1y return*
ASC-US	Negative	Any	1.7 (0.02-3.5)	2.3 (0.23-4.4)	2.7 (0.35-5.1)	6-12mo return	(Not stated)
	Unknown	≥500	1.5 (0-3.5)	2.5 (0-5.0)	3.2 (0.06-6.4)	6-12mo return	6-12mo return
		<500	4.0 (1.9-6.0)	5.4 (2.9-7.9)	6.4 (3.5-9.3)	Colposcopy	
	Positive	Any	3.3 (0-6.7)	4.5 (0.46-8.5)	5.4 (0.75-10.0)	Colposcopy	Colposcopy

Three-year risk benchmarks based on general population risks were 0.36% (3y return), 3.4% (6-12mo return), and 4.7% (colposcopy). Risks after combined cytology/HPV testing (co-testing) were calculated only among women aged 30 years and older, consistent with U.S. Preventive Services Task Force and American Cancer Society guidelines. CD4 count was measured at the time of cytology/HPV testing.

$_b$HSIL+, biopsy-confirmed high grade squamous intraepithelial lesion or worse; CIN3+, cervical intraepithelial neoplasia grade 3 or higher; WLHIV, women living with HIV; CDC, Centers for Disease Control and Prevention.

* Colposcopy if HPV16+ or HPV16/18+*. We did not have sufficient data to evaluate this guideline.

Figure 2.1 Generation of $_{b}$HSIL+ (CIN2+) risk benchmarks for a 3-year return (after negative cytology, panel A), a 6-12 month return (after ASC-US cytology, panel B), and immediate colposcopy (after LSIL cytology, panel C). Black lines depict summary risks generated by linear models with random intercepts, and black points indicate the 3-year risk benchmarks used for comparison to risks among women living with HIV.

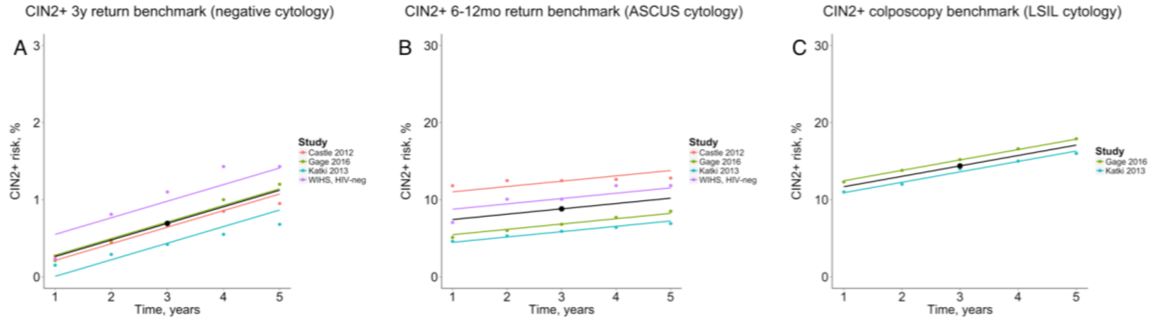
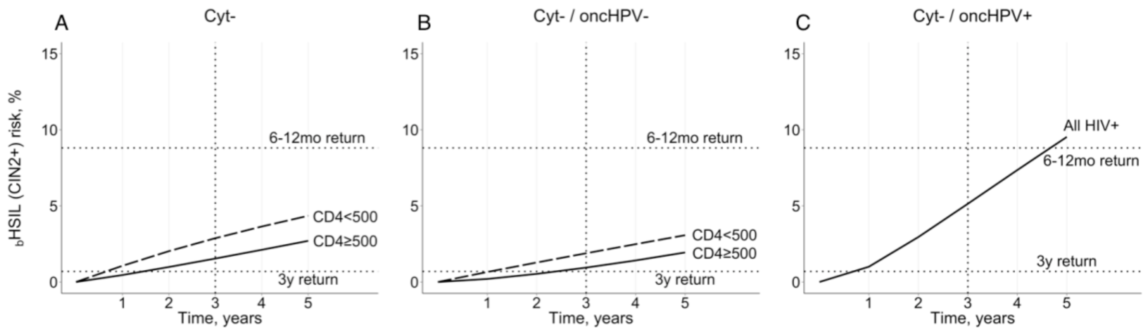
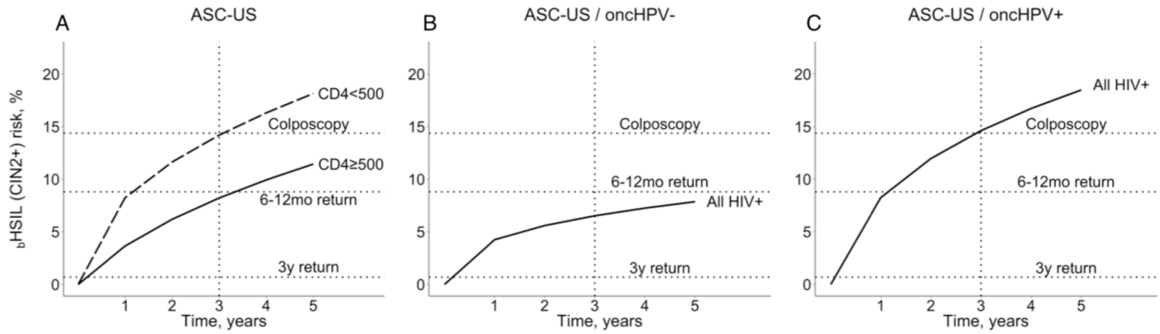


Figure 2.2 Risk of cervical $_{b}$HSIL+ (CIN2+) among 2,049 women living with HIV (WLHIV) following negative cytology, by CD4 cell count at the time of cytology and oncogenic HPV status, compared to general population risk benchmarks for recommending women be re-screened in 3 years (3y return) or 6-12 months (6-12mo return). The Figure includes panels for: any oncogenic HPV result (positive, negative or unknown) (panel A), oncHPV-negative (panel B), or oncHPV-positive (panel C). Calculation of risks following a co-test result (panels B and C) was restricted to 1,194 women aged 30 years and older.



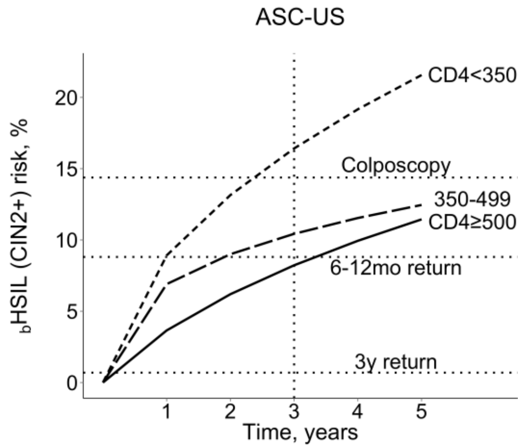
Among WLHIV with negative cytology, there were 20 $_{b}$HSIL+ (CIN2+) events over 5 years among 1,042 women with CD4≥500 and 33 events among 985 women with CD4<500. Among women with negative cytology and a negative oncHPV co-test, there were 9 $_{b}$HSIL+ events among 511 women with CD4≥500 and 15 events among 553 women with CD4<500. Among women with negative cytology and a positive oncHPV co-test, there were 10 $_{b}$HSIL+ events among 124 women. CD4 cell count was measured at the time of cytology and was unknown for 22 women.

Figure 2.3 Risk of cervical $_b$HSIL+ (CIN2+) among 374 women living with HIV (WLHIV) following ASC-US cytology, by CD4 cell count at the time of cytology and oncogenic HPV co-test status, compared to general population risk benchmarks for recommending women be re-screened in 3 years (3y return), 6-12 months (6-12mo return), or referred for immediate colposcopy. The Figure includes panels for: any oncogenic HPV result (positive, negative or unknown) (panel A), oncHPV-negative (panel B), or oncHPV-positive (panel C). Calculation of risks following a co-test result (panels B and C) was restricted to 245 women aged 30 years and older.



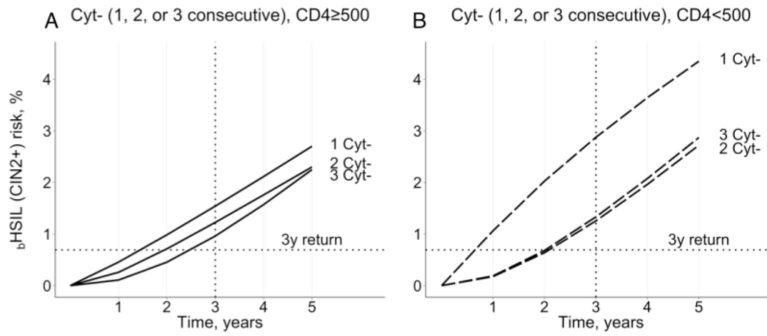
Among WLHIV with ASC-US cytology, there were 10 $_b$HSIL+ (CIN2+) events over 5 years among 108 women with CD4≥500 and 41 events among 265 women with CD4<500. Among women with ASC-US cytology and a negative HPV co-test, there were 12 $_b$HSIL+ events among 163 women. Among women with ASC-US cytology and a positive HPV co-test, there were 14 $_b$HSIL+ events among 82 women. CD4 cell count was measured at the time of cytology and was unknown for 1 woman.

Figure 2.4 Risk of cervical $_{b}$HSIL+ (CIN2+) among 374 women living with HIV (WLHIV) following ASC-US cytology, by CD4 cell count at the time of cytology, compared to general population risk benchmarks for recommending women be re-screened in 3 years (3y return), 6-12 months (6-12mo return), or referred for immediate colposcopy.



Among WLHIV with ASC-US cytology, there were 10 $_{b}$HSIL+ (CIN2+) events over 5 years among 108 women with CD4≥500, 10 events among 90 women with CD4 350-499, and 31 events among 175 women with CD4<350. CD4 cell count was measured at the time of cytology and was missing for 1 woman.

Figure 2.5 Risk of cervical $_b$HSIL+ (CIN2+) among women living with HIV (WLHIV) following 1, 2, or 3 consecutive negative cytology results, by CD4 cell count at final cytology (≥500 panel A, <500 panel B), compared to a general population risk benchmark for recommending women be re-screened in 3 years (3y return).



Among WLHIV with CD4≥500, there were 1,042, 846, and 716 women with 20, 14, and 12 $_b$HSIL+ (CIN2+) events, respectively, for the analysis of 1, 2, and 3 consecutive negative cytology results. Among WLHIV with CD4<500, there were 985, 785, and 620 women with 33, 16, and 14 $_b$HSIL+ events, respectively, for analysis of 1, 2, and 3 consecutive negative cytology results.

Figure 2.6 Generation of $_{b}$HSIL+ (CIN3+) risk benchmarks for a 3y return (after negative cytology, panel A), a 6-12mo return (after ASC-US cytology, panel B), and immediate colposcopy (after LSIL cytology, panel C). Black lines depict summary risks generated by linear models with random intercepts, and black points indicate the 3-year risk benchmarks used for comparison to risks among women living with HIV.

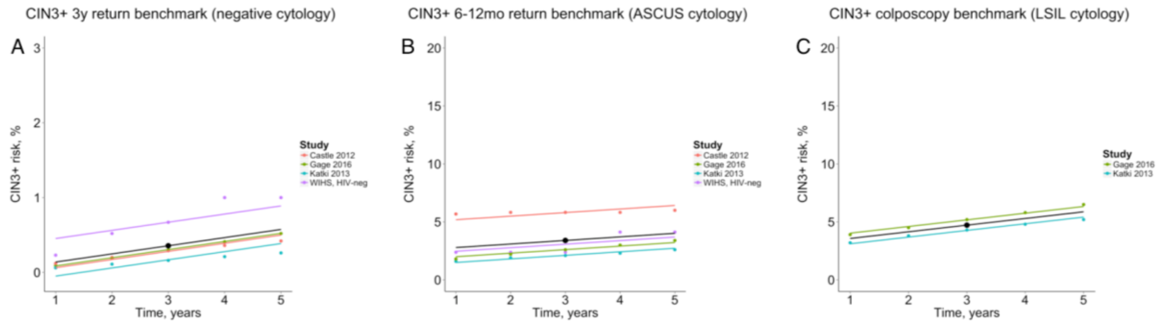
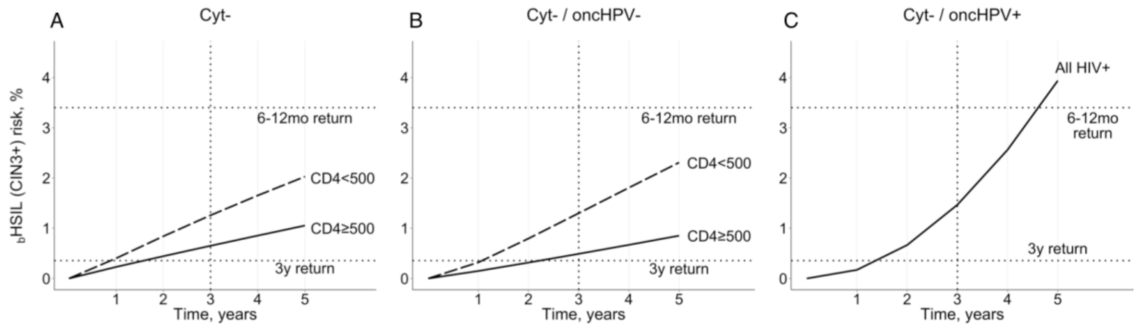
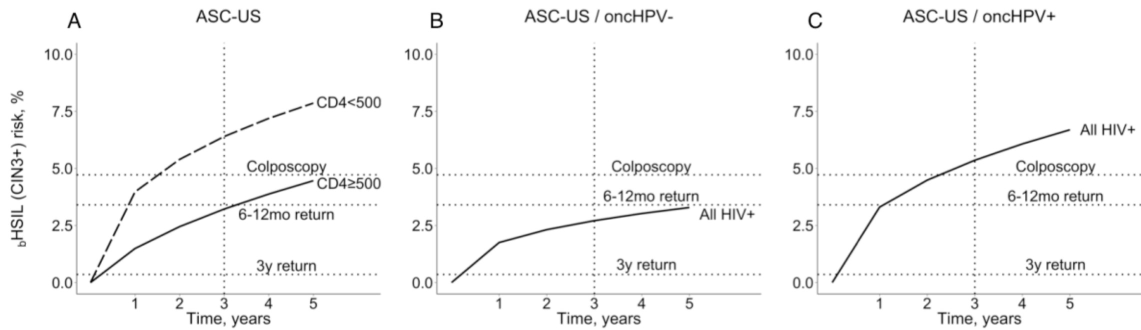


Figure 2.7 Risk of cervical $_b$HSIL+ (CIN3+) among 2,049 women living with HIV (WLHIV) following negative cytology, by CD4 cell count at the time of cytology and oncogenic HPV status, compared to general population risk benchmarks for recommending women be re-screened in 3 years (3y return) or 6-12 months (6-12mo return). The Figure includes panels for: any oncogenic HPV result (positive, negative or unknown) (panel A), oncHPV-negative (panel B), or oncHPV-positive (panel C). Calculation of risks following a co-test result (panels B and C) was restricted to 1,194 women aged 30 years and older.



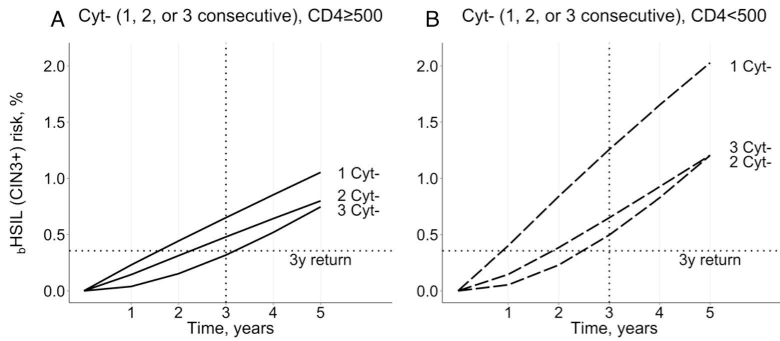
Among WLHIV with negative cytology, there were 8 $_b$HSIL+ (CIN3+) events over 5 years among 1,042 women with CD4≥500 and 15 events among 985 women with CD4<500. Among women with negative cytology and a negative HPV co-test, there were 4 $_b$HSIL+ events among 511 women with CD4≥500 and 11 events among 553 women with CD4<500. Among women with negative cytology and a positive HPV co-test, there were 4 $_b$HSIL+ events among 120 women. CD4 cell count was measured at the time of cytology and was unknown for 22 women.

Figure 2.8 Risk of cervical $_{b}$HSIL+ (CIN3+) among 374 women living with HIV (WLHIV) following ASC-US cytology, by CD4 cell count at the time of cytology and oncogenic HPV co-test status, compared to general population risk benchmarks for recommending women be re-screened in 3 years (3y return), 6-12 months (6-12mo return), or referred immediately for colposcopy. The Figure includes panels for: any oncogenic HPV result (positive, negative or unknown) (panel A), oncHPV-negative (panel B), or oncHPV-positive (panel C). Calculation of risks following a co-test result (panels B and C) was restricted to 245 women aged 30 years and older.



Among WLHIV with ASC-US cytology, there were 4 $_{b}$HSIL+ (CIN3+) events over 5 years among 108 women with CD4≥500 and 18 events among 265 women with CD4<500. Among women with ASC-US cytology and a negative HPV co-test, there were 5 $_{b}$HSIL+ events among 163 women. Among women with ASC-US cytology and a positive HPV co-test, there were 5 $_{b}$HSIL+ events among 82 women. CD4 cell count was measured at the time of cytology and was unknown for 1 woman.

Figure 2.9 Risk of cervical $_b$HSIL+ (CIN3+) among women living with HIV (WLHIV) following 1, 2, or 3 consecutive negative cytology results, by CD4 cell count at final cytology (≥500 panel A, <500 panel B), compared to general population risk benchmarks for recommending women be re-screened in 3 years (3y return).



Among WLHIV with CD4≥500, there were 1,042, 846, and 716 women with 8, 5, and 4, $_b$HSIL+ (CIN3+) events, respectively, for the analysis of 1, 2, and 3 consecutive negative cytology results. Among WLHIV with CD4<500, there were 985, 785, and 620 women with 15, 7, and 6, $_b$HSIL+ events, respectively, for analysis of 1, 2, and 3 consecutive negative cytology results.

Chapter 3: Patterns of Repeated Anal Cytology Testing among HIV-positive and HIV-negative Men who have Sex with Men

3.1 Abstract

Background: Men who have sex with men (MSM) are at increased risk for anal cancer. In cervical cancer screening, patterns of repeated cytology are used to identify low- and high-risk women, but little is known about these patterns for anal cytology among MSM.

Methods: We analyzed Multicenter AIDS Cohort Study (MACS) data for MSM who were offered anal cytology testing annually (HIV-positive, n=708) or every 2 years (HIV-negative, n=796) for 4 years. After excluding men with anal dysplasia treatment during testing, at least 2 valid anal cytology results were available for 474 HIV-negative and 502 HIV-positive MSM, and at least 3 valid results for 328 HIV-positive MSM. Inverse probability weighting was used to address possible selection bias.

Results: Following an initial negative (normal) cytology, the frequency of a second negative cytology was lower among HIV-positive MSM with CD4≥500 (74%) or CD4<500 (68%) than HIV-negative MSM (83%) ($p<0.001$). After an initial abnormal cytology, the frequency of a second abnormal cytology was highest among HIV-positive MSM with CD4<500 (70%) compared to CD4≥500 (53%) or HIV-negative MSM (46%) ($p=0.003$). Among HIV-positive MSM with at least three results, 37% had 3 consecutive negative results; 3 consecutive abnormal results were more frequent among CD4<500 (22%) than CD4≥500 (10%) ($p=0.008$).

Conclusions: More than one-third of HIV-positive MSM have consistently negative anal cytology over three years. Following abnormal anal cytology, a repeated cytology is commonly negative in

HIV-negative or immunocompetent HIV-positive men, while persistent cytological abnormality is more likely among HIV-positive men with CD4<500.

3.2 Introduction

Anal cancer is rare in the United States general population (1.8 per 100,000),[45,46] though rates are increasing.[47] In contrast, incidence among HIV-seropositive men who have sex with men (HIV-positive MSM) is extremely high, estimated at 131 per 100,000,[48] due to increased human papillomavirus (HPV) prevalence and HIV-associated immunosuppression.[51] During 2001-2005, approximately 28% of U.S. anal cancers in males occurred in men living with HIV, the vast majority in HIV-positive MSM.[106] This burden is likely growing as the HIV-positive population size increases,[5,7] though the trend in anal cancer incidence is unclear.[4,107] Anal cancer is also a concern for HIV-negative MSM, who have incidence 30-fold higher than the general population.[49,108]

There is an urgent need for effective anal cancer screening methods among MSM. Though no national or international guidelines exist,[50] the primary strategy is screening by anal cytology (collected with an anal swab) with referral to high-resolution anoscopy (HRA) for possible biopsy, diagnosis, and treatment of anal precancer/cancer.[32,51,52] This approach is analogous to cervical cancer screening by cytology with referral to colposcopy, but is not as well described.[51,53,54] Using a threshold of ASC-US (atypical squamous cells of undetermined significance) and higher grades of cellular dysplasia on cytology as a positive screen, the sensitivity of both anal and cervical cytology for biopsy-confirmed high-grade dysplasia are estimated at 90%; however, specificity appears lower for anal vs. cervical cytology (33% vs. 53%).[109]

Due to the challenges and uncertainty associated with anal cytology, some have proposed that HIV-positive MSM be referred directly to HRA.[55] However, while anal cytology has high acceptability among MSM,[56,57] there are a limited number of trained and experienced HRA providers, a higher cost for the procedure, and uncertain benefits of screening using this diagnostic tool. Thus,

evaluating whether using cytology may be appropriate to identify men who do or do not need HRA is an important goal.

At the cervix, the predictive value of repeated cytology results (e.g., 3 consecutive negative results) is frequently utilized in screening guidelines.[40,63] For anal cytology, however, it is not known what proportion of HIV-positive MSM have consistently negative results. Further, different transition probabilities, such as the likelihood of a negative cytology if the previous cytology was abnormal, have not been described for anal cytology nor compared by HIV or immune status. Such data could inform decisions regarding when and whether to repeat anal cytology or refer MSM to HRA.

3.3 Methods

Study Population

We analyzed data from the Multicenter AIDS Cohort Study (MACS), a cohort study of HIV-positive and HIV-negative men who have sex with men (MSM). The MACS has 4 United States sites (Baltimore, Chicago, Pittsburgh, and Los Angeles) and has been ongoing since 1984. Visits occur every 6 months and include routine collection of biological and behavioral covariates of interest. For this sub-study, all MACS participants who attended any study visits between June 2010 and July 2011 were offered a free anal cytology test, with collection and testing done as previously described.[54] Men with unsatisfactory cytology results were offered another test at their next visit. By design, over the study period, HIV-positive men were offered annual cytology (up to 4 cytologies total), whereas HIV-negative men were offered a second cytology 2 years later (2 cytologies total). Thus, our analyses including both HIV-positive and HIV-negative MSM describe 2 cytology results typically collected 1 and 2 years apart, respectively. Analyses examining 3 or more cytology results could be performed among HIV-positive MSM only. Information about HRA and treatment of anal dysplasia occurring outside of regular MACS visits was collected using participant questionnaires and

subsequent medical record review. This MACS sub-study was approved by the institutional review boards of each participating site.

Statistical Analysis

A substantial proportion (18%) of cytology results were classified as being unsatisfactory for evaluation. For the purposes of this analysis (excluding the generation of inverse probability weights described below) we omitted these results and only considered results deemed sufficient for interpretation. Adequate (valid) specimens were classified as negative (normal) or abnormal: ASC-US, low-grade squamous intraepithelial lesion (LSIL), atypical squamous cells cannot exclude HSIL (ASC-H), or high-grade squamous intraepithelial lesion (HSIL). As we stratify by HIV status, we excluded 1 man who acquired HIV after his first cytology. Men who had treatment of anal dysplasia (including imiquimod cream, trichloroacetic acid, cryotherapy, electrocautery, infrared coagulation, or surgery) between their first and second cytology (N=38) were excluded from all analyses. For analyses considering 3 consecutive cytologies (HIV-positive MSM only), 14 additional men with treatment between the second and third cytology were excluded.

Among men with at least 2 valid cytology tests, and considering only the first 2 valid (consecutive) results, we calculated frequencies of having a negative (vs. abnormal) cytology following a negative or abnormal cytology. We compared these frequencies across HIV-negative MSM and HIV-positive MSM with absolute CD4+ T cell counts (CD4) ≥500 cells/μL (immunocompetent) and <500 cells/μL (potentially immunocompromised) at the first cytology; p-values were calculated using chi-square tests across all three groups. We also present this analysis after dividing abnormal results into more detailed categories. Among HIV-positive MSM with at least 3 valid results, we also calculated frequencies of having a negative (vs. abnormal) cytology at the third consecutive anal cytology following 2 consecutive negative or 2 consecutive abnormal cytologies, and compared these frequencies by CD4 count at the first cytology; p-values were calculated using chi-square tests across the two HIV-positive groups.

We recognized potential for selection bias in our analysis set of HIV-positive MSM with at least 3 valid results and no anal dysplasia treatment (N=328), as this group represented less than half of the HIV-positive MSM who originally had at least one anal swab for cytology collected (N=708). Therefore, we applied inverse probability weights in the analyses of cytology patterns conducted among this group. We generated the weights using a logistic regression model including variables potentially related to consistent participation in cytology testing, including study center, wave of enrollment into cohort, age, race/ethnicity, educational level, first cytology result (including inadequate), HAART status, and number of sexual partners. Weights were stabilized by dividing the overall proportion with complete data by each individual's model-predicted probability of having complete data. We then applied these stabilized weights when calculating the prevalence of cytology patterns among HIV-positive MSM, and when fitting a logistic model comparing characteristics of men with consistently abnormal vs. consistently negative cytology (described below).

Among HIV-positive MSM with at least 3 valid cytologies, we classified men as having different patterns of negative and abnormal results (e.g., negative-abnormal-negative) by considering the first 3 valid results. As a descriptive analysis, we further restricted to HIV-positive MSM with either consistently abnormal results (i.e., 3 consecutive abnormal cytologies) or consistently negative results (i.e., 3 consecutive negative cytologies) and fit a logistic regression model to compare demographic, behavioral, and biological characteristics between these two groups.

3.4 Results

A total of 796 HIV-negative and 708 HIV-positive MSM had at least one anal swab collected and evaluated for anal cytology, including inadequate results (Table 3.1, top portion). Since the focus of this analysis was on patterns in repeated anal cytology, all analyses were restricted to MSM with at least two valid cytology results (Table 3.1, bottom portion). Among the HIV-negative MSM, who typically only had 2 opportunities to have anal cytology collected, 474/796 (60%) had 2 valid results after excluding 6 men with anal dysplasia treatment between their first and second cytology; the

median time interval between valid cytologies for HIV-negative MSM was 2.0 years (IQR 1.9-2.2). Among the HIV-positive MSM, who had up to 4 anal cytologies collected, 502/708 (71%) had at least 2 valid results after excluding 32 men with anal dysplasia treatment; the median time interval between valid cytologies was 1.0 years (IQR 0.96-1.3). Among these MSM, the median age was 58 years for HIV-negative and 54 years for HIV-positive MSM. Consistent with the MACS participants overall, most men in this sub-study were non-Hispanic White and had at least a college education. Among HIV-positive MSM, the median current CD4 cell count (at the first cytology) was 579 cells/μL, while the median nadir CD4 count (prior to first cytology) was 252 cells/μL. When summarizing all MACS visits over the last 5 years, the mean number of condomless receptive anal sex partners reported at each visit was 1.0 or more for 12% of HIV-negative and 27% of HIV-positive men.

We compared the frequency of a negative (vs. abnormal) cytology following an initial negative or abnormal cytology by HIV and CD4 status at the first cytology (Table 3.2). After an initial negative cytology, the frequency of a negative result on the second cytology (without accounting for differences in time interval) was 83%, 74%, and 68% among HIV-negative MSM, HIV-positive MSM with CD4≥500, and HIV-positive MSM with CD4<500, respectively ($p<0.001$). After an initial abnormal cytology, corresponding frequencies of an abnormal result on the second cytology (without accounting for differences in time interval) were 46%, 53%, and 70% ($p=0.003$). When the analyses were restricted to cytologies that were within 18-30 months of each other, so that HIV-negative and HIV-positive MSM had similar time intervals between tests (Table 3.3), consecutive negative cytologies were still most frequent in HIV-negative MSM (83%), but there was no appreciable difference between the HIV-positive groups based on CD4 count (73-74%; overall $p=0.02$). For consecutive abnormal cytologies, as in the primary analysis, the results showed comparable frequencies in HIV-negative MSM and HIV-positive MSM with CD4≥500 (43% and 40%, respectively), and higher frequency in HIV-positive MSM with CD4<500 (65%, overall $p=0.02$).

Further stratification of results from the first and second cytologies (Table 3.2) revealed that ASC-US results at the second cytology accounted for more than three-quarters of abnormal results following an initial negative cytology, with LSIL or higher grade results occurring in 6% of men or less, regardless of HIV or CD4 status. After an initial ASC-US cytology, more than one-quarter of men (27-31%) had ASC-US at their second cytology in all groups, while LSIL was more common in HIV-positive MSM with CD4<500 (27%) than CD4≥500 (14%) or HIV-negative MSM (6%) (overall p=0.07). ASC-H and HSIL results were generally uncommon, but did represent 6-10% of results following an initial cytology of LSIL or higher grade.

Among HIV-positive MSM only, we also compared the frequency of a negative or abnormal cytology following 2 consecutive negative or abnormal cytologies (Table 3.2). After 2 consecutive negative cytologies, the frequency of the third cytology remaining negative was high (74-77%) regardless of CD4 count (p=0.84). However, after 2 consecutive abnormal cytologies, the frequency of the third cytology remaining abnormal was higher among HIV-positive MSM with CD4<500 (79%) compared to CD4≥500 (60%), though the difference did not quite reach statistical significance (p=0.08).

Among the 708 HIV-positive MSM who had at least one cytology collected, 328 (46%) had at least 3 valid results and no treatment. Among these 328 HIV-positive MSM, we explored frequencies of different patterns of results observed over the first 3 cytologies, using inverse-probability weighting to approximate what would have been observed in the original 708 MSM (Table 3.4). Across categories of CD4 count, 37-38% of HIV-positive MSM had consistently (3 out of 3) negative cytology; thus, a high proportion (62-63%) had abnormal results for at least 1 of the 3 cytologies. However, most men did not have consistently abnormal cytology, and the proportion of men with consistently abnormal cytology was higher among HIV-positive MSM with CD4<500 than CD4≥500 (22% vs. 10%, p=0.008). Conversely, the proportion of men with 2 negative and 1 abnormal cytology was lower among HIV-positive MSM with CD4<500 vs. CD4≥500 (25% vs. 35%). A pattern of 1 negative and 2 abnormal cytologies was also common in both groups (16-17%).

A detailed description of all patterns across the first 3 consecutive cytologies in HIV-positive MSM is provided in Table 3.5.

Finally, we explored demographic, behavioral, and biological risk factors for a consistently (over 3 consecutive results) abnormal cytology pattern, compared to a consistently negative pattern, using inverse-probability weighted logistic regression (Table 3.6). The odds of consistently abnormal cytology increased by 28% with each 100 cells/μL decrease in CD4 cell count at the first cytology (95%CI 4-59%). Additionally, a nadir CD4 cell count less than 100 cells/μL (threshold chosen based on exploratory analysis) indicated 4.4-fold higher odds of consistently abnormal cytology (95%CI 1.2-16.5). Men who reported a mean of 1 or more condomless receptive anal sex partners at each visit over the past 5 years had 5.7-fold higher odds (95%CI 2.1-15.2) compared to men who reported fewer or none of these partners. Odds of consistently abnormal cytology were increased in men aged 60 and older (OR 6.1, 95%CI 1.3-27.6) and of non-white race/ethnicity (OR 6.2, 95%CI 1.9-20.0).

3.5 Discussion

Using anal cytology to assist in identifying MSM who might (or might not) have risk for anal dysplasia is an important goal. This is particularly true for HIV-positive MSM, who are at high risk of anal cancer. In one of few studies to repeatedly collect and evaluate anal swabs for cytological abnormalities, our data show that more than one-third of our population of HIV-positive MSM have consistently negative (normal) anal cytology when tested three times over the course of approximately three years. Since negative anal cytology may indicate lower risk of ultimate development of anal cancer, it is possible that repeatedly negative cytology might define a subset of HIV-positive MSM who are at lower anal cancer risk and thus less likely to benefit from an invasive procedure such as HRA. Conversely, consistently abnormal anal cytology in HIV-positive MSM over a three-year period may identify men at higher risk of anal dysplasia. A fluctuating pattern of negative and abnormal cytology was very common, but additional research is necessary to understand how such a pattern should be interpreted.

Even among MSM with the same recent cytology result, we found that the likelihood of the next cytology being abnormal was related to HIV status or to the level of HIV-associated immunosuppression. After a negative cytology result, a second negative cytology was seen in the majority of men regardless of HIV or CD4 status, but the frequency was lower in HIV-positive MSM. When the first cytology was abnormal, the likelihood that the next result would remain abnormal was highest among HIV-positive MSM with CD4<500 cells/μL, with much lower frequencies of a second abnormal Pap in HIV-positive MSM with CD4>500 cells/μL and HIV-negative MSM. One of multiple possible explanations for this finding is that anal dysplasia was less likely to regress in more immunosuppressed men, but this topic is poorly studied.[110,111] Some data do suggest that HIV reduces clearance of anal HPV.[58,112,113]

Our findings motivate further study of the utility of repeated cytology for managing an initial abnormal cytology. For example, MSM with an initial ASC-US cytology (the least severe of the abnormal cytology results) were likely to have a negative second cytology if HIV-negative (60%) or HIV-positive with CD4>500 cells/μL (58%). If this accurately represents a low-risk status (which we did not investigate here), then repeating cytology after an ASC-US result may provide one way to distinguish between men who are not at high risk of anal dysplasia and men who might benefit from prompt referral to HRA. Repeated cytology was less likely to revert to negative among HIV-positive MSM with lower CD4 counts, particularly when the initial result was LSIL or worse.

Compared to HIV-positive MSM with 3 consecutive negative anal cytologies, we found that HIV-positive MSM with 3 consecutive abnormal cytologies were more likely to be older, of race/ethnicity other than non-Hispanic white, to have lower CD4 counts at first cytology as well as lower nadir CD4 counts, and to have more condomless receptive anal sex partners. These characteristics are largely consistent with known risk factors for having anal lesions/cancer or for acquiring anal HPV.[108,114–116] One possible explanation for the higher likelihood of persistently abnormal cytology among non-white HIV-positive MSM is that, in our data, the likelihood of treatment for anal dysplasia after a first abnormal cytology was 30% among white non-Hispanic men

compared to only 12% among other men (p=0.002). Thus, white non-Hispanic men with a first abnormal cytology were more likely to be excluded from the cytology-patterns analysis, and the racial difference that we observed might be due to other factors related to treatment access or treatment-seeking behavior. We recommend further study of this difference in the likelihood of referral and potential treatment, as an analogous disparity in follow-up after abnormal cervical cytology has produced a substantial racial disparity in cervical cancer incidence among older U.S. women.[117]

Our results show that using repeated anal cytology over time identifies patterns of negative and abnormal anal cytology. These patterns may have potential to identify men at low and high risk of anal lesions. We emphasize that anal cytology screening is not diagnostic, and cannot prevent anal cancer without the possibility of referral to HRA among those identified to be at risk. Digital anorectal examination should always be included in the evaluation of individuals at risk for anal dysplasia, and can be used to identify some anal cancers at earlier stages if HRA is not readily available.[118,119] Importantly, our analyses did not relate anal cytology patterns (from anal swabs) to histologically verified anal dysplasia (from anal biopsies). The utility of repeated anal cytology can only be confirmed through unbiased follow-up by HRA (i.e., HRA in MSM with both negative and abnormal anal cytology results) and biopsy when indicated.

It is not yet clear whether, as in cervical cancer screening, molecular testing of anal swabs for the presence of oncogenic HPV subtypes, or co-testing for HPV subtype and cytology, will help overcome the current suboptimal diagnostic accuracy of anal cytology testing alone.[120] The prevalence of anal HPV is very high among HIV-positive MSM, though testing specifically for HPV16 (which confers higher risk) may have utility in screening, including for triage of lower-risk abnormal cytology results.[58,121]

Our analysis did not directly relate cytology patterns to histologically verified anal precancer, and thus we cannot say (for example) that risk of biopsy-confirmed anal HSIL is truly lower among those with consistently negative cytology. While this is likely to be true, it must be studied directly. In addition, treatment of anal HSIL has not yet been conclusively shown to prevent anal cancer; this is

the topic of an ongoing randomized trial.[59] We did not have complete data on serial anal cytology for all participants, but we attempted to correct for potential selection bias using inverse probability weighting. We also did not attempt to describe or account for differences in demographic, biological, or behavioral characteristics by HIV status or CD4 count when calculating the prevalence of different transition probabilities and cytology patterns. Such differences, such as higher numbers of condomless receptive anal sex partners among HIV-positive MSM, could contribute to some of the differences in cytology patterns across groups. Finally, while the MACS study is a large and rich data source for studying HIV among MSM, it may not be representative of all HIV-positive MSM in the U.S.[122] Despite these limitations, we hope that our comprehensive description of anal cytology patterns by HIV and CD4 status may inform management of anal cytology results and suggest new avenues for future research.

In conclusion, for HIV-negative and HIV-positive MSM, patterns of repeated anal cytology may prove useful as an indicator of low or high risk of anal disease. More than one-third of HIV-positive MSM have consistently negative annual anal cytology over 3 years, and lower CD4 counts are associated with consistently abnormal anal cytology and with a transition to abnormal cytology after a negative cytology. Further study of the cytology patterns we described, including direct relation of cytology patterns to biopsy-confirmed anal precancer, will be important to enable more effective anal cancer prevention for MSM.

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3.7 Tables and Figures

Table 3.1 Description of HIV-negative and HIV-positive men who have sex with men (MSM) in the MACS study with anal cytology testing

Number of anal cytology tests	**HIV-negative MSM**	**HIV-positive MSM**
	N with valid results (N with any results)	
1 or more	752 (796)	665 (708)
2 or more	480 (625)	534 (593)
3 or more	NA	369 (484)

Characteristics of MSM included in analyses (2 or more valid anal cytologies, no anal dysplasia treatment)	**HIV-negative MSM**	**HIV-positive MSM**
	N (%) or median (IQR)	
Total number MSM	474	502
Age, years (at first cytology)	58 (51-64)	54 (50-59)
Race/ethnicity		
Non-Hispanic white	410 (86)	325 (65)
Non-Hispanic black	39 (8)	129 (26)
Hispanic	19 (4)	40 (8)
Other	6 (1)	8 (2)
Education		
12th grade or less	95 (20)	194 (39)
College graduate	158 (33)	173 (34)
Post-graduate	173 (36)	107 (21)
Unknown	48 (10)	28 (6)
Study site		
Baltimore	130 (27)	131 (26)
Chicago	37 (8)	150 (30)
Pittsburgh	149 (31)	102 (20)
Los Angeles	158 (33)	119 (24)
CD4 count at first cytology, cells/μL	NA	579 (429-749)
Nadir CD4 count (as of first cytology), cells/μL	NA	252 (154-354)
Currently on HAART (at first cytology)	NA	433 (88)
Time since first HAART (at first cytology), years	NA	11.8 (7.4-13.8)
Mean number of condomless receptive anal sex partners reported at each visit during the previous 5 years		
0	307 (65)	254 (52)
0.1-0.9	107 (23)	103 (21)
1.0 or more	58 (12)	135 (27)

MSM, men who have sex with men; HAART, highly active antiretroviral therapy; MACS, Multicenter AIDS Cohort Study. Small numbers of missing values are excluded and percentages may not sum exactly to 100 due to rounding. Men with treatment of anal dysplasia between the 1st and 2nd cytology (N=38) are excluded in the lower portion of the table. For analyses involving 3 cytology results, HIV-positive men with treatment between the 2nd and 3rd cytology (N=14) were additionally excluded.

Table 3.2 Frequencies of the next anal cytology result following 1 or 2 initial cytologies that were negative or abnormal among 976 MSM, by HIV and CD4 status at first cytology

	HIV-negative MSM	HIV-positive MSM, CD4≥500	HIV-positive MSM, CD4<500	p-value
After 1 negative cytology	355	206	114	<0.001
Negative cytology	295 (83)	153 (74)	77 (68)	
Abnormal cytology	60 (17)	53 (26)	37 (33)	
After 1 abnormal cytology	119	99	81	0.003
Negative cytology	64 (54)	47 (48)	24 (30)	
Abnormal cytology	55 (46)	52 (53)	57 (70)	
After 1 negative cytology	355	206	114	0.005
Negative cytology	295 (83)	153 (74)	77 (68)	
ASC-US cytology	46 (13)	44 (21)	30 (26)	
LSIL/ASC-H/HSIL cytology	14 (4)	9 (4)	7 (6)	
After 1 ASC-US cytology	85	59	41	0.07
Negative cytology	51 (60)	34 (58)	17 (41)	
ASC-US cytology	26 (31)	16 (27)	12 (29)	
LSIL cytology	5 (6)	8 (14)	11 (27)	
ASC-H/HSIL cytology	3 (4)	1 (2)	1 (2)	
After 1 LSIL/ASC-H/HSIL cytology	34	40	40	0.49
Negative cytology	13 (38)	13 (33)	7 (18)	
ASC-US cytology	11 (32)	12 (30)	14 (35)	
LSIL cytology	8 (24)	11 (28)	16 (40)	
ASC-H/HSIL cytology	2 (6)	4 (10)	3 (8)	
After 2 negative cytologies	--	102	51	0.84
Negative cytology	--	75 (74)	39 (77)	
Abnormal cytology	--	27 (27)	12 (24)	
After 2 abnormal cytologies	--	35	38	0.08
Negative cytology	--	14 (40)	8 (21)	
Abnormal cytology	--	21 (60)	30 (79)	

N or N (%). MSM, men who have sex with men; ASC-US, atypical squamous cells of undetermined significance; LSIL, low-grade squamous intraepithelial lesion; ASC-H, atypical squamous cells cannot exclude HSIL; HSIL, high-grade squamous intraepithelial lesion. Men with treatment of anal dysplasia during the cytologies being considered were excluded for each analysis (see Methods), as were 2 HIV-positive men with missing CD4 cell counts. Data are unweighted and p-values were calculated using chi-square tests. Due to differences in study design, the median length of time between cytologies was longer for HIV-negative MSM (2.0 [IQR 1.9-2.2] than for HIV-positive MSM (1.0 years [IQR 0.96-1.3]). Percentages may not sum exactly to 100 due to rounding.

Table 3.3 Frequencies of the next anal cytology result following an initial negative or abnormal cytology result among 687 MSM, by HIV and CD4 status at first cytology, requiring an 18-30 month interval between cytology results

	HIV-negative	HIV-positive, CD4≥500	HIV-positive, CD4<500	p-value
After 1 negative cytology	279	140	69	0.02
Negative cytology	233 (83)	102 (73)	51 (74)	
Abnormal cytology	46 (17)	38 (27)	18 (26)	
After 1 abnormal cytology	93	55	51	0.02
Negative cytology	53 (57)	33 (60)	18 (35)	
Abnormal cytology	40 (43)	22 (40)	33 (65)	

N or N (%). MSM, men who have sex with men. Men with treatment of anal dysplasia during the cytologies being considered were excluded for each analysis. Data are unweighted and p-values were calculated using chi-square tests. This analysis was performed to assess the impact of differential intervals between cytologies for HIV-negative vs. HIV-positive MSM; in this table, data are restricted to cytology results spaced by 18-30 months. Results can be compared to Table 2, where intervals between cytologies tended to be longer for HIV-negative MSM than for HIV-positive MSM. Percentages may not sum exactly to 100 due to rounding.

Table 3.4 Patterns of the first 3 consecutive anal cytology results among 328 HIV-positive MSM with at least 3 valid cytology results

Pattern	HIV-positive MSM, CD4≥500	HIV-positive MSM, CD4<500
Consistently negative	37%	38%
Negative – Negative – Negative	37%	38%
2 negative, 1 abnormal	35%	25%
Negative – Negative – Abnormal	11%	7%
Negative – Abnormal – Negative	9%	8%
Abnormal – Negative – Negative	15%	9%
1 negative, 2 abnormal	17%	16%
Abnormal – Abnormal – Negative	8%	5%
Abnormal – Negative – Abnormal	4%	4%
Negative – Abnormal – Abnormal	7%	7%
Consistently abnormal	10%	22%
Abnormal – Abnormal – Abnormal	10%	22%

MSM, men who have sex with men. Percentages are weighted to correct for missing cytology-pattern data among 708 eligible HIV-positive MSM (i.e., 708 HIV-positive MSM with at least one anal cytology specimen collected). Men with treatment for anal dysplasia between the first and third cytology were excluded, as were 2 men with missing CD4 cell counts. Numbers may not sum exactly to 100 due to rounding.

Table 3.5 Prevalence of detailed anal cytology patterns among 328 HIV-positive men who have sex with men (MSM) with at least 3 valid cytologies

Pattern	Percent	Pattern	Percent
Negative – negative – negative	37.4%	ASC-H – negative – ASC-US	0.6%
Negative – negative – ASC-US	8.0%	ASC-H – negative – LSIL	0.5%
Negative – negative – LSIL	0.8%	ASC-H – ASC-US – negative	0.2%
Negative – negative – ASC-H	0.6%	ASC-H – ASC-US – ASC-US	0.3%
Negative – ASC-US – negative	6.1%	ASC-H – ASC-US – LSIL	0.4%
Negative – ASC-US – ASC-US	4.3%	ASC-H – ASC-H – LSIL	0.5%
Negative – ASC-US – LSIL	1.0%	LSIL – negative – negative	1.5%
Negative – ASC-US – ASC-H	0.3%	LSIL – negative – ASC-US	1.2%
Negative – ASC-US – HSIL	0.2%	LSIL – ASC-US – negative	0.8%
Negative – LSIL – negative	2.6%	LSIL – ASC-US – ASC-US	3.3%
Negative – LSIL – ASC-US	0.2%	LSIL – ASC-US – LSIL	0.9%
Negative – LSIL – LSIL	0.5%	LSIL – LSIL – negative	1.9%
Negative – ASC-H – ASC-US	0.2%	LSIL – LSIL – ASC-US	1.8%
ASC-US – negative – negative	11.0%	LSIL – LSIL – LSIL	1.8%
ASC-US – negative – ASC-US	1.2%	LSIL – ASC-H – negative	0.3%
ASC-US – negative – LSIL	0.6%	LSIL – HSIL – LSIL	0.2%
ASC-US – ASC-US – negative	2.9%	HSIL – ASC-US – ASC-H	0.2%
ASC-US – ASC-US – ASC-US	1.3%	HSIL – LSIL – ASC-US	0.2%
ASC-US – ASC-US – LSIL	0.9%	HSIL – HSIL – ASC-US	0.2%
ASC-US – LSIL – negative	0.5%	HSIL – HSIL – HSIL	0.3%
ASC-US – LSIL – ASC-US	1.5%		
ASC-US – LSIL – LSIL	0.4%		
ASC-US – ASC-H – negative	0.2%		
ASC-US – HSIL – LSIL	0.2%		

Percentages are weighted to correct for missing cytology-pattern data among 708 eligible HIV-positive MSM (i.e., 708 HIV-positive MSM with at least one anal cytology specimen collected); unweighted results were similar. Men with treatment for anal dysplasia between the first and third cytology were excluded.

Table 3.6 Logistic regression model identifying risk factors for a pattern of first 3 consecutive abnormal anal cytologies (N=51) compared to first 3 consecutive negative cytologies (N=115) among HIV-positive MSM

Characteristic at first cytology	Adjusted odds ratio (95% CI)
Absolute CD4 cell count, per 100 cells/μL decrease	1.28 (1.04-1.59)
Nadir CD4 count as of first cytology	
≥100 cells/μL	Reference
<100 cells/μL	4.4 (1.2-16.5)
Mean number of condomless receptive anal sex partners reported at each visit during the previous 5 years	
0-0.9	Reference
1.0 or more	5.7 (2.1-15.2)
Age, years	
<50	Reference
50-59	1.2 (0.32-4.5)
≥60	6.1 (1.3-27.6)
Race/ethnicity	
Non-Hispanic white	Reference
Any other	6.2 (1.9-20.0)

Higher odds ratios indicate a higher likelihood of having 3 consistently abnormal cytologies, as compared with having 3 consistently negative cytologies. Cytology was tested approximately annually. Odds ratios are weighted to correct for missing cytology-pattern data among 708 eligible HIV-positive MSM (i.e., 708 HIV-positive MSM with at least one anal cytology specimen collected). Men with treatment for anal dysplasia between the first and third cytology were excluded. Two observations were excluded due to missing data, leaving 164 in the analysis set.

Chapter 4: Updating Individual Lung Cancer Risk during CT Screening to Identify those who Might Lengthen Screening Intervals

4.1 Abstract

Background: To facilitate individual decisions regarding when to return for screening, individual disease risk should be updated after screening tests. We calculated how individual lung cancer risk evolved based on CT findings during the National Lung Screening Trial (NLST).

Methods: We developed a simple model for risks of interval and screen-detected ("next-screen") lung cancer among 25,762 NLST CT-group participants, all of whom underwent yearly screening. First, each participant's 1-year lung cancer risk in the absence of screening ("pre-screening risk") is calculated based on their risk factors using a validated model. Then, risks of interval and next-screen lung cancer are calculated to be the pre-screening risk raised to a power determined by the results of the screen.

Results: Median 1-year pre-screening risk was 0.32% (IQR=0.19%-0.53%). Only the most recent screening result, not prior results, affected the risk prediction ($p>0.2$). Among screen-negatives, median interval-cancer risk decreased 6.4-fold to 0.05% (IQR=0.02%-0.09%), but next-screen lung cancer detection changed little from pre-screening risk (median=0.29%). However, for the 70% of screen-negatives without CT-detected emphysema or consolidation (51% of participants), next-screen detection was 1.8-fold lower than pre-screening risk (median=0.18%). In contrast, after a false-positive screen, median next-screen lung cancer detection increased 4.9-fold to 1.5% (IQR=1.1%-2.3%) and varied widely by false-positive nodule features (size, location, growth, and margins).

Conclusions: Screen-negatives without CT-detected emphysema or consolidation, comprising half of NLST participants, maintained reduced lung cancer risk at the next annual screen and thus might safely return at longer intervals. In contrast, most false-positives experienced substantially increased lung cancer detection at the next screen.

4.2 Introduction

The National Lung Screening Trial (NLST) demonstrated a 20% reduction in lung cancer mortality with 3 rounds of CT screening versus chest radiography.[11] The U.S. Preventive Services Task Force now recommends annual CT screening for ever-smokers aged 55-80 years who smoked at least 30 pack-years and quit no more than 15 years ago.[71] However, selecting ever-smokers for screening based on individualized pre-screening risk calculations may improve the effectiveness, efficiency, and cost-effectiveness of screening,[21,72–74] and National Comprehensive Cancer Network guidelines now allow this approach.[123] Online risk tools[124,125] enumerate individualized benefits and harms of screening to aid decision-making.

Once beginning screening, risk-based decisions could also be made regarding screening intervals, triage testing, and exiting from screening. For example, in diabetic retinopathy screening, choosing screening frequency based on risk substantially reduced patient burden and costs, yet maintained safety against clinically significant disease.[126] Considering risk-based screening intervals is particularly important for CT lung screening, which has high rates of false-positivity that lead to excess complications, harm, and costs. The NLST had 24% screen-positivity, of which 96.4% were false-positives.[11] A Veterans Health Administration screening demonstration project experienced 60% screen-positivity, of which 97.5% were false-positives.[12] Allowing longer intervals for those at lower risk would reduce the number of screens and false-positives, thus enabling individualized cost-effective screening that maintains safety.

Risk-based intervals require that individual risk – originally calculated prior to screening – be updated as test results accrue. Several validated models predict individual risk of lung cancer in the

absence of screening based on demographic, smoking, and health-related risk factors,[72,73,127–133] and others calculate the *current* probability of lung cancer when a nodule is identified on CT.[134] However, for screened individuals believed to be cancer-free (i.e., the screen result was negative or false-positive), no model provides an updated estimate of *future* risk based on the current screen result and individual risk factors.

We developed a simple model that quantifies how individual risk evolved during annual CT screening in the NLST. First, individual pre-screening 1-year lung cancer risk is calculated using the validated Lung Cancer Risk Assessment Tool (LCRAT).[73,124] Then, the model calculates how pre-screening risk is modified by screen results (negative or false-positive) and CT features such as nodule characteristics or CT-diagnosed emphysema. This model encapsulates the effects of a negative or false-positive result on future risk, which, along with individual risk factors, determine when an individual should return for screening.

4.3 Methods

Data Source and Definitions

The NLST randomized 53,454 ever-smokers to 3 annual screens (denoted T0, T1, and T2) with either low-dose CT or radiography.[11] Eligibility required age 55-74 years, 30 or more pack-years of smoking, and 15 or fewer quit-years. We analyzed lung cancer risk among 25,762 participants randomized to CT screening, where a positive screen was defined by at least one non-calcified nodule with longest diameter at least 4 mm or other suspicious abnormalities (NLST modified Fleischner criteria[11,135]). Screen-negatives returned for re-screening in 1 year while screen-positives had complex follow-up, often involving repeat CTs, at the discretion of providers.[11,136]

We related CT screening results to lung cancer risk over the subsequent 1-year interval and at the next annual screen. "Interval cancers" were defined as cases developing within 1 year of a negative CT and before the next screen.[137] Individuals were at risk for interval cancer during each of the three 1-year intervals that followed a negative CT. We defined a screen-detected (i.e., "next-

screen") cancer as a case most likely diagnosed because of a positive CT (Supplementary Methods). Individuals were at risk for screen-detected cancer at each screen preceded by a negative or false-positive result (thus, we could not analyze risk at the first [T0] screen), not preceded by diagnosis with interval cancer, and with a valid result (so that lung cancer might be detected).

We created variables to describe different features noted on CT, specific to person and screen. These included the presence, number, diameter, location, margins, attenuation, and growth of nodules, as well as non-nodule features such as emphysema, atelectasis, adenopathy, consolidation, and fibrosis (detailed list in Table 4.1). These variables combined information across multiple nodules as needed to create a summary variable.

Statistical Analysis

We developed first-order Markov transition models[138] for the binary indicator of lung cancer status to estimate individual interval or next-screen lung cancer risk based on pre-screening risk and screen results (details in Supplementary Methods). Given risk factors x, the models first calculate 1-year pre-screening risk, $r_0(x)$, using the Lung Cancer Risk Assessment Tool (LCRAT)[73], a validated model for lung cancer risk in the absence of screening. LCRAT risk-factors include age, education, sex, race, smoking intensity/duration/quit-years, body mass index, family history of lung cancer, and self-reported emphysema.[73] Next, we fit log-binomial regression models that calculate future risk by raising pre-screening risk $r_0(x)$ to an exponent specific to screen results. For example, following is the model for next-screen lung cancer, denoting s as the recent screen result (0=negative, 1=false-positive):

$$r(x) = \{r_0(x)\}^{\beta_0 + s\beta_1}$$

Thus, after a negative screen, pre-screening risk is raised to power β_0, and after a false-positive screen, pre-screening risk is raised to power $\beta_0+\beta_1$. If two people have the same screen result, then the person who had higher pre-screening risk will also have higher next-screen risk. Logistic regression models yield similar results but have a more complex risk equation.

We examined lung cancer risk in 3 separate settings: interval-cancer risk (among screen-negatives only), next-screen cancer among screen-negatives, and next-screen cancer among false-positives. We did not consider risk following true-positive results, as these participants already had cancer.

We tested whether risk calculations depended only on the most recent screen result (and not prior results), by comparing exponents at the T2 screen between groups with the *same* T1 result but *different* T0 results. Differing exponents would imply that prior screen results continue to influence risk calculations. In addition, we tested for equality of exponents across the different NLST screens and intervals.

For the 3 settings described above, we examined the effects of specific features noted on CT. In each setting, we separately applied backwards-stepwise selection and the lasso (least absolute shrinkage and selection operator)[139] to identify strongly associated and biologically plausible features (from among 50 features) to include in models (Table 4.1 and Table 4.2). We validated each final model using 10-fold cross-validation. Separately, for comparison to the final model for false-positives, we fit a model for next-screen cancer using retrospectively-assigned Lung-RADS categories.[140,141]

Finally, we conducted a proof-of-principle analysis to examine the utility of our model for identifying individuals who might extend screening intervals. Among participants with a negative or false-positive result at the final (T2) screen, we predicted 1-year total risk of interval and next-screen cancer using the T2 findings. Then, within quintiles of predicted risk, we calculated the observed incidence of lung cancer over the 4 years following screening cessation.

4.4 Results

Model Development

Following a negative or false-positive screen, exponents were similar for calculating interval-cancer risk following T0, T1, or T2 (p=0.32) and for calculating screen-detected lung cancer risk at

T1 or T2 (p=0.07) (Supplementary Results). Accounting for the most recent screen, prior results did not additionally influence risk calculations, either for interval cancers (p=0.97) or screen-detected cancers (p=0.47) (Supplementary Results, Figure 4.1). Thus, we fit models combining data across intervals and screens, considering only the most recent screen.

<u>Risk after a Negative or False-positive CT</u>

Median 1-year pre-screening risk was 0.32%, and individual risks for the middle 50% of participants (IQR) ranged from 0.19% to 0.53% (Figure 4.2). Following 56,927 negative screens from 23,331 unique individuals, cancer was detected in the 1-year interval following 43 (0.08%) screens (Table 4.3). Based on our model incorporating pre-screening risk, $r_0(x)$, interval-cancer risk following a negative screen decreased per the equation $r_0(x)^{1.32}$ (*n.b.* exponents greater than 1 imply decreased risk). Using the T0 screen result and the T0-T1 interval for illustration, median risk decreased 6.7-fold from 0.32% pre-screening risk to 0.05% interval-cancer risk between T0 and T1 (IQR=0.02%-0.09%) (Figure 4.2).

For diagnosis of screen-detected cancer, we analyzed 35,534 negative and 12,994 false-positive screens from 19,752 and 8,300 unique individuals, respectively (Table 4.3). Cancer was detected at the next screen among 0.39% of the negative screens and 1.8% of the false-positive screens, with next-screen detection among screen-negatives calculated as $r_0(x)^{1.01}$. In contrast, detection among false-positives increased as $r(x)^{0.74}$. Using the T0 result and the T1 screen for illustration, lung cancer detection at T1 following a negative T0 CT approximated pre-screening risk (medians 0.29% vs. 0.32%), while detection at T1 following a false-positive at T0 increased 4.9-fold from 0.32% pre-screening risk to 1.5% detection (IQR=1.1%-2.3%) (Figure 4.2).

<u>Risk based on Specific Features found on a Negative or False-positive CT Screen</u>

Following a negative or false-positive screen, interval and next-screen lung cancer risks varied substantially based on specific CT-image features. These models cross-validated well (Table 4.4), and the false-positive model out-performed one using Lung-RADS categories (Supplementary Results, Table 4.5).

Following a negative screen, next-screen risk was elevated if the CT identified either emphysema (median risk increased from 0.31% to 0.53%) or consolidation (median risk increased from 0.31% to 1.6%) (Figure 4.3). Thirty percent of screen-negatives had CT-diagnosed emphysema, regardless of their baseline self-reported emphysema status (7% self-reported emphysema), and 0.6% had consolidation. Thus, a large majority (70%) of screen-negatives had neither emphysema nor consolidation, and for this group, next-screen lung cancer detection was 1.7-fold lower than pre-screening risk (from 0.31% to 0.18%).

Also among screen-negatives, median interval-cancer risk *increased* over pre-screening risk (0.31% vs. 0.66%) for the 2% of screen-negatives with consolidation or adenopathy. Further analysis suggests that these should have been classified as positive screens (Supplementary Results, Figure 4.4).

Following a false-positive screen, specific features of the nodule(s) strongly modified next-screen risk (Figure 4.5). Median risk varied widely with longest nodule diameter: 0.49% (4-5mm), 0.80% (6-7mm), 1.9% (8-10mm), 4.1% (11-13mm), and 4.0% (≥14mm) (Table 4.6). Risk was higher if any nodule was in the upper lobes (median 1.4%) or had spiculated margins (4.0%), but was lower if all nodules had smooth margins (0.71%). Those with a nodule that grew from T0 to T1 had 22-fold higher risk at T2 (median 7.7%). The number of nodules did not influence risk after accounting for these features (p=0.50).

For individuals, each CT feature contributes to the risk calculation. For example, for the 19% of false-positives in the lowest-risk category (only 4-5mm smooth-margins nodules with no growth and not in upper lobes), next-screen risk nearly equaled pre-screening risk ($r_0(x)^{0.99}$). Thus, the lowest-risk false-positives have similar next-screen risk as screen-negatives.

<u>Lung cancer Incidence after Cessation of Screening: Potential for Extending Screening Intervals</u>

Among 23,881 participants with a negative or false-positive T2 result, 1-year risk predicted by our model ranged from 0.05% at the first percentile to 9.5% at the 99th percentile. Among the 4,777 participants in the lowest-risk quintile, observed lung cancer incidence during the 4 years

following T2 was only 0.08%. Incidence increased in each quintile, reaching 37-fold higher incidence (3.1%) among the highest-risk participants (Table 4.7).

4.5 Discussion

Although many models calculate individual lung cancer risk in the absence of screening, risk-based decisions during screening require that risk be updated as test results accrue. To identify individuals who might safely lengthen their screening interval, we developed a simple model that quantifies how individual lung cancer risk evolved during annual CT screening in the NLST. Risk calculations depended only on pre-screening risk and the most recent screen result; prior results did not further influence risk. Following a negative screen, risk was very low during the next year, but lung cancer detection at the next screen nearly equaled pre-screening risk. However, screen-negatives without emphysema or consolidation maintained reduced risk at the next screen, suggesting that some of them could safely return at a longer interval. Since these participants comprised 51% of the NLST, major reductions may be possible in the patient burden and financial costs associated with CT lung screening. In contrast, next-screen lung cancer detection was increased for a large majority of false-positives, for whom screening intervals should not be extended.

As expected, a negative screen indicated extremely low risk of lung cancer over the following 1-year interval. When screen-negatives returned for their next screen, they comprised 2 distinct groups: the 30% with CT-detected emphysema or consolidation had higher next-screen detection than pre-screening risk, while the 70% without such findings (51% of all participants) maintained lower next-screen detection. The subset of these without strong risk factors are potential candidates for waiting longer than 1 year to return to screening. Over 4 years following cessation of NLST screening, participants with the lowest predicted risks had very low lung cancer incidence, suggesting that extended intervals might be safe in practice.

Surprisingly, a recent false-positive screen indicated substantially higher next-screen lung cancer detection. Possible explanations include incorrect determination of false-positivity from

images or biopsies, or that a nodule, even if not cancer, may indicate a "field effect" of underlying malignant processes that presage incipient cancer elsewhere in the lung. Importantly, nodule features identified on a false-positive CT accounted for elevated risk, and some of these also predict nodule malignancy at the *current* screen (i.e., for true-positive screens).[134] There is heterogeneity among false-positives: individuals with strong risk factors and dangerous CT features have high next-screen lung cancer detection, while the 19% of false-positives with only low-risk CT features (no growth, smooth margins, small nodules not in upper lobes) have next-screen detection similar to that following a negative screen. Further research should explore what follow-up testing is appropriate in very high-risk individuals, and whether some low-risk false-positives could consider longer screening intervals.

We found that the most recent screen result sufficed to calculate risk, and that including prior screens did not significantly change risk calculations. This is not inconsistent with findings by Patz et al. that lung cancer incidence successively decreased with multiple negative screens.[75] Patz et al. examined whether, given a prior negative screen (e.g. T0), the most recent screen modified risk (e.g. T1), whereas we considered the opposite: whether, given the recent screen result (e.g. T1), prior results (e.g. T0) further affect risk. Although our findings suggest prior screen results are uninformative, there may be small reassurance from sequential negative screens, or small differences in detection across different NLST screens (Supplementary Results). Further study of these issues requires data describing more than 3 annual screens.

Our study has limitations. We could not calculate risk under longer screening intervals because the NLST had only annual screening. External validation of our model in other annual screening settings is crucial. We used our validated LCRAT model to predict 1-year pre-screening risk and did not investigate whether other models can be substituted. For simplicity, we also did not "update" pre-screening risk if individuals quit smoking or as age, pack-years, and quit-years accumulated. Updating risk factors would have negligible effect over 3 screens, but could be done periodically in practice. We did not consider specific CT features (e.g. nodule size) in evaluating the potential utility of prior screens for risk prediction.

Existing risk tools, such as shouldiscreen.com[125] and the Risk-based NLST Outcomes Tool,[124] only assist in shared decision-making for entering screening. Our model allows risk to be continually updated during screening, requiring that participants be provided counseling and support as risks fluctuate. To illustrate how individual lung cancer risk can vary over time, consider a man with the median 1-year pre-screening risk (0.32%). If his first CT identifies an 8-mm false-positive nodule in the upper lobes with smooth margins, then his next-screen risk increases to $(0.32\%)^{(0.73-0.10+0.07)}=1.8\%$. If at the next screen, his result is negative with no emphysema or consolidation, his interval-cancer risk is $0.32\%^{1.32}=0.05\%$, and his next-screen risk is $0.32\%^{1.07}=0.21\%$. Thus, his 1-year next-screen risk will be lower than his pre-screening risk (0.21% vs. 0.32%), even though it had once been 8.5-fold higher (1.8%).

Our findings illustrate that even within the CT-screening context, traditional risk factors such as smoking history maintain a strong influence on lung cancer risk. More research is needed to understand the harms and benefits associated with extending screening intervals in low-risk individuals, and to develop shared decision-making processes that allow patients to understand these in the context of their individual risks. Our model's risk calculations take one step toward enabling truly risk-based personalized medicine throughout the course of screening: from entry to screening intervals, triage testing, and eventual exit from lifetime screening.

4.6 Supplementary Methods

Definition of Screen-detected ("Next-screen") Lung Cancer

Data collected in the NLST do not allow direct identification of lung cancers as "screen-detected." Our definition of a screen-detected cancer at T1 or T2 required the following: a positive screen and a lung cancer diagnosis before the next screen that occurred either a) within 12 months of the positive screen or b) after a continuous sequence of diagnostic procedures that was not broken by a gap of greater than 12 months between the screen date and diagnosis date. To consider all

relevant cancers, we also included 3 cases that arose more than 1 year after the most recent screen and within the window for the subsequent screen but before the screen took place.

Detailed Description of Modeling Approach

A priori, we considered that risk within a screening program is likely to be related to risk in the absence of screening. Indeed, in preliminary models, we found that accounting for pre-screening risk resulted in strong improvement over a model including screen result only (AIC 4013 vs. 4163). We built on our previous work in which we developed and validated a risk model for incident lung cancer in the absence of screening called the Lung Cancer Risk Assessment Tool (LCRAT).[73] The LCRAT was fit to data on 39,180 ever-smokers in the PLCO community care arm, and we have validated it in 4 cohorts to ensure it is well-calibrated and has good discrimination: the PLCO chest radiography arm,[73] NLST chest radiography arm,[73] NIH-AARP (under review), and the ACS CPS-II (under review). LCRAT is available in our R package *lcrisks* that also calculates risks from our Lung Cancer Death Risk Assessment Tool (LCDRAT) (http://dceg.cancer.gov/tools/risk-assessment/lcrisks). LCRAT and LCDRAT are also available as part of our R package *lcmodels* which calculates risks from 9 prominent lung cancer risk models (http://dceg.cancer.gov/tools/risk-assessment/lcmodels). We used LCRAT to predict, for each individual in the NLST CT arm, 1-year pre-screening lung cancer risk at baseline.

Since follow-up and compliance in the NLST CT arm was very complete, our analysis considers risk within 1-year intervals only. We began by fitting logistic regression models separately for interval and screen-detected cancers, and separately for each screen. As such, these initially included (1) 3 models for interval-cancer risk in the 1-year periods following T0, T1, and T2 screens and (2) 2 models for screen-detected cancers (risk at T1 as a function of the T0 screen result, and risk at T2 as a function of the T1 screen result). Later, upon observing that coefficients were similar across screens (see below Supplementary Results), we combined these models to obtain one overall model for interval cancers and one for screen-detected cancers.

We considered multiple approaches for model parameterization. We used log and logit transformations for 1-year pre-screening risk, which gave better fit by likelihood-ratio statistics than modeling untransformed risk (data not shown). Initial models included separate terms for transformed pre-screening risk and screen result, but we subsequently found and included interactions (i.e., products) between these terms. Finally, we removed intercept terms and the main effect for screen result, as they did not improve fit and could not be straightforwardly interpreted. Throughout analysis, we used logistic regression for model development, as log-binomial models frequently encounter challenges with convergence. We changed final models to log-binomial with a log transformation of pre-screening risk. This had a negligible effect on model fit but has advantages for interpretation, as it allows model coefficients to act as simple exponents of pre-screening risk as described below.

This final approach produced models of the following general form:

$$\log r = \beta_1 \log r_0(x) + s\beta_2 \log r_0(x)$$

where:

r = predicted risk of interval or screen-detected lung cancer

$r_0(x)$ = individual 1-year pre-screening risk (calculated using LCRAT[73])

s = result from most recent screen (e.g. 0=negative, 1=false-positive)

We can rearrange this equation as follows to show that this allows coefficients to act as exponents of pre-screening risk:

$$r = \{r_0(x)\}^{\beta_0 + s\beta_1}$$

For example, in the model for risk of next-screen lung cancer based on overall screening result, $s = 0$ for a recent negative result and $s = 1$ for a recent false-positive result. Thus, β_0 is the exponent for an individual with a recent negative result, and $\beta_0 + \beta_1$ is the exponent for an individual with a recent false-positive result.

Subsequent models including features noted on CT were formulated analogously, such that coefficients are added together to obtain exponents for pre-screening risk. For example, the final

model for next-screen lung cancer detection following a false-positive screen based on CT features was parameterized as:

$$r = \{r_0(x)\}^{d_0\beta_0 + d_1\beta_1 + d_2\beta_2 + d_3\beta_3 + d_4\beta_4 + d_5\beta_5 + p\beta_6 + m\beta_7 + u\beta_8 + g\beta_9}$$

where:

r = predicted risk of screen-detected lung cancer

$r_0(x)$ = individual 1-year pre-screening risk

d_0 = no nodule present

d_1 = longest diameter among all nodules was 4-5 mm

d_2 = longest diameter among all nodules was 6-7 mm

d_3 = longest diameter among all nodules was 8-10 mm

d_4 = longest diameter among all nodules was 11-13 mm

d_5 = longest diameter among all nodules was 14 mm or larger

p = at least one nodule with spiculated margins was present

m = at least one nodule with smooth margins was present

u = at least one nodule was present in the upper lobes

g = if evaluable, an existing nodule grew during the most recent screening interval

Approach for Selecting Detailed CT Features for Inclusion in Models

We considered detailed CT features that might relate to future lung cancer risk in 3 separate settings: interval cancers among recent screen-negatives, screen-detected cancers among recent screen-negatives, and screen-detected cancers among recent false-positives. In each instance, we considered a set of relevant variables that we created to reflect the overall features observed on a CT screen (Table 4.1). Each variable was modeled as an interaction with the logit of pre-screening risk. Using the set of relevant variables, we applied two approaches for variable selection in each case:

a) Backwards-stepwise selection: We performed backwards-stepwise selection using the “step” function in R. This technique begins with the inclusion of all variables and then removes them

one-by-one to find the model with the minimum value of the Akaike Information Criterion (AIC).

b) Lasso: The lasso (least absolute shrinkage and selection operator) is a penalized variable selection technique that "shrinks" coefficient values toward zero depending on the value of a penalization parameter, thus selecting only a subset of variables for inclusion in a regression model.[139] For the penalization parameter, we averaged between the value that a) gave the minimum cross-validated error and b) was the largest value such that the cross-validated error was within 1 standard error of the minimum error. Although ad hoc, we found that this was the best approach to yield a reasonable number of selected variables.

Given that we considered many potential variables, we took a cautious approach for including variables in final models. Among the variables selected by at least one approach, we selected variables for final models by excluding those that a) were not strongly statistically significant, b) lacked strong biological plausibility or interpretability, c) appeared to be driven by a small number of cases within a small group, or d) were better captured by other features also included in the model. The variables selected by each technique, along with the variables included in final models, are shown below in Table 4.2. A description of each variable is given in Table 4.1.

4.7 Supplementary Results

Consistency of Exponents across Intervals and Screens

In initial analyses, we separately evaluated risk at each NLST screen (T1, T2) and during each interval (T0-T1, T1-T2, 1 year following T2). For interval cancers, estimating exponents separately by interval gave risk calculations of $\{r_0(x)\}^{1.29}$ for the T0-T1 interval, $\{r_0(x)\}^{1.40}$ for the T1-T2 interval, and $\{r_0(x)\}^{1.31}$ for the 1-year interval following T2. Based on a likelihood ratio test (2 df), there was not statistically significant heterogeneity among these exponents (p=0.32).

For screen-detected cancers, among screen-negatives, estimating exponents separately by screen gave risk calculations of $\{r_0(x)\}^{1.03}$ for risk at the T1 screen and $\{r_0(x)\}^{0.99}$ for risk at the T2

screen. Among false-positives, estimating exponents separately by screen gave $\{r_0(x)\}^{0.76}$ at the T1 screen and $\{r_0(x)\}^{0.72}$ at the T2 screen. A likelihood ratio test (2 df) indicated that these exponents did not vary significantly across screens (p=0.07).

Effect of Prior Screen Results Once a More Recent Result is Known

Our first-order Markov transition model assumes that future risk depends on the most recent screen result, but not on results occurring before that. To test this assumption, we compared individuals with the same result for the most recent screen, but a different result for the prior screen; risk calculations would differ between these groups if they are influenced by the prior result.

For interval cancers, the most recent screen result is negative by definition. In one combined model, we examined risks for a) interval cancer during the T1-T2 interval, comparing those who screened negative at both T0 and T1 to those who screened false-positive at T0 but negative at T1; and b) interval cancer during the one-year period following T2, comparing those who screened negative at both T1 and T2 to those who screened false-positive at T1 but negative at T2. For the negative/negative group, the risk calculation was $\{r_0(x)\}^{1.35}$, compared to $\{r_0(x)\}^{1.33}$ for the false-positive/negative group. These exponents were not statistically significantly different (p=0.97).

For screen-detected cancers, we compared risks for screen-detected cancer at T2 (since at the T2 screen, two past screen results are known). We first compared risk of screen-detected cancer at T2 between those who screened negative at both T1 and T0 and those who screened negative at T1 but false-positive at T0. For the T0-negative/T1-negative group, the risk calculation at T2 was $\{r_0(x)\}^{1.00}$, compared to $\{r_0(x)\}^{0.92}$ for the T0-false-positive/T1-negative group. These exponents were not statistically significantly different (p=0.23), though we note that the point estimates for the exponents do suggest that there may be some small reassurance provided by sequential negative CTs.

Next, we compared risk of screen-detected cancer at T2 between those who screened false-positive at both T1 and T0 to those who screened false-positive at T1 but negative at T0. For the T0-false-positive/T1-false-positive group, the risk calculation at T2 was $\{r_0(x)\}^{0.72}$, compared to $\{r_0(x)\}^{0.70}$ for the T0-negative/T1-false-positive group. These exponents were not statistically

significantly different (p=0.63). A likelihood ratio test (2 df) for the overall hypothesis that prior screen results do not contribute to risk calculations (i.e., regardless of most recent screen result) for screen-detected cancer was also not significant (p=0.47). The result for screen-detected cancer is shown graphically in Figure 4.1.

Model Estimation using GEE

Most individuals contributed multiple observations to each model (i.e., one observation per screen or interval), although they could only be a case once. To ensure our results were not impacted by correlation between screen results within the same individual, we re-estimated our final log-binomial models using generalized estimating equations (GEE) as a sensitivity analysis. The impact on the variance of our estimates was negligible (data not shown).

Estimation of Screen-detected Cancer Risk using Lung-RADS

Exponents based on Lung-RADS categories to calculate screen-detected lung cancer risk following a false-positive CT screen are shown in Table 4.6. As expected, the model assigned higher future risk of screen-detected cancer to higher Lung-RADS categories; e.g., the exponent for pre-screening risk for category 4B was 0.51 compared to 0.84 for category 2 (smaller exponents imply increased risk). Based on a comparison of the AIC, our false-positive model based directly on CT-image features (Figure 4.5) performed better than the model based on Lung-RADS categorization (AIC 1903 vs. 1978, Table 4.6) and also substantially better than a model including Lung-RADS categories alone and excluding pre-screening risk (AIC 2023, model not shown).

CT Features and Risk of Interval Cancers

We defined an “interval cancer” as a cancer arising within 12 months of a negative screen and before the subsequent screen occurred. As we did for screen-detected cancers, we investigated the association between specific features noted on a (negative) CT and the subsequent risk of diagnosis with an interval cancer. We found that risk of an interval cancer was very low, but was notably higher among those whose CT noted either adenopathy or consolidation (Figure 4.4).

To better understand this observation, we investigated the recommended follow-up for these cases. Among 43 total interval cancers, 9 had either adenopathy or consolidation noted on the negative CT preceding their diagnosis. Among these 9, 4 were recommended to follow up after their "negative" CT with a diagnostic CT (N=2), biopsy (N=1), or repeat CT in 3 months (N=1). Among the overall group of participants with a negative CT that noted adenopathy or consolidation, a much larger proportion were recommended to follow up sooner than 12 months (23%) compared to those without such features on CT (2%).

Thus, we concluded that although these features confer increased risk of lung cancer diagnosis, they do not appropriately represent features associated with risk of an interval cancer following a negative CT. Rather, CTs noting adenopathy or consolidation should arguably be defined as positive screens and followed up as such. Indeed, a retrospective review of the negative CTs that immediately preceded NLST interval cancers found that 91% of such CTs, upon re-review, met the NLST criteria for a positive screen.[137]

4.8 Tables and Figures

Table 4.1 List and description of all variables that describe specific features identified on CT

Variable	Description: Except where indicated, all variables were binary and indicated the presence or absence of the factor described.
Adenopathy	Any non-calcified hilar/mediastinal adenopathy or mass (≥10 mm on short axis)
Any nodule	At least one non-calcified nodule or mass with a diameter ≥4 mm
Atelectasis	Atelectasis, segmental or greater
Benign nodule	Any benign lung nodule(s)
Consolidation	Consolidation
Emphysema	Emphysema
Ground glass attenuation	Any non-calcified nodule or mass with diameter ≥4 mm whose predominant attenuation is ground glass
Growth during previous interval	Any non-calcified nodule or mass with diameter ≥4 mm that had interval growth based on comparison with prior CT
Lingular location	Any non-calcified nodule or mass with diameter ≥4 mm whose epicenter is in the lingula
Longest nodule diameter	Continuous*: longest diameter in millimeters among all non-calcified nodules or masses with diameter ≥4 mm
Lower lobe(s)	Any non-calcified nodule or mass with diameter ≥4 mm whose epicenter is in the right or left lower lobe
Micronodule	Any non-calcified micronodule(s) (opacity <4 mm)
Mixed attenuation	Any non-calcified nodule or mass with diameter ≥4 mm whose predominant attenuation is mixed
Multi-nodules	Six or more nodules not suspicious for cancer (opacity ≥4 mm)
Number of nodules	Continuous: number of nodules as described in “any nodule”
Opacities, fibrosis, scarring	Any reticular/reticulonodular opacities, honeycombing, fibrosis, or scar
Other abnormality (high)	Other potentially significant abnormality above the diaphragm
Other abnormality (low)	Other potentially significant abnormality below the diaphragm
Other attenuation	Any non-calcified nodule or mass with diameter ≥4 mm whose predominant attenuation is other than those described above
Pleural thickening or effusion	Pleural thickening or effusion
Poorly defined margins	Any non-calcified nodule or mass with diameter ≥4 mm whose margins are poorly defined
Right middle lobe	Any non-calcified nodule or mass with diameter ≥4 mm whose epicenter is in the right middle lobe
Smooth margins	Any non-calcified nodule or mass with diameter ≥4 mm whose margins are smooth
Soft tissue attenuation	Any non-calcified nodule or mass with diameter ≥4 mm whose predominant attenuation is soft tissue
Spiculated margins	Any non-calcified nodule or mass with diameter ≥4 mm whose margins are spiculated (stellate)
Suspicious change in attenuation	Any non-calcified nodule or mass with diameter ≥4 mm that had an interval suspicious change in attenuation based on comparison with prior CT
Unclassifiable attenuation	Any non-calcified nodule or mass with diameter ≥4 mm whose predominant attenuation cannot be determined
Unclassifiable margins	Any non-calcified nodule or mass with diameter ≥4 mm whose margin type cannot be determined
Upper lobe(s)	Any non-calcified nodule or mass with diameter ≥4 mm whose epicenter is in the right or left upper lobe

*Subsequently categorized; see footnote for Table 4.2.

Table 4.2 Selection of variables describing features identified on CT for inclusion in models of interval cancers, screen-detected cancer among screen-negatives, and screen-detected cancer among false-positives

Interval cancer among screen-negatives[a]	Screen-detected cancer among screen-negatives[b]	Screen-detected cancer among false-positives[c]
• Adenopathy [SW,L,F]	• Adenopathy	• Adenopathy
• Atelectasis	• Atelectasis	• Any nodule [SW, F*]
• Benign nodule [SW]	• Benign nodule	• Atelectasis
• Consolidation [SW,L,F]	• Consolidation [SW, F]	• Benign nodule
• Emphysema	• Emphysema [SW, F]	• Consolidation
• Micronodule	• Micronodule	• Emphysema [SW]
• Multi-nodules	• Multi-nodules [SW]	• Ground glass attenuation
• Opacities, fibrosis, scarring	• Opacities, fibrosis, scarring [SW]	• Growth during previous interval [SW, L, F]
• Other abnormality (high) [SW]	• Other abnormality (high)	• Lingula
• Other abnormality (low)	• Other abnormality (low)	• Longest nodule diameter [SW, L, F**]
• Pleural thickening or effusion	• Pleural thickening or effusion	• Lower lobe(s)
		• Micronodule
		• Mixed attenuation [SW, L]
		• Multi-nodules
		• Number of nodules
		• Opacities, fibrosis, scarring
		• Other abnormality (high)
		• Other abnormality (low)
		• Other attenuation [SW, L]
		• Pleural thickening or effusion
		• Poorly defined margins [SW]
		• Right middle lobe [SW]
		• Smooth margins [L, F]
		• Soft tissue attenuation
		• Spiculated margins [SW, L, F]
		• Suspicious change in attenuation
		• Unclassifiable attenuation [SW]
		• Unclassifiable margins [SW]
		• Upper lobe(s) [SW, L, F]

[SW] Selected by backwards stepwise approach
[L] Selected by lasso
[F] Selected for inclusion in final model
[a] Final model shown in Figure 4.4
[b] Final model shown in Figure 4.3
[c] Final model shown in Figure 4.5
*In the final model, this effect is essentially included in the diameter variable.
**Diameter was modeled continuously during variable selection. For the final model described in Figure 3, we considered different parameterizations including continuous, categorical, and log, square-root, and square transformations. We chose the categorical approach because it gave the lowest AIC.

Table 4.3 Individuals and screens from the National Lung Screening Trial included in analysis of risk for interval and screen-detected lung cancer

	At risk for interval cancer	At risk for screen-detected cancer	
	Screen-negative	Screen-negative	False-positive
Total number individuals, N	23,331	19,752	8,300
Screens per person, N (%)			
1 screen	4,445 (19%)	3,970 (20%)	3,606 (43%)
2 screens	4,176 (18%)	15,782 (80%)	4,694 (57%)
3 screens	14,710 (63%)	--	--
Total number screens, N	56,927	35,534	12,994
NLST screening round, N (%)			
T0	19,076 (34%)	18,247 (51%)	6,484 (50%)
T1	17,804 (31%)	17,287 (49%)	6,510 (50%)
T2	20,047 (35%)	--	--
1-year pre-screening risk, median (IQR)	0.31% (0.19-0.51%)	0.31% (0.19-0.50%)	0.35% (0.21-0.58%)
Lung cancer detected, N (%)	43 (0.076%)	138 (0.39%)	235 (1.8%)
Lung-RADS category, N (%)			
1	39,593 (70%)	26,512 (75%)	4 (0%)
2	16,867 (30%)	8.991 (25%)	8,661 (67%)
3	12 (0%)	5 (0%)	1,844 (14%)
4A	26 (0%)	18 (0%)	1,329 (10%)
4B	10 (0%)	6 (0%)	542 (4%)
4X	0 (0%)	0 (0%)	239 (2%)
Indeterminate or missing	418 (1%)	2 (0%)	375 (3%)

We analyzed 25,762 unique individuals. Percentages may not sum exactly to 100 due to rounding. See Methods for detailed definitions of interval and screen-detected cancer and a description of who was considered at risk for each. Lung-RADS categories were assigned retrospectively as described in Pinsky et al., *Ann Intern Med* 2015.[141]

Table 4.4 Cross-validation for models of next-screen lung cancer detection and interval lung cancer risk that incorporate specific CT-image features[a]

Predicted risk quintile	Next-screen cancer among screen-negatives, N[b]		Next-screen cancer among false-positives, N[c]		Interval cancer among screen-negatives, N[d]	
	Predicted	Observed	Predicted	Observed	Predicted	Observed
Lowest	5.8	3	6.5	7	1.2	2
Low	11.1	19	13.9	13	2.5	2
Moderate	17.9	13	24.3	31	4.3	8
High	29.9	33	45.3	43	7.6	8
Highest	73.7	70	147.9	141	29.1	23
Total	138.4	138	238.0	235	44.8	43

[a] Ten-fold cross-validation was performed: each model was fit 10 times using 90% of the data to generate predicted risks for the other 10% of the data. Data for all NLST screens (T1 and T2) and intervals (T0-T1, T1-T2, 1-year post-T2) was used. For each model, the model-predicted number of lung cancers is compared to the observed number of lung cancers within each quintile of risk.
[b] Model for next-screen cancer among screen-negatives includes CT-detected emphysema and consolidation. Ten-fold cross-validation estimate of prediction error was 0.39%
[c] Model for next-screen cancer among false-positives includes spiculated margins, smooth margins, nodule(s) in upper lobe(s), growing nodule(s), and longest nodule diameter. Ten-fold cross-validation estimate of prediction error was 1.72%.
[d] Model for interval cancer among screen-negatives includes a binary indicator of whether adenopathy or consolidation (or both) were diagnosed on the CT image. Ten-fold cross-validation estimate of prediction error was 0.08%.

Table 4.5 Calculation of next-screen lung cancer risk following a false-positive screen, based on Lung-RADS categories

Risk at next screen = $r_0(x)^y$ with exponent y given as follows:		
Characteristic	Exponent, y (95% CI)	Prevalence
Lung-RADS category at screen		
2	0.84 (0.80-0.88)	69%
3	0.81 (0.73-0.89)	15%
4A	0.60 (0.55-0.65)	10%
4B	0.51 (0.45-0.57)	4%
4X	0.76 (0.60-0.98)	2%

Model was fit among 12,615 individuals with a false-positive result at T0 or T1 and evaluates risk of cancer detection at T1 or T2, respectively. We restricted to individuals in whom a Lung-RADS category could be conclusively retrospectively assigned, as described in Pinsky et al., *Ann Intern Med* 2015.[141] The Akaike Information Criterion (AIC) for this model was 1978, as compared to 1903 for our false-positive model (Figure 4.5) fit among the same individuals.

Table 4.6 Effect of features noted on a false-positive CT screen on 1-year risk of screen-detected lung cancer among participants in the National Lung Screening Trial

Characteristic	Prevalence	Median	IQR	Median risk difference	Median risk ratio
Pre-screening risk	(100%)	0.34%	0.21-0.57%	Ref	Ref
Risk at next screen by:					
All T1 false-positives	(100%)	0.91%	0.45-2.0%	+0.56%	2.6
All low-risk factors**	18.9%	0.32%	0.20-0.53%	-0.02%	0.94
Spiculated margins					
No	90.4%	0.79%	0.42-1.7%	+0.45%	2.3
Yes	9.6%	4.0%	2.0-7.4%	+3.7%	11.7
Smooth margins					
No	26.8%	1.9%	0.90-3.9%	+1.6%	5.5
Yes	73.2%	0.71%	0.37-1.5%	+0.36%	2.1
Nodule(s) in upper lobe(s)					
No	55.1%	0.62%	0.32-1.3%	+0.28%	1.8
Yes	44.9%	1.4%	0.71-3.1%	+1.1%	4.2
Growing nodule(s)					
No	94.0%	0.83%	0.43-1.7%	+0.48%	2.4
Yes	6.0%	7.7%	3.7-15.4%	+7.4%	22.4
Longest nodule diameter					
N/A*	1.9%	1.5%	1.1-2.2%	+1.2%	4.4
4-5 mm	39.0%	0.49%	0.28-0.85%	+0.15%	1.4
6-7 mm	29.8%	0.80%	0.46-1.4%	+0.45%	2.3
8-10 mm	16.4%	1.9%	1.2-3.3%	+1.6%	5.5
11-13 mm	5.7%	4.1%	2.5-7.5%	+3.8%	11.9
14+ mm	7.2%	4.0%	2.2-7.6%	+3.6%	11.5

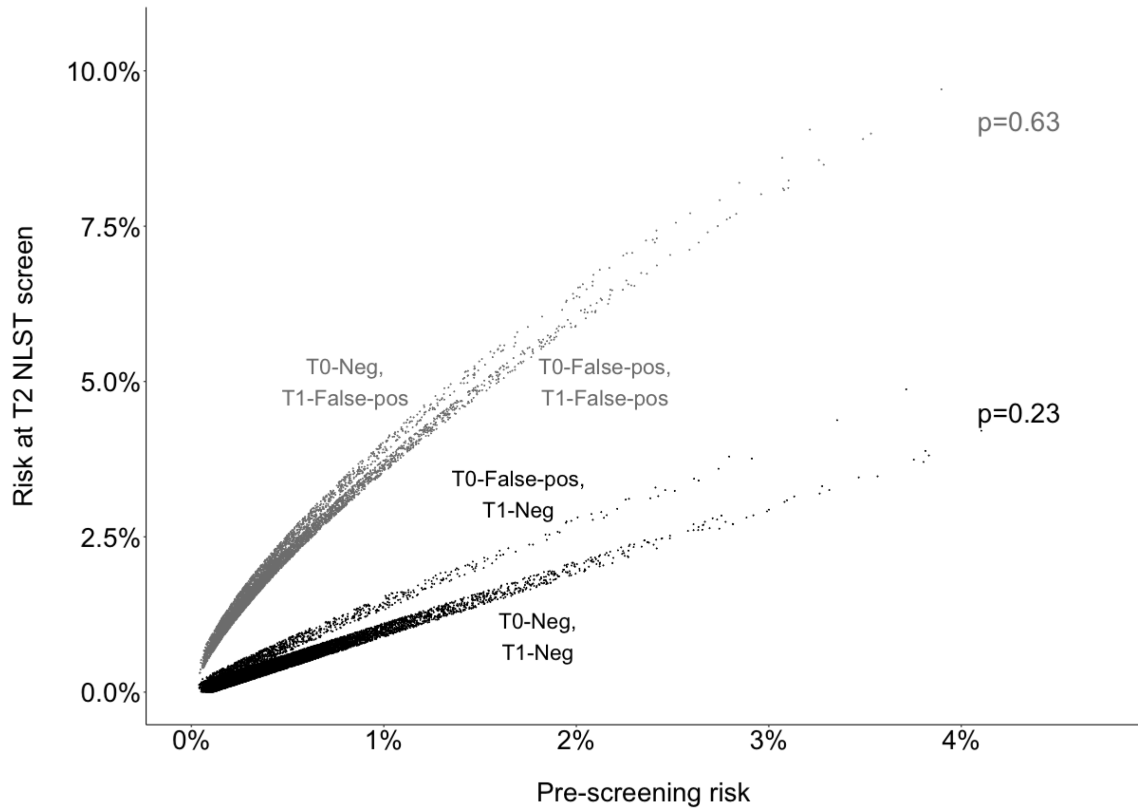
These data describe individuals who screened positive at the second NLST screen (T1) but in whom lung cancer was not immediately detected, and were subsequently at risk for lung cancer at the third screen (T2) (N=6,510). The second and third screens were selected to allow for evaluation of nodule growth between the first and second screens, and thus presentation of its relation to risk at the third screen. Outliers are included in the calculations. We note that the median risk among all T1 false-positives (0.91%) differs from that in Figure 4.2 (1.5%) because the distribution of risks becomes much wider after accounting for specific CT features. The means of the two risk distributions are similar.
*Screen was positive for a reason other than a nodule ≥4 mm
**Defined as follows: largest nodule diameter = 4-5 mm, at least one nodule with smooth margins, and no nodules in upper lobe(s), with spiculation, or growth. The exponent for such an individual's pre-screening risk would be 0.99 (95% CI 0.92-1.06); in other words, the calculation for next-screen risk is very similar to that for a negative screen.

Table 4.7 Observed lung cancer incidence over 4 years following the final (T2) NLST screen, by quintile of model-predicted 1-year total lung cancer risk

Predicted risk quintile	N	Range (median) of 1-year predicted risks	Observed 4-year lung cancer incidence
Lowest	4,777	0.03% to 0.15% (0.11%)	0.08%
Low	4,776	0.15% to 0.27% (0.21%)	0.48%
Moderate	4,776	0.27% to 0.46% (0.35%)	0.77%
High	4,776	0.46% to 0.90% (0.62%)	2.0%
Highest	4,776	0.90% to 41% (1.6%)	3.1%

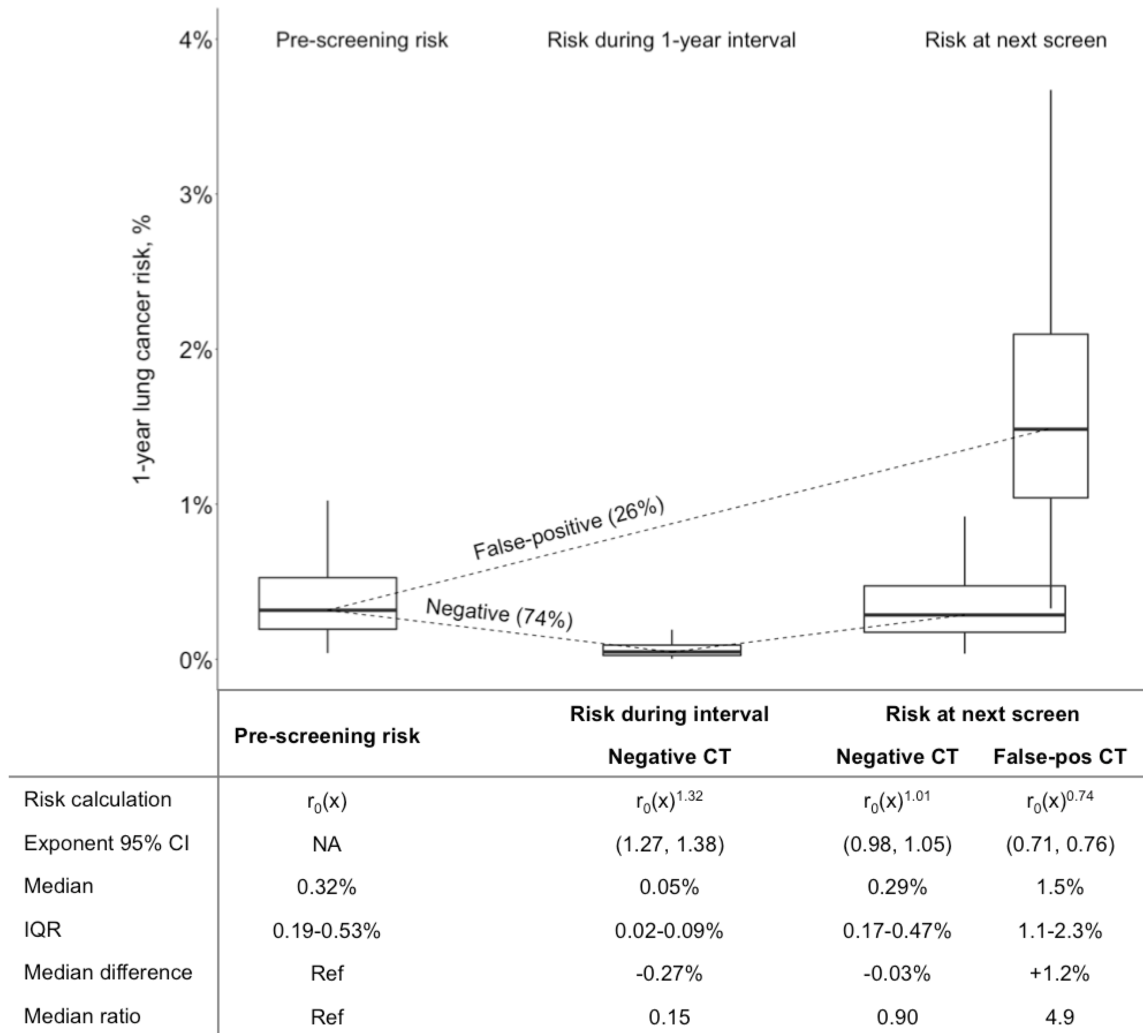
Analysis included 23,881 individuals who had a negative or false-positive T2 CT screen result and no prior lung cancer diagnosis. Following the T2 screen, 98% of participants had at least 4 years of follow-up for lung cancer incidence. One-year total predicted risk was calculated using our models for interval-cancer risk among screen-negatives (Figure 4.4), next-screen cancer risk among screen-negatives (Figure 4.3), and next-screen cancer risk among false-positives (Figure 4.5). For screen-negatives, interval and next-screen cancer risks were summed.

Figure 4.1 Comparison of T2 screen-detected lung cancer risk between groups with the same screen result at T1, but a different result at T0 in the National Lung Screening Trial



This analysis evaluated our first-order Markov assumption, in other words, evaluated whether prior screen-results continue to influence risk calculations once a more recent screen result is known. Exponents for risk calculation at T2 did not statistically significantly differ between groups whose T1 screen was negative but whose T0 screen differed (p=0.23) or between groups whose T1 screen was false-positive but whose T0 screen differed (p=0.63). A global likelihood ratio test (2 df) also indicated that prior screen results (regardless of whether the most recent result was negative or false-positive) do not contribute to risk calculations (p=0.47).

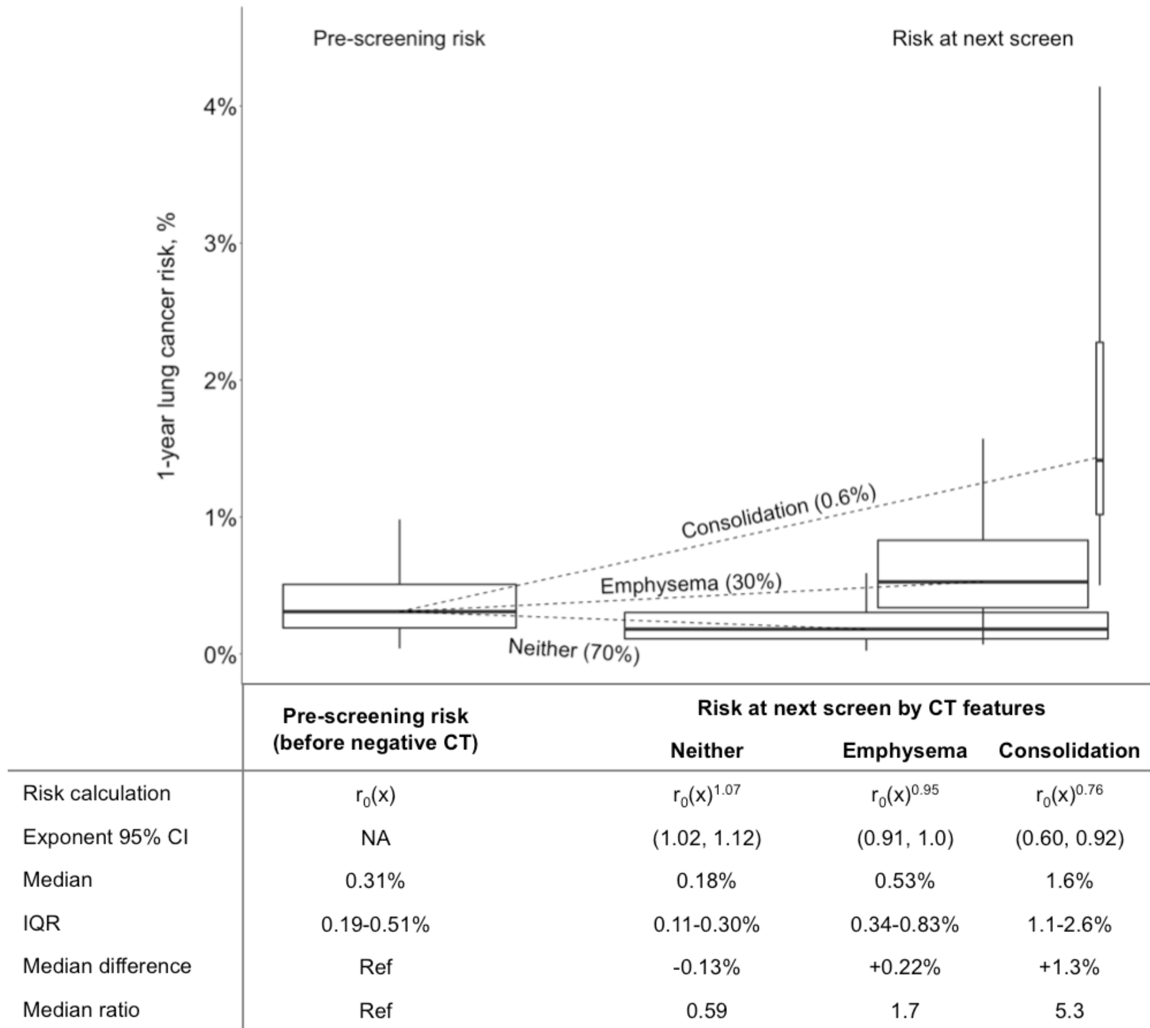
Figure 4.2 Overall effect of a negative or false-positive CT screening result on 1-year risk of an interval or screen-detected lung cancer among participants in the National Lung Screening Trial



	Pre-screening risk	Risk during interval	Risk at next screen	
		Negative CT	Negative CT	False-pos CT
Risk calculation	$r_0(x)$	$r_0(x)^{1.32}$	$r_0(x)^{1.01}$	$r_0(x)^{0.74}$
Exponent 95% CI	NA	(1.27, 1.38)	(0.98, 1.05)	(0.71, 0.76)
Median	0.32%	0.05%	0.29%	1.5%
IQR	0.19-0.53%	0.02-0.09%	0.17-0.47%	1.1-2.3%
Median difference	Ref	-0.27%	-0.03%	+1.2%
Median ratio	Ref	0.15	0.90	4.9

For illustration, this figure was constructed using data from individuals who underwent the first (T0) NLST screen and were at risk for lung cancer during the subsequent interval (i.e., screened negative, N=19,076) or at the subsequent (T1) screen (i.e., screened negative or false-positive and had a valid T1 screen result, N=24,731). Individuals for whom lung cancer was detected at T0 (N=270) were excluded. After this exclusion, 26% of individuals had a false-positive CT and the other 74% had a negative CT. Pre-screening risk $r_0(x)$ was calculated using the Lung Cancer Risk Assessment Tool.[73] Outliers are not included in the figure, but are included in the calculations in the table. Within each group of boxplots, boxplot widths are scaled by the percentage of the population represented, and vertical lines in boxplots represent the range of data excluding outliers. IQR, interquartile range.

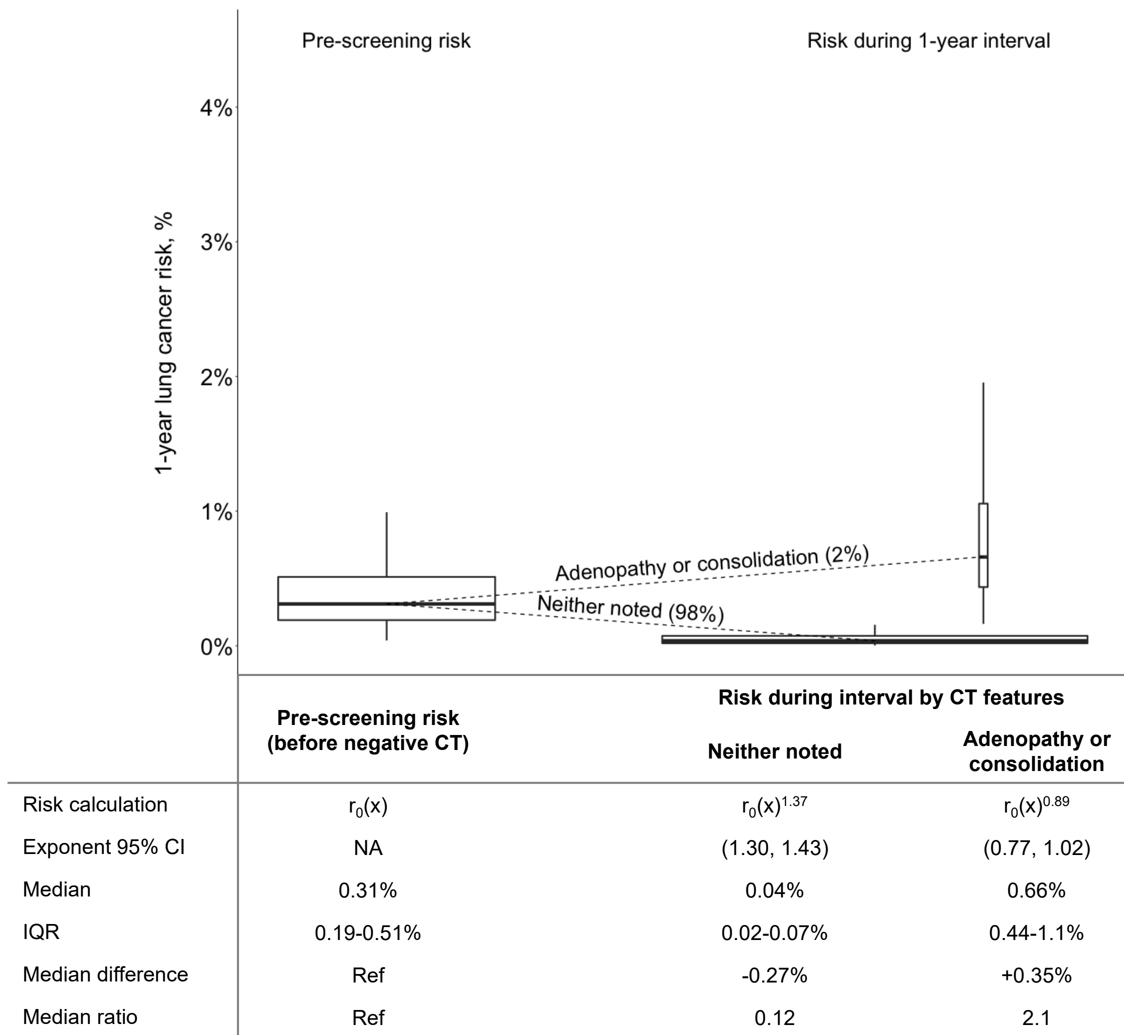
Figure 4.3 Effect of features noted on a negative CT screen on 1-year risk of screen-detected lung cancer among participants in the National Lung Screening Trial



	Pre-screening risk (before negative CT)	Risk at next screen by CT features		
		Neither	Emphysema	Consolidation
Risk calculation	$r_0(x)$	$r_0(x)^{1.07}$	$r_0(x)^{0.95}$	$r_0(x)^{0.76}$
Exponent 95% CI	NA	(1.02, 1.12)	(0.91, 1.0)	(0.60, 0.92)
Median	0.31%	0.18%	0.53%	1.6%
IQR	0.19-0.51%	0.11-0.30%	0.34-0.83%	1.1-2.6%
Median difference	Ref	-0.13%	+0.22%	+1.3%
Median ratio	Ref	0.59	1.7	5.3

For illustration, this figure was constructed using data from individuals who screened negative at the first NLST screen (T0) and were subsequently at risk for lung cancer at the second screen (T1) (N=18,247). Among these individuals, 0.6% had consolidation identified on their negative CT, 30% had emphysema, and 70% had neither. A small number of individuals with both consolidation and emphysema noted at T0 were included in both corresponding risk distributions. Pre-screening risk $r_0(x)$ was calculated using the Lung Cancer Risk Assessment Tool.[73] Outliers are not included in the figure, but are included in the calculations in the table. Within each group of boxplots, boxplot widths are scaled by the percentage of the population represented, and vertical lines in boxplots represent the range of data excluding outliers. IQR, interquartile range.

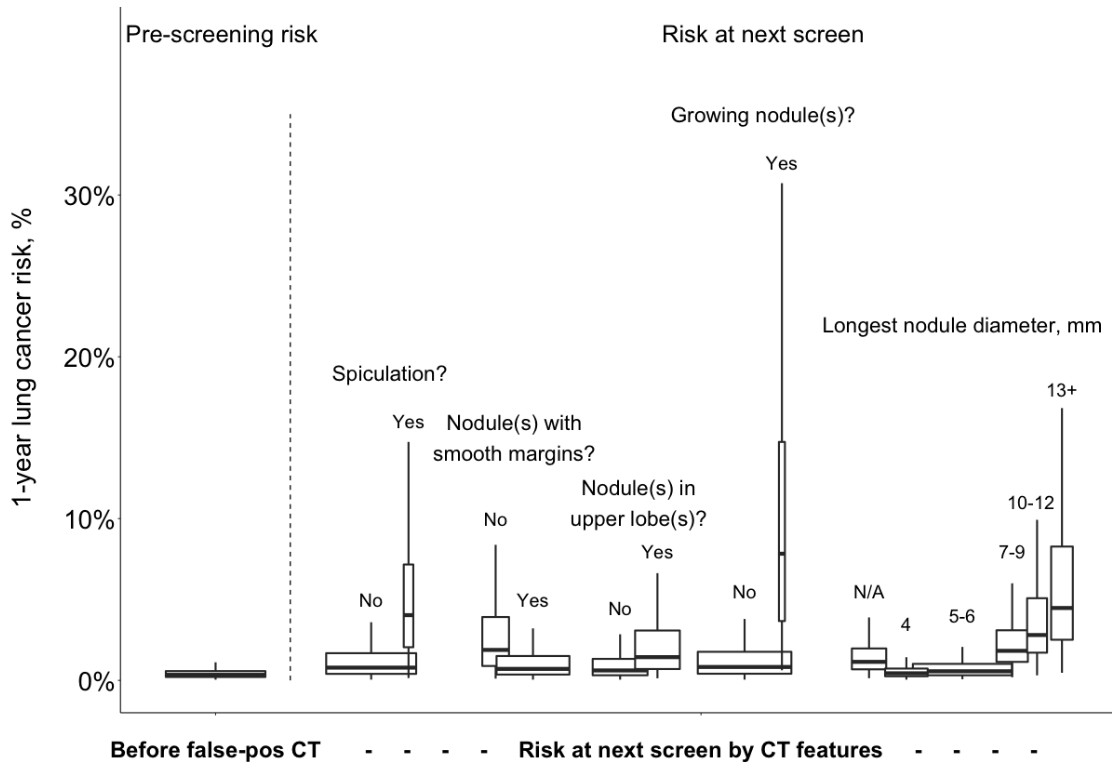
Figure 4.4 Effect of features noted on a negative CT screen on 1-year risk of interval lung cancer among participants in the National Lung Screening Trial



	Pre-screening risk (before negative CT)	Risk during interval by CT features	
		Neither noted	Adenopathy or consolidation
Risk calculation	$r_0(x)$	$r_0(x)^{1.37}$	$r_0(x)^{0.89}$
Exponent 95% CI	NA	(1.30, 1.43)	(0.77, 1.02)
Median	0.31%	0.04%	0.66%
IQR	0.19-0.51%	0.02-0.07%	0.44-1.1%
Median difference	Ref	-0.27%	+0.35%
Median ratio	Ref	0.12	2.1

For illustration, this figure was constructed using data from individuals who screened negative at the first NLST screen and were subsequently at risk for lung cancer during the interval between the first and second screens (N=19,076). Pre-screening risk (r) was calculated using the Lung Cancer Risk Assessment Tool.[73] Outliers are not included in the figure, but are included in the calculations in the table. Within each group of boxplots, boxplot widths are scaled by the percentage of the population represented, and vertical lines in boxplots represent the range of data excluding outliers. IQR, interquartile range.

Figure 4.5 Effect of features noted on a false-positive CT screen on 1-year risk of screen-detected lung cancer among participants in the National Lung Screening Trial



Risk at next screen after a false-positive screen = $r_0(x)^y$ with exponent y calculated as follows:

Characteristic	Value (95% CI)
What was the longest diameter among all nodules?	This gives the initial value
N/A*	0.76 (0.62-0.95)
4-5 mm	0.92 (0.84-1.00)
6-7 mm	0.85 (0.78-0.93)
8-10 mm	0.73 (0.66-0.80)
11-13 mm	0.63 (0.56-0.71)
14 mm or larger	0.68 (0.62-0.76)
Was any nodule with spiculated margins present?	If yes, subtract 0.10 (-0.15, -0.04)
Was any nodule with smooth margins present?	If yes, add 0.07 (0.02, 0.12)
Was any nodule present in the upper lobes?	If yes, subtract 0.10 (-0.15, -0.04)
If evaluable, did an existing nodule grow during the most recent screening interval?	If yes, subtract 0.28 (-0.34, -0.22)

*Screen was positive for a reason other than a nodule ≥4 mm
For illustration, this figure was constructed using data from individuals who screened positive at the second NLST screen (T1) but in whom lung cancer was not immediately detected, and were subsequently at risk for lung cancer detection at the third screen (T2) (N=6,510). The second and third screens were selected to allow for evaluation of nodule growth between the first and second screens, and thus presentation of its relation to risk at the third screen. Pre-screening risk $r_0(x)$ was calculated using the Lung Cancer Risk Assessment Tool.[73] Outliers are not included in the figure, but are included in the calculations in the table. Within each group of boxplots, boxplot widths are scaled by the percentage of the population represented, and vertical lines in boxplots represent the range of data excluding outliers. IQR, interquartile range.

Chapter 5: Conclusions

5.1 Summary of Results

This dissertation applied precision approaches for cancer screening in two high-risk populations (PLHIV and heavy smokers), and for three types of cancer (cervical, anal, and lung cancers). While each context was unique, the ultimate goal of this work is the same in each case: to identify ways that cancer screening can be tailored to each individual, thus achieving a better overall balance of benefits and harms at the population level.

Chapter 2 used a risk benchmarking framework to compare cervical precancer risks between U.S. WLHIV (in the Women's Interagency HIV Study) and general population women. This framework allowed explicit suggestion of particular screening or management strategies following different cytology and/or oncHPV testing results. We found that most existing CDC guidelines for WLHIV were supported by this risk comparison, including: a 3-year return after 3 consecutive negative cytologies or a negative cytology/oncHPV co-test for WLHIV with CD4≥500; a 1-year return after negative cytology with either a positive oncHPV co-test or a CD4<500; and a 6-12 month return after ASC-US cytology for CD4≥350. Other findings differed from current guidelines, including: colposcopy instead of a 6-12 month return for WLHIV with ASC-US and CD4<350; and a 2-year instead of 1-year interval for WLHIV with CD4≥500 after negative cytology. In sum, our findings largely supported current guidelines for cervical cancer screening in WLHIV, but also suggested that CD4 cell count might be considered in some instances to permit more tailored screening strategies.

Chapter 3 analyzed data from the Multicenter AIDS Cohort Study to describe patterns of repeated anal cytology among HIV-positive and HIV-negative MSM. We found that among men with an initial negative cytology, the second cytology was most likely to remain negative among HIV-negative men (83%) and less likely to remain negative among HIV-positive men with CD4≥500 (74%) or CD4<500 (68%). Similarly, after an initial abnormal cytology, the second cytology was least likely to remain abnormal among HIV-negative men (46%) or HIV-positive men with CD4≥500

(53%), and most likely to remain abnormal among HIV-positive men with CD4<500 (70%). Among HIV-positive MSM, about 37% have consistently negative cytology over 3 years, which may identify a low-risk group in whom an invasive procedure such as HRA is unlikely to be beneficial. HIV-positive men with consistently negative cytology, as compared to those with consistently abnormal cytology, were likely to have higher current and nadir CD4 counts and fewer recent condomless receptive anal sex partners, consistent with known risk factors for anal lesions and cancer.

Finally, Chapter 4 analyzed data from the National Lung Screening Trial to develop a risk model that continually updates individual lung cancer risk during CT screening. We found that those with a false-positive CT have overall increased lung cancer detection at the next annual screen, while screen-negatives have detection similar to their one-year risk prior to screening. However, there is heterogeneity in each of these groups. Screen-negatives with CT-detected emphysema or consolidation have increased risk when they return for the next screen, while the 70% without either of these features have 1.8-fold reduced next-screen detection. This 70% of screen-negatives, who comprised 51% of National Lung Screening Trial participants, represents a logical first group to consider for longer screening intervals. Next-screen detection among false-positives varies widely by nodule features, but for false-positives with all low-risk features (19%), future risk is equivalent to that following a negative screen.

5.2 Opportunities for Future Research

Each of the three contexts studied within this dissertation has unique opportunities for future research, and there are additional research avenues that are relevant across all three aims. To optimize cervical cancer screening in WLHIV, there are a few scenarios that we could not address but that should be studied in future work. These include risk-based screening strategies following primary (standalone) HPV testing, the utility of type-specific HPV testing for risk stratification including in conjunction with CD4 count, risk-tailored screening strategies appropriate for WLHIV in low-resource settings, the utility of HIV viral load measurements for risk stratification, whether full

immunosuppression (CD4 count) history must be considered for screening decisions, and whether broad screening recommendations are appropriate for special groups of WLHIV such as those with a history of cervical precancer treatment.

Anal cancer screening among MSM is a context with a substantial and wide-ranging need for additional research, and multiple specific questions follow directly from our results. In particular, patterns of anal cytology (e.g., consistently negative cytology over 3 years) should be studied in their relation to the risk of biopsy-confirmed HSIL: here we would expect that consistently negative cytology might indicate sufficiently low risk to safely avoid referral to HRA. We examined the effect of current CD4 cell count on the likelihood of transitioning from one cytology result to another (e.g., from normal to abnormal), but it is possible that other factors such as nadir CD4 cell count, HIV viral load, or demographic factors such as age also play an important role. Finally, since there are major demographic differences between our study population (MACS participants) and the current population of HIV-positive MSM in the U.S., it would be of interest to examine statistically whether our pap-pattern prevalence estimates are likely to represent HIV-positive MSM more broadly.

Similarly, CT lung cancer screening is a new field with a multitude of research needs. Following from our findings, perhaps most importantly, it will be critical to externally validate our risk model in an appropriate population before it can be applied in practice. Our finding that only the most recent CT result contributed to risk calculations is novel and important, but should be re-examined using data describing more than 3 annual CT screens. We identified a subset of CT participants – namely, those with a negative CT result and no emphysema or consolidation – who are likely candidates for extended screening intervals, and additional research is needed to identify precise appropriate risk thresholds for longer intervals and to examine the impact of such a strategy on CT screening programs overall. Similarly, at the other end of the risk spectrum, our findings identify a small subset of false-positives who have very high predicted probabilities of next-screen lung cancer detection. Future studies should seek to describe these participants and to examine potential

strategies for appropriate follow-up testing that may occur sooner than the recommended next annual screen.

Finally, there are avenues of future work that are applicable to precision cancer screening in general and thus common to all three dissertation aims. Precision cancer screening strategies, by their nature, require individualized assessment of patients' cancer risks and the application of screening strategies that are complex and differ across patients. Research is needed to understand the implications of such strategies for clinical workflows, to identify approaches that automate and streamline processes for clinicians, and to develop tools that allow clinicians to effectively and efficiently communicate with patients in a way that improves shared decision-making. Success in implementation will require interdisciplinary research efforts that engage clinicians, patients, and researchers from a variety of fields.

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Chapter 7: Curriculum Vitae

Hilary A. Robbins
PhD Candidate, Department of Epidemiology
Johns Hopkins Bloomberg School of Public Health
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Education and Training

PhD *(2018)* **Epidemiology**
Johns Hopkins Bloomberg School of Public Health, Baltimore, MD
Advisor: Dr. Gypsyamber D'Souza

MHS 2017 **Biostatistics**
Johns Hopkins Bloomberg School of Public Health, Baltimore, MD
Advisors: Dr. Scott Zeger and Dr. Hormuzd Katki (NCI)

MSPH 2012 **International Health**
Johns Hopkins Bloomberg School of Public Health, Baltimore, MD
Advisor: Dr. Li Liu

BS 2010 **Chemistry**
Duke University, Durham, NC

Professional Experience

Sep. – Dec. 2016 **Site Coordinator**
Oral HPV Infection and Persistence in HIV (OHIP) Study
Johns Hopkins Bloomberg School of Public Health, Baltimore, MD

Oct. 2012 – Aug. 2014 **Post-Baccalaureate Fellow**
Division of Cancer Epidemiology and Genetics, NCI, NIH, Rockville, MD
Mentors: Dr. Eric Engels and Dr. Mahboobeh Safaeian

May – Sep. 2012 **Epi Scholar**
Los Angeles County Department of Public Health, Los Angeles, CA

Jan. – Apr. 2012 **Research Assistant**
Center for American Indian Health, Johns Hopkins, Baltimore, MD

Jan. – June 2011 **Community Health Volunteer Researcher**
ATRAVES, Managua, Nicaragua

July – Dec. 2010 **Math Teacher**
Colegio Bilingüe New Horizons, Santo Domingo, Dominican Republic

May 2007 – Dec. 2009 **Undergraduate Researcher**
Dr. Eric Toone's chemistry laboratory, Duke University, Durham, NC
Dr. Blanche Capel's biology laboratory, Duke University, Durham, NC
Dr. Thomas Schmedake's biochemistry laboratory, UNCC, Charlotte, NC

Honors and Awards

June 2017	**Kocherlakota Award** Awarded to a biostatistics master's student for the best performance on the first-year written comprehensive examination. Department of Biostatistics, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD
June 2017	**ICSN Conference Travel Award** International Cancer Screening Nework Meeting, Bethesda, MD
May 2017	**1st Place Poster, Clinical and Translational Research** Johns Hopkins Sidney Kimmel Comprehensive Cancer Center (SKCCC) Fellow Research Day 2017, Baltimore, MD
May 2017	**ATS Abstract Travel Scholarship** American Thoracic Society (ATS) 2017 Conference, Washington, DC
May 2017	**ATS Student Scholars Program** American Thoracic Society (ATS) 2017 Conference, Washington, DC
April 2017	**David and Elinor Bodian Scholarship** Awarded to a doctoral student whose dissertation research is at a critical juncture. Johns Hopkins Bloomberg School of Public Health, Baltimore, MD
Mar. 2017	**Alison Snow Jones Prize in Health Policy & Management** Awarded to a doctoral student for excellence in a thesis research manuscript. Johns Hopkins Bloomberg School of Public Health, Baltimore, MD
Mar. 2017	**3rd Place Poster, Applied Research** Delta Omega Poster Competition, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD
Feb. 2017	**International Papillomavirus Society Travel Award** HPV 2017: 31st International Papillomavirus Conference, Cape Town, South Africa
Nov. 2016	**Scholar-in-Training Travel Award** AACR Special Conference on Improving Cancer Risk Prediction for Prevention and Early Detection, Orlando, FL
May 2016	**Honorable Mention Poster, Clinical and Translational Research** Johns Hopkins Sidney Kimmel Comprehensive Cancer Center (SKCCC) Fellow Research Day 2016, Baltimore, MD
Apr. 2016	**Carol Eliasberg Martin Scholarship** Awarded to a doctoral student or post-doc whose research holds promise for preventing cancers that affect women. Johns Hopkins Bloomberg School of Public Health, Baltimore, MD
Feb. 2016	**Women in Cancer Research (WICR) Scholar Travel Award** AACR 2016 Annual Meeting, New Orleans, LA
Oct. 2015	**Translating Cancer Epidemiology Conference Travel Award** Translating Cancer Epidemiology: From Cells to Clinic and Population, Huntsman Cancer Institute, Salt Lake City, UT
Mar. 2015	**Jean Coombs Award** Awarded to a doctoral student whose dissertation concerns cancer or childhood diseases. Johns Hopkins Bloomberg School of Public Health, Baltimore, MD

Aug. 2014 **Cancer Epidemiology, Prevention, and Control Training Grant**
Johns Hopkins Bloomberg School of Public Health, Baltimore, MD

Dec. 2013 **CROI Young Investigator Travel Award**
Conference on Retroviruses and Opportunistic Infections (CROI) 2014

Nov. 2013 **DCEG Fellows Award for Research Excellence**
Provides funding for travel to scientific meetings to fellows who have made exceptional contributions to research projects. Division of Cancer Epidemiology and Genetics, NCI, NIH, Rockville, MD

June 2013 **Fellowship Achievement Award**
Awards a stipend increase to fellows for excellence in research during the prior year. Division of Cancer Epidemiology and Genetics, NCI, NIH, Rockville, MD

May 2013 **Outstanding Poster Award**
Post-Baccalaureate Poster Day, NIH, Bethesda, MD

Apr. 2013 **Delta Omega Honor Society**
Members are inducted through a selective process that assesses their outstanding performance and devotion to the field of public health. Johns Hopkins Bloomberg School of Public Health, Baltimore, MD

Jan. 2013 **Consortium of Universities in Global Health Annual Meeting Travel Award**
Center for Global Health, Johns Hopkins University, Baltimore, MD

Dec. 2011 **Sara's Wish Foundation Scholarship**
Awarded to young women who exhibit qualities of leadership, service, and adventure to support travel for international humanitarian work. Sara's Wish Foundation, Amherst, MA

May 2010 **Magna Cum Laude**
Duke University, Durham, NC

Dec. 2009 **Phi Beta Kappa**
Duke University, Durham, NC

May 2006 **National Merit Scholar**
Northwest Cabarrus High School, Concord, NC

Teaching, Mentoring, Leadership, and Service

June 2017 – present — **Student Representative to Epidemiology Faculty**
Johns Hopkins Bloomberg School of Public Health, Baltimore, MD

May 2017 – present — **MHS Student Representative to Biostatistics Faculty**
Johns Hopkins Bloomberg School of Public Health, Baltimore, MD

Jan. 2014 – present — **Tutor, Epidemiology and Biostatistics**
Johns Hopkins Bloomberg School of Public Health, Baltimore, MD

Jan. 2014 – present — **Reader, Duke Reader Project**
Duke University, Durham, NC

Oct. 2013 – present — **Interviewer, Duke University Alumni Admissions Advisory Committee**
Duke University, Durham, NC

June – Aug. 2017 — **Mentor to Brooke Gipson, undergraduate summer student**
Diversity Summer Internship Program, Johns Hopkins University

May 2016 – May 2017 — **Member, Doctoral Student Council**
Johns Hopkins Bloomberg School of Public Health, Baltimore, MD

Feb. 2016 – June 2017 — **Student Representative for Schools of Public Health, Medicine, and Nursing, Johns Hopkins University Doctor of Philosophy Board**
Johns Hopkins University, Baltimore, MD

Aug. – Dec. 2016 — **Co-Coordinator, Cancer Epidemiology Journal Club**
Johns Hopkins Bloomberg School of Public Health, Baltimore, MD

Aug. 2015 – May 2016 — **Co-Coordinator, Cancer Epidemiology Research in Progress Seminar**
Johns Hopkins Bloomberg School of Public Health, Baltimore, MD

May 2015 – May 2016 — **Student Representative, Epidemiology Curriculum Committee**
Johns Hopkins Bloomberg School of Public Health, Baltimore, MD

Sep. – Dec. 2015 — **Lab Instructor, Fundamentals of Epidemiology**
Johns Hopkins University, Baltimore, MD

Aug. – Sep. 2015 — **Member, Scientific Support Committee**
"Precision Cancer Screening in the General Population" symposium
National Cancer Institute, Rockvile, MD

May – Aug. 2015 — **Mentor to Victoria Buckman, undergraduate summer student**
Diversity Summer Internship Program, Johns Hopkins University

Oct. – Dec. 2014 — **Teaching Assistant, Epidemiologic Methods II**
Johns Hopkins Bloomberg School of Public Health, Baltimore, MD

May 2013 – Aug. 2014 — **Co-Chair, New Fellows Welcome Committee**
Division of Cancer Epidemiology and Genetics, NCI, Rockville, MD

Nov. 2013 – Aug. 2014 — **Member, Technical Evaluation of Questionnaires (TEQ) Committee**
Division of Cancer Epidemiology and Genetics, NCI, Rockville, MD

Dec. 2012 – June 2013 — **Member, DCEG Fellows' Training Symposium Planning Committee**
Division of Cancer Epidemiology and Genetics, NCI, Rockville, MD

Research Grants and Funding

NIH/NCI Individual National Research Service Award (NRSA) F31 CA210660
"Optimizing Screening for HPV-Related Cancers Among People Living with HIV"
Objective: Use risk-tailored methods to optimize screening strategies for cervical cancer among HIV-positive women and for anal cancer among HIV-positive and -negative men who have sex with men.
This NRSA F31 application received a perfect overall impact score (10).

Practice Activities

May 2016 Wrote article about skin cancer among transplant recipients for the Skin Cancer Foundation's annual layperson magazine:
"After A Transplant: New Dangers" by Hilary A. Robbins, Eric A. Engels, John P. Roberts, and Sarah T. Arron. The Skin Cancer Foundation Journal 2016, p. 36-38.
Available at: http://www.skincancer.org/prevention/are-you-at-risk/transplants

Jan. 2015 Created page of "Common questions and answers about oral HPV infection" for the Oral Cancer Foundation's website.

Peer-Reviewed Publications

1. **Robbins HA**, Wiley D, Ho K, Plankey M, Reddy S, Joste N, Darragh TM, Breen EC, Young S, D'Souza G. Patterns of repeated anal cytology testing among HIV-positive and HIV-negative men who have sex with men. *Papillomavirus Research*, in press.

2. **Robbins HA***, Gipson BJ*, Fakhry C, D'Souza G. Sensitivity and specificity of oral HPV detection for HPV-positive head and neck cancer. *Oral Oncology* 2018;77:52-56. PMID 29362127.

3. **Robbins HA**, Strickler H, Massad LS, Pierce CB, Darragh TM, Minkoff H, Keller MJ, Fischl M, Palefsky J, Flowers L, Rahangdale L, Milam J, Shrestha S, Colie C, D'Souza G. Cervical cancer screening intervals and management for women living with HIV: A risk benchmarking approach. *AIDS* 2017 Apr 24;31(7):1035-1044. PMC5531443.

4. D'Souza G, Zhang Y, Merritt S, Gold D, **Robbins HA**, Buckman V, Gerber J, Eisele D, Ha P, Califano J, Fakhry C. Patient experience and anxiety during and after treatment for an HPV-related oropharyngeal cancer. *Oral Oncology* 2016 Sep;60:90-95. PMID 27531878.

5. Safaeian M, **Robbins HA**, Berndt SI, Lynch CF, Fraumeni JF, Engels EA. Risk of colorectal cancer after solid organ transplantation in the United States. *Am J Transplant* 2016 Mar;16(3):960-7. PMC5218822.

6. **Robbins HA**, Fennel C, Gillison M, Xiao W, Guo Y, Kirk GD, Mehta SH, D'Souza G. Prevalence of and risk factors for oral human papillomavirus infection among HIV-infected and HIV-uninfected people who inject drugs. *PLoS One* 2015 Nov 24;10(11):e0143698. PMC4657972.

7. **Robbins HA**, Clarke CA, Arron ST, Tatalovich Z, Kahn AR, Hernandez BY, Paddock L, Yanik EL, Lynch CF, Kasiske BL, Snyder J, Engels EA. Melanoma risk and survival among organ transplant recipients. *J Invest Dermatol* 2015; 135(11):2657-65. PMC4640996.

8. **Robbins HA,** Pfeiffer RM, Shiels MS, Li J, Hall HI, Engels EA. Excess cancers among HIV-infected people in the United States. *J Natl Cancer Inst* 2015 Feb 6;107(4). PMC4334816.

9. **Robbins HA**, Engels EA, Pfeiffer RM, Shiels MS. Age at cancer diagnosis for blacks compared to whites in the United States. *J Natl Cancer Inst* 2015 Jan 31;107(3). PMC4326308.

10. **Robbins HA,** Hurley EA, Liu L, Chao S. Multilevel correlates of broadly- and narrowly-defined intimate partner violence among pregnant women in Los Angeles. *Matern Child Health J* 2015 Jul;19(7):1643-51. PMC4544841.

11. Li Y, Safaeian M, **Robbins HA**, Graubard B. Logistic analysis of epidemiologic and survey studies with augmentation sampling involving re-stratification and population expansion. *Biostatistics* 2015 Jan;16(1):169-78. PMC4263221.

12. Clarke CA, **Robbins HA**, Tatalovich Z, Lynch CF, Pawlish KS, Finch JL, Hernandez BY, Fraumeni JF, Madeleine MM, Engels EA. Risk of Merkel cell carcinoma after solid organ transplantation. *J Natl Cancer Inst* 2015 Jan 8;107(2). PMC4311175.

13. **Robbins HA**, Waterboer T, Porras C, Kemp TJ, Pawlita M, Rodriguez AC, Wacholder S, Gonzalez P, Schiller JT, Lowy DR, Esser M, Matys K, Poncelet S, Herrero R, Hildesheim A, Pinto LA, Safaeian M. Immunogenicity assessment of HPV16/18 vaccine using the glutathione S-transferase L1 multiplex serology assay. Hum Vaccin Immunother 2014 Oct 3;10(10):2965-74. PMC5443057.

14. **Robbins HA,** Li Y, Porras C, Pawlita M, Ghosh A, Rodriguez AC, Schiffman M, Wacholder S, Kemp T, Gonzalez P, Schiller J, Lowy D, Esser M, Matys K, Quint W, van Doorn L-J, Herrero R, Pinto LA, Hildesheim A, Waterboer T, Safaeian M. Glutathione S-transferase L1 multiplex serology as a measure of cumulative infection with human papillomavirus. *BMC Infect Dis* 2014 Mar 3;14(1):120. PMC3973893.

15. **Robbins HA,** Shiels M, Pfeiffer R, Engels EA. Epidemiologic contributions to recent cancer trends among HIV-infected people in the United States. *AIDS* 2014 Mar 27;28(6):881-90. PMC5015650.

16. **Robbins HA,** Kemp TJ, Porras C, Rodriguez AC, Schiffman M, Wacholder S, Gonzalez P, Schiller J, Lowy D, Poncelet S, Esser M, Matys K, Hildesheim A, Pinto LA, Herrero R, Safaeian M. Comparison of antibody responses to human papillomavirus vaccination as measured by three assays. *Front Oncol* 2014 Jan 13;3:328. PMC3888946.

Published Commentaries, Editorials, and Letters

1. **Robbins HA**. CT lung cancer screening in people living with HIV: Modeling to bridge the evidence. Invited commentary on "Benefits and harms of lung cancer screening in HIV-infected individuals with CD4+≥500: A simulation study" by Kong et al. *AIDS*, in press.

2. D'Souza G and **Robbins HA**. Sexual and relationship health among survivors of oropharyngeal or oral cavity squamous cell carcinoma. Invited commentary on "Significant changes in sexual behavior after a diagnosis of HPV-positive and negative oral cancer" by Taberna et al. *Cancer* 2017 Apr 1;123(7):1092-109. PMC5538106.

3. Marcus PM, Pashayan N, Church TR, Doria-Rose VP, Gould MK, Hubbard RA, Marrone M, Miglioretti DL, Pharoah PD, Pinsky PF, Rendle K, **Robbins HA**, Roberts MC, Rolland B, Schiffman M, Tiro JA, Zauber AG, Winn DM, Freedman AN, Khoury MJ. Population-based precision cancer screening: a symposium on evidence, epidemiology, and next steps. *Cancer Epidemiol Biomark Prev* 2016 25(11):1449–55. PMC5165650.

4. Shiels MS, **Robbins HA,** Engels EA. Younger age at cancer diagnosis may be driven by age structure of the HCV population. *J Hepatol* 2016 Feb;64(2):516-7. PMC5373652.

Invited Oral Presentations

Dec. 1, 2017 — "Human Papillomavirus"
Lecture to Epidemiology of Infectious Diseases course
Johns Hopkins Bloomberg School of Public Health, Baltimore, MD

July 4, 2017 — "Precision Medicine for Cancer Screening: Applications in Lung and Cervical Cancers"
Genetic Epidemiology Group, International Agency for Research on Cancer (IARC), Lyon, France

Jan. 19, 2017 — "Precision Medicine for Cancer Screening: Applications in Lung and Cervical Cancers"
Epidemiology and Clinical Outcomes Research Seminar Series
Washington University in St. Louis School of Medicine, St. Louis, MO

July 1, 2014 — "Measurement of Human Papillomavirus Immune Responses"
With Dr. Mahboobeh Safaeian, as a section of "Human Papillomavirus Seroepidemiology in Natural History and Vaccination Studies"
MedImmune, Gaithersburg, MD

Proffered Oral Presentations

June 20, 2017 — "Effect of Screening CT Results on Lung Cancer Risk Prediction within the National Lung Screening Trial"
International Cancer Screening Network (ICSN) Meeting, Bethesda, MD

May 24, 2017 — "Effect of Screening CT Findings on Lung Cancer Risk Prediction Within the National Lung Screening Trial"
American Thoracic Society (ATS) 2017 International Conference, Washington, DC

Mar. 4, 2017 — "Cervical Cancer Screening Intervals and Management of Abnormal Results for Women Living with HIV: A Risk Benchmarking Approach"
HPV 2017: 31st International Papillomavirus Conference, Cape Town, South Africa

Nov. 18, 2016 — "Effect of Screening CT Findings on Lung Cancer Risk Prediction within the National Lung Screening Trial"
AACR Conference on Improving Cancer Risk Prediction for Prevention and Early Detection, Orlando, FL

Mar. 8, 2016 — "Optimizing Screening for HPV-related Cancers among People Living with HIV"
Doctoral Proposal Seminar, JHSPH, Baltimore, MD

June 18, 2014 — "Measurement of HPV Immune Responses: Comparing Serology Assays"
Post-baccalaureate Seminar Series, NIH, Bethesda, MD

Apr. 10, 2014 — "Epidemiologic Factors Contributing to Cancer Trends in the U.S. HIV-Infected Population"
Seminars by DFARE Winners, DCEG, NCI, NIH, Rockville, MD

Dec. 12, 2013 — "Epidemiologic Contributions to Cancer Trends Among HIV-Infected People"
Registry Database Studies Seminar Series, DCEG, NCI, NIH, Rockville, MD

Nov. 14, 2013 — "Excess Burden of Cancer among HIV-Infected Persons in the United States"
Seminars by Fellowship Achievement Award Winners, DCEG, NCI, NIH

Nov. 13, 2013 — "Epidemiologic Contributions to Recent Cancer Trends Among HIV-Infected People in the United States"
14th International Conference on Malignancies in AIDS and Other Acquired Immunodeficiencies (ICMAOI), NIH, Bethesda, MD

Apr. 13, 2013 — "Correlates of Intimate Partner Violence during Pregnancy: A Multilevel Analysis of the Los Angeles Mommy and Baby Project"
Student Leaders in Global Health, Unite for Sight Global Health and Innovation Conference, New Haven, CT

Poster Presentations

Apr. 5, 2017 — "Effect of Screening CT Findings on Lung Cancer Risk Prediction Within the National Lung Screening Trial"
American Association for Cancer Research (AACR) 2017, Washington, DC

Apr. 18, 2016 — "Optimizing Cervical Cancer Screening for HIV-infected Women: A Risk-based Approach"
American Association for Cancer Research (AACR) 2016, New Orleans, LA

Oct. 26, 2015 — "Screening Interval after Normal Cervical Cytology among HIV-infected Women: A Risk-based Approach"
15th International Conference on Malignancies in AIDS and Other Acquired Immunodeficiencies (ICMAOI), NIH, Bethesda, MD

Oct. 24, 2015 — "Excess Cancers among HIV-infected People in the United States"
Translating Cancer Epidemiology: From Cells to Clinic and Population
Huntsman Cancer Institute, Salt Lake City, UT

June 16, 2015 — "Age at Cancer Diagnosis for Blacks Compared with Whites in the United States"
Society for Epidemiologic Research 2015 Annual Meeting, Denver, CO

Aug. 24, 2014 — "Immunogenicity Assessment of HPV16/18 Vaccine using the Glutathione S-Transferase Multiplex Serology Assay"
HPV 2014: 29th International Papillomavirus Conference, Seattle, WA

May 1, 2014 — "Immunogenicity Assessment of HPV16/18 Vaccine using the Glutathione S-Transferase Multiplex Serology Assay"
Post-Baccalaureate Poster Day, NIH, Bethesda, MD

Mar. 5, 2014 — "Excess Burden of Cancer Among HIV-Infected Persons in the United States"
Conference on Retroviruses and Opportunistic Infections (CROI), Boston, MA

June 18, 2013 — "Epidemiologic Contributions to Changing Cancer Incidence in the U.S. HIV Population, 1996-2008"
Society for Epidemiologic Research Annual Meeting, Boston, MA

May 1, 2013 — "Utility of Glutathione S-Transferase Multiplex Serology as a Measure of Exposure and Immunity to Human Papillomavirus among Unvaccinated Women"
Post-Baccalaureate Poster Day, NIH, Bethesda, MD

Mar. 15, 2013 — "Correlates of Intimate Partner Violence during Pregnancy: A Multilevel Analysis of the Los Angeles Mommy and Baby Project"
Consortium of Universities for Global Health Annual Meeting, Washington, DC

Manuscript Review

AIDS (2014, 2017, 2018)
AIDS Research and Human Retroviruses (2016)
Annals of the American Thoracic Society (2017)
British Journal of Dermatology (2017)
Cancer Epidemiology (2015)
Cancer Epidemiology, Biomarkers & Prevention (2015, 2018)
Cancer Medicine (2017)
Clinical and Vaccine Immunology (2015)
Epidemiology and Infection (2016)
Human Vaccines & Immunotherapeutics (2014, 2015)
JAIDS (2016, 2017)
Journal of Clinical Microbiology (2016)
Journal of Infection (2014)
Journal of Infectious Diseases (2016)
PLoS One (2015)
Preventive Medicine (2017)
Public Health Reports (2016)
Sexually Transmitted Infections (2014)
Vaccine (2016)

Professional Memberships

2015 – present	American Association for Cancer Research (AACR)
2014 – present	International Papillomavirus Society (IPVS)
2012 – present	Society for Epidemiologic Research (SER)
2015 – 2017	American Statistical Association (ASA)
2016 – 2017	American Thoracic Society (ATS)
2012 – 2013	American Public Health Association (APHA)

Professional Skills

Software: R, Stata, SAS, SEER*Stat; Joinpoint, Endnote, Reference Manager, Mendeley, ArcGIS (basic), RedCap (basic), Microsoft Word, Excel, PowerPoint, and Outlook
Languages: English (native), Spanish (full professional proficiency)