Efficacy of Cervical Cancer Screening to Prevent Cervical Cancer Mortality Among Women Ages 55 to 79 Years: A Population-Based, Case-Control Study

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Abstract

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Aim. Though cervical cytology screening has been shown to reduce cervical cancer incidence and mortality among reproductive-age women, there are but limited data regarding the efficacy of screening older women. Analyses from Sweden and Finland suggest that participation by older women in organized cytology screening programs reduces the incidence of cervical cancer by 51-64%. In the United States, results from Kamineni and colleagues suggest that cytology screening reduces cervical cancer incidence by 77% among women ages 55-79 years. We sought to quantify the efficacy of cervical cancer screening among older American women with respect to mortality.

Methods. Among enrollees of two U.S. health plans, we compared cervical screening histories of women ages 55-79 who died of cervical cancer during 1980-2010 (cases) to those of women who were at risk of developing this malignancy (controls). Controls were sampled from women with an intact cervix, matched 2:1 to cases on health plan, age, and enrollment duration. Medical records were reviewed to ascertain each woman's receipt of cytology screening during the detectable pre-clinical phase (DPP), estimated to be the 5 to 7 years prior to diagnosis during which cervical neoplasia is asymptomatic but cytologically detectable. Logistic regression models were used to estimate the risk of cervical cancer mortality associated with screening.

Results. 39 cases and 80 controls were eligible for the study. Screening during the presumed DPP was associated with a 74% (95% CI: 37-90%) reduction in cervical cancer mortality, adjusting for matching characteristics and covariates that were associated with case status (smoking, marital status, race/ethnicity).

Significance. Screening of older women by means of cervical cytology was strongly associated with reduced cervical cancer mortality. These results provide a minimum efficacy estimate of human papillomavirus DNA screening – a more sensitive test that may be increasingly utilized in the future — to reduce mortality among older women.

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INTRODUCTION

Cervical cancer screening by means of cytology, or the Papanicolaou (Pap) smear, seeks to detect pre-cancerous or frankly invasive cancerous cervical lesions prior to the onset of symptoms. Ideally, such detection leads to removal of cervical intraepithelial neoplasia (CIN) prior to its malignant transformation, or treatment of cancer earlier than would otherwise have occurred in the absence of screening. Cervical cytology screening has been consistently observed to have high efficacy with respect to invasive cervical cancer (ICC) incidence and mortality among women of reproductive age.[1-3] Though over three million Pap smears are performed annually in the United States among women older than 65 years,[4] data regarding the utility of screening such women for cervical cancer are limited. Analyses of the national organized cervical cancer screening programs in Sweden and Finland suggest that participation in such programs is associated with reductions cervical cancer incidence by 51-64% among older women.[5,6] In the United States, data from Kamineni and colleagues suggest that cervical cancer screening among women 55 to 79 years of age is associated with a 77-79% reduction in cervical cancer incidence.[7]

Whether cytological screening reduces ICC mortality to a similar degree as its apparent reduction of ICC incidence has not been well evaluated in older women. Screening may preferentially detect slow-growing lesions and/or those lesions that are more responsive to treatment, in which case screening would not be as efficacious in reducing ICC mortality as its apparent reduction of incidence.[8] However, two recent analyses from national screening programs suggest that organized cytology screening is in fact associated with a substantial mortality benefit for older women. A case-only analysis of data from Sweden's cervical cancer

screening registry found that women ≥66 years at cervical cancer diagnosis experienced a 36% increase in long-term survival if their cancers were detected by organized screening tests rather than clinically.[9] A Finnish analysis of fatal cervical cancer cases and controls observed receipt of a negative Pap smear predicted a reduction in cervical cancer mortality among women ages 55-69 years.[10] However, limitations of the information available from these national registries – such as lack of data on the presence of signs and/or symptoms at the time of a Pap smear, potential confounders, hysterectomy status, and the receipt of "opportunistic" smears – restrict the conclusions that can be derived from these results.

Among women enrolled in one of two integrated healthcare delivery systems in the United States, we compared receipt of screening between women ages 55 to 79 years who died of ICC and demographically-similar women at risk of cervical cancer, to quantify the efficacy of cervical cancer screening to reduce mortality from cervical cancer among older American women.

BACKGROUND

Cervical cancer screening by means of cytology aims to identify either (1) cervical intraepithelial neoplasia (CIN), which may then be removed prior to its progression to invasive carcinoma, or (2) frankly invasive cervical cancer (ICC) that has not yet become symptomatic. Consequently, cervical cancer screening has the potential to reduce both the incidence of and mortality due to ICC. Though no randomized trials of cervical cancer screening have been conducted, observational evidence has consistently suggested that cervical cytology screening is highly efficacious at reducing the incidence of and mortality from cervical cancer among women of reproductive age.[1-3,11-14]

I. Natural History of Cervical Cancer

Viruses of the human papillomavirus (HPV) family appear to be a necessary, but not sufficient, cause of invasive cervical cancer.[15] Of the approximately 100 types of HPV, 12 to 14 types are oncogenic ("high risk"), and of those, two types, HPV-16 and HPV-18, account for approximately 70% of all cervical cancers worldwide.[16] Infection with high-risk HPV confers a 189-fold increased risk of squamous cell carcinoma (SCC) and a 110-fold increased risk for adenocarcinoma, compared to women without detectable HPV.[17] However, many women clear HPV within months of infection; the median time to clearance is 8 to 14 months for high risk HPV types, and 5 to 6 months for low risk types.[18] Other risk factors, such as cell-mediated immune function, are believed to be cofactors in the development of cervical cancer subsequent to HPV infection.[19] A small proportion (~5%) of oncogenic HPV infections do not clear within three years of initial infection, but instead become persistent and can induce the cervical

epithelium to become neoplastic.[20] CIN develops slowly: approximately 10 years elapse between persistent infection and detection of CIN grade 3 (CIN3), which may then regress, be removed if detected via screening, or progress to become invasive.[21] Approximately half of untreated CIN3 lesions progress to ICC within 30 years.[22] Thus, several decades can elapse between initial HPV infection and symptomatic cervical cancer, during which screening may offer some benefit in terms of incidence or mortality.

II. Current Cervical Cancer Screening Guidelines

There is consensus that older women who have been inadequately or never screened should receive screening after the age of 65.[23-25] Disagreement exists regarding whether to continue to screen "adequately-screened" women older than 65 years of age. Current recommendations by the American Cancer Society (ACS), the U.S. Preventive Services Task Force (USPSTF), and the American Congress of Obstetrics and Gynecology (ACOG) do not promote the use of Pap tests among otherwise low-risk women above 65 years of age with three consecutive, adequate, negative cytology results or two consecutive negative co-tests (concurrent HPV and cytology testing) and no history of CIN grade 2 or worse (CIN2+) in the prior 20 years.[23-25] However, these groups acknowledge that these recommendations are based on weak evidence; the ACS rated the single study[26] it included as evidence for stopping screening as being of "moderate to low" quality,[23] though it did ignore several informative observational studies.[27] The ACOG based its recommendation to cease screening at age 65 on only three studies: a 2011 modeling study,[26,28] a 2001 case series,[28] and a 2000 follow-up of women with negative screening results.[29] The USPSTF, which conducted a comprehensive evidence review,

stated that the existing evidence provided only "moderate certainty that the benefits of screening do not outweigh the potential harms."[24]

III. Controversy of Whether to Screen Older Women

Several studies have proposed that older women who have previously been well-screened may be released from cytological screening, based on inferences that older women experience a low incidence rate of cervical cancer following regular screening. In an analysis of women diagnosed with CIN or ICC during 1989-1990 through the organized cervical cytology screening program in northeastern Scotland, Van Wijngaarden and Ducan reported that all cases (n=26) of ICC among women older than 50 years occurred in women who had never been screened or had been screened less frequently than every 3 years, whereas no cases occurred among women previously screened every 3 years.[30] Based on 229 ICC cases ≥50 years of age, and the number of women in each stratum of age and screening history, Cruickshank and colleagues estimated that the incidence rate of ICC among Scottish women ages 50 to 60 years with ≥3 consecutive negative cervical screens prior to age 50 was approximately one-fifth that of the entire population over the study's 5-year follow-up period (11 versus 59 per 100,000).[31] Similarly, Cecchini and colleagues reported the incidence rate of ICC among 11,342 screen-negative Italian women over the age of 60 who were adequately screened (defined as receiving ≥2 negative cytology results, one of which occurred between ages 58 and 60) was 7% of the expected rate based on age-specific incidence rates in the overall population over the study's 10 year follow up period.[32]

However, these data are insufficient to infer that women older than 50 years who were previously adequately screened with negative results will remain at low risk of cervical cancer for several reasons. First, Van Wijngaarden and Duncan's analysis did not provide denominator data for the total number of women in each category of screening history, and therefore differences in the numbers of cases by screening history may simply be proportional to underlying differences in the size of the populations at risk. Second, a low-incidence period following a negative screen may be a simple consequence of the removal of antecedent lesions and occult invasive cases of cervical cancer from the screen-negative cohort, and the fact that the cohort of women eligible to be screened must, by definition, be free of cervical cancer and its symptoms.[8,33] Due to this "healthy screenee" bias, these data alone are inadequate to evaluate the efficacy of cervical cancer screening to prevent cervical cancer incidence or mortality. Studies of cancer incidence or mortality in women who screened negative are useful in the design of screening recommendations (specifically regarding the frequency of screening), assuming *additional* evidence exists in support of the efficacy of a screening test to prevent undesirable outcomes such as incidence or mortality.[8] Finally, the follow-up periods of Cruickshank et al. and Cecchini et al. may have been too brief to capture the rise in ICC incidence several years after negative cytology tests, and therefore cannot support the inference that adequately-screened older women are at permanently low risk of ICC. A large, multi-country analysis of data from the late 1950s to the mid-1980s from women up to age ~64 years by the International Agency of Research on Cancer (IARC) found that ICC incidence is low for at most 7 years following two negative screening tests.[34] More recent studies that included older women observed that ICC incidence following a single negative screening result extends for no more than 6.5 years among women ages 55 to 69 years,[35] and no more than 5 to 7 years among women ages 55 to 79 years.[7]

Cruickshank et al. followed women for at most 5 years after cessation of regular screening. Cecchini et al. followed women up to 10 years, but the median follow-up period was 5.9 years, within the duration of the low risk interval. The length of the observation in these studies relative to the duration of low ICC risk would obscure the rise in incidence 5 to 7 years after negative cervical screening test(s).

To inform a decision that women should be released from cervical cancer screening above a certain age, it would be useful to compare the rate of cervical abnormalities following consecutive negative smears among older women to that among younger women. Rebolj and colleagues conducted such a study using the Dutch national registry of cytopathology and histopathology, and found no differences in the incidence of ICC following three consecutive negative cytology results between two groups: women ages 30 to 44 years and those ages 45 to 54 years at the time of the third negative smear.[36] The authors did observe a significantly higher rate of preinvasive lesions among younger women, emphasizing that detection rates of preinvasive lesions alone cannot be used to infer that cytological screening benefits younger women more than older women. Since women with consecutive negative screening results experience equally low incidence rates of cervical cancer at younger and older ages, any recommendation to cease screening women with a history of negative smears should not be selectively applied to women above a certain age (unless a woman's expected remaining years of life limits the possible benefits she could accrue by continued cervical cancer screening).[8]

Another argument, used by Gustafsson and colleagues to justify the cessation of screening at older ages, is the decline in the percentage of abnormal Pap smears as women age. Among women older than 50 years, the percentage of abnormal Pap smears was one-fifth of that

among women ages 30 to 34 years.[37] First, while such data are useful in calculating the predictive value of a positive result, they provide no information on the efficacy of earlier treatment enabled by screening or the accuracy of the test.[8] Second, because there is evidence that the likelihood that a given cytological abnormality will become malignant is higher among older women,[22,36,38,39] the lower percentage of positive smears cannot be used as a direct surrogate for the relative number of invasive cancers potentially averted by screening. Finally, more recent data indicate that the absolute rate of dysplasia among older women is not negligible even within the low-incidence period following a negative cytological test. An analysis of data from 1991-1999 from 128,805 women in the National Breast and Cervical Cancer Early Detection Program (NBCCEDP), which provides breast and cervical cancer screening to low-income women in the United States, found that within three years of a negative smear, the incidence of high-grade cytological changes (high-grade squamous intraepithelial lesion (HSIL) or suggestive of squamous cell cancer) was 150 per 100,000 and 103 per 100,000 among women ages 50 to 64 years and ≥65 years, respectively.[40] Among 36,512 Scottish women with two or more negative cytology results (of which one occurred within the five years prior to age 50) and at least one cytological screening test after age 50, 1.8% were found to have dyskaryosis (i.e., abnormal cytology) after age 50.[41] This percentage is likely an under-estimate, because women without detected dyskaryosis had a significantly shorter follow-up period (median 33.2 months) than those with detected dyskaryosis (median 62 months). Had the follow-up period been longer for women who were apparently dyskaryosis-free, a higher percentage would likely have been found to subsequently develop cervical abnormalities.

An international analysis of cervical cancer trends before[42] and after[1] the introduction of organized cervical cancer screening programs conducted by Gustafsson and colleagues observed the relative reduction in age-specific ICC incidence rates was attenuated among older women compared to that among women younger than 55 years. However, because these inferences were based on ecologic data, any differences in efficacy may reflect age-correlated differences in population coverage and/or implementation. The authors postulated that the age-related decline in relative efficacy was due to a decline in test sensitivity and/or "that women without preinvasive lesions at *e.g.* age 50 will remain at low risk for the rest of their lives."[1] While the sensitivity of Pap smear testing is lower among women ages 30 to 50 years compared to those younger than 30 years[43] the IARC meta-analysis from 8 countries indicated that the sensitivity of the Pap smear does not decrease appreciably after age 50.[34] Furthermore, as stated above, subsequent research indicates that screen-negative older women are at low risk of ICC for no more than 7 years.[7,34,35] Finally, all results from the international analyses by Gustafsson and colleagues are presented in relative terms; the increase in absolute ICC incidence rates at older ages[44] could account for the smaller *relative* reduction in ICC incidence among older women, if the absolute reduction did not vary by age. Together, these results suggest that older women may benefit from continued screening regardless of prior screening history.

IV. Rationale for the Present Study

Given that the period of low ICC incidence after one or two negative cytological screening tests does not extend indefinitely, but returns to that of unscreened women after 5 to 7 years,[7,34,35] its duration does not vary with age,[36] and the incidence of cervical lesions even during this period is not trivial,[40,41] it is reasonable to investigate whether cervical cancer

screening can reduce cervical cancer incidence and mortality among older women. There is strong evidence in support of the former; whether cervical cancer screening can prevent cervical cancer mortality among older women is less clear.

A handful of studies have evaluated cervical cancer screening efficacy among older women with respect to incidence, with consistent results. At a population level, Sasieni and colleagues noted that the United States is currently the only country to regularly screen women over 70 years (despite lack of support for this practice in clinical guidelines), and is also the only country in which ICC incidence has declined between 50 to 59 years and 70 to 79 years of age.[45] Sasieni and colleagues also conducted an analysis of data from the United Kingdom's screening program and found cytological screening had a similar efficacy among women ages 55 to 69 as those ages 40 to 54.[35] An audit of Sweden's organized cervical cancer screening program found that, among 390 ICC cases and 1,940 age-matched controls who were ≥66 years old at the time of diagnosis, participation in organized cytology screening was associated with a 64% reduction (OR=0.36, 95% confidence interval (CI): 0.24-0.53) in ICC incidence.[5] A case-control study from Finland that included 79 cases and 478 controls who were 60-64 years of age, and 17 cases and 87 controls who were 65-69 years of age, found that participation in organized cytology screening was associated with an estimated 51% reduction in ICC incidence in each of these age groups (60-64 year old women: OR=0.49, 95% CI: 0.28-0.84; 65-69 year old women: OR=0.49, 95% CI: 0.10-2.41).[6] Neither of these registry-based incidence studies[5,6] had information regarding the presence of signs and/or symptoms at the time of a Pap smear; in the absence of such information, each author group excluded uniform periods of time prior to diagnosis in an attempt to exclude from the analysis exams that took place after a lesion became invasive (at

which point the cancer can no longer be averted). In a given instance, this approach may be less valid than one in which the occult invasive phase (OIP) is defined with consideration of the onset of signs/symptoms of cervical disease and varied in sensitivity analyses.[46] Further, data on hysterectomy status among controls are not available in registries, which may give a falsely low estimate of the percentage of screened women among those at risk of cervical cancer and therefore falsely minimize the efficacy of screening. Finally, in the Finnish study, no data were available on opportunistic screens (i.e., screening tests that occur outside the national organized screening program), which exceed those that occur within the organized national program by 1.5-fold.[47] Nonetheless, a medical record-based case-control study from the Pacific Northwest was able to ascertain these variables and drew similar conclusions. The results of that study, which was conducted at the same health plans as the present study during 1980 to 1999, suggests that screening women ages 55 to 79 years reduces the risk of invasive disease by 77% (OR=0.23, 95% CI: 0.11-0.44).[7]

Given these favorable results regarding cervical cancer incidence, the next question is whether cervical cancer screening is similarly efficacious with respect to reducing cervical cancer mortality in this older age group. If cytology were to preferentially detect slow-growing lesions and/or those that are responsive to cervical cancer treatment, then screening would be less efficacious in reducing cervical cancer mortality than incidence. Also, advances in the treatment of cervical cancer may render cervical cancer screening relatively less efficacious with respect to mortality. The efficacy of a screening test to prevent mortality from a disease is due in part to the relative benefit of effective treatment at early rather than later stages at diagnosis.[8] If improvements in the treatment of ICC were so successful as to equalize the survival of

individuals diagnosed at an early stage via screening and those diagnosed at a later stage due to signs/symptoms, then a previously efficacious screening test would offer less benefit. At all stages of diagnosis, the 5-year observed survival of patients diagnosed with ICC in the United States has improved between 1973 and 2006, based on data from the Surveillance, Epidemiology, and End Results (SEER) registries (Figure 1 and Table 1).[48] Five-year survival improved from 11.2% (95% CI: 8.9-13.7%) to 16.0% (95% CI: 14.4-17.7%) among women diagnosed with distant disease during 1973 to 1979 versus 2000 to 2006, and from 82.5% (95% CI: 81.4- 83.6%) to 88.4% (95% CI: 87.7-89.1%) among those diagnosed with local disease during the same time periods. This trend is consistent with the hypothesis that treatment for cervical cancer has truly become more efficacious over the last 40 years, though more accurate classification of women with truly advanced disease from local or regional stages may have occurred over time (Table 2) and could contribute to such a trend.[49] In the case of cervical cancer, however, survival of early stage ICC remains far superior to that of late stage disease. If cervical cancer screening does offer a mortality benefit, it is unlikely to have been substantially attenuated by improved treatment efficacy.

Ecologic data from the Nordic countries suggest that cervical cancer screening of older women is indeed associated with lower cervical cancer mortality: cervical cancer mortality fell by 40 to 66% in women 50 to 59 years of age in Iceland, Finland and Sweden, during the first 15 years after the introduction of organized cervical cancer screening programs in those countries. In contrast, 50 to 59 year-old women in Norway, which lacked an organized cervical cancer screening program until the early 1980s, experienced only a 2% decline in cervical cancer mortality from the mid-1960s through the early 1980s. Rates fell by 66% among women ages 60

to 69 years in Iceland, the only country to screen women in this age group. However, mortality rates among 60 to 69 year old women also fell by 32% in Finland, complicating the interpretation of these data.[3] Similarly, a report from northeastern Scotland, a region in which women ages 25 to 60 years old have been invited for screening every five years since 1960,[30] found that women ages 45 to 64 years old were most likely to have been screened and rescreened, and experienced a greater decrease in cervical cancer mortality from 1974 to 1991 than younger or older women.[50]

More recently, two analytic studies from national screening registries in Scandinavia suggest that cervical cancer screening is efficacious among older women with respect to ICC mortality. In the first, from Sweden, Andrae and colleagues compared the "cure proportions" of women with screen- versus symptomatically-detected ICC.[9] The cure proportion is the relative survival at the point in time after which diseased persons no longer experience excess mortality compared to non-diseased persons of the same age and gender; a plot of relative survival will plateau at the cure proportion. In the absence of over-detection (or "pseudo-disease"), it is likely a valid measure of efficacy. Andrae et al. observed that, among women ages ≥66 years at diagnosis, those with screen-detected ICC experienced an absolute 36% (95% CI: 11-80%) increase in cure proportion over that of women with clinically-detected ICC. Importantly, there was no appreciable difference in this percentage between women with guideline-adherent or non-adherent screening histories, implying that even guideline-adherent women (defined as having received a Pap smear in the previous 3.5 years for women under age 54, or within the previous 5.5 years for women age 54 or older) would benefit from continued screening above age 65 years. In the second study, Lönnberg et al. compared past participation in Finland's organized screening program of 506 women who died of cervical cancer during 2000-2009 and 3,036 age-

matched controls, including 75 cases and 465 controls who were 55 to 69 years at the time of their (or their matched case's) diagnosis.[10] They observed a 71% (95% CI: 46-84%) reduction in ICC mortality associated with participation in the national organized cervical cancer screening program among 55 to 69 year-old women.

While their results are informative, these two studies are not without potential limitations. First, neither study could assess the presence of signs and/or symptoms of cervical cancer at the time of each Pap smear, as these data are not recorded in Sweden's or Finland's national screening registries.[5,10] Ideally, one would exclude all cytology tests performed in the presence of signs or symptoms of cervical cancer, as such tests are diagnostic in nature.[51] To compensate, each group of the investigators used the timing of the test in relation to diagnosis in an attempt to exclude diagnostic tests. In Andrae et al., smears within <1 month of diagnosis date were considered diagnostic, whereas those within 1-6 months were screens. In Lönnberg et al., the authors elected to exclude all Pap smears that led to the diagnosis of cancer (defined as a positive test within 12 months of diagnosis), though ideally all such tests should be included if they were truly screening in nature.[51] The exposure window was then defined as either (a) within 66 months of ICC diagnosis (if the case was not screen-detected) or (b) within 12-78 months of diagnosis (if the case was "screen-detected," meaning the Pap smear within 0-12 months of diagnosis was positive). Each of these approaches likely introduced some misclassification of screening status. In the case-only analysis, this may have attenuated the measured cure proportion (assuming the misclassification was non-differential with respect to survival). In the case-control analysis, this likely excluded a large proportion of the screening Pap smears among cases, most of whom are screened relatively close to diagnosis (Figure 2).[51] As a result, the calculated screening prevalence among cases would be spuriously low, and the OR would be

further from 1 (i.e., the calculated efficacy may be exaggerated). Second, as in their incidence analysis, Lönnberg et al. were unable to exclude controls with a history of hysterectomy. The percentage of controls who participated in organized screening would be falsely low compared to the true percentage among eligible controls, and thus the efficacy associated with screening would be minimized. Third, no data on potential confounders were available, such as smoking, which is strongly related to both screening status[52] and to cervical cancer risk.[53] Finally, no data were available on opportunistic screening in the Finnish case-control analysis[10] though such screening is widespread; indeed, an estimated 60% of Pap smears in Finland occur outside the national organized screening program.[47] Opportunistic screening does decline with age, from 40% in the youngest women to 10% among the oldest,[47] so this potential source of bias may impact the estimated efficacy of cytology at older ages more weakly than that at younger ages.

These results suggest that cytological screening of older women may be efficacious in preventing cervical cancer mortality among older women, though further research – ideally incorporating reliable information on hysterectomy status and signs and symptoms at the time of the cytology test, and including all screening cytology tests administered to a given woman during that period of time corresponding to the preclinical duration of cervical cancer – is warranted.

METHODS

I. Study Design

In our population-based case-control study, we compared the cervical cytology screening histories of women who died of cervical cancer (cases) to that of a sample of women at risk of cervical cancer who were otherwise similar to the cases (controls) from two health plans in the Pacific Northwest. Receipt of cervical cancer screening during the presumed detectable pre-clinical phase (DPP) of cervical cancer development was the primary exposure (bolded along the x-axis in Figure 2). For cervical cytology screening, the DPP begins when a pre-malignant cervical lesion is detectable by cytology, and ends with the onset of clinical signs or symptoms due to cervical cancer that has invaded the basement membrane. This is the appropriate window during which to ascertain screening history, because a deficit of screening among cases relative to controls should be observable during this period if the test is beneficial.[51,54] Inclusion of the periods prior to, or after, the DPP in the analysis attenuates the estimate of benefit.[51,55]

The DPP was defined in a standardized way. First, the date of onset of clinical signs or symptoms that led to the diagnosis of cervical cancer, the index date, was determined for cases by standardized medical record review. Signs or symptoms of cervical cancer in the 12 months prior to the cervical cancer diagnosis were defined as post-menopausal bleeding, post-coital bleeding, vaginal bleeding, non-specific bleeding, abdominal pain, vaginal discharge, weight loss, obstructive uropathy, or ascites. If a case was screen-detected, then the date of screening was the index date. The index date for each control matched that of her respective case. Second, whether a subject was screened for cervical cancer in the 7 years prior to the index date was ascertained from the medical record. Only screening tests that occurred within 7 years prior to

the index date were included in the analysis, as the incidence of ICC among cytologically-negative women ages 55 to 79 years returns to that of unscreened women 5 to 7 years after a negative test. Numerous studies[7,34,45] have corroborated this 7-year estimate of the DPP for cervical cancer, though some studies have estimated that cervical cancer is detectable for up to 30 years.[22] If the true DPP did in fact start more than 7 years prior to the index date, then the under-counting of screening Pap smears would be relatively greater among controls; controls' screening prevalence is expected to have been relatively uniform during the duration of the case's DPP, whereas any screens that took place among cases would likely have been close to the end of the DPP (Figure 2). Thus, the calculated OR would underestimate the beneficial effect of screening.[51,55]

II. Study Setting

Study subjects were identified from enrollees of two integrated health plans: Group Health (GH), based in Seattle, Washington; and Kaiser Permanente Northwest (KPNW), based in Portland, Oregon. At present, GH and KPNW respectively cover 478,000 members and 600,000 members, or nearly 1.1 million individuals in total.

The screening policies at these health plans have recently incorporated HPV DNA testing. Equivocal cytology results have been triaged with "reflex" HPV DNA testing at GH since 2005, and at KPNW from 2008 to mid-2010. (In mid-2010, after the study period ended, KPNW began screening with both cytology and HPV DNA concurrently ("co-testing").) The result of the HPV DNA assay did not influence whether cytology was performed during any portion of the study period. Because cytology continued to be applied independently of HPV DNA testing, the use of HPV DNA to triage uncertain cytology results does not undermine the

ability of the proposed study to ascertain the beneficial effect of cytological cervical cancer screening. Only if HPV DNA assays were used as the sole or primary screening test – which has not been implemented at either study site, and indeed, is not recommended by any clinical guidelines group – would isolation of the effect of cytology screening during the DPP be compromised.

III. Study Subjects

Cases were women who died of cervical cancer and/or its treatment during the years 1980 to 2010 at ages 55 to 79 years. Cases were ascertained from the Cancer Surveillance System (CSS) for GH enrollees (part of the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program), and from the Kaiser Tumor Registry for KPNW enrollees. Cases who possibly died due to treatment of cervical cancer were identified as follows. Women who died from one of a small number of pre-determined causes of death (including sepsis, renal failure, bowel obstruction or perforation, hemorrhage, necrotizing fasciitis, pulmonary infection, and venous thromboembolism) within 5 years of an ICC diagnosis were enumerated. The medical records of these potential cases (n=3) were reviewed with a clinician (without knowledge of screening history) to adjudicate whether cervical cancer treatment led to the fatality, but in none of these potential cases was cervical cancer treatment determined to have been responsible.

Controls were a sample of all women ages 55 to 79 years enrolled in GH or KPNW at any point during the years 1980 to 2010. To be a match, a control must have been enrolled in the health plan at the time of her case's tumor registry diagnosis date (reference date). Matching was based on health plan, age (within 6 months), and duration of enrollment in the health plan prior

to the reference date (equal to or greater than that of the case, by no more than 6 months). For both cases and their matched controls, eligibility was restricted to women with at least 6 years of enrollment prior to the reference date, with no gaps in enrollment longer than 6 months. For GH controls, eligibility was restricted to women residing in the 13 counties in western Washington surveyed by CSS. The eligible controls were ordered in terms of how well they matched the case, measured as the sum of two numbers: the number of days between (1) the case's and potential control's birth dates and (2) the case's and potential control's health plan enrollment dates. The two potential controls with the lowest sums of these two numbers were selected for medical record review. Upon review, any potential control who had a hysterectomy prior to the reference date, or whose medical record documented that she received care outside the health plan, was excluded and replaced with the next best-matched control, until 2 eligible controls with an intact cervix were identified per case.

IV. Data Collection

The data collection relied on methods previously validated by Kamineni and colleagues.[7] Cervical cancer screening history was recorded from medical records using a standardized medical record abstraction database developed with ACCESS software. The reason(s) for the test, whether diagnostic or screening in nature, were ascertained for each Pap smear; only screening tests were included (i.e., those performed in the absence of ICC signs or symptoms). No distinction was made between conventional cytology (i.e., Pap smears) and liquid-based cytology, because these two methods of cytology slide preparation differ only in terms of slide adequacy, not test accuracy.[56,57] Data on covariates to be considered in the analysis were also obtained from the medical record, including marital status, body mass index (BMI), smoking

history, race/ethnicity, parity, menopausal status, oral contraceptive use, and immunosuppressive status. Data were not available on sexual history or human papillomavirus (HPV) infection, the primary etiologic agent of cervical cancer.[15] Smoking is the most plausible confounder, as it is a strong ICC risk factor[53] and is negatively associated with cytology screening in 50-74 year-old women in the Pacific Northwest.[52] Smoking status was ascertained for all subjects. Finally, the medical records of a random 10% sample of all subjects were re-abstracted and any discrepancies between initial and subsequent re-abstraction were analyzed using κ or weighted κ, as appropriate.[58]

The institutional review boards at GH and KPNW each approved the study protocol.

V. Analysis

Multivariate logistic regression was used to quantify the odds ratio (OR) of cervical cancer mortality associated with receipt of screening during the DPP, adjusting for matching variables and covariates that were associated ($p<0.10$) with case status. Unconditional logistic regression was used because matching variables were easily quantified and because conditional logistic regression would decrease study efficiency.[59,60] Since the observed effect of screening may differ with the estimated DPP length,[51] sensitivity analyses were performed by varying the start of the DPP in 6-month intervals, from 5 to 7 years prior to the index date. Three exploratory analyses were planned: 1) stratification by age at the index date, <65 or ≥65 years old, the age at which the USPSTF, ACOG, and the ACS recommend screening cessation for most women,[23-25] 2) restriction to cases with squamous cell carcinoma (SCC), as cytology screening may be more efficacious against SCC than adenocarcinoma of the uterine cervix,[61] and 3) stratification by year of diagnosis (1999 or earlier vs. 2000 or later), since the addition of chemotherapy to radiation

therapy-based treatment occurred in 1999, which was a major advance in cervical cancer treatment.[62]

The primary data analysis software was STATA (version 12.0, College Station, Texas).

RESULTS

Forty cases and 80 controls were identified as eligible for inclusion in the study. After medical record abstraction, 1 case with less than 6 years of pre-diagnosis enrollment was excluded, leaving 39 eligible cases and 80 eligible controls in the study. Prior to abstraction, 4 cases were excluded because no medical records were available, and 3 were excluded because they had likely received outside care (Table 3). Among controls with sufficient enrollment, the most common reason for exclusion prior to abstraction was evidence of hysterectomy before the reference date (n=69), followed by lack of availability of medical records (n=18), and documentation of care outside the medical plan (n=16).

There were no appreciable differences between cases and controls in most measured demographic characteristics (Table 4). A majority (61%) of study subjects were younger than age 65 years at diagnosis; half (49%) of cases were younger than 65 years at death. Cases were more likely to be current smokers at the time of ICC diagnosis (31%) than controls (14%), and had higher BMIs than controls (32% vs. 15% with BMI $\geq$ 35 kg/m^2). The overwhelming majority of both cases (95%) and controls (97%) were white. Controls were more likely than cases to have been married at the reference date (68% vs. 56%). Fewer cases (5%) than controls (11%) were nulliparous, and cases were more likely than controls have had 3 or more births (72% vs. 50%).

Among cases, the most common cervical tumor pathology was squamous cell carcinoma (51%), followed by adenocarcinoma (31%), undifferentiated carcinoma (10%), and adenosquamous carcinoma (3%). Tumor pathology was unknown for 5% of cases (Table 5).

Screening histories differed substantially between cases and controls. In the 7 years prior to the index date, cervical cytology screening was documented for 51% of cases and 81% of controls. The univariate OR associated with one or more screens was 0.24 (95% CI: 0.10 – 0.56) (Table 6). After adjustment for variables that were associated ($p<0.10$) with case status (smoking status, marital status, and race/ethnicity), screening was associated with a 74% reduction in cervical cancer mortality (OR=0.26, 95% CI: 0.10 – 0.63). Inclusion of all measured covariates did not alter the magnitude of the association (OR=0.26, 95% CI: 0.09 – 0.77).

Exclusion of the 10 subjects with fewer than 7 years of enrollment prior to reference date did not affect the magnitude of the calculated OR (adjusted OR=0.26, 95% CI: 0.10 – 0.67). Similarly, use of conditional logistic regression did not alter the OR substantially (adjusted OR=0.25, 95% CI: 0.09-0.68). In sensitivity analyses, the length of the DPP was varied from 5 to 6.5 years prior to the index date (Table 7). As the DPP shortened, the magnitude of the risk estimate was not appreciably affected. The adjusted associations ranged from OR=0.20 (95% CI: 0.08 – 0.50) with a DPP length of 5.5 years to OR=0.30 (95% CI: 0.12 – 0.72) with a DPP length of 6.5 years.

Three pre-planned exploratory analyses were conducted. To explore whether age modified the association between cervical cancer screening and cervical cancer mortality, subjects were stratified by age at reference date. The associations did differ somewhat by age (<65 years vs. ≥65 years at reference date; Table 8), but a sharply reduced risk associated with screening was present in both groups. Second, to investigate the impact of improved cervical cancer treatment on the relative mortality benefit afforded by cervical cancer screening, subjects were stratified by year of diagnosis, 1999 or earlier vs. 2000 or later. The size of the reduced risk of cervical cancer mortality associated with screening was similar during the two intervals (Table

9). Finally, restriction to cases with SCC tumor pathology (n=20) yielded a lower adjusted OR (OR=0.13, 95% CI: 0.03 – 0.54) (Table 10). For each of these three exploratory analyses, the precision of the estimates was necessarily limited by the small numbers of women in each sub-group.

Analysis of subjects whose medical records were abstracted twice revealed high degrees of intra-abstractor reliability. No discrepancies between first and second abstraction occurred for index date, exposure status, tumor pathology type (for cases only), or marital status. Measures of intra-rater reliability (κ or weighted κ, as appropriate for nominal or ordinal variables, respectively[58]) are shown in Table 11; they range from 0.778 for race/ethnicity to 0.949 for BMI.

DISCUSSION

This study observed that cervical cancer screening by means of cytology during the DPP, estimated as the 7 years prior to symptom onset or screen-detected diagnosis, was associated with a 74% reduction in cervical cancer mortality among women aged 55 to 79 years. This is nearly identical to Kamineni et al's estimate of efficacy with respect to incidence (77%) from the same two health plans and during a similar time period (1980-1999).[7] This suggests that cervical cytology screening does not preferentially detect slow-growing lesions and/or those that are more likely to respond to treatment.

This study was designed to answer a direct and interpretable question of public health significance. Outcome and exposure data were drawn from valid sources: established tumor registries and medical record review, respectively. Previous research has repeatedly documented that the medical record is a more accurate source of Pap smear screening history than self-report.[63-66] Unlike previous studies addressing this research question,[9,10] hysterectomy status and the presence of signs and/or symptoms of cervical cancer at the time of each cytology test were ascertained, and women who had any evidence of care outside of the health plan were excluded in an attempt to ensure that complete exposure information could be ascertained. Medical record review in this study was highly reliable. The results were robust to analyses in which subjects with fewer than 7 years of enrollment prior to the reference date were excluded, and to sensitivity analyses in which the length of the DPP was varied. Further, the observed efficacy of 74% may actually be an under-estimate if the true duration of the DPP is longer than 7 years.[51,55]

Given the small number of total cases in the main analysis, the precision of the three prespecified exploratory analyses was limited and the results of these analyses must be interpreted cautiously. First, although the efficacy among women older than 65 years was less than that among women younger than 65 years, the breadth of the confidence intervals of these estimates precludes any strong inferences about the differential efficacy of cytology screening by age. Indeed, other cervical screening studies that have included a broad age range of women have observed a slightly higher efficacy among older women than younger women,[2,5,7] though the differences in risk estimates by age were not of large magnitude (nor statistically significant) and these studies examined the outcome of incidence rather than mortality. Andrae et al., who did examine the outcome of mortality, observed a substantially increased cure proportion associated with screen detection among women older than 66 years than for those 23 to 65 years of age.[9] Second, the similarity of the ORs in the two time intervals, 1999 or earlier vs. 2000 or later, does not support the inference that dramatic improvements in cervical cancer treatment – primarily, the addition of chemotherapy to radiation-based treatment regimens – have rendered screening relatively less efficacious with respect to mortality. Third, the somewhat higher efficacy observed for squamous cell carcinoma (SCC) cases corroborates the conclusions of other studies[10,17,61] that cytology screening is likely to be more efficacious against SCC tumors than against adenocarcinomas.

No data were available on sexual history or the presence of HPV infection. However, ascertainment of neither sexual history nor HPV infection is performed routinely for post-menopausal women and therefore is unlikely to influence a clinician's decision to screen for cervical cancer. During the study period, clinical screening guidelines at GH and KPNW ignored HPV status. Age at sexual debut was considered, but it influenced only the age at screening

initiation, not cessation (Erin Masterson and Aruna Kamineni, personal communications). Furthermore, age at first sexual intercourse, total number of sexual partners, and HPV-16 status are not associated with receipt of cervical cancer screening among 50 to 74 year-old women in the Pacific Northwest.[52] For these reasons, lack of ascertainment and adjustment for sexual history and HPV status is not likely to substantially confound the measured OR. Finally, this study could not address the impact of recent screening as a function of the adequacy of screening earlier in life, because data on screening prior to health plan enrollment were not available. However, previous research indicates that older women with negative screening tests experience a low incidence of cervical cancer for no more than 7 years following one or two negative tests.[7,34,35] Further, the benefits from screening with respect to cure proportion did not differ with prior screening history among women older than 66 years of age at diagnosis.[9] Thus, it is reasonable to infer that the results of the present study are applicable to older women regardless of prior screening history.

While randomization would be ideal to evaluate the efficacy of a screening test, a randomized trial is not feasible to address cervical cancer screening efficacy due to the rarity of cervical cancer, the lengthy duration of follow-up necessary to observe the effects of screening, the widespread use of cervical cancer screening among the general population, and the lack of ethical justification to randomize women to not receive screening by an efficacious test – not to mention the cost and logistical complexity of such a study.[8] When screening status and potential confounders can be accurately ascertained, the case-control study design is a valid and efficient means of gauging screening efficacy.[67]

Irrespective of the study's strengths and the robustness of its results, some may consider its research question obsolete. Cytological screening may become less utilized in the future in

favor of HPV-based screening[68] due to its superiority over cytology in the two characteristics[8] that influence test efficacy: HPV DNA testing can detect risk of ICC for a longer period than cytology,[69,70] and its sensitivity is an absolute 40% higher than that of cytology.[71,72] Indeed, these two characteristics are intertwined due to the clinical practice algorithms that currently govern the use of HPV DNA testing. If followed, such algorithms recommend that HPV DNA tests be administered concurrently with a Pap smear only among women older than 30 years of age. A positive HPV DNA result combined with negative cytology results in a more frequent screening schedule (i.e., rescreen with both HPV DNA and cytology tests in 12 months)[73] than if a woman had received a negative screening cytology result alone (i.e., rescreen with cytology in 2-3 years).[23,24,74] Thus, utilization of HPV DNA testing as currently recommended is likely to result in increased probability of diagnosis and/or earlier diagnosis of cervical cancer.

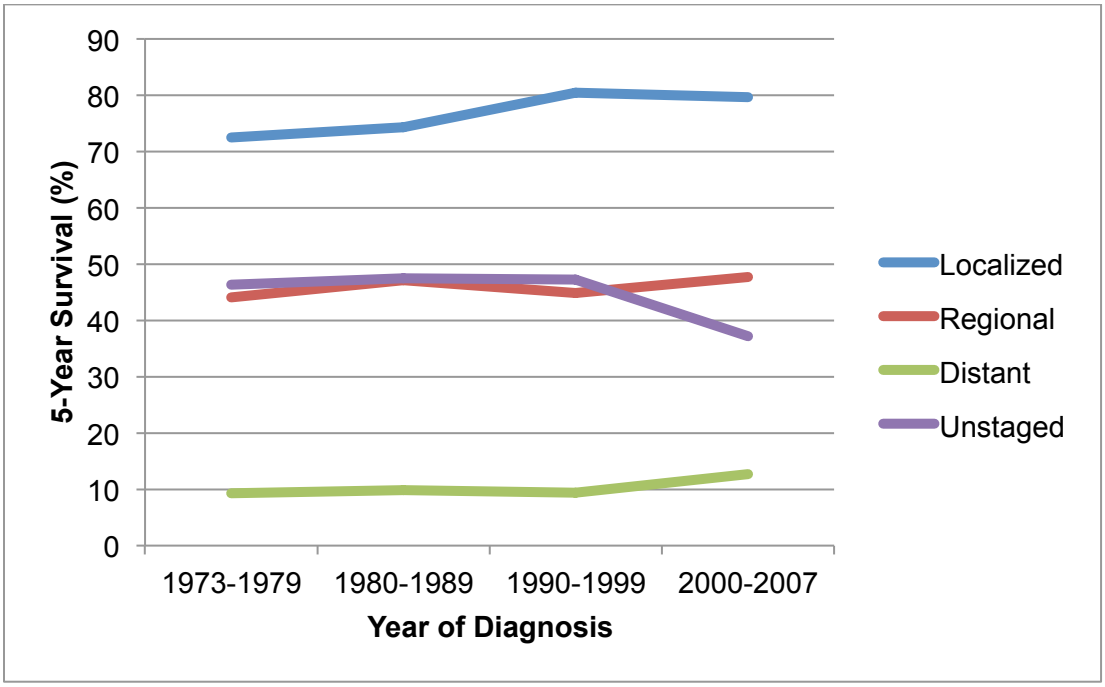
However, screening by cytology alone still remains an acceptable option under all current clinical guidelines, and Pap smears continue to be widely used in clinical practice as a method of choice to screen for cervical cancer.[23,24,74] Because the relationship between these screening modalities' efficacies is knowable –the efficacy of HPV-based screening will exceed that of cytology, all things equal – analysis of extant data on cytology screening offers a minimum estimate of HPV-based screening efficacy among older women. In effect, the present study provides insight into *whether* to screen older women, not the best modality to do so. A study to evaluate the efficacy of HPV DNA testing among older women will not be possible until several years after the introduction of an HPV DNA-based screening program when a sufficient number of deaths have occurred to make meaningful comparisons based on prior HPV DNA screening history. The results of the present study regarding the efficacy of cytology-based screening of older women with respect to mortality may shed light on the potential efficacy of an HPV-based

screening program to prevent cervical cancer mortality among older women, until such data are available.

In the meantime, national guidelines groups acknowledge that lack of evidence hampers their ability to make evidence-based recommendations for older women. The present study addresses this critical research gap. Based on the OR and the observed screening prevalence among the cases from the present study, and assuming the association observed in this study is causal, 36.2% of cervical cancer deaths among 55-79 year-old women in the United States, or approximately 801 deaths per year,[75] could have been averted by screening in the 7 years prior to symptom onset or screen-detected diagnosis. Based on its superior performance characteristics, it is likely that a larger number of deaths could be averted in an HPV-based screening strategy.

This study, in conjunction with previous analyses, provides evidence on the benefits of extending screening guidelines to include women older than 65 years. Cervical cytology screening is not without harms, though, such as invasive diagnostic procedures, short-term psychological distress, and over-diagnosis.[24] If, after quantifying the costs and potential harms of screening older women, such benefits are deemed to outweigh potential harms, national guidelines groups could consider an expansion of the age group for which screening is currently recommended.

Figure 1. Five-Year Survival of Invasive Cervical Cancer Among Women 55 to 79 Years of Age by Stage at Diagnosis from Surveillance, Epidemiology, and End Results (SEER) Registries, 1973-2006. Stage at diagnosis is classified according to the SEER historic staging system, which is consistent across time periods.



Source: Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) SEER*Stat Database: Incidence - SEER 17 Regs Research Data + Hurricane Katrina Impacted Louisiana Cases, Nov 2010 Sub (1973-2008 varying) - Linked To County Attributes - Total U.S., 1969-2009 Counties, National Cancer Institute, DCCPS, Surveillance Research Program, Cancer Statistics Branch, released April 2011, based on the November 2010 submission.

Figure 2. Screening during the detectable preclinical phase (DPP) of persons who died of their cancer (cases) and during the corresponding period among controls. The DPP is shown in bold along the x-axis. This figure assumes that the DPP is 7 years for all cases, that screening during the first 6 years of the DPP inevitably leads to the cancer being cured (i.e., odds ratio = 0), and that screening after that time is of no benefit to survival. Adapted from Weiss, McKnight, and Stevens 1992.

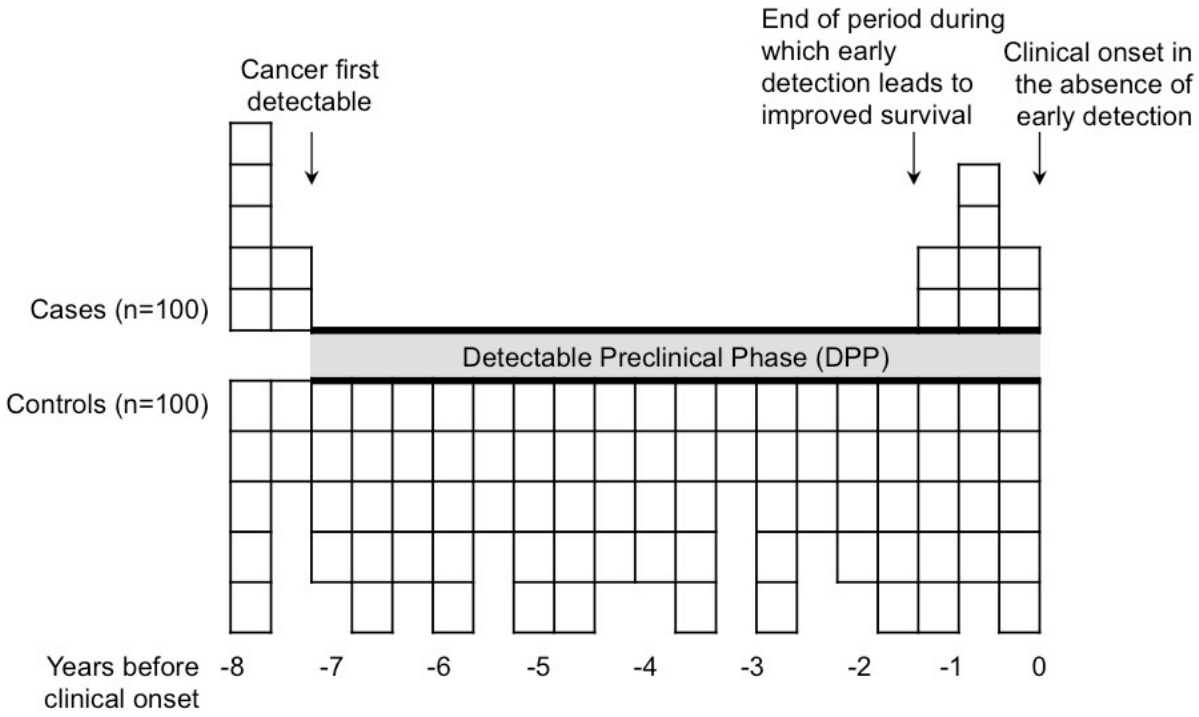


Table 1. Observed 5-Year Survival of Women 55-79 Years of Age Diagnosed with Invasive Cervical Cancer by Stage at Diagnosis from Surveillance, Epidemiology, and End Results (SEER) Registries, 1973-2007. Stage at diagnosis is classified according to the SEER historic staging system, which is consistent across time periods.

	Localized			Regional			Distant			Unstaged		
Year at Diagnosis	Survival (%)	95% CI		Survival (%)	95% CI		Survival (%)	95% CI		Survival (%)	95% CI	
1973-1979	72.5	(70.1,	74.7)	44.1	(41.2,	46.9)	9.30	(6.7,	12.4)	46.4	(40.8,	51.9)
1980-1989	74.3	(71.9,	76.5)	47.2	(44.8,	49.6)	9.80	(7.4,	12.6)	47.5	(41.2,	53.5)
1990-1999	80.5	(78.6,	82.3)	44.9	(42.6,	47.1)	9.40	(7.1,	12.0)	47.3	(42.1,	52.4)
2000-2007	79.7	(77.8,	81.5)	47.7	(45.6,	49.7)	12.70	(10.5,	15.1)	37.2	(31.5,	43.0)

Abbreviation: CI: confidence interval.
Confidence interval: log(-log()) transformation.

Source: Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) SEER*Stat Database: Incidence - SEER 17 Regs Research Data + Hurricane Katrina Impacted Louisiana Cases, Nov 2011 Sub (1973-2009 varying) - Linked To County Attributes - Total U.S., 1969-2010 Counties, National Cancer Institute, DCCPS, Surveillance Research Program, Cancer Statistics Branch, based on the November 2011 submission.

Table 2. Observed Cases of Invasive Cervical Cancer Among Women 55-79 Years of Age by Stage at Diagnosis from Surveillance, Epidemiology, and End Results (SEER) Registries, 1973-2007. Stage at diagnosis is classified according to the SEER historic staging system, which is consistent across time periods. Note: Absolute numbers are not presented, as they may reflect increases in the number of SEER registries since 1973.

Year at Diagnosis	Localized row %	Regional row %	Distant row %	Unstaged row %
1973-1979	43.3	35.1	11.5	10.1
1980-1989	36.8	42.4	13.0	7.7
1990-1999	38.3	41.0	11.5	9.2
2000-2007	33.9	44.9	14.9	6.3

Source: Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) SEER*Stat Database: Incidence - SEER 17 Regs Research Data + Hurricane Katrina Impacted Louisiana Cases, Nov 2011 Sub (1973-2009 varying) - Linked To County Attributes - Total U.S., 1969-2010 Counties, National Cancer Institute, DCCPS, Surveillance Research Program, Cancer Statistics Branch, based on the November 2011 submission.

Table 3. Reasons for exclusion of cases and controls.

	Cases n (%)	Controls n (%)
Hysterectomy prior to diagnosis date	n/a	69 (62.2)
No medical records available	4 (50.0)	18 (16.2)
Documentation of care outside the health plan	0 (0)	16 (14.4)
Likely receiving care outside the health plan	3 (37.5)	4 (3.6)
Died/disenrolled before diagnosis date (evident from chart review)	n/a	3 (2.0)
Documentation of invasive cervical cancer prior to health plan enrollment	0 (0)	1 (0.9)
<6 years enrollment prior to diagnosis	1 (12.5)	0 (0)
Total	8 (100)	111 (100)

Table 4. Demographic characteristics of cases and controls. "At diagnosis" refers to the diagnosis date of the case or of the control's matched case.

Health plan	Cases (n=39) n (%)[a]	Controls (n=80) n (%)[a]
Group Health	16 (41.0)	34 (42.5)
Kaiser Permanente Northwest	23 (59.0)	46 (57.5)
Age at diagnosis		
55-59 years	15 (38.5)	28 (35.0)
60-<65	9 (23.1)	20 (25.0)
65-<70	5 (12.8)	10 (12.5)
70-<75	6 (15.4)	12 (15.0)
75+	4 (10.3)	10 (12.5)
Age at death		
55-59 years	8 (20.5)	n/a
60-<65	11 (28.2)	n/a
65-<70	7 (17.9)	n/a
70-<75	6 (15.4)	n/a
75+	7 (17.9)	n/a
Enrollment length prior to diagnosis		
<10 years	15 (38.5)	31 (38.8)
10-14 years	13 (33.3)	27 (33.8)
15+ years	11 (28.2)	22 (27.5)
Smoking history		
Never	12 (30.8)	33 (41.3)
Non-smoker[b]	7 (17.9)	14 (17.5)
Former smoker[c]	8 (20.5)	22 (27.5)
Current smoker	12 (30.8)	11 (13.8)
Body Mass Index (BMI)		
<18.5 kg/m^2	1 (3.2)	1 (1.3)
18.5 - <25	11 (35.5)	29 (38.7)
25 - <30	5 (16.1)	24 (32.0)
30 - <35	4 (12.9)	10 (13.3)
35+	10 (32.3)	11 (14.7)
Unknown	8	5
Race		
White	36 (94.7)	74 (97.4)
Hispanic	1 (2.6)	0 (0)
Asian	1 (2.6)	2 (2.6)
Unknown	1	4
Marital status		
Never married	0 (0)	2 (2.5)
Married	20 (55.6)	54 (68.4)
Divorced	5 (13.9)	12 (15.2)

	Widowed	10 (27.8)	11 (13.9)
	Separated	1 (2.8)	0 (0)
	Unknown	3	1
Parity			
	0	2 (5.1)	9 (11.3)
	1	2 (5.1)	8 (10.0)
	2	7 (17.9)	23 (28.8)
	3	11 (28.2)	12 (15.0)
	4	10 (25.6)	13 (16.3)
	5+	7 (17.9)	15 (18.8)

[a] Percentage excludes unknowns, if any.

[b] Documented as a current non-smoker as of index date; past smoking habits unknown.

[c] Documented as a current non-smoker as of index date; documentation of smoking in the past.

Table 5. Pathology of invasive cervical cancer tumors among cases (n=39). Histopathological types not listed were not found among cases.

Pathology	n (%)[a]
Squamous cell carcinoma	20 (54.1)
Adenocarcinoma	12 (32.4)
Adenosquamous carcinoma	1 (2.7)
Undifferentiated carcinoma	4 (10.8)
Unknown	2
Total	39 (100)

[a] Percentage excludes unknowns.

Table 6. Odds ratios (OR) and 95% confidence intervals (CI) of the association between cervical cancer screening during the seven years prior to index date and cervical cancer mortality among women ages 55-79 using multivariate logistic regression.

	Cases (n=39) n (%)	Controls (n=80) n (%)	Univariate model[a] OR (95% CI)	Adjusted model[b] OR (95% CI)
Unscreened	19 (49)	15 (19)	1.00 (referent)	1.00 (referent)
Screened	20 (51)	65 (81)	0.24 (0.10 - 0.56)	0.26 (0.10 - 0.63)

[a] Adjusted for matching variables only (controls matched to cases on health plan (Group Health or Kaiser Permanente Northwest), duration of enrollment prior to diagnosis (continuous, in months), age (continuous))

[b] Adjusted for matching variables, plus those that were significant in full model ($p<0.10$): smoking status (never smoker, non-smoker, former smoker, current smoker), marital status (never married, married, divorced, widowed, separated, unknown), race/ethnicity (White, Hispanic, Asian, unknown)

Table 7. Sensitivity analyses of odds ratios (OR) and 95% confidence intervals (CI) of the association between cervical cancer screening during the seven years prior to index date and cervical cancer mortality among women ages 55-79 using multivariate logistic regression. The interval during which screening was considered was varied in 6-month intervals, from 6.5 years prior to index date to 5 years prior to index date. The primary analysis in Table 6 utilized a DPP estimate of 7 years.

Number of years prior to index date that DPP starts		Cases (n=39)	Controls (n=80)	Adjusted model[a]
6.5 years		n(%)	n(%)	OR (95% CI)
	Unscreened	20 (51)	18 (22)	1.00 (referent)
	Screened	19 (49)	62 (78)	0.30 (0.12 - 0.72)
6 years				
	Unscreened	23 (59)	19 (24)	1.00 (referent)
	Screened	16 (41)	61 (76)	0.24 (0.10 - 0.57)
5.5 years				
	Unscreened	25 (64)	20 (25)	1.00 (referent)
	Screened	14 (36)	60 (75)	0.20 (0.08 - 0.50)
5 years				
	Unscreened	25 (64)	21 (26)	1.00 (referent)
	Screened	14 (36)	59 (74)	0.22 (0.09 - 0.53)

[a] Adjusted for matching variables, plus those that were significant in full model ($p<0.10$): smoking status (never smoker, non-smoker, former smoker, current smoker), marital status (never married, married, divorced, widowed, separated, unknown), race/ethnicity (White, Hispanic, Asian, unknown)

Table 8. Odds ratios (OR) and 95% confidence intervals (CI) of the association between cervical cancer screening during the seven years prior to index date and cervical cancer mortality, stratified by age at diagnosis.

Age at diagnosis	Cases (n=39)	Controls (n=80)	Adjusted model[a]
<65 years of age	n (%)	n (%)	OR (95% CI)
Unscreened	14 (58)	8 (17)	1.00 (referent)
Screened	10 (42)	40 (83)	0.18 (0.06 - 0.57)
≥65 years of age			
Unscreened	5 (33)	7 (23)	1.00 (referent)
Screened	10 (67)	25 (78)	0.47 (0.14 - 1.63)

[a] Adjusted for matching variables, plus those that were significant in full model ($p<0.10$): smoking status (never smoker, non-smoker, former smoker, current smoker), marital status (never married, married, divorced, widowed, separated, unknown), race/ethnicity (White, Hispanic, Asian, unknown)

Table 9. Odds ratios (OR) and 95% confidence intervals (CI) of the association between cervical cancer screening during the seven years prior to index date and cervical cancer mortality, stratified by year of diagnosis of the case (1999 or earlier vs. 2000 or later).

Year of diagnosis	Cases (n=39)	Controls (n=80)	Adjusted model[a]
1999 or earlier	n (%)	n (%)	OR (95% CI)
Unscreened	12 (57)	8 (19)	1.00 (referent)
Screened	9 (43)	34 (81)	0.23 (0.08 - 0.67)
2000 or later			
Unscreened	7 (39)	7 (18)	1.00 (referent)
Screened	11 (61)	31 (82)	0.29 (0.10 - 0.84)

[a] Adjusted for matching variables, plus those that were significant in full model ($p<0.10$): smoking status (never smoker, non-smoker, former smoker, current smoker), marital status (never married, married, divorced, widowed, separated, unknown), race/ethnicity (White, Hispanic, Asian, unknown)

Table 10. Odds ratios (OR) and 95% confidence intervals (CI) of the association between cervical cancer screening during the seven years prior to index date and cervical cancer mortality, restricted to cases with squamous cell carcinoma (SCC) pathology.

	Cases (n=20) n (%)	Controls (n=40) n (%)	Adjusted model[a] OR (95% CI)
Unscreened	11 (55)	6 (15)	1.00 (referent)
Screened	9 (45)	34 (85)	0.13 (0.03 - 0.54)

[a] Adjusted for matching variables, plus those that were significant in full model ($p<0.10$): smoking status (never smoker, non-smoker, former smoker, current smoker), marital status (never married, married, divorced, widowed, separated, unknown), race/ethnicity (White, Hispanic, Asian, unknown)

Table 11. Measures of intra-rater reliability of 4 variables with any discrepancy between first and second abstraction. A random 10% sample (n=12) of subjects' medical records were re-abstracted. No discrepancies between first and second abstraction were found for index date, tumor pathology type (cases only), or marital status. Standard methods for calculating kappa or weighted kappa were used, as appropriate.

	Discrepancies	Reliability	95% CI lower bound[d]
Race/ethnicity[a]	1	0.778	0.388
Menopausal status[b]	2	0.779	0.386
Parity[b]	2	0.928	0.530
Smoking status[b]	3	0.946	0.549
BMI[b,c]	3	0.949	0.534

[a] Kappa calculated (nominal categories; categories match those used in Table 4)

[b] Weighted kappa calculated (ordinal categories; categories match those used in Table 4)

[c] BMI could not be calculated for one subject because height was not found in the medical record in neither first nor second abstraction.

[d] Upper bound is 1.000.

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VITA

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