Impact of screening on cervical cancer incidence. A population-based case-control study in the United States

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Abbreviations:

HPV: human papillomavirus

NM: New Mexico

NMHPVPR: New Mexico HPV Pap Registry

NMTR: New Mexico Tumor Registry

SM: supplementary material

Novelty and Impact (limit: 75 words. Currently 75)

For the first time, we estimate the impact of cervical screening at a state-wide level, linking the only US population-based screening registry with a SEER cancer registry. We show that 3-yearly screening prevents 83% of stage 2+ cancer, with no additional benefit from more frequent screening. The safety of 3-yearly cytology and lack of benefit of more frequent screening should reassure clinicians who remain skeptical of US guidelines and enable them to become willingly adherent.

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Abstract:

Cervical cancer is widely preventable through screening, but little is known about the duration of protection offered by a negative screen in North America. A case-control study was conducted with records from population-based registries in New Mexico. Cases were obtained from the Tumor Registry diagnosed with cervical cancer in 2006-2016. Five controls per case from the New Mexico HPV Pap Registry were matched to cases by sex, age and place of residence. Dates and results of all cervical screening and diagnostic tests since 2006 were identified from the pap registry. We estimated the odds ratio of non-localized (stage 2+) and localized (stage 1) cervical cancer associated with attending screening in the 3yrs prior to case-diagnosis compared to women not screened in 5yrs. Of 876 cases, 527 were aged 25-64y with ≥3yrs of potential screening data. 38% of cases and 61% of controls attended screening in a 3yr period. Women screened in the 3yrs prior to diagnosis had 83% lower risk of non-localized cancer (odds ratio (OR)=0.17,95%CI:0.12-0.24), and 48% lower odds of localized cancer (OR=0.52,95%CI:0.38-0.72), compared with women not screened in the 5yrs prior to diagnosis. Women remained at low risk of non-localized cancer for 3.5-5yrs after a negative screen compared to women with no negative screens in the 5yrs prior to diagnosis. Routine cervical screening is effective at preventing localized and non-localized cervical cancers; 3-yearly screening prevents 83% of non-localized cancers, with no additional benefit of more frequent screening. Increasing screening coverage remains essential to further reduce cervical cancer incidence.

Introduction

Cervical cancer is largely preventable, yet an estimated 13,170 women in the United States (US) will be diagnosed with invasive cervical cancer in 2019, an age-standardized rate of 7.6 per 100,000 women in 2011-16[1]. Cervical screening and human papillomavirus (HPV) vaccination are two methods of preventing cervical cancer. In 2012 consensus guidelines were issued for cervical screening in US populations, recommending screening begin at age 21yrs; 3-yearly cytology for women aged 21-29yrs, and either 3-yearly cytology or 5-yearly co-testing (co-occurring HPV and cytology testing) for women 30-64yrs[2, 3]. In 2018 the US Preventive Services Task Force (USPSTF) released updated guidelines, adding 5-yearly primary HPV testing as an option for women aged 30-65yrs[4]. Most women aged >65yrs can cease cervical screening[2, 4]. The first HPV vaccine was licensed in the US in 2006[5] and the Centers for Disease Control and Prevention first recommended routine HPV vaccination for girls aged 11-12yrs in 2007[6].

Screening has been shown to be effective at preventing cervical cancer on a population level since the 1960s[7]. Although the effectiveness of screening has been evaluated in numerous European populations[7-13], the sensitivity of cytology varies between screening settings[14]. Previous research on the effectiveness of cervical screening within the US has focused on women enrolled in health plans or integrated health systems[15, 16], and/or has focused on women of specific ages[17]. In 2006 HPV was added to the list of reportable conditions for individuals residing in New Mexico. All cervical screening test results (HPV, Pap cytology and co-testing) and all pathology for the cervix, vagina and vulva are reported to the New Mexico HPV Pap Registry (NMHPVPR)[18]. The NMHPVPR has previously been described in detail[19]. New Mexico is the only State in the US with a complete record of all cervical screening, diagnosis and treatment, providing appropriate high-quality data to evaluate the effectiveness of cervical screening on a population basis, across a variety of diverse healthcare delivery settings and populations. The population of New Mexico is diverse; according to 2018

123 population estimates, 49.1% of the population were of Hispanic or Latino origin, 10.9% were
124 American Indian or Alaska natives, and 2.6% were African American[20].

125 We assessed the effectiveness of cervical screening in New Mexico using a case-control
126 study design. We addressed three questions (outlined in the Methods) which together provide
127 insights into the effectiveness of screening on a state-wide basis. This study was approved by the
128 University of New Mexico Human Research Review Committee.

129 **Methods**

130 *Cervical Cancer Cases*

131 We collected data on all cervical cancer diagnoses in the population-based New Mexico
132 Tumor Registry (NMTR) during 2006-2016. For each case, the NMTR provided information on the
133 month/year of birth, month/year of diagnosis, morphology and stage at diagnosis (using the derived
134 AJCC-6 stage classification system). NMTR records were linked with the NMHPVPR to provide
135 information on each case's history of cervical screening, diagnostic and treatment results within New
136 Mexico since January 2006. The reason why each test was performed was not available; see
137 **Supplementary Materials 1 (SM1)** for details on how we determined which tests were likely due to
138 symptoms. Only colposcopy procedures resulting in a biopsy were captured. With few exceptions,
139 information was available for each woman's census tract of residence at cancer diagnosis and at
140 each screening or diagnostic test.

141 Since cancers histologically diagnosed within 5 months of an abnormal screening result were almost
142 certainly present at the time of the screen, and in most cases will have been screen-detected, we
143 took the date of the first abnormal cytology or positive HPV test within 5 months of histological
144 diagnosis as the "date of index diagnosis". The date of index diagnosis for cases with no such
145 abnormal test result was the date of diagnosis. We note that this definition primarily affects results

when considering “time since last screen” since this definition does not count a positive test less than five months before histological diagnosis as a pre-diagnostic test.

Controls

Controls were selected from the NMHPVPR. Five women were selected per case, matched on date of birth and census tract of residence at diagnosis. To be eligible as a control, women had to be alive without a known hysterectomy or diagnosis of cervical cancer recorded at the date of the case’s diagnosis. Since women were only in the NMHPVPR if they had attended screening from January 2006-December 2016, we added a fractional number of unscreened “virtual-controls” for each case, to represent women who had not attended screening between January 2006-December 2016, and were therefore not in the NMHPVPR. The number of virtual controls was determined by comparing numbers of women in NMHPVPR with numbers from the census. Details on how the weights were calculated to determine the fractional number of unscreened women are available in **SM2**, and additional details on matching in **SM3**. All controls were assigned their matched case’s date of diagnosis as a date of pseudo-diagnosis.

Measures to evaluate the effectiveness of cervical screening

We address the following primary questions:

1) What is the risk of (i) stage 1 (localized), and (ii) stage 2+ (non-localized) cervical cancer within 3 years of attending screening compared with the risk in women who did not attend screening within the previous 5 years?
2) For how long do women remain at lower risk of non-localized cancer after a negative screen?
3) How does the risk among women who attend screening frequently (at least once every 2.5 years), regardless of the screening result, compare with the risk among women who do not attend screening, or who attend infrequently?

We examined the effect of attending screening on the risk of cervical cancer using the following measures to answer each question. 1) Existence of a satisfactory screen in the 3yrs prior (versus none in the 5yrs prior) to the case's date of index diagnosis. This analysis was restricted to women with ≥3yrs of potential pre-diagnosis screening history. 2) Time between the last negative screening test and the case's date of index diagnosis, among women with ≥5 years of screening history available. A screening test was defined to be negative if there was a negative cytology or HPV test which was not taken as part of a positive co-test, nor was it the first negative cytology/HPV test within 12 months of an abnormal screening test. We used the following categories: ≤1.5yrs, 1.5-2.5yrs, 2.5-3.5yrs and 3.5-5yrs, compared with women with no recorded negative screening tests within 5 years of the case's date of index diagnosis. 3) We defined a woman to have been frequently screened if she had at least 2 screens a minimum of 10 months apart, with no interval >30 months between screens, in the 5yrs prior to the date of indexdiagnosis/pseudo-diagnosis. Women with some screening in the 5yrs prior to the date of index diagnosis who did not meet the criteria of frequent screening were considered to have attended screening infrequently. This analysis was restricted to women with at least 5yrs of screening history, to allow us to distinguish unscreened from infrequently screened women.

Since women are only recommended to attend routine screening until age 65yrs, we restrict the main analyses to women aged 25-64yrs. Except where explicitly stated otherwise, when analyses considered screening in a 5yr period, we excluded cases and their matched controls diagnosed before 1st January 2011. All analyses were carried out for all stages combined and separately by stage at diagnosis.

We carried out seven sensitivity analyses on the first question addressed (What is the risk of (i) stage 1 (localized), and (ii) stage 2+ (non-localized) cervical cancer within 3 years of attending screening compared with women who did not attend screening within the previous 5 years?). The first sensitivity analyses (SA1) adjusted for the census-tract level sociodemographic variables shown

in **Table S1**, since the controls were matched to the cases on census tract, and we do not have individual-level sociodemographic data. SA2 excluded women whose address was a P.O. Box or zip code (see **SM3**). SA3 used an alternative set of weights, where control women from the NMTR who were diagnosed with potentially screen-detected cancers (breast or colorectal) were excluded when calculating the weights. SA4 excluded the virtual (unscreened) controls from the analysis, to examine the impact of merely selecting controls from the NMHPVPR, without allowing for the fact that it is not a population register, and that women who did not attend screening from January 2006-December 2016 could not be selected as a control. SA5 included women of all ages, regardless of whether they were recommended to attend screening, and SA6 included women aged 25-69y, since 65y was only introduced as the upper age limit of screening in 2012 [3]. Finally, SA7 used a reference category of women who had not attended screening in a 3-year period, rather than a 5-year period.

Statistical Methods

We present results from unadjusted weighted logistic regression analyses (having broken the matching, to allow for the weights) as the primary results.

Results

A total of 876 women were diagnosed with cervical cancer in New Mexico between 1st January 2006 and 31st December 2016. Of these 876 cancers, 70% were squamous, 19% adenocarcinoma, 2% adenosquamous and 8% other morphologies. A total of 646 women were diagnosed from January 2009-December 2016, with ≥3yrs of potential screening history recorded. Of these, 47.9% were diagnosed at ages 35-54yrs, with only 2.3% (N=15) diagnosed before age 25yrs, and 15.8% (N=102) diagnosed aged ≥65yrs (**Figure 1**, **Table 1**). The stage at diagnosis was strongly related to age at diagnosis; in women <35yrs, 75.0% with a known stage were stage 1, compared to 41.1% among women aged ≥65yrs.

Approximately 40% (38.0%) of cases diagnosed aged 25-64yrs attended screening in the 3 years prior to the date of index diagnosis (**Table 2**), compared with 61.2% of controls (weighted for women without a record of screening in the NMHPVPR). Women aged 25-64yrs who attended screening in a 3yr period had a lower risk of diagnosis for each cancer stage compared to women not screened in the last 5yrs (**Table 2, S2**). 22.5% of women with stage 3+ cancer had been screened in the 3yrs prior to the date of index diagnosis, compared to 59.3% of women with stage 1A cancer (**Table S2**). The effect of attending screening in the last 3yrs increased with increasing cancer stage, from no effect on the odds of stage 1A cancer (odds ratio (OR)=0.78, 95%CI:0.48-1.28) to strong effects on stage 3+ cancer (OR=0.16, 95%CI:0.10-0.23) compared to women who did not attend in the last 5yrs. **Figure 2** shows there were effects of screening on non-localized cancers for all ages, but only for ages 35-49yrs and 50-64yrs for stage 1 cancers.

The results from sensitivity analyses (SA) are presented in **Figure S1**. Most of the SA provided extremely similar results, more details are provided in **SM4**. When we assumed that the population at risk of cervical cancer excluded women with a hysterectomy (who guidelines have recommended against screening since 2012[2]), and that all hysterectomized women had not attended screening, the proportion of unscreened women was 0 for women aged 20-69. This is equivalent to SA4, when the virtual-controls were excluded from the analyses; this sensitivity analysis showed a larger effect of screening (SA4).

For time since the last negative screen (**Table 3**), when restricted to women with ≥5yrs of potential screening history, women aged 25-64yrs with a negative screen remained at lower risk of both stage 1 (OR=0.20, 95%CI:0.14-0.28) and non-localized cancer (OR=0.11, 95%CI:0.07-0.17) for at least 3.5yrs compared to women with no negative screening in the last 5yrs (a mix of women with no screening and those with only abnormal screening results). The risk for stage 2+ cancers remained constant over the first 3.5yrs. Results were similar in the sensitivity analyses, adjusting for census-level socioeconomic variables, and using alternative weights (**Table S3**). There was a significant

reduction in risk of non-localized cervical cancer for at least 3.5yrs following a negative test relative to women with no negative tests in 5yrs for women in each age group considered (25-34yrs, 35-49yrs, 50-64yrs, ≥65yrs), except stage 1 for women aged ≥65y (**Figure S2**). In sensitivity analyses, when the analysis was extended to women with ≥3yrs potential screening history rather than 5yrs, the results were very similar (**Table S4**).

Women who attended screening frequently (at least 2 screens a minimum of 10 months apart, with no interval >30 months between screens) were at significantly lower risk of both non-localized (OR=0.10, 95%CI:0.05-0.19) and stage 1 cancer (OR=0.43, 95%CI:0.28-0.65) than women who did not attend screening in a 5yr period (**Table 4**). Women who attended screening in the previous 5yrs, but did not meet the criteria for frequent screening (' infrequently' screened) were at significantly reduced risk of both non-localized (OR=0.26, 95%CI:0.18-0.37) and stage 1 cancer (OR=0.58, 95%CI:0.40-0.82) compared with women not screened in 5yrs, but at significantly greater risk of non-localized cancer compared with those screened frequently (OR=2.54, 95%CI:1.33-4.84). Sensitivity analyses produced very similar results (**Table S5**). When restricted to women who attended screening in the 2.5yrs prior to the date of index diagnosis or who had not attended in 5yrs, the results were also very similar (**Table S6**).

When restricted to women who had only cytology screening (i.e. no HPV tests prior to diagnosis), results of the 3 main analyses were very similar (**Tables S7-S9**).

Discussion

This study addressed three key relevant questions related to the performance of cervical screening. First, attending screening within a 3yr period reduced the odds of non-localized cancer by 83%, and stage 1 cancer by 48% compared to women not screened in 5 years. Second, women who had a negative screening test were at much lower risk of both non-localized and stage 1 cancer for up to 5yrs compared to women without a negative screen in the last 5yrs, with a larger benefit in the first 3.5yrs. Third, frequently attending cervical screening (at least 2 screens a minimum of 10

268 months apart, with no interval >30 months between screens) was associated with a 90% reduction in
269 the odds of non-localized cervical cancer, and a 57% reduction in the odds of stage 1 cervical cancer,
270 compared to women who did not attend screening for 5yrs. Notably, we found similar relative
271 benefits of screening at ages 25-34yrs, 35-49yrs, 50-64yrs, and aged ≥65yrs for non-localized cancer.

272 It is important to acknowledge that cancers diagnosed before symptoms developed should
273 be considered a success of cervical screening; 23% of cancers diagnosed at a known stage in New
274 Mexico 2006-16 were diagnosed at stage 1A. The stage distributions of cervical cancers diagnosed in
275 New Mexico over the study time period including stage 1A were very similar to that computed for
276 SEER18 registries overall (SEER*Stat November 2018; data not shown).

277 Women who were screened at least once every 2.5yrs ('frequently') had a relative risk of
278 non-localized cancer of 0.39 compared with women screened infrequently. This was also the case
279 when restricted to women who were screened within the 2.5yrs prior to the date of index diagnosis,
280 indicating that this is not purely due to the presence of a recent test, but to having had multiple tests
281 in the 5yr period. This was largely a study of cytology, with little co-testing. The sensitivity of
282 cytology for CIN2+ is around 71-75%[21]; therefore there is an advantage to having more frequent
283 screenings, due to the high level of false negatives for a single cytology test. However, this does not
284 mean that annual testing is an improvement, as demonstrated by the very similar risk of non-
285 localized cancer 0-1.5yrs after a negative screen compared with 2.5-3.5yrs after a negative screen.
286 On the contrary, while this study was not designed to assess the disadvantages of screening more
287 frequently than current guidelines recommend, there are many reasons to dissuade this practice.
288 First, more frequent screening increases the probability of having a false-positive test (when either
289 no precancerous lesion is present, or the precancerous lesion would regress without requiring
290 intervention). Second, false-positive rests have the potential to increase stress and anxiety if further
291 diagnostic testing is required, in addition to the discomfort from a colposcopy. Additionally, there is

292 the time and expense associated with unnecessary testing; in New Mexico 28% of women who
293 reside in rural areas must travel more than 30 minutes each-way to seek diagnostic services[22].

294 Recent guidelines recommend routine HPV co-testing in women aged 30-65yrs[4]. The
295 majority of screening records in New Mexico in 2006-2016 were cytology tests taken alone, though
296 the proportion of HPV tests or co-tests increased with time (from 4.2% in 2006 to 54.7% in 2016),
297 and when restricted to women aged 30-65yrs, where co-tests are routinely recommended, 67.8%
298 were observed in 2016. Co-testing will increase the sensitivity of a single round of screening, and
299 potentially support longer screening intervals versus intervals when screening by cytology alone[23].
300 Whether longer screening intervals can be successfully adopted by the US in the absence of
301 organized call-recall systems should be given careful consideration. As cervical screening intervals
302 lengthen for primary HPV testing and co-testing over time, it will be critical to monitor the
303 proportion of women who fail to rescreen at 5 year intervals. Although HPV-based technologies are
304 directed at improving screening efficiencies and reducing potential harms from screening,
305 lengthening cervical cancer screening intervals in the US may not be readily implemented due to the
306 lack of organized screening programs. Furthermore, the continuously changing landscape of cervical
307 screening could result in an increase in cervical cancer incidence if women fail to return for screening
308 or return beyond the duration of protection afforded.

309 Whilst we have shown that cervical screening in New Mexico is effective at preventing
310 cervical cancer, only 61% of controls aged 25-64yrs had attended cervical screening in a 3yr period.
311 Therefore, initiatives which increase screening coverage are likely the best investment for improving
312 the prevention of cervical cancer, especially among women from birth cohorts which did not benefit
313 from HPV vaccination prior to sexual initiation. Since not all attendees return for their next screen, it
314 is important to use the most sensitive screening test available.

315 Similar methods have been used to explore the effectiveness of cervical screening in
316 Europe[8-11, 24, 25] and Australia[26]. Andrae et al[8] found a slightly lower effect of screening in women

aged 30-65 in Sweden for all stages (OR=2.52) and stage 2+ (OR=4.82), when considering women who weren't screened compared to women who were screened in the recommended interval (3-yearly for women aged 30-50 and 5-yearly for women ages 50-60). Yang et al[26] found that even infrequent screening in Australia, defined as a pap test in only one year of a four year period, was associated with an 85% reduction in risk of all stages of cervical cancer, and frequent screening (a pap in at least two years in a four year period) was associated with around a 95% reduction in risk. These effects are slightly larger than those found for infrequently and frequent screening in our study, though our definition of frequent screening differs slightly.

New Mexico is the only state within the US where cervical screening data of this quality exist on a population basis, enabling the evaluation of cervical screening as practiced across a wide range of healthcare delivery settings. Screening recommendations and implementation approaches vary widely between countries[27], so results from one setting may not apply to another; for example, in the US the vast majority of screening is opportunistic whereas in Sweden there is a national program where women are invited for screening[28]. The importance of comprehensive audits of screening programs including the full target population is widely recognized[29, 30]. Previous research on the effectiveness of cervical screening in the US has relied on data from women enrolled in health plans or integrated health systems[15, 16] who may be at different risk of cervical cancer than the general population. Screening guidelines for the US have been almost exclusively based on the analysis of cervical screening data which are not representative of women and/or providers in the general population[2, 31]. Furthermore, studies of cervical screening effectiveness in the US have been conducted in settings where screening is implemented by system-specific screening guidelines. For example Kaiser Permanente Northern California introduced HPV as part of a co-test in 2003[32], whereas HPV co-testing did not even begin utilization in mainstream clinical practice in New Mexico until 2013, following national cervical screening guidelines issued in 2012[3].

It was not possible to select controls from a population register and link to their screening history. Only women who have attended screening at least once could be identified from the NMHPVPR; it was therefore important to augment this with virtual-controls (who had not been screened since January 2006) based on the census. Had we not included virtual-controls, we would have overestimated the impact of screening. We weighted the controls selected from the NMHPVPR by identifying the age-specific proportion of matched women in the NMTR who had a screening record in the NMHPVPR. However, women who develop non-cervical cancer may have different screening behaviors compared with the general population; we therefore re-weighted the controls excluding women diagnosed with cancers which could have been screen-detected (breast and colorectal), and the results were extremely similar (**Figure S1, Tables S3, S5**). Our results estimated 75% of controls aged 25-65yrs had been screened in the past 5 years; this is consistent with previous investigations which estimated the 5-year screening coverage for women aged 21-65yrs in New Mexico to be around 80%[19].

Whilst we have not included any woman who we know to have had a hysterectomy, we only have incomplete information on hysterectomies (particularly prior to 2006). The situation is further complicated in that prior to 2012, the majority of women with a hysterectomy were still offered screening. If we add together the number of women in the screening registry with the number of women in New Mexico who have had a hysterectomy, the sum, in most age-groups, is greater than the number in the census. Analysing the data in this way would be equivalent to not allowing for unscreened (virtual) controls – it makes screening appear better than it is.

We have used the date of the first abnormal cytology or positive HPV within 5 months of diagnosis as the date of index diagnosis rather than the definitive date of diagnosis used by the NMTR[33], and considered screening in a 3- or 5yr period prior to this date. We only have records of screening tests performed on women where addresses were recorded as a resident of New Mexico or which were taken from a New Mexico provider; whereas some women may have attended

366 screening in other States which would have been missed. Some of the women selected as
367 NMHPVPR controls may only have been resident in New Mexico for a limited period, for example
368 due to migration, therefore our data may not represent their full screening history since 2006. When
369 limiting the analyses to women diagnosed with cervical cancer at age 25-64yrs who had at least 5yrs
370 of screening history data, our sample was reduced to 410 cases. Screening guidelines varied both
371 between and within organizations across the period of this study, so we could not evaluate the
372 effect of screening among women who complied with screening guidelines. We have not linked HPV
373 vaccination status to screening histories, but this is likely to have minimal impact on our results due
374 to the long natural history from HPV infection to cervical cancer versus the introduction of HPV
375 vaccination. We do not have sufficient women who were only screened using HPV testing to
376 compare the effect of screening using cytology alone to those with HPV testing, nor sufficient
377 numbers of women with adenocarcinomas who have at least 3 years of screening data when broken
378 down by stage and screening history in order to investigate the effect of screening by histologic
379 subtype.

380 In conclusion, our study demonstrates that routine screening at a population level has had a
381 beneficial effect in preventing cervical cancer. However, only 61% of controls in this study had
382 attended screening in a 3yr period. Thus, increasing screening coverage will have the greatest impact
383 in achieving further reductions in cervical cancer rates.

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Table titles

Table 1: Stage distribution by age of the 646 cervical cancers diagnosed in New Mexico 2009-2016 among women with ≥3 years of screening history

Table 2: Odds ratios and 95% confidence intervals of cervical cancer by screening attendance and stage at diagnosis, among women aged 25-64 years with at least 3 years of potential screening history

Table 3: Odds ratios and 95% confidence intervals of cervical cancer by time since last negative screen and stage at diagnosis, among women aged 25-64 years with at least 5 years of potential screening history

Table 4: Odds ratios and 95% confidence intervals of cervical cancer for women who were frequently and infrequently screened by stage at diagnosis, among women aged 25-64 years with at least 5 years of potential screening history

Figure titles

Figure 1: Stage distribution by age of the 646 cervical cancers diagnosed in New Mexico 2009-2016 among women with ≥3 years of screening history

Figure 2: Odds ratios and 95% confidence intervals for risk of cervical cancer by stage for women screened within the last 3 years compared to women not screened in the last 5 years, restricted to women with ≥3 years of screening history