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Cervical Cancer in the USA: Prevention, Detection, and Disease Outcomes in Relation to Novel Factors and Disparities

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Abstract

Due to the availability of HPV vaccines and cervical cancer screening services, cervical cancer has recently become preventable in the United State (USA) given adequate healthcare infrastructure and women's ability and willingness to follow health guidelines. Any case of invasive cervical cancer should be viewed as a failure of screening or vaccination. Although the number of cervical cancer cases has been gradually/generally decreasing over the past 20 years, in 2024 alone about 13,000 women were diagnosed with late-stage cervical cancer in the USA and about 4,000 women died from it. Clearly, efforts to improve prevention via the HPV vaccine and adherence to screening/PAP smears guidelines remain important research topics. Moreover, because cervical cancer and treatment outcomes in the USA are well known to suffer from systemic racial and ethnic disparities, research and efforts to alleviate cervical cancer burden in the USA must consider the presence of these disparities.

The purpose of this study was to identify the impacts of potentially important novel factors on cervical cancer prevention and disease outcomes. The specific aims were to evaluate (1) childhood sexual abuse (CSA) as a risk factor for non-adherence to cervical cancer screening guidelines, (2) individual and joint impacts of adverse childhood experiences (ACEs) and obesity on HPV vaccination, and (3) impacts of COVID-19 on cervical cancer outcomes. Women with CSA may find screening procedures to be retraumatizing but impacts of CSA of cervical cancer screening are poorly understood. CSA and other forms of adverse forms of childhood (ACE) also increase the risk for cancer and associated risk behaviors including obesity, smoking, alcohol and drug misuse, high-risk sexual behavior, and may be related to other important factors such as trust/distrust of authority figures.

The results of this dissertation increase knowledge needed to lower cervical cancer burdens in the USA. By considering the influence of childhood trauma on cervical cancer screening and HPV vaccination, these findings will help advance cervical cancer prevention research though enhanced understanding of novel risk factors that may be important for cancer risk behaviors and cancer risk. This dissertation also builds upon knowledge of disparities in cervical cancer outcomes by investigating impacts of the novel COVID-19 pandemic and impacts on existing cancer disparities like race/ethnicity.

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Chapter 1: Introduction & Literature Review

Background

Over 4,000 women die each year in the United States (US) from cervical cancer (CDC 2024). There are two main types of cervical cancer which are named after the type of cell where the malignant tumor starts: Squamous cell carcinoma (SCC) and adenocarcinoma (ADC). According to the American Cancer Society, nine out of 10 cervical cancers are SCC. Nearly all cervical cancers are caused by the Human Papilloma Virus (HPV) with estimates ranging from 90-100% of cervical cancer cases being accounted to HPV (De Martel 2017). Cervical cancer can be prevented or mitigated through screening (early detection of abnormal cells prior to cancer) and the use of the HPV vaccine, yet many women do not follow screening guidelines and many young women remain unvaccinated for HPV. According to the American Cancer Society, five year survival for cervical cancer is around 91% when diagnosed early but only 19% when diagnosed at a late stage, highlighting the importance of early detection and intervention. The focus of this dissertation is reducing the burden of cervical cancer in the US through identifying novel factors that limit screening and HPV vaccination, we well as provide new information about sources of inequities in cervical cancer diagnosis and treatment for remediation.

Cervical Cancer Screening

Left untreated, most HPV infections will go away, but ongoing infection with oncogenic types can lead to precancerous lesions and cancer. HPV causes changes in the DNA of cervical cells that lead to abnormal growth defined as cervical intraepithelial neoplasia (CIN) or squamous intraepithelial lesions (SIL), which lead to cancer. Within three years of HPV infection, about 70% of moderate neoplasia resolves without treatment and 15-22% progresses to high-grade dysplasia (De Martel et al, 2017).

Introduced in the 19503, Papanicolaou tests (also called “PAP smears”) were introduced to detect cell changes in the cervix caused by HPV that if left untreated may lead to cervical cancer (Kessler, 2017). PAP smears involve collecting cells from the cervix for examination to detect cell changes that could lead to cancer or cervical cancer cells, and have proven to be a highly effective method of reducing cervical cancer in the US, where cervical cancer incidence and death rates went down over 60% in the 40 years following the introduction of PAP smears (Kessler, 2017).

Because PAP smears reduce cancer incidence and improve early detection and treatment, the American Cancer Society recommends women aged 25-65 years old be screened every three years or every five years if they’re also given a primary HPV test at the same time. However, many women do not adhere to cervical cancer screening guidelines: In 2020, an estimated 46.2% of women aged 25-64 years in the US did not meet recommended American Cancer Society guidelines for cervical cancer screening (Orji et al. 2024). Main risk factors that have been associated with reduced screening are healthcare infrastructure, race/ethnicity, sociocultural and religious factors, income, cost of accessing services, body mass index (BMI), obesity and diet, and marital status (Devarapalli et al., 2018; Gnade et al., 2020; Lim & Ojo, 2017; Miles-Richardson et al., 2016; Musselwhite et al., 2016).

More recently, childhood sexual abuse (CSA) has been recognized as a potential risk factor for non-adherence to cervical cancer screening guidelines. Women with a history of CSA may find screening procedures to be retraumatizing (Marshall et al., 2023) and CSA also increases the risk for engaging in health risk behaviors including smoking, alcohol and drug misuse, and high-risk sexual behavior (Cadman et al., 2012) which increase the risk of cancer (Holman et al., 2016). Among the few studies that have been published on the link between CSA and cervical cancer screening, results have been mixed with some showing a positive association (Farley et al., 2002; Olesen et al., 2012; Alcalá et al., 2017), and no association in others (Alcalá et al., 2018; Brandford, 2023). Differences between studies may be due to differences in cohort characteristics or study methods, but to date a systematic review and meta-analysis to look at sources of heterogeneity in effect size estimates for CSA and adherence to PAP screening guidelines has not been done.

Given that over 45% of women in the US do not follow cervical cancer screening guidelines, improving cervical cancer screening adherence remains an important area for research and improvement, especially for at risk groups of women and women for whom the HPV vaccine is not recommended (i.e., women over 26 years old).

HPV Vaccine

Cervical cancer can be prevented through the prevention of HPV. Since HPV vaccines were first introduced the prevalence of HPV infection and incidence of cervical cancers among females aged 14 to 29 years have declined nationally in the US by over 80% (Mix et al., 2021; Rosenblum et al., 2022). The first HPV vaccine was released in the United States in 2006 for use in girls and young women (CDCFDA, 2010). Since 2006, two more HPV vaccines have been released with each providing protection against additional HPV strains (Markowitz et al., 2013). All three vaccines are considered highly efficacious at preventing HPV-attributable cancers with efficacy of over 80% for cervical cancer prevention with just one dose (Markowitz et al., 2013). In 2011, the United States adopted a gender-neutral vaccination approach because HPV causes cancer in men and HPV is spread between the sexes (Meites, 2019). The Advisory Committee on

Immunization Practices (ACIP) has recommended catch-up HPV vaccination for all men and women through age 26 years since 2019 (Meites, 2019).

The CDC's Health People 2030 target for HPV vaccination is 80%, but actual vaccination rates remain around 60%, leaving many young people unvaccinated and a lower-than desired herd immunity level (Healthy People 2030). In most states, individuals under the age of 18 years need parental consent to receive the HPV vaccine. Key reasons for vaccine hesitancy among the parents of adolescents in the US include safety/side effect concerns, and beliefs that the vaccine is not necessary and/or effective (Szilagyi et al., 2020; White et al., 2023). Reasons for vaccine hesitancy among young adults aged 18 to 26 years old are not as well studied although vaccination rates are lower in this group than their younger peers (around 36%; Arevalo et al., 2023), and include beliefs that the vaccine is not safe and/or effective, having a primary care provider, gender (males have lower vaccination than females), and level of education (Adjei et al. 2018; Muthurkishnan et al., 2022).

More recently, obesity and adverse childhood experiences (ACEs) have been identified as possible factors associated with HPV vaccination. ACE are traumatic exposures that occur before the age of 18 years old. Examples of ACE include: physical, sexual, or emotional abuse, living with a someone who was suicidal, abused drugs/alcohol, or the incarceration of a family member (Felitti et al., 1998). ACE and obesity are both known to increase cancer risk (Calle et al., 2003; Kalra et al., 2023) and impact healthcare service utilization (Felitti et al., 2010; Wee et al., 2000), yet they are poorly understood in regard to HPV vaccination behaviors, both individually and in combination, despite being associated with one another (the odds of obesity in adulthood are approximately 46 times higher among individuals with multiple ACE relative to those with one or none; Wiss and Brewerton 2020; Schroeder et al., 2021). Identifying key groups at risk of

HPV vaccine hesitancy, such as individuals with obesity and ACE, is an important area of research for public health efforts needed to increase HPV vaccination rates.

Stage at diagnosis & Days to treatment

For women who are diagnosed with cervical cancer, key determinants of survival include the stage at which the cancer was diagnosed, and time from diagnosis to treatment. When diagnosed with early, localized cervical cancer in the US, the survival rate is about 85% but if diagnosed later at a regional or distant stage, survival drops to 53% and 16% respectively, and the frequency of late-stage diagnoses has been increasing over time (Benard et al., 2017). Delays in starting treatment after diagnosis have also been increasing in the US, and delays in treatment for cancer patients are correlated with increased patient distress, decreased disease control, and lower survival (Ramey et al., 2018).

Significant disparities in stage at diagnosis and survival exist in the US. Non-Hispanic Blacks and Hispanics more likely to be diagnosed with later stages of cervical cancer and have worse treatment and survival outcomes than their non-Hispanic White counterparts (Beavis et al., 2017; Coker et al., 2009; Islami et al., 2019). Women in rural versus urban populations in the US are also at increased risk for late stage of diagnosis and treatment delays for cervical cancer (Yu et al., 2019; Zahnd et al., 2018). Factors that impact racial and rural/urban disparities in cervical cancer stage at diagnosis and/or time from diagnosis to treatment, are important avenues of research to reduce existing disparities and optimize strategies for early detection and treatment more equitably for all Americans.

Dissertation Objectives

The focus of this dissertation is reducing the burden of cervical cancer in the US through the identification of possible novel sources of screening and HPV vaccination hesitancy, as well as the identification of inequities in cervical cancer diagnosis and treatment for remediation. The specific research objectives were to:

(1) systematically review the literature reporting on associations between childhood sexual abuse and adherence to cervical cancer screening guidelines, to produce a pooled estimate of the effect size using meta-analysis, and to identify research gaps in and the overall quality of the literature on the topic (Chapter 2).

(2) both (a) assess associations of ACEs and obesity on HPV vaccination and (b) explore the joint associations of ACEs and obesity on HPV vaccination, controlling for known confounding demographic variables using a nationally representative cross-sectional sample from the Behavioral Risk Factor Surveillance System (BRFSS 2021-2023; Chapter 3); and,

(3) estimate COVID-19 pandemic impacts on frequency of late-stage cervical cancer diagnosis and time in days from diagnosis to treatment, among women who were diagnosed with cervical cancer and reported to the Surveillance and Epidemiologic End Results Cancer Registry (SEER) from 2015 to 2021 and potential sources of disparities such as race/ethnicity and rural/urban residency (Chapter 4).

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Chapter 2: Childhood Sexual Abuse and Adherence to Cervical Cancer Screening Guidelines: A Systematic Review and Meta-analysis

Abstract

Background: Cancer screening is critical for early detection and reduced mortality risk. Growing evidence suggests that childhood sexual abuse (CSA) increases the risk of cervical cancer in part, through decreased adherence to screening guidelines. Previous reviews and meta-analyses require updating and exploration of sub-groups to explain heterogeneity of effect in the observed literature.

Materials & Methods: We searched PubMed, Embase, and Google Scholar through May, 2024 using PRISMA guidelines and keywords related to cervical cancer, cancer screening, and CSA. Eligible studies were English language peer-reviewed articles reporting associations between CSA and adherence to cervical cancer screening guidelines on subjects ≥18 years old. Data were extracted from included studies on the association between CSA and adherence to screening guidelines, study characteristics, and study quality. We used random effects meta-analysis to calculate pooled odds ratio (OR), and meta-regression methods to test sources of heterogeneity among estimates.

Results: 250 articles related to the key words were located. Eight of the studies reporting on 24,139 individuals were eligible for inclusion in the synthesis. Relative to none, exposure to CSA did not significantly change the odds of adherence to cervical cancer screening guidelines (OR= 0.7645, 95%CI= 0.5138-1.1377, I^2=72.9%, P=0.1856). Subgroup analyses showed that significant heterogeneity was explained by percentage of white women in each cohort (β=-0.0187, se=0.0068, p=0.0056), mean age (β =-0.0756, SE=0.0249, p=0.0024), and overall study quality(β =-0.2644, SE=0.0749, p=0.0004).

Conclusions: Our results support an association between CSA and adherence to cervical cancer screening guidelines in the general population.

Keywords: *adverse childhood experiences, child abuse, cancer screening, cervical cancer, pap test*

Introduction

Cervical cancer is one of the most common cancers among women globally, with over half a million women diagnosed and around 300,000 deaths annually (Cohen et al., 2019). Nearly all cases of cervical cancer are linked to human papillomavirus (HPV; (Lees et al., 2016). Papanicolaou tests, also called PAP smears, were introduced in the 1950s to detect cell changes in the cervix caused by HPV that if left untreated may lead to cervical cancer (Kessler, 2017). Screening is critical for the early detection and treatment of cervical cancer in order to reduce mortality of this common cancer, currently responsible for over 7% of all cancer-related deaths among women globally (Rerucha et al., 2018). In the 40 years following the introduction of the pap test, cervical cancer incidence and death rates went down over 60% in the United States (Kessler, 2017). The American Academy of Family Physicians and U.S. Preventive Services Task Force recommends screening women aged 21-29 years old every three years, and that women 30-65 be screened every three years or every five years if they're also tested for HPV at the same time (Rerucha et al., 2018).

Despite the effectiveness of PAP smears for reducing cervical cancer mortality, well known barriers to screening exist. One of the largest barriers to screening is living in a country that lacks organized screening and HPV vaccination services (Small Jr et al., 2017). Around 90% of cervical cancer occurs in low and middle-income countries that meet this description (Cohen et al., 2019), and the mortality rate is 18 times higher in these countries compared to wealthier countries (Small Jr et al., 2017). Cervical cancer incidence has also been increasing in China (Zhang et al., 2020).

Within countries, cancer incidence is related to sexual practices (e.g., age at initiation, number of partners and partners number of partners), smoking, obesity, nutritional/dietary factors, genetics (Momenimovahed & Salehiniya, 2017)(Kashyap et al., 2019). Main risk factors that have been associated with reduced screening are sociocultural and religious factors (Devarapalli et al., 2018), income and cost of accessing services (Lim & Ojo, 2017), body mass index (BMI), obesity and diet (Gnade et al., 2020), and race/ethnicity (Musselwhite et al., 2016).

Another potential barrier to cervical cancer screening which has received recent attention is childhood sexual abuse (CSA). Women with a history of CSA may find screening procedures in body regions involved in the trauma to be retraumatizing and cause avoidance of screening (Marshall et al., 2023). Women who have been sexually abused are also more likely to engage in health risk behaviors including smoking, alcohol and drug misuse, and high-risk sexual behavior (Cadman et al., 2012) which increase the risk of cancer (Holman et al., 2016) or possibly be linked to ambivalence about health. Theories as to why childhood abuse is linked to cancer in adulthood include increased risky health behaviors, neurobiological alterations linked to prolonged states of stress, and decreased health care use (Nurius et al., 2019). Recent evidence suggests the link between CSA and lack of adherence to cervical cancer screening guidelines may be one pathway from CSA to cancer (Farley et al., 2002;Olesen et al., 2012; Alcalá et al., 2017), but in some studies no association was found (Alcalá et al., 2018;Brandford, 2023).

The aim of this study was to systematically review the literature reporting on associations between CSA and adherence to cervical cancer screening guidelines, to produce a pooled estimate of the effect size using meta-analysis, and to identify research gaps in and the overall quality of the literature on the topic. This research is important because screening helps cancer be caught and treated early given that treatment is most effective early on in the disease process. Barriers to screening such as CSA need to be identified in particular, because CSA has been shown to be associated with cervical cancer.

Materials and Methods

Study selection

An exhaustive online literature search was performed using PubMed, Embase, and Google Scholar databases. Our search and reporting were carried out in accordance with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) guidelines. The final search string was “('adverse childhood experiences' OR 'childhood trauma' OR 'sexual abuse' AND ('cervical cancer screening' OR 'pelvic exam' OR 'pap smear')”, and the search was conducted in May of 2024. For our Google Scholar search, we searched the first 15 pages of results, after which results became irrelevant to the search string. Once the keyword search across the online databases was complete, we subsequently reviewed the reference lists of eligible articles and related/previous review articles to locate additional eligible studies.

To be eligible for inclusion, articles needed to be written in the English language, and report on: women aged 18 years or older, childhood sexual abuse, and adherence to cervical cancer screening guidelines. There were no limits on the publication dates of included articles and articles from all countries were eligible. Studies need to either provide a measure of association between history of CSA and adherence to cervical cancer screening guidelines or else provide adequate data for calculating the odds ratio for the association.

Data extraction

For each eligible study the following data were collected: Title, first author, year of publication, sample size, response rate, study population characteristics (country, special population/nationally representative, percent Caucasian, average age, etc.), study design, measure of childhood sexual abuse, cancer screening data and the source (i.e., medical record or self-report), measures of association (both overall and adjusted), variables included in the adjusted analyses (if appropriate), and any other relevant information.

The quality of the included articles was assessed using a modified version of the Downs and Black quality checklist (Downs & Black, 1998). This method originally uses 27 questions to evaluate the quality of reporting, internal validity, and external validity of studies. We removed eight questions that were not relevant to cross-sectional studies and slightly rephrased four questions to better fit our study population (Table 1). The result was 19 questions from which overall quality scores could range from 0-20 (Downs & Black, 1998; Table 1). The quality of reporting scores could range from 0-9, external validity from 0-2, and internal validity from 0-8 (Downs & Black, 1998).

This study was exempt from IRB review because no primary data were collected.

Analytic procedures

For this quantitative review, we used R studio (R Foundation for Statistical Computing, Vienna, Austria) and the metagen function of the meta-package (Balduzzi & Schwarzer, 2019)to calculate pooled odds ratios and 95% confidence intervals. The main source of information for the pooled odds ratios was from adjusted odds ratios provided in the articles but in one case was from crude/unadjusted odds ratios. To evaluate how adjustments to the main association were related to the estimate provided, we used meta-regression to test if the unadjusted and adjusted

ORs were significantly different in a subgroup test. We also tested population source as a binary subgroup to see if there were differences in the association based on inference on women from the general population versus those from special populations (i.e., incarcerated women or homeless women). Race (proportion white) and mean age were additionally tested as a source of heterogeneity in effect size via subgroup tests. We used random effects models with the inverse variance method for pooling and analyze the heterogeneity across studies using the Maximum-likelihood estimator, Higgins' I2 and Cochran's Q. Publication bias was assessed by visual inspection of funnel plots. In all cases, significance was defined at $\alpha = 0.05$.

Results

The initial database searches returned a total of 250 articles. After reviewing the titles and abstracts of each article, 127 were excluded and 26 articles were eligible for full text review. Of the 26 articles that underwent full text review, eight met the eligibility criteria and were included in the study (Figure 1).

The characteristics of each included study are summarized in Table 2. Seven of the eight eligible studies were carried out in the USA with the only non-USA study taking place in Australia. The data used was collected between 2003 and 2020, although one study failed to mention the dates of data collection (Farley et al., 2002). Three of the eight studies reported on special populations (n=2 incarcerated, n=1 homeless). Of the five studies that reported on the general population, 60% (n=3) used state-level Behavioral Risk Factor Surveillance Data (BRFSS: Tennessee, Kansas, and Texas). Seven of the eight studies used a cross-sectional survey/interview design while the last study used a case-control design(Farley et al., 2002). The average overall score on the quality assessment was 15.7 ± 0.51 SE (range 14-17; Table 2). The average reporting score was 7.0 ± 0.24 SE; external validity was 1.7 ± 0.19 SE; and internal validity was 6.0 ± 0.33 SE (Table 2).

The eight included studies reported on a total of 24,139 women. Six of the studies presented either the percentage of women who were White or else data from which the percentage could be calculated: the range was 33.0% to 95.3% with the mean percentage White at 60.6% ± 9.17 SE. The average age of women in each cohort could be extracted or calculated for five studies with the range being 33.9 to 49.3 years old (mean = 42.2 ± 3.1 SE).

Using adjusted ORs when available and ORs when they were not (n=1 case), four of the six studies showed significantly lower odds of adhering to PAP guidelines among individuals with CSA compared to those without CSA (Figure 2). However, the overall meta-regression for the association between CSA and adherence to PAP screening guidelines in adulthood was not significant (pooled random effects OR=0.76, 95% CI=0.51-1.14). A subgroup test showed that crude and adjusted ORs did not produce significantly different pooled effect estimates (p=0.8168; Figure 3). The most commonly adjusted for confounding variables were race/ethnicity (n=6), age (n=4), education (n=4), insurance status (n=3), marital status (n=2), and cancer status (n=2); 15 other covariates were used in a single study/effect measure estimate (Table 3). Our subgroup test for the effect of population used (general vs special) also showed no significant difference in the pooled effect estimate (p=0.6343; Figure 3). Cohorts that had a higher average age and higher percentage of white women showed significantly lower estimates of effect size (p=0.002 and p=0.0056, respectively; Figure 4, Table 4). The overall quality score of articles also explained significant heterogeneity in effect estimates with higher quality articles estimating smaller effect sizes (p=0.0004; Figure 4, Table 4).

Discussion

There was substantial heterogeneity across the eight studies with four showing lower adherence to cervical cancer screening guidelines among women with CSA relative to those without CSA (three showed no difference and one showed higher adherence). The overall pooled random effects estimate from the eight studies was not significant showing no overall association between CSA and screening (OR=0.76, 95% CI=0.51-1.14) with high heterogeneity (I^2= 73%). We found that some of the variability in results between studies was related to differences in the age and ethnicity of the women being studied and related to differences in the overall quality score articles received from the quality assessment (in all cases $p<0.0056$). Heterogeneity did not appear to be due to differences in adjustment for confounding between studies.

Although three studies reported on women from special populations (incarcerated or homeless), population type also did not show significance in the subgroup test. However, visual inspection of the forest plot shows that most studies are near OR=1 but for the general population all studies are to the left of OR=1, and for the special populations, two of the three fall above OR=1. Given that there were only three studies on the women in these special populations and that we pooled data on incarcerated and homeless women, the result of no differences based on population may be due to type II error given small sample size and heterogeneity in the special population group. It is also notable that all the women studied except for in one study were from the USA highlighting a knowledge gap for providers and public health professional regarding the association between CSA and cervical cancer screening outside of the USA.

We found that overall, the quality of reporting and internal validity among the studies diminishes the reliability of the evidence produced. Specifically, only two of the studies used medical records for screening adherence while the other six used self-report which is subject to recall bias and possibly social desirability bias. Studies that use medical records to collect screening data rather than self-report may better explain relationships between CSA and screening behaviors. Studies that lost points on reporting lost points due to not including a clear description of the patient's characteristics and/or don't describe the distributions of principal confounders. Internal validity was lower mainly due to studies using self-report for the main outcome (adherence to PAP screening) and due to subjects knowing the exposure and outcome of interest in three of the studies.

It is likely that using self-reporting of CSA results in reporting bias whereby fewer participants disclose the abuse than those who actually experienced it (Chandran et al., 2018; Katzenstein & Fontes, 2017) which could be due to feelings of embarrassment, desire for privacy, suppressed memories, etc. The result is that measures of CSA are likely underestimates that bias the results of studies towards the null, but the magnitude of that bias is not understood and difficult to study (Langeland et al., 2015). Future studies should work to estimate the frequency of unreported CSA among women of different demographic groups to better help estimate the impact of CSA on healthcare and health outcomes.

Given that barriers to in-person testing like embarrassment, transport and service costs, and a person's health characteristics exist, the development of self-sampling kits for HPV testing have been gaining attention. Numerous randomized clinical trials have shown that self-sampling can increase screening uptake by 113% compared to controls, and that self-screening had only a marginal effect linkage to clinical assessment and/or treatment (Yeh et al., 2019) and the FDA has approved self-collection of a vaginal sample for HPV. Primary care providers who suspect patients may be at risk for not getting recommended cervical cancer screenings should consider offering information about self-screening kits to increase screening uptake among hesitant women (Parker et al., 2024).

We did not find an overall association between CSA and screening and observed considerable differences in effect measures from the different studies. Some differences between studies were explained by differences in the age and ethnicity of the women being studied with the odds of following screening guidelines being lower among studies with a higher average age, higher percentage of white participants, and higher quality score. More studies that use medical record data for screening history and are on persons living in countries outside of the USA would help provide a more complete understanding of CSA and cervical cancer screening. Despite the overall effect measure being insignificant the studies showed that many women with history of CSA are at increased discomfort during pelvic exams. Therefore, it would likely be beneficial to women with CSA to be offered a self-sample test.

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Tables

Table 2.1. Modified Downs & Black quality assessment form

Original criteria	Scoring	Included?	Re-worded?
Is the objective of the study clear?	Yes= 1, No=0	yes	No
Are the main outcomes clearly described in the introduction or methods?	Yes= 1, No=0	yes	No
Are characteristics of the patients included in the study clearly described?	Yes= 1, No=0	yes	No
Are the interventions clearly described?	Yes= 1, No=0	yes	No
Are the distributions of principal confounders in each group of subjects clearly described?	Yes= 2, Partially=1, No=0	yes	No
Are the main findings of the study clearly described?	Yes= 1, No=0	yes	No
Does the study estimate random variability in data for main outcomes?	Yes= 1, No=0	yes	No
Have all the important adverse events consequential to the intervention been reported?	Yes= 1, No=0	no	n/a
Have characteristics of patients lost to follow-up been described?	Yes= 1, No=0	no	n/a
Have actual probability values been reported for the main outcomes except probability <0.001?	Yes= 1, No=0		No
Were subjects who were asked to participate in the study representative of the entire population recruited?	Yes=1, No=0, Unclear=0		No
Were those subjects who were prepared to participate representative of the recruited population?	Yes=1, No=0, Unclear=0		No
Were staff, places, and facilities where patients were treated representative of treatment most received?	Yes=1, No=0, Unclear=0	no	n/a
Was an attempt made to blind study subjects to the intervention?	Yes=1, No=0, Unclear=0	no	n/a
Was an attempt made to blind those measuring the main outcomes?	Yes=1, No=0, Unclear=0	Yes	Yes
If any of the results of the study were based on data dredging was this made clear?	Yes=1, No=0, Unclear=0	Yes	No
Was the time period between intervention and outcomes the same for intervention and control groups or adjusted for?	Yes=1, No=0, Unclear=0	No	n/a
Were the statistical tests used to assess main outcomes appropriate?	Yes=1, No=0, Unclear=0	Yes	No
Was compliance with the interventions reliable?	Yes=1, No=0, Unclear=0	Yes	Yes
Were main outcome measures used accurate? (valid and reliable)	Yes=1, No=0, Unclear=0	Yes	No
Were patients in different intervention groups recruited from the same population?	Yes=1, No=0, Unclear=0	Yes	Yes
Were study subjects in different intervention groups recruited over the same period of time?	Yes=1, No=0, Unclear=0	Yes	Yes
Were study subjects randomized to intervention groups?	Yes=1, No=0, Unclear=0	no	n/a
Was the randomized intervention assignment concealed from patients and staff until recruitment was complete?	Yes=1, No=0, Unclear=0	no	n/a
Was there adequate adjustment for confounding in the analyses from which main findings were drawn?	Yes=1, No=0, Unclear=0	Yes	No
Were losses of patients to follow-up taken into account?	Yes=1, No=0, Unclear=0	No	n/a

Table 2.2. Summary of study characteristics and scoring from the quality assessment for studies reporting on adherence to PAP screening guidelines

First Author, Year	Country	Year(s) data collected	N	Source of screening data	Adherence measure	Reporting score	External validity score	Internal validity score	Overall quality score
Alcala, 2017	USA	2009	1527	Self-report	PAP in last 3 yrs	7	2	6	16
Alcala, 2018	USA	2014	11,794	Self-report	PAP in last 3 yrs	6	2	6	15
Brandford, 2023	USA	2020	7464	Self-report	PAP in last 3 yrs	8	2	6	17
Farley, 2002	USA	n/a	736	Medical records	PAP in last 2 yrs	7	2	7	17
Kelly, 2018	USA	2010	290	Self-report	PAP in last 3 yrs	7	1	5	14
Kohler, 2021	USA	2017-2018	29	Self-report	PAP in last 3 yrs	7	0	4	11
Olesen, 2012	Australia	2003-2004	2095	Medical records	PAP in last 2 yrs	6	2	7	16
Ramaswamy, 2011	USA	2010	204	Self-report	PAP in last 3 yrs	7	1	5	14

Table 2.3. Summary of confounding variables using in multivariable models based on number of studies

Variable	**N studies**
Race/ethnicity	6
Age	4
Education	4
Insurance status	3
Marital status	2
Cancer status	2
Hysterectomy status	1
Cancer status	1
Language of survey	1
Annual household income	1
Physical abuse	1
Emotional abuse	1
Clinic location	1
Attitudes toward PAP	1
PTSD diagnosis	1
Has child/children	1
Welfare receipt	1
Employment	1
BMI	1
Smoking status	1
Illicit drug use	1

Table 2.4. Summary of results of meta-regressions for the effects of percentage white women in each cohort who were white, mean cohort age, and overall quality score on heterogeneity in effect size estimate for the association between CSA and adherence to PAP in adulthood

Subgroup test	**Estimate (β)**	**SE**	**p-value**
Mean age	-0.076	0.025	0.0024
Percent white	-0.019	0.007	0.0056
Overall quality score	-0.264	0.075	0.0004

Figures

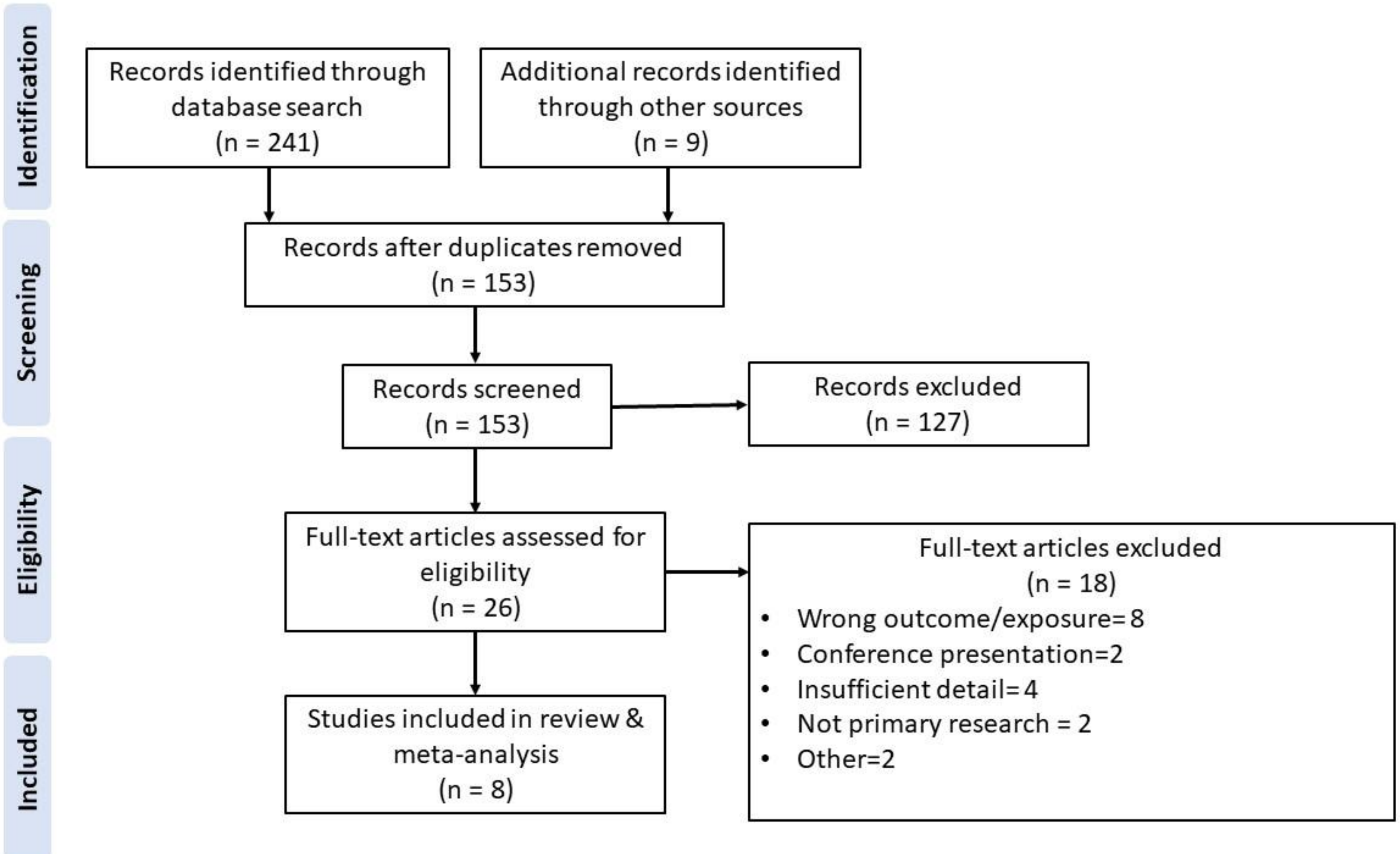

Figure 2.1. PRISMA diagram for study selection

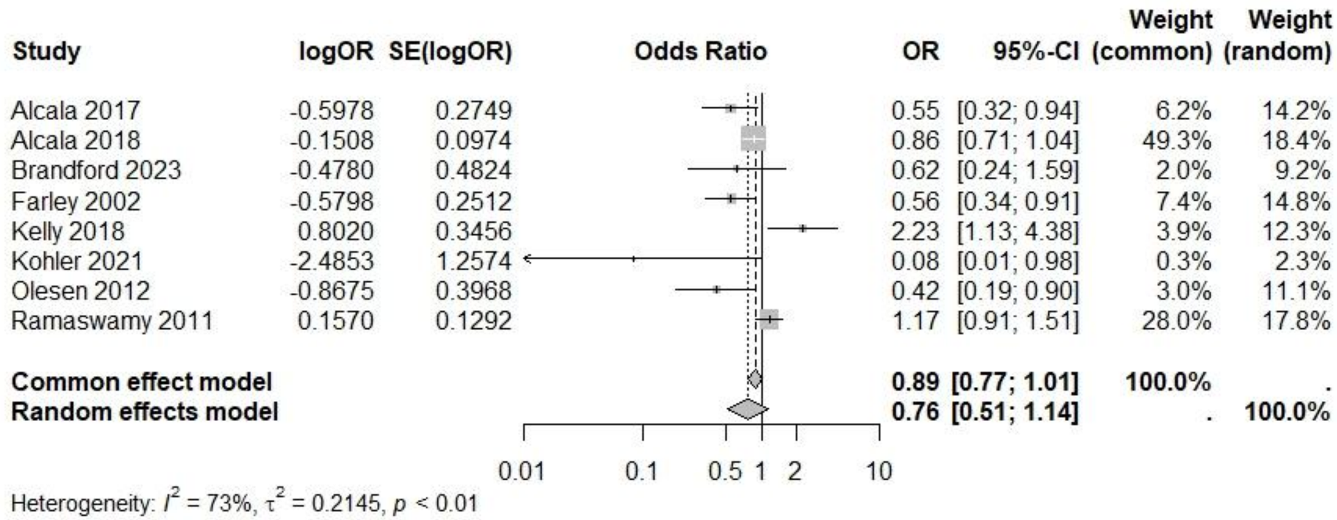

Figure 2.2. Results of overall meta-analysis for the association between CSA and adherence to PAP screening guidelines in adulthood.

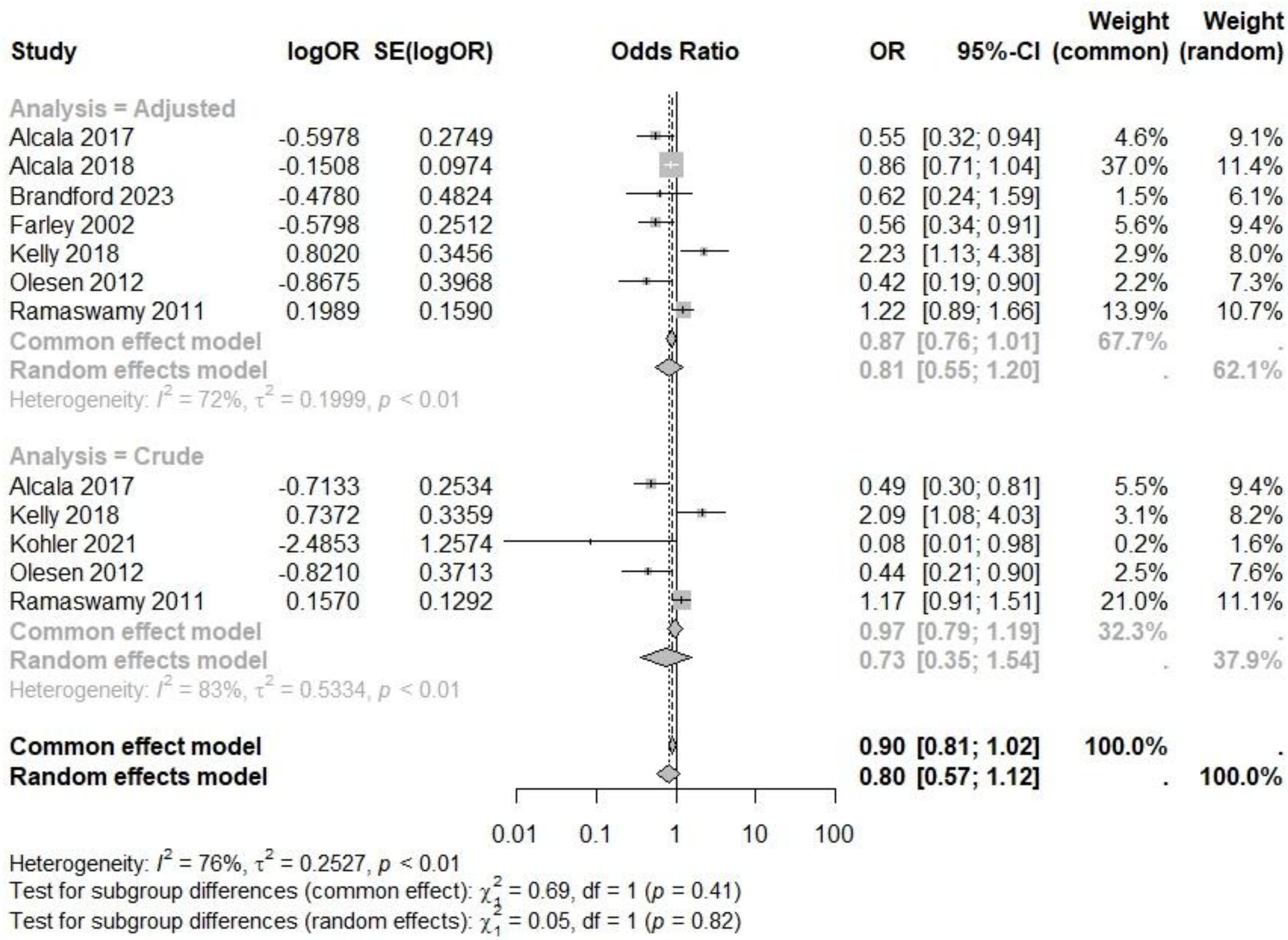

Figure 2.3. Forest plot showing results of subgroup test for differences in the association between CSA and adherence to PAP screening guidelines in adulthood based on if studies reported crude or adjusted odds ratios (OR).

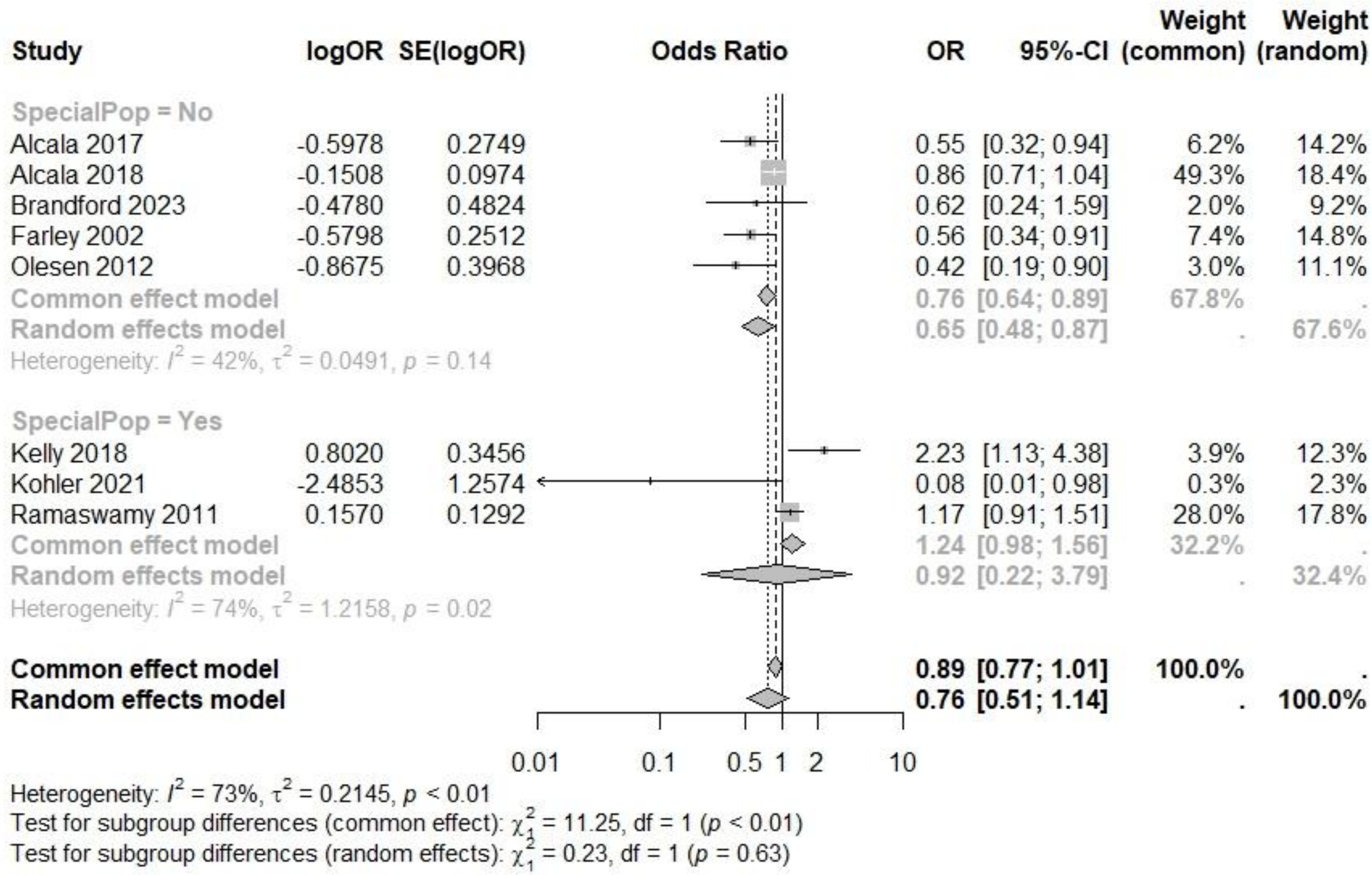

Figure 2.4. Forest plot showing results of subgroup test for differences in the association between CSA and adherence to PAP screening guidelines in adulthood based on if studies reported on the general population for a special population (either incarcerated or homeless women).

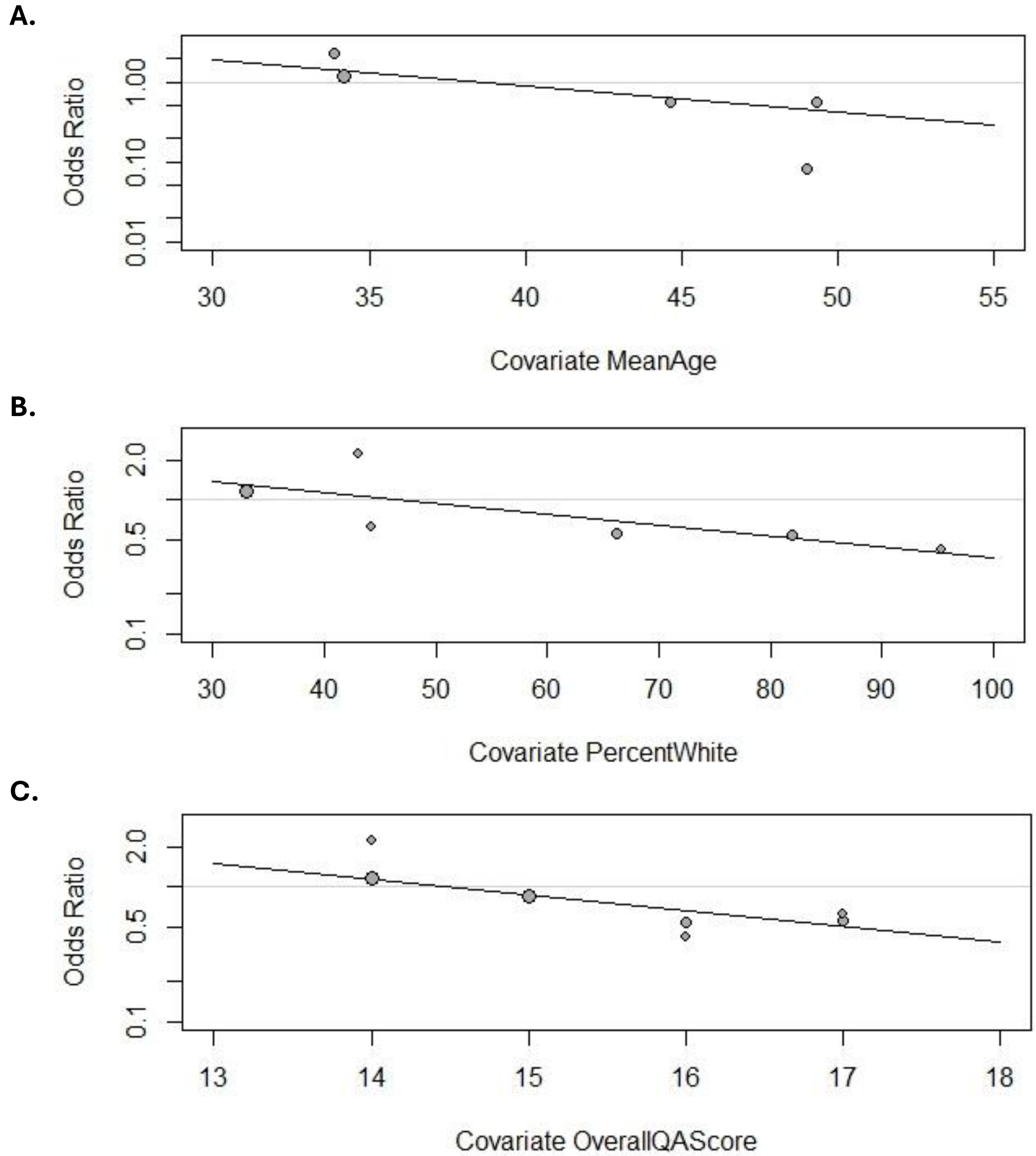

Figure 2.5. Bubble plots showing relationships between differences in the association between CSA and adherence to PAP screening guidelines in adulthood based on (A) the mean age and (B) the percentage of participants who were white in the study cohorts, and (C) the overall quality assessment score of each study.

Chapter 3: Adverse childhood experiences, obesity, and HPV vaccination among young adults in USA: A cross-sectional population-based study

Abstract

Introduction: Adverse childhood experiences (ACEs) and obesity are related to increased cancer risk and to one another, but their associations with HPV vaccination are not well studied and joint associations have not been evaluated. We examined individual and joint associations between ACEs, obesity, and HPV vaccination status using a national sample of 18–26-year-old adults.

Methods: Data from the 2021-2023 Behavioral Risk Factor Surveillance System (BRFSS) were analyzed. The primary outcome was HPV vaccination initiation (no shots vs one or more) and the exposure of interest was low vs high ACE exposure (0-2 vs ≥ 3ACE). We used eight measures of ACEs before the age of 18 years old to construct the binary ACE exposure variable**.** Weighted generalized linear regression (GLM) using the binomial distribution and the logit link were used to calculate adjusted prevalence ratios (aPR) and corresponding 95% CI for HPV vaccination. Additive and multiplicative interactions between ACE and obesity on HPV vaccination were also tested.

Results: The total analytical sample after data cleaning and inclusion criteria was 1,596 individuals. The weighted prevalence of HPV vaccination was 38.9% for men and 53.9% for women. In the weighted adjusted models, respondents with high ACE exposure (aPR= 1.801, 95%CI=1.777-1.826) and those with obesity (aPR=1.038, 95%CI= 1.022-1.054) had a higher prevalence of HPV vaccination compared to those with low ACE and without obesity, respectively. There was evidence for negative interaction between ACE and obesity on both the additive and multiplicative scales.

Conclusions: Our results suggest positive associations between ACEs, obesity, and HPV vaccination, but that in combination, the joint effects are antagonistic (less than additive and less than multiplicative combined effects). Overall vaccination was under 40% for males and 54% for females, highlighting the need for a higher rate of catch-up vaccinations among 18-26 year olds in the USA.

Keywords: *HPV, vaccination, Adverse Childhood experience, Obesity, BMI, cancer*

Introduction

Human papillomavirus (HPV) is the most common sexually transmitted infection worldwide (Forman et al., 2012). Left untreated, most HPV infections go away, but ongoing infection with oncogenic types can lead to precancerous lesions and cancer (De Martel et al, 2017). Nearly 100% of all cervical cancer cases are caused by HPV infection and HPV is responsible for a substantial fraction of other anogenital and oropharyngeal cancers in both men and women including: penis, vulva, vagina, anus, tongue and tonsils (Markowitz et al. 2018). Worldwide, an estimated 630,000 new cancer cases were attributed to HPV in 2017 (Markowitz et al. 2018), an attributable fraction of 4.5% of all cancers (Parkin et al. 2006; Forman et al. 2012). Although HPV-related incident cancer is still high, rates have been decreasing, particularly in developed countries, due to increased preventative screening and more recently, the HPV vaccine (Markowitz et al. 2018).

There are currently three HPV vaccines available, and all are considered highly efficacious at preventing HPV-attributable cancers with efficacy of over 80% for cervical cancer prevention with just one dose (Markowitz et al., 2013). Since HPV vaccines were first introduced, the prevalence of HPV infection and incidence of cervical cancers among females aged 14 to 29 years have declined nationally in the US by over 80% (Mix et al., 2021; Rosenblum et al., 2022). The Advisory Committee on Immunization Practices (ACIP) has recommended HPV vaccination for all boys and girls at 13 years of age, and catch-up HPV vaccination for all men and women through age 26 years since 2019 (Meites, 2019).

Despite high efficacy for HPV-related cancer prevention, many young people do not to receive the HPV vaccine. Among adolescents in 2020, coverage (at least one dose) was 75.4% (73.7% for males and 76.8% for females; Lu et al., 2022). Although some states allow minors to obtain an HPV vaccine, in most states parental permission is required. Because 18-26 year-olds are old enough to legally self-consent for vaccination and are still at ages recommended for catch-up vaccination, they are a key demographic group for improving vaccine uptake. Although not as well studied as adolescents, approximately 36% percent of 18-26 y/o individuals have received at least one HPV vaccine (Arevalo et al., 2023). The CDC's Healthy People 2030 goal for reaching desired herd immunity is 80% HPV vaccination coverage, leaving about a 44% percentage gap to be filled through public health efforts.

Obesity is associated with reduced preventative care services utilization but not well studied as a potential source of HPV vaccine hesitancy. Defined as having a body mass index (BMI) of greater or equal to 30kg/m^2, obesity is a common risk factor in the USA with a prevalence of ~28% among 18-25 year-olds (Ellison-Barnes et al., 2021). Women with obesity have reported avoiding preventive women's healthcare services due to embarrassment, perceived provider judgment/disrespect, unsolicited weight loss advice, and equipment problems (Amy et al., 2006). Women with obesity are less likely to receive cervical and breast cancer screening than their non-obese counterparts (Wee et al., 2000), despite obesity being associated with higher cancer risk and mortality (Calle et al., 2003). The few studies that exist on obesity and HVP vaccination have shown mixed results: one found individuals with obesity were as likely to begin HPV vaccine as normal weight peers (Sundaram et al., 2016), another found that adolescent girls and young women with obesity were less likely to report HPV vaccination and reported vaccination at a later age (Harris et al., 2019). Given that obesity is a risk factor for cancer mortality, prevalent in the population, and associated with disparities in preventive care services, more evidence on the association between obesity and HPV vaccination is needed.

Another poorly understood but potentially important factor for HPV vaccination is Adverse Childhood Experiences (ACEs). ACEs are traumatic exposures that occur before the age of 18 years old. Examples of ACEs include: physical, sexual, or emotional abuse, living with a someone who was suicidal, abused drugs/alcohol, or the incarceration of a family member (Felitti et al., 1998). ACEs are prevalent with ~64% of the USA adult population experiencing one or more ACE and ~17% experiencing four or more (Swedo, 2023). ACEs can impact the body directly (e.g., altered metabolic and hypo-pituitary axis function; Berens, et al. 2017) as well as via changes to the social and emotional development of survivors which can lead to avoidance behaviors, emotion dysregulation, feelings of powerlessness, distrust of authority, and risky health behaviors in adulthood (Felitti et al., 2010). Having three or more ACEs has been found to be associated with 52.6% higher risk of HPV-related cancer (Kalra et al., 2023) yet the impact of ACEs on HPV vaccination is not well understood. Early evidence has shown surprising results with some individual ACEs, and the number of ACEs, being positively associated with HPV vaccination (Poudel et al., 2024; Zhang et al. 2023). Given that ACEs are known to increase cancer risk and impact risky-health behaviors, more research is needed on the impact of ACEs on HPV vaccination behavior.

ACEs are associated with obesity: the odds of obesity in adulthood are approximately 46 times higher among individuals with multiple ACEs relative to those with one or none (Wiss & Brewerton 2020; Schroeder et al., 2021). Potential mediating mechanisms that drive the relationship between ACEs and adult obesity include: depression, anxiety, substance abuse, somatization, and eating disorders. Adults with four or more ACEs have 4- to 12-fold increased risks for alcoholism and depression (Felitti et al. 1998). Obesity can be used as a defense mechanism as, for example, survivors of childhood sexual abuse sometimes overeat to appear undesirable and ward off unwanted advances, while adults raised with food insecurity sometimes eat to feel safe (Martin & Ferris, 2007; Yokiel, 2012). Individuals who experience ACE may be more likely to have obesity that influences key health decisions like whether to receive the HPV vaccine or not. For patients with obesity and high ACE, behavioral interventions that incorporate psychotherapy, such as CBT, may be more successful for changing risky health behaviors than educational approaches that appeal to health needs alone.

The purpose of the current study is to (1) assess associations of ACEs and obesity on HPV vaccination and (2) explore the joint associations of ACEs and obesity on HPV vaccination, controlling for known confounding demographic variables using a nationally representative cross-sectional sample from the Behavioral Risk Factor Surveillance System (BRFSS). If ACE interact with obesity to influence vaccination behavior, then ACE screening can be used to provide trauma-informed care to better treat symptoms (and thus indirectly health behaviors) among at-risk patients.

Methods

Study Design

This cross-sectional study used data from the Behavioral Risk Factor Surveillance System (BRFSS), one of the largest ongoing surveillance systems in the world. The BRFSS is led by the Centers for Disease Control and Prevention (CDC) and 50 U.S. states participate annually. Each state has a State Coordinator who works with the CDC to lead data collection, reporting, and interviewer training/contracting in their state. The BRFSS uses a standardized core questionnaire that has optional additional modules to collect data on chronic health conditions, health-related risk behaviors, and use of preventative services nationwide. Trained interviewers administer the BRFSS continuously each year using Random Digit Dialing (RDD) techniques on landlines and cell phones. To adjust for non-response, the BRFSS uses iterative proportional fitting/ranking to weight survey data for demographic variables in a complex procedure to ensure that weighted data are representative of the populations included in the survey. Data used for weighting include age, race and ethnicity, sex, education level, marital status, home ownership, and type of telephone ownership (landline and/or cellular telephone) for geographic regions within states.

BRFSS data from 2021-2023 were used in this study. We followed guidance from BRFSS and the CDC on combining data across years to create one dataset with indicators for each year. The average overall BRFSS response rate across 2021, 2022, and 2023 was 44.6% (range 44-45%). A total of 15 states administered the HPV module during the three years eligible for our study (Appendix 2). After reducing the sample to the states that administered the HPV and ACEs modules, respondent age to 18-26 years old, and the sample to responses that answered "yes" or "no" to the HPV vaccination question, the final analytical sample contained 1,596 people. This study used only publicly available secondary data and did not require IRB approval.

Measures

Outcome

Data on HPV vaccination status came from the optional BRFSS module HPV Vaccination and was characterized as "yes/no". Specifically, responses to the question, "Have you ever had an H.P.V. vaccination?" were coded as 1= yes, 0= no, with don't know/unsure/blank responses removed from the dataset. Although not well studied, we expect the accuracy of self-reporting on this question to be high given that our study population is young adults and that parental recall of adolescents vaccination status has been shown to be comparable to provider reporting (Boakye et al., 2017).

Exposures

Obesity

Two BRFSS questions are used to calculate BMI data for participants: self-reported weight and height. A standard formula of weight in kilograms divided by the square height in meters produced BMI estimates is used by BRFSS to produce a calculated variable for BMI category according to CDC definitions of obesity with BMI $\geq$ 30 (May et al., 2013).

Adverse Childhood Experiences (ACEs)

We used the 11 survey questions in the BRFSS state-added ACE module to quantify eight categories of ACE occurring before the age of 18 years old: (1) sexual abuse, (2) emotional abuse, (3) physical abuse, (4) intimate partner violence, (5) mental illness in the household, (6) substance abuse in the household, (7) parental separation or divorce, and (8) familial incarceration (Appendix 1). Any form of sexual abuse (touched, made to touch, or raped) constituted a "yes" code for sexual abuse while no forms of sexual abuse were assigned a "no". Sexual, emotional, and physical abuse as well as witnessing intimate partner violence were labelled "yes" if it occurred once or more than once. All other ACE questions were asked as yes or no and coded as such. The eight individual ACEs were summed to create an ACE score which was then dichotomized into high ($\geq$3) and low (0-2) ACE exposure as done previously (Clements-Nolle et al., 2018; Thomas et al., 2023).

Covariates

Data on demographic characteristics of the participants was also extracted for use in the analyses. Specifically, we extracted (and coded) the variables: sex (M/F), age (18-22 yrs/23-26 yrs), race (white/non-white), ethnicity (Hispanic/non-Hispanic), income (less than $25k, $25-

50K, ≥50K), education (college degree/no college degree), and marital status (married/unmarried). We also controlled for having a primary care provider (yes/no).

Analyses

We used weighting procedures to estimate the weighted prevalence of demographic, exposure, and outcome data with 95% confidence intervals (CI). The prevalence of HPV vaccination was compared to the demographic variables, obesity, and ACE status, using weighted Chi-square tests with 95% CI. Weighted generalized linear regression (GLM) using the binomial distribution and the logit link were used to calculate adjusted prevalence ratios (aPR) and corresponding 95% CI for HPV vaccination. To examine the association between ACE status and HPV vaccination our GLM included ACE status and adjusted for sex, age, race, ethnicity, income, education, marital and primary care provider status. We then repeated this procedure replacing the ACE status variable with the obesity status variable. Interaction between obesity and ACE status on HPV vaccination was assessed on both the multiplicative and additive scales. Multiplicative interaction examines relative differences while additive interaction examines absolute risk (i.e., If the combined effect of two exposures is larger or smaller than the product of their individual effects vs. if the combined effect is larger or smaller than the sum of the individual effects; VanderWeele & Knoll, 2014). Prevalence ratios (PRs) were calculated because the outcome (HPV vaccination) was not rare (~45.9%) making PRs more appropriate for the interaction tests than odds ratios (VanderWeele et al., 2014). We used adjusted prevalence ratios based on the demographic factors and primary care provider status in our interaction tests to control for confounding. Relative excess risk due to interaction (RERI) was used to examine evidence of interaction on the additive scale and corresponding 95% CI were calculated using the delta method (Hosmer & Lemeshow, 1992; VanderWeele & Knoll, 2014). In all cases significance was assessed at $\alpha = 0.05$ and all analyses were carried out in SAS version 9.4 (SAS Institute Inc.).

Results

Sample characteristics

The total analytic sample contained 1, 596 individuals who were aged 18-26 years old and provided a “yes” or “no” answer to the HPV vaccination question and were given the ACE module. The majority of participants were female (50.8%), 18-22 years old (60.1%), and white non-Hispanic (51.2%; Table 1). Most participants were unmarried (89.9%) and reported having at least one primary care provider (71.0; Table 1). A total of 37.8% of participants reported high exposure (≥3 ACE) and 21.4% reported weight and height data corresponding to obesity (Table 1). HPV vaccination of one or more doses was reported by 46.5% (95% CI 43.4-49.7) of participants (Table 1).

The prevalence of HPV vaccination was related to several factors. Females reported higher vaccination than males (53.9% vs. 38.9%, $p<0.001$; Table 2). Vaccination was highest among those with an annual income over $50k (59.6% vs. 35.5% and 40.3% for $25-50k and less than $25k, respectively; Table 2). The prevalence of HPV vaccination was almost 20% higher among individuals with a college degree compared to those without a college degree ($p<0.001$; Table 2). Unmarried participants had higher vaccination than married participants (47.6% vs. 37.5%, $p=0.0482$; Table 2). Participants who reported having one or more primary care providers also had a higher proportion of vaccinated individuals than among those who reported not having a primary care provider (52.4% vs. 31.7%; Table 2). Obese and non-obese individuals had similar vaccination levels (48.7% and 45.9%, respectively) while individuals reporting high ACE exposure had a higher proportion of vaccinated individuals (53.1%) than those reporting low ACE exposure (42.5%; Table 2).

Individual associations

After controlling for demographic factors, the adjusted prevalence ratios showed significant positive associations (Table 3). People with obesity (aPR=1.038, 95%CI= 1.022-1.054) were slightly more likely to be vaccinated for HPV compared to those without obesity. For ACEs, people reporting high ACE exposure had 80% higher prevalence of HPV vaccination (aPR= 1.801, 95%CI=1.777-1.826) compared to those who reported low ACE exposure.

Joint associations

There was evidence of interaction on the additive and multiplicative scales (Table 4). The additive scale showed a negative/subadditive interaction (RERI=-1.917, 95% CI= -2.01, -1.82). The multiplicative interaction estimate was 0.302 (95% CI= 0.29, 0.31) indicating a negative, antagonistic interaction on the multiplicative scale.

Discussion

ACE and obesity are important factors that influence both cancer risk and healthcare service utilization but are poorly understood individually and have not been studied in combination despite being related to one another (Wiss & Brewerton 2020; Schroeder et al., 2021). The purpose of the current study was to assess associations of ACEs and obesity on HPV vaccination and explore the joint associations of ACEs and obesity on HPV vaccination, controlling for known confounding demographic variables using a nationally representative sample. Similar to other population-based studies (Ellison-Barnes et al., 2021; Swedo, 2023), we found both exposures to be common: two in ten respondents reported obesity and almost four of ten reported high ACE exposure (≥3 ACEs). We found evidence that ACEs were positively associated with HPV vaccination, a small positive effect of obesity on HPV vaccination, and a negative, antagonistic interaction between ACEs and obesity on vaccination status.

Although somewhat counterintuitive, our finding of a positive association between ACEs and HPV vaccination is consistent with most other early studies (Proudel et al., 2024; Zhang et al. 2023) and published abstracts (Kalra et al., 2023) on this topic (but see Nunes, 2020). The positive association between ACEs and HPV vaccination could be due in part to increased provider recommendations for vaccination and/or resilience and post-traumatic growth. Survivors of childhood sexual abuse are recommended the HPV vaccine, even at ages under 13 years of old, due to possible HPV exposure during abuse and because survivors of childhood abuse are more likely to engage in risk behaviors associated with cancer (Garland et al., 2015; Holman et al., 2016). Moreover, some individuals experience positive psychological changes after healing form negative life experiences, and this post-traumatic growth may have positive influences on some health behaviors such as HPV vaccination (Klika & Herrenkohl, 2013; Widyorini et al., 2022). Future work would benefit from examining factors related to ACE resilience and health behaviors. To date, all studies have utilized BRFSS data so future research should also aim to diversify the data used for this research topic.

The association we found between obesity and HPV vaccination was very small (3.8% higher adjusted prevalence) and early results in the literature have been mixed. One previous population-based study found a negative association between obesity and HPV vaccination status as well as later age at vaccination (Harris et al., 2019). However, in a university-based pediatric sample no association between HPV vaccination status and BMI was observed (Manickavasagam et al., 2014), and in a national sample, vaccine uptake was the same among overweight/obese individuals and their normal weight peers (Sundaram et al., 2016). Given the mixed results in the literature on HPV vaccination and obesity combined with known risk factors associated with obesity (i.e., lower healthcare utilization and higher cancer rates), this topic merits further research.

To our knowledge, this is the first study to assess the joint effects of obesity and ACEs on HPV vaccination status and we found evidence of a negative, antagonistic interaction. This result suggests that one exposure might be partially negating the protective effect of the other, either obesity reducing the positive impact of ACEs, or ACEs reducing the small impact of obesity, on the prevalence of HPV vaccination. It's possible that people who have both obesity and ACEs may have lower resilience than those who have one or the other, or that because ACEs and obesity are related, they overlap rather increase the resulting prevalence. Therefore, future work should consider that obesity may be an effect mediator rather than effect modifier, for the relationship between ACEs and HPV vaccination.

Limitations

The limitations of this study include reliance on self-reported data, sample sizes, and survey response rate. Self-reported compared to clinician measured height/weight data used to estimate obesity have shown sensitivity and specificity of 71% and 98% for males, and 78% and 96% for females (Lucca et al. 2010). Therefore, false negatives may skew results toward the null by including some obese individuals in the nonobese category, especially for males. In a sample of young adults, the self-reported prevalence of overweight/obesity was 33% and based on the measured data was 39% (P=0.16; Bowing et al., 2012). In terms of ACEs, survivors of abuse are often hesitant to report incidents because of shame and fear of retribution. Thus, the prevalence of childhood abuse is likely underestimated (Garland et al., 2015) also causing misclassification and biasing the results towards the null. Additionally, the results of this study are generalizable only to people who 18-26 years old, and who answered the ACE and HPV questions. This was a relatively small sample size (1,596 individuals) representative of only the 15 states that administered the ACE and HPV questions in 2021-2023. And finally, the BRFSS had a response rate of 44.6% for the years included in this study which may result in response bias in the study sample.

Conclusions

In this study and very limited existing literature, ACEs were positively associated with HPV vaccination. We found that obesity had a small positive association with HPV vaccination and evidence of negative additive and multiplicative interaction between ACEs and obesity. Increased screening for ACEs in primary care and referrals for HPV vaccination services may contribute to the observed association. Further research on the relationship between obesity and HPV vaccination, individually and in joint association with ACEs is warranted.

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Tables

Table 3.1. Descriptive statistics of US young adult sample from BRFSS 2021-2023

Total *N* = 1,596		
Variable	Unweighted N	Weighted % (95% CI)
Sex		
Male	854	49.2 (45.9, 52.5)
Female	742	50.8 (47.5, 54.1)
Age		
18-22 years	841	60.1 (57.0, 63.2)
23-26 years	755	39.9 (36.8, 43.0)
Race/Ethnicity		
White	862	51.2 (48.0, 54.5)
Hispanic	268	17.3 (14.8, 19.8)
Other[a]	451	31.5 (28.4, 34.6)
Annual Income		
Less than $25 k	212	17.6 (14.7, 20.5)
$25 k-50 k	364	29.9 (26.5, 33.2)
$50 +	625	52.5 (48.8, 56.2)
Education		
No college degree	1,178	84.4 (82.4, 86.3)
College degree	414	15.6 (13.7, 17.6)
Marital Status		
Married	170	10.1 (8.3, 11.8)
Unmarried	1,416	89.9 (88.2, 91.7)
Primary Care Provider		
No (no or unsure)	480	29.0 (26.2, 31.92)
Yes (one or more)	1,110	71.0 (68.1, 73.8)
Body Mass Index (BMI)		
Not obese (BMI < 30)	1,251	78.6 (75.9, 81.2)
Obese (BMI ≥ 30)	345	21.4 (18.8, 24.1)
ACE Exposure		
Low: 0-2 ACEs	992	62.2 (59.1, 65.4)
High: ≥3 ACEs	604	37.8 (34.6, 40.9)
HPV Vaccination Initiation		
Yes (≥1 dose)	705	46.5 (43.4, 49.7)
No (0 doses)	891	53.5 (50.3, 56.6)
HPV Vaccination Completion		
No (1 dose)	410	75.2 (70.2, 80.2)
Yes (≥1 doses)	132	24.8 (19.8, 29.8)

Notes: N= sample size; 95% CI indicates 95% confidence interval; ACE= Adverse Childhood Experience.
[a]Other Race/Ethnicity includes Asian, Black, Native Hawaiian and Pacific Islander, and American Indian/Alaskan Native.

Table 3.2. Distribution of weighted prevalence of HPV vaccination initiation and completion by demographics among US young adult sample from BRFSS data 2021-2023.

	HPV Vaccine Initiation	
Variable	Weighted % (95% CI)	p-value
Sex		
Male	38.9 (34.4, 43.3)	<0.0001
Female	53.9 (49.3, 58.6)	
Age		
18-22 years	47.4 (43.0, 51.7)	0.5372
23-26 years	45.3 (40.6, 50.0)	
Race/Ethnicity		
White	48.0 (43.8, 52.3)	0.0585
Hispanic	37.4 (29.2, 45.6)	
Other[a]	48.0 (43.8, 52.3)	
Annual Income		
Less than $25 k	40.3 (31.1, 49.6)	<0.0001
$25 k-50 k	35.5 (29.1, 42.0)	
$50 +	59.6 (31.1, 49.6)	
Education		
No college degree	43.2 (39.5, 46.8)	<0.0001
College degree	64.2 (58.5, 69.9)	
Marital Status		
Unmarried	47.6 (44.2, 51.0)	0.0482
Married	37.5 (28.5, 46.6)	
Primary Care Provider		
No (no or unsure)	31.7 (26.2, 37.1)	<0.0001
Yes (one or more)	52.4 (48.6, 56.3)	
Body Mass Index (BMI)		
Not obese (BMI < 30)	45.9 (42.3, 49.5)	0.4979
Obese (BMI ≥ 30)	48.7 (41.7, 55.6)	
ACE Exposure		
Low: 0-2 ACEs	42.5 (38.4, 46.7)	0.0017
High: ≥3 ACEs	53.1 (48.1, 58.1)	

[a]Other Race/Ethnicity includes Asian, Black, Native Hawaiian and Pacific Islander, and American Indian/Alaskan Native.

Table 3.3. Association between HPV vaccination outcomes (initiation and completion), demographic factors, and ACEs among US young adult study sample from BRFSS data 2021-2023.

	HPV Vaccination Initiation	
Variable	**aOR**	**95% CI**
Body Mass Index (BMI)		
Not obese (BMI <30)	1 (ref)	-
Obese (BMI ≥ 30)	1.038	1.022, 1.054
ACE Exposure		
Low: 0-2 ACEs	1 (ref)	-
High: ≥3 ACEs	1.801	1.777, 1.826
Both models were adjusted for sex, age, race, ethnicity, education, income, marital status, and having a primary care provider.		

Table 3.4. Multiplicative and additive interaction between ACEs and obesity on HPV vaccination status, BRFSS, 2021-2023

	HPV Vaccination	
	aPR (95% CI)	**aPR (95% CI)**
Obesity		
1. Multiplicative Interaction	**Low ACEs[a]**	**High ACEs[b]**
Not Obese[c]	Reference	2.02 (1.98, 2.06)
Obese[d]	2.302 (2.24, 2.37)	1.405 (1.36, 1.45)
Multiplicative Interaction Estimate	**0.302 (0.29, 0.31)**	
2. Additive Interaction (RERI)	**-1.917 (-2.01, -1.82)**	

ACEs: adverse childhood experiences; aPR: adjusted prevalence ratio; CI: confidence interval.
All models were adjusted for sex, age, race, ethnicity, education, income, marital status, and primary care provider status.
[a]Low ACEs=0-2. [b]High ACEs=3+. [c]BMI<30. [d]BMI≥30.

Appendices

Appendix 3.1. Summary of ACE BRFSS items used in study

ACE Survey Questions	Response options	ACE Category
Did you live with anyone who was depressed, mentally ill, or suicidal?	1=Yes 2=No 7=DK/NS 9=Refused	Mental illness in household
Did you live with anyone who was a problem drinker or alcoholic?	1=Yes 2=No 7=DK/NS 9=Refused	Substance abuse in household
Did you live with anyone who used illegal street drugs or who abused prescription medications?	1=Yes 2=No 7=DK/NS 9=Refused	
Did you live with anyone who served time or was sentenced to serve time in a prison, jail, or other correctional facility?	1=Yes 2=No 7=DK/NS 9=Refused	Familial incarceration
Were your parents separated or divorced?	1=Yes 2=No 8=Parents not married 7=DK/NS 9=Refused	Parental separation/divorce
How often did your parents or adults in your home ever slap, hit, kick, punch or beat each other up?	1=Never 2=Once 3= >once 7=DK/NS 9=Refused	Witness intimate partner violence
Before age 18, how often did a parent or adult in your home ever hit, beat, kick, or physically hurt you in any way? Do not include spanking. Would you say—	1=Never 2=Once 3= >once 7=DK/NS 9=Refused	Physical abuse
How often did a parent or adult in your home ever swear at you, insult you, or put you down?	1=Never 2=Once 3= >once 7=DK/NS 9=Refused	Emotional abuse
How often did anyone at least 5 years older than you or an adult, ever touch you sexually?	1=Never 2=Once 3= >once 7=DK/NS 9=Refused	Sexual abuse
How often did anyone at least 5 years older than you or an adult, try to make you touch sexually?	1=Never 2=Once 3= >once 7=DK/NS 9=Refused	
How often did anyone at least 5 years older than you or an adult, force you to have sex?	1=Never 2=Once 3= >once 7=DK/NS 9=Refused	

Appendix 3.2. States that administered the HPV & ACEs modules BRFSS 2021-2023

Year	**HPV Module States**	**ACEs Module States**
2021	Delaware, Georgia, Hawaii, Massachusetts, Mississippi, New Jersey, Tennessee, & West Virginia	Arkansas, Iowa, Mississippi, Nevada, N: Alabamaew Hampshire, North Dakota, Oregon, South Carolina, Virginia, Wisconsin, Kansas, Maine, New York, Ohio, New Jersey
2022	Arkansas, Delaware, Hawaii, Massachusetts, New Jersey, Oklahoma, & New York	Arkansas, Florida, Iowa, Nevada, North Dakota, Oregon, South Dakota, Virginia, Arizona, Ohio, New Jersey, Oklahoma
2023	Delaware, Illinois, Maryland, Massachusetts, Missouri, & New Jersey	Delaware, Florida, Georgia, Missouri, Nevada, New Jersey, Oregon, Rhode Island, Tennessee, Virginia, Ohio, Maryland

Chapter 4: Impacts of COVID-19 on late-stage cervical diagnosis and first course treatment delays among at risk groups

Abstract

Background. During the COVID-19 pandemic, US states issued stay-at-home orders, social distancing guidelines, and temporarily banned all non-elective medical procedures. Women's health service utilization went down markedly for cervical exams during this time, with reductions over 80% compared the average of the preceding five years. However, associated impacts of COVID-19-related disease outcomes are less understood. The purpose of this study was to detect pandemic-related impacts to cervical cancer stage at diagnosis and treatment initiation, and to evaluate if well-known existing disparities were worsened by the pandemic.

Methods. Data on 22,828 incident cancer cases were obtained from the National Cancer Institute's SEER Research Plus Database (SEER-22). Logistic regression was used to model the likelihood of late-stage diagnosis, and a zero-inflated Gamma Generalized Linear Model was used to estimate the number of days from diagnosis to treatment, both before (2015-2019) and during the first two years of the COVID-19 pandemic (2020-2021) based on race, ethnicity, income, age, and residency (rural vs urban). Next, we used the baseline data (2015-2019) to construct pre-COVID models, incorporating the covariates, to establish predicted values for the first (2020) and second (2021) year of the pandemic. The observed proportion (O) of late-stage diagnoses, and mean time from diagnosis to treatment, were compared to the expected values (E) using the ratio of O:E and 95% confidence interval to determine significance.

Results. The percentage of participants with late-stage diagnosis was higher both years (60.9% and 61.5% for 2020-2021, respectively) of the pandemic than in the preceding five years (56.4%; O:E=1.02, 95% CI=1.00-1.04). Around 24-28% of participants each year were given treatment the same day they were diagnosed and mean number of days from diagnosis to treatment was lower in 2015-2019 (36.0 days ±0.3 SE) than during the second year of the pandemic (40.12 ± 0.7 SE days, O:E= 1.08, 95% CI=1.04-1.13). Both before and during the pandemic, Black and Hispanic women were more likely to be diagnosed at a late stage, and to experience longer treatment wait times than their White and non-Hispanic peers (in all cases $p \leq 0.017$). For Hispanic women, disproportionate impacts were widened by the COVID-19 pandemic (both outcomes in 2020 and late-stage diagnosis in 2021, O:E ≥ 1.040 in all cases).

Conclusion. Our study highlights that racial and ethnic disparities remain important areas of public health equity for cervical cancer treatment and outcomes, independent of COVID-19. More work is needed to identify and establish mitigating measures for these disparities, particularly among certain racial and ethnic groups that are disproportionately impacted. Future studies should also aim to better evaluate disproportionate impacts of COVID-19 on cervical cancer outcomes among rural and urban areas.

Key words: *Covid-19, coronavirus, cervical cancer, stage at diagnosis, treatment delays, cancer disparities*

Introduction

During the COVID-19 pandemic women's healthcare service utilization went down due to nonessential medical service bans, social distancing guidelines, and public concerns about safety (Becker et al., 2021; Behera 2023; Whaley et al. 2020). Advisement by the Surgeon General on the 17th of March, 2020, led to the Centers for Medicare & Medicaid Services (CMS) announcement that all elective surgeries, non-essential medical, surgical, and dental procedures would be delayed during the 2019 Novel Coronavirus (COVID-19) outbreak to save resources for responding to the pandemic: this is when most states issued non-essential medical services bans. As a result, there was a decrease in HPV vaccination uptake and coverage starting from March 2020 (Ferrara et al., 2022). From Mar-April 2020 the US HPV vaccination rate was 23% of the rate for previous years (Daniels et al., 2021). Changes in cervical screening test volumes related to COVID-19 are well studied, and show decrease in the number of cervical exams performed during 2020 compared to previous years of over 50% (Ferrara et al., 2022). Cervical exam rates were the lowest in April 2020, at 84% lower than 5-year average (DeGroff et al., 2021).

Compared to HPV vaccination and screening impacts, less is known about how disease outcomes may have been impacted by COVID-19 related care disruptions. To date, only three studies have examined COVID-19 related disruptions to the cancer care outcomes of stage at diagnosis (Bonadio et al., 2021), time from diagnosis to treatment (Patel et al., 2022), or both (Popescu et al., 2022). These studies were carried out in Brazil (Bonadio et al., 2021), Romania (Popescu et al., 202), and the US (Patel et al., 2022; Mumper 2025). Results from these studies consistently indicated that the COVID-19 pandemic was associated with a higher percentage of late-stage cervical cancer diagnoses, and increased treatment delays. One study from the US (Patel et al., 2022) was an online survey distributed through listservs for patient groups/organizations and on social media evaluating care delays, and the other used a sample of just over 300 incident cervical cancer cases from the state of Utah to look at late stage diagnoses, but a population-based US study on COVID-19 impacts to cervical cancer diagnosis stage and/or time to treatment is needed.

Standard treatment for cervical cancer depends on the stage at diagnosis and other factors like patient age, overall health, and concerns about fertility. Surgical treatment approaches are generally recommended for women with early-stage cervical cancer: radical hysterectomy (removal of the utuerus, cervix, and parts of the vagina and parametrium) has long been the recommended treatment while simple hysterectomy (uterus and cervix removal only) has been more widely used recently due to similar recurrence rates as the more invasive/extensive radical procedure (Plante et al., 2024). If women do not desire to maintain fertility, radiation therapy is another treatment option which is often combined with chemotherapy to treat advanced cervical cancer (Chargari et al., 2022). Immunotherapies like Pembrolizumab are an emerging approach to target cancer cells but are not yet widely used or available (Lorusso et al., 2024).

Pandemic-related disruptions in preventive services may have widened existing cancer disparities among key at risk groups. In the US, Non-Hispanic Blacks and Hispanics are more likely to be diagnosed with later stages of cervical cancer and have worse treatment and survival outcomes than their non-Hispanic White counterparts (Beavis et al., 2017; Coker et al., 2009; Islami et al., 2019). For PAP screening, early evidence indicates that Hispanic women experienced a greater decrease during COVID-19 than non-Hispanic White women (Nguyen et al., 2024). Limited existing literature has also indicated a negative effect of COVID-19 on treatment delays among Black and Hispanic women (Patel et al., 2022). Women in rural versus urban populations in the US are also at increased risk for late stage of diagnosis and treatment delays for cervical cancer (Yu et al., 2019; Zahnd et al., 2018), and saw greater reductions in cervical cancer screening during the pandemic than their urban counterparts (Bermudez et al., 2024; Borders & Wiggins, 2024; DeGroff et al., 2021) but effects on disease and treatment outcomes are not known. If COVID-19 worsened racial and rural/urban disparities in cervical cancer stage at diagnosis and/or time from diagnosis to treatment, then strategies to reduce these disparities are needed more than ever to reverse trends and optimize recovery strategies.

The purpose of this study is to estimate COVID-19 related disparities in cervical cancer stage at diagnosis and days from diagnosis to treatment among women who were diagnosed with cervical cancer and reported to the Surveillance and Epidemiologic End Results Cancer Registry (SEER) from 2018 to 2021 and two potential sources of disparities: race (Black/Hispanic/Other) and residence (rural/urban).

Methods

Study design

Data on incident cancer cases for the years 2015-2021 were obtained from the National Cancer Institute's SEER Research Plus Database (SEER-22), November 2023 Submission. This study used data on patients who were diagnosed with cervical cancer between 2018 and 2021 via SEER*Stat software (version 8.4.4; https://seer.cancer.gov/seerstat/). The SEER program includes 22 population-based cancer registries and reports from across the US (full list available from: https://seer.cancer.gov/registries/terms.html). Because we utilized pre-existing, de-identified and publicly available secondary data, this study was considered exempt by the Institutional Review Board of the University of Nevada, Reno.

Women were eligible for inclusion if they had a diagnosis of cervical cancer made during the years 2018-2021, and had known urban/rural residence, race/ethnicity. Included participants need to also have a known AJCC stage and days from diagnosis to treatment to be included in this study.

Measures

Dependent variables

The two outcomes of interest in this study were late-stage diagnosis and time from diagnosis to treatment. Late-stage at diagnosis was evaluated as binary using SEER's combined summary stage (2004+) criteria of: 0= Localized, 1= Regional or Distant (SEER-22, Ferrante et al., 2000). Time from diagnosis to treatment was measured in days and treated as continuous.

Independent variables

The key exposure of interest in this study is the COVID-19 pandemic. We defined the pre-pandemic period as Jan 2015 to Jan 2019, Year 1 of the pandemic as 2020, and Year 2 as 2021. The other independent variables of interest focus on disproportionate risk groups (Table 1). Race and ethnicity were treated as categorical with "White", "Black", and "Other" used as the three options for Race, and "Hispanic"/"non-Hispanic" as the two possible levels for Ethnicity. We coded residency as binary with rural/urban levels based on SEERs rural-urban continuum codes which categorize counties to metro (urban: codes 1-3) and nonmetro (rural: codes 4-9) based on population size and proximity to metro areas. We also use age and median household income as covariates to control for confounding. Insurance status was not available in the SEER dataset but income likely provided some control for confounding due to healthcare access.

Statistical Methods

We compared year of diagnosis and sociodemographic, staging, and treatment time characteristics of patients with descriptive statistics. For inferential statistics, we first used logistic regressions to predict the likelihood of late-stage diagnosis (Hosmer et al. 2013), and a zero-inflated Gamma Generalized Linear Model to predict the number of days from diagnosis to treatment (Belotti et al., 2015) both before and during the first two years of the COVID-19 pandemic (before=2015-2019, during= 2020-2021). For each time period, we modeled the outcomes using a multivariable model with the independent variables of race, ethnicity, location, age, income (as well as late-stage diagnosis for the time to treatment outcome). Next, we used the preceding five years as baseline data (2015-2019) to construct pre-COVID models, incorporating the covariates, to establish predicted values for the first (2020) and second (2021) year of the pandemic.

The logistic model for late-stage diagnosis was:

$$Logit\ (P(Late\text{-}Stage)) = \beta_0 + \beta_1\ (Race/Black) + \beta_2\ (Race/Other) + \beta_3\ (Ethnicity/Hispanic) + \beta_4\ (Residency/Rural) + \beta_5\ (Age/39\text{-}63\ years) + \beta_6\ (Age/{>}63\ years) + \beta_7\ (Income/\$40\text{-}\$100k) + \beta_8\ (Income/{>}\$100k) + \beta_9\ (Year) + \epsilon_1$$

Where:

P = Probability of Late-Stage Cancer diagnosis

β_0 = intercept

$\beta_1 - \beta_9$ = coefficients for the predictor variables

The outcome variable time to treatment (in days) had a semi-continuous nature with many zeros (Table 2) and a right skewed distribution (Figure 1). To account for the zeros and skewed nature of the outcome, a two-part model was employed: the two-part model is used to analyze data with this kind of mixture nature of zeros and positive continuous values (Belotti et al., 2015; Olsen & Schafer, 2001). Two-part regression models also known as hurdle model or zero inflated models which are used to analyze data when there are excess zeros, which is common in count data.

The first part of two-part models uses logistic regression to model the probability of a non-zero response based on the independent variables. Specifically, the binary logistic regression component was used to fit the probability of no treatment delay (treatment time =0) versus the probability of a delay (treatment time > 0):

$$Logit\ (P(Y>0)) = \beta_0 + \beta_1\ (Race/Black) + \beta_2\ (Race/Other) + \beta_3\ (Ethnicity/Hispanic) + \beta_4\ (Residency/Rural) + \beta_5\ (Age/39\text{-}63\ years) + \beta_6\ (Age/>63\ years) + \beta_7\ (Income/\$40\text{-}\$100k) + \beta_8\ (Income/>\$100k) + \beta_9\ (Year) + \epsilon_1$$

The second part of the model used a generalized linear model (GLM) with the gamma distribution and log link function to model the number of days from diagnosis to treatment based on the sociodemographic variables and year, for cases in which a treatment delay was observed (Belotti et al., 2015):

$$Log\ (E[Y \mid Y>0]) = \gamma_0 + \gamma_1\ (Race/Black) + \gamma_2\ (Race/Other) + \gamma_3\ (Ethnicity/Hispanic) + \gamma_4\ (Residency/Rural) + \gamma_5\ (Age/39\text{-}63\ years) + \gamma_6\ (Age/>63\ years) + \gamma_7\ (Income/\$40\text{-}\$100k) + \gamma_8\ (Income/>\$100k) + \gamma_9\ (Year) + \epsilon_2$$

To predict the expected proportion of late-stage diagnosis and mean days from diagnosis to treatment during the first two years of the pandemic, the parameter estimates from the pre-pandemic baseline models were applied to the years 2020 and 2021. This approach assumes that if pre-pandemic trends had continued, the outcomes would have followed the same pattern. COVID-19 impacts on the outcomes were assessed as observed (O) minus expected (E) values from the basic models with expected values estimated directly for the population average. We then quantified deviations using observed/expected (O/E) ratios with corresponding 95% confidence intervals (CI). O/E ratios with 95% CIs that do not include the null value of one are considered statistically significant.

In all cases significance was assessed at $\alpha=0.05$. Software from Rstudio was used for analyses (Posit team 2024).

Results

Sample Characteristics

The final analytical sample contained 22,828 individuals with around 3,000 incident cases per year (Table 1). The race and ethnicity of the participants was primarily White (74.8%) or Black (15.0%), and non-Hispanic (71.7%). Almost 90% of the individuals sampled lived in urban locations (89.9%). Over half of the sample was aged 39-63 years at the time of their diagnosis, with about 25% being under 39 years and 20% being over 63 years of age. Most participants reported a median income of 40-100k (84%) of over 100k (14.9%), with only 1.3% reporting an income of under 40k.

Stage at Diagnosis

During all study years combined, 57.6% of participants were diagnosed at a late-stage (Regional or Distant; Table 1). There was a 4.5 percentage point increase in in year 1 (60.9%), and a 5.1 percentage point increase in year 2 (61.5%) of the pandemic in percentage of participants with late-stage diagnosis was compared to the average of preceding five years (56.4%). Consequently, most diagnoses were late-stage in all time periods (Figure 2).

Associations

Our multivariable logistic regressions showed that age, race, and ethnicity were related to the odds of a late-stage cervical cancer diagnosis both before (2015-2019) and during (2020-2021) the Covid-19 pandemic (Table 3). Specifically, the odds of a late-stage diagnosis were 34% (95%CI= 22-47%) higher pre- and 26% (95% CI= 11-54%) higher post-COVID for Black women relative to White women (in both cases $p<002$). Women of Hispanic origin showed higher odds of a late-stage diagnosis than non-Hispanic women both pre- and during the COVID-19 pandemic with 9% (95%CI=2-18%) and 21% (95%CI= 7-38%) higher odds of a late stage diagnosis, respectively (Table 3). During both time periods age showed a strong relationship with stage at diagnosis (in all cases $p<0.0001$) with individuals aged 39-63 years having around 2x, and those over 63 years having almost 4x the odds of receiving a late-stage diagnosis (Table 3). Income (in all cases $p\geq 0.551$) and residency (in all cases $p\geq 0.124$) were not related to the proportion of women with a late-stage diagnosis before or during the COVID period.

Observed vs. Predicted Proportions

When we used the baseline (2015-2019) data to predict the proportion of late-stage diagnosis overall and by demographic factors the overall ratio of observed proportion late-stage diagnosis to the predicted proportion was higher in 2020 with an O:P ratio of 1.020 (95% CI= 1.00-1.040) but not significantly different from predicted in 2021 (O:P ratio= 1.010, 95% CI= 0.996-1.030).

In 2020, we observed a higher proportion of late-stage diagnosis than expected for White women (1.020, 95% CI= 1.00-1.04), Hispanic women (1.04, 95% CI=1.01-1.07), urban residents (1.06, 95% CI= 1.01-1.12), those under 63 years of age (<39 years = 1.04, 95%CI=1.00-1.08; 39-63 years= 1.02, 95%CI=1.00-1.05), and those with an income of 40-100k (1.020, 95% CI= 1.00-1.04).

The data from 2021 also showed higher than expected proportions of late-stage diagnoses for White and Hispanic women, those under 39 years of age, and those who made under 100k per year (both 40-100k and <40k; Table 4). A >5% increase was found for the observed:expected proportion of late-stage diagnoses was also observed among individuals who reported annual incomes of over 100k per year (0.947, 95% CI= 0.904-0.991).

Time from Diagnosis to Treatment

Around 24-28% of participants each year were given treatment the same day they were diagnosed (i.e., on day zero), resulting in some level of treatment delay for over 70% of diagnosed individuals each year (Table 2). The mean number of days from diagnosis to treatment was lower from 2015-2019 (36.0 days ±0.3 SE) than during the first and second years of the pandemic: 36.6 days ± 0.7 SE, and 40.12 days ± 0.7 SE, respectively (Table 1).

Associations

Results of the zero-inflated Gamma Generalized Linear Model very similar trends before and during the COVID-19 pandemic. During the five year period before the pandemic, Black patients had somewhat higher odds of experiencing a treatment delay than White patients (OR=1.11, 95% CI= 0.99-1.24) but among those who were delayed, Black women had significantly longer wait times (17% longer, $\beta = 0.160$, SE=0.02, $p < 0.001$; Table 5). This was similar to during the first two years of the pandemic where the odds of a treatment delay were not significantly different for Black relative to White women (OR=1.07, 95% CI=0.87-1.3), while among those with delays, the time spent waiting was significantly longer for Black women (10% longer, β=0.93, SE= 0.14, $p<0.001$; Table 6).

Prior to the pandemic, Hispanic patients had 18% higher odds of a treatment delay (OR= 1.18, 95% CI=1.08-1.29), and among delayed patients, Hispanic patients waited 22% longer than their non-Hispanic peers (β=0.20, SE= 0.02, $p<0.001$; Table 5). Similarly, during the first two years of the pandemic, where the odds of a treatment delay were 13% higher for Hispanic relative to non-Hispanic women (95%CI= 1-38%), and the average wait time among the delayed was 22% longer (β=0.20, SE= 0.03, $p<0.001$; Table 6).

Late-diagnosis was also significantly related to both increased odds of a treatment delay and increased time to treatment among the delayed, both before and during the pandemic (in all cases $p<0.001$; Tables 5 & 6.). Both women aged 39-63 and >63 year old women had higher odds of a treatment delay relative to women < 39 years old, before and during the pandemic (24-78% higher, in all cases $p \leq 0.006$). However, among the delayed age was not related to treatment time for either age group or time period (Tables 5 & 6). Residency of women was not related to the odds of a treatment delay in either time period (in both cases $p \geq 0.560$; Table 5). However, among patients who experienced a treatment delay, during the pre-COVID-19 period there were shorter wait times among rural versus urban patients (8% shorter, $\beta=-0.08$, SE= 0.03, p=0.002; Table 5). Surprisingly, income was not related to treatment delays or delay times either before or during the pandemic (in all cases $p\geq0.238$; Tables 5&6).

Observed vs. Predicted Treatment Time

During the first year of the pandemic, we found no significant differences between observed and predicted times from diagnosis to treatment overall or for any of the sociodemographic variables (Table 7). In the second year of the pandemic (2021), the overall observed mean number of days from diagnosis to treatment was 40.12 while the predicted number based on the five years of preceding data was 37.0 days (O/P ratio= 1.08, 95% CI= 1.04-1.13; Table 7). Longer observed than expected wait times were observed for White women (O/P ratio= 1.10, 95% CI=1.05-1.15), rural residents (O/P ratio= 1.08, 95% CI= 1.04-1.13), women aged 39-63 years old (O/P ratio= 1.12, 95% CI= 1.06-1.18), and those who earned 40-100k per year (O/P ratio= 1.09, 95% CI= 1.05-1.14; Table 7).

Discussion

Growing evidence shows that the COVID-19 pandemic negatively impacted women's health service utilization (Becker et al., 2021; Behera 2023), but impacts of the pandemic on women's health outcomes such as cervical cancer, are poorly understood. The purpose of this study was to investigate COVID-19 impacts on cervical cancer stage at diagnosis and days from diagnosis to treatment, and to evaluate if well-known sources of disparities were worsened by pandemic related care disruptions (race, ethnicity, and rural/urban residence).

Although fewer women sought cancer testing during the pandemic (Janczewski et al. 2023), our results showed that those who did, and tested positive, were treated as quickly as expected based on rates observed in the five years preceding the pandemic for the first (2020), but not the second (2021) year of the pandemic. The observed reduction in number of cancer patients treated (Janczewski et al., 2023) may have actually helped cancer treatment teams recover from other pandemic-related disruptions and deliver normally-time cancer care to those who did seek care during the pandemic. Evidence suggests that women's health service utilization, including PAP smears, was lowest in the Spring of 2020 (60% to 90%) with impacts lasting into mid-summer to fall that year (Becker et al. 2021; Miller et al. 2021). More women being tested increases the number of cancers detected and that more women were tested in 2021 than 2020 fits with our finding of longer than expected treatment times (both overall and based on several of the sociodemographic factors) during the second year of the pandemic. A subsequent "Catch-up" in the second year of the pandemic could result in the minor but observed increase in care delays in 2021.

Overall, our data showed an increase in time to treatment initiation during each subsequent year of the study period which is similar to other non-pandemic related studies (Ramey 2018; Roy et al. 2022). Despite the increasing trend, observed mean treatment times were still low (below 40 days in all cases in this study) and within generally desired treatment times of about 35-40 days (Hack et al. 2022), especially compared to the rate of disease progression which usually occurs over a number of years (Boon et al. 2022; Matsuo 2020).

We found that the proportion of women with a late-stage diagnosis was higher than expected during the first but not the second year of the pandemic. This was different than existing data on 308 cervical cancer cases in Utah residents from 2018/2019 to 2020/2021 (Mumper et al. 2025). Given that the number of women screened and diagnosed with cervical cancer was lowest in the spring of 2020, when social distancing guidelines were strongest and nonessential medical service bans were in effect (Miller et al. 2021), it's possible that a higher proportion of the women who did go to be tested did so due to symptoms rather than routine screening scheduling. Early-stage cervical cancer often has no noticeable symptoms while later stage cancer can cause unusual vaginal discharge, painful sex, and general pelvic pain (Singh et al. 2018).

Well known trends in disparities were present in our dataset both during the pre-COVID time period and during both years of the pandemic period. The odds of a late-stage cervical cancer diagnosis and longer wait times were significantly higher for Black and Hispanic women relative to their White and non-Hispanic counterparts. Similarly, a recent survey of US adults found Black and Latino women reported less timely cancer care than their White counterparts during the pandemic (Patel et al., 2022) although this study did not control for changes over time unrelated to the pandemic making it difficult to know if disparities were worsened due to COVID or just consistent with overall time trends. In this study, the disparities mostly did not appear to be worsened by the COVID-19 pandemic, with the notable exception of larger than expected late-stage diagnoses and treatment delays in 2021, and a larger than expected proportion of late-stage diagnoses in 2020, for Hispanic women relative to non-Hispanic women. Our results show that racial and ethnic disparities in cervical cancer care are still strongly present and are an ongoing important area for public health efforts to intervene and improve equity in healthcare. Efforts are especially needed to reverse disparities related to ethnicity, given that we observed well known negative impacts to treatment time and stage at diagnosis, and that we found novel evidence some of these disparities may have been worsened by the COVID-19 pandemic.

Our dataset also highlighted novel differences in late-stage diagnosis and treatment times among women of different ages and incomes during the pandemic. For young women (those under 39 years of age) a higher proportion of late-stage cervical cancer was observed than expected in both years of the pandemic with differences being greater in 2021 than 2020. Women aged 39-63 also showed pandemic related differences with higher observed than predicted proportion of late-stage diagnosis in 2020 and higher than expected treatment times in 2021. Although women over age 65 with no history of abnormal PAP are considered extremely low risk for cervical cancer, they are also generally more likely to be diagnosed with late-stage disease when it does occur probably due to lower screening rates (Cooley et al., 2023). Our study shows novel evidence that this trend may have been reversed during COVID-19 possibly due to differences in the daily lives of working women related to the pandemic such as impacts of social distancing guidelines on normal behaviors spilling over into health behaviors. Future work should evaluate lower than expected PAP screening differences based on age and consider how to prevent age-related missed abnormal cervical cell changes during public health emergencies such as pandemics.

It's also notable that the only time in this study in which observed values were smaller than expected was for the proportion of late-stage diagnoses among women with annual income of over 100k in 2021 (5% lower than expected). Conversely, rates were 2-24% higher for women making <40 or 40-100k annually. Income is a known source of disparities in cervical cancer care, particularly across the globe but also within the USA (Buskwofie et al., 2020). Our findings add a new possible mechanism to recent concerning evidence that declining cervical cancer incidence in low-income regions in the USA may be reversing (Amboree et al., 2024).

Study limitations & future research

Key limitations of this study were related to the sample characteristics. First, the sample was comprised of predominantly urban (~90%) cervical cancer reports with only a few hundred rural cervical cancer cases reported in 2020 and 2021. This reduces the statistical power and increases the chances of type II error (Akobeng 2016). We found that the proportion of late-stage diagnoses was higher among rural women during the first year of the pandemic, but no differences during the pre-COVID and later COVID time periods, which is counter to expected based on the literature (Hung et al. 2021). These results taken with the small and inconsistent results we found for the tests on residency and treatment time, may have been biased due to the imbalance in our study population and increased type II error.

The SEER dataset also included 13 of the 52 US States which made the examination of possible state effects difficult, although known differences in cervical cancer incidence and mortality exit between states and regions (Yoo et al. 2017). Cancer care was considered an essential medical service and continued during the pandemic in all states, but different states had varying social distancing measures and lengths of time nonessential medical service bans were in effect (NASHP 2021). Cancer care utilization may have impacted stage at diagnosis (e.g., more symptomatic and fewer asymptomatic participated in screening during COVID in 2020) and time to treatment (e.g, fewer total women present to treat in 2020) different in various states in part due to differences in the length of time the measures were in effect. State differences in the current dataset and research question are complicated to test due to data being available from a relatively small number of states and confounding with other state-level differences like vaccination rates, healthcare provider to patient ratios, and variations/inconsistencies in how the registries that participate in SEER collect and report data.

Our results would also be improved (1) if we had been able to differentiate cases who did not get any treatment from those who were lost to follow-up/treated in a facility or state that did not report to a SEER registry, (2) if data on insurance status, having a primary healthcare provider, and education were available, and (3) if temporal resolution was higher than annual with monthly statistics available (e.g., the first few months of 2020 are included in the current study as pandemic due to the annual time frame but were too early for services to be impacted). However, SEER unfortunately does not make this differentiation or these data available.

Another key limitation is the possibility of misclassification due to reporting procedures. Registries reporting to SEER have reporting delays that could indicate a patient has not been treated when they have actually been treated. Moreover, in some vases when a diagnosis date is not identified, the treatment date is recorded as the diagnosis date as a registry rule. Future work should consider how reporting by different registries/facilities (e.g., outpatient vs cancer centers) impacts treatment time data and if the COVID-19 pandemic impacted the number of false same day diagnosis and treatment reports (misclassification rate).

Finally, we didn't consider the impact of different types of treatment on the time from diagnosis to treatment outcome. Patients with cervical cancer may be initially treated by surgery, chemoradiation, chemotherapy, or enrolled in a clinical trial, which have differences in associated wait times. Clinical trial enrollment is the slowest but often provides the most cutting edge/current forms of treatment (Roy et al. 2022). Future studies should aim to consider both how treatment time and course of treatment impact racial, ethnic, and rural/urban disparities in cervical cancer care delivery.

Conclusion

Independent of COVID-19, our results underscore that improving cervical cancer screening rates and HPV vaccination uptake remain important public health priorities, given that most diagnoses in this study were late-stage. Timely HPV vaccination can prevent new cases of cervical cancer, and the number of late-state diagnoses could be drastically reduced if screening recommendations were more widely followed.

Our study represents one of the first to evaluate the impact of COVID-19 on cervical cancer outcomes directly (i.e., not screening) in the USA. Overall, it seems COVID-19 social distancing guidelines and nonessential medical services bans had a larger impact on missed preventative services than extended treatment times and increase proportion of late-stage at diagnoses. Our study highlights that racial and ethnic disparities remain important areas of public health equity for cervical cancer treatment and outcomes, independent of COVID-19 and sheds new light on impacts of COVID-19 on cervical cancer based on women's age and income. More work is needed to establish and evaluate mitigating measures for these disparities, especially among Hispanic women who showed consistent evidence of disproportionately high COVID-19 impacts on top of existing known disparities.

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Tables

Table 4.1. Participant demographics overall and by time period (pre-Pandemic=2015-2019; Pandemic= 2021 and 2022)

	Overall	**Pre-pandemic**	**Year 1**	**Year 2**
Group	**N (%)**	**N (%)**	**N (%)**	**N (%)**
Overall	22,828 (100)	16,971 (100)	2,936 (100)	2,921 (100)
Race				
White	17,069 (74.8)	12,697 (74.8)	2,196 (74.8)	2,176 (74.5)
Black	3,425 (15.0)	2,572 (15.2)	437 (14.9)	416 (14.2)
Other	2,334 (10.2)	1,702 (10.0)	303 (10.3)	329 (11.3)
Ethnicity				
Non-Hispanic	16,361 (71.7)	12,260 (72.2)	2,093 (71.3)	2,008 (68.7)
Hispanic	6,467 (28.3)	4,711 (27.8)	843 (28.7)	913 (31.3)
Location				
Urban	20,297 (88.9)	15,054 (88.7)	2,620 (89.2)	2,623 (89.8)
Rural	2,531 (11.1)	1,917 (11.3)	316 (10.8)	298 (10.2)
Age				
< 39 years	5,676 (24.9)	4,270 (25.2)	713 (24.3)	693 (23.7)
39-63 years	12,581 (55.1)	9,391 (55.3)	1,573 (53.6)	1,617 (55.4)
> 63 years	4,571 (20.0)	3,310 (19.5)	650 (22.1)	611 (20.9)
Income				
>100k	3,392 (14.9)	2,379 (14.0)	514 (17.5)	499 (17.1)
40-100k	19,150 (83.9)	14,359 (84.6)	2,390 (81.4)	2,401 (82.2)
<40 k	286 (1.3)	233 (1.4)	32 (1.1)	21 (0.7)
Late-Stage Diagnosis				
Yes	13,149 (57.6)	9,566 (56.4)	1,788 (60.9)	1,795 (61.5)
No	9,679 (42.4)	7,405 (43.6)	1,148 (39.1)	1,126 (38.6)
	Mean (SE)	**Mean (SE)**	**Mean (SE)**	**Mean (SE)**
Days to treatment	36.59 (0.28)	35.98 (0.33)	36.58 (0.68)	40.12 (0.74)

Notes: N= sample size, %= percentage of sample, SE= standard error of mean, Days to treatment= the average number of days from cancer diagnosis to first treatment.

Table 4.2. Percentage of respondents treated the same day as they were diagnosed by year (SEEER 2015-2021)

Year of diagnosis	N Total	N Zero count	Percentage
2015	3510	955	27.2
2016	3462	932	26.9
2017	3420	942	27.5
2018	3270	869	26.6
2019	3306	858	26.0
2020	2936	764	26.0
2021	2921	720	24.7

Notes: N= sample size

Table 4.3. Multivariable logistic regression results predicting late-stage cervical cancer diagnosis before (2015-2019) and during (2020-2021) the COVID-19 pandemic

	Pre-Covid Logistic regression (2015 - 2019)				**Covid Logistic regression (2020-2021)**			
Variable	**Estimate (β)**	**aOR**	**95% CI**	***p*-value**	**Estimate (β)**	**aOR**	**95% CI**	***p*-value**
Race								
White	*ref*	*ref*	*ref*		*ref*	*ref*	*ref*	
Black	0.29	1.34	1.22-1.47	< .001	0.26	1.30	1.11-1.54	0.002
Others	-0.04	0.96	0.86-1.07	0.438	-0.02	0.98	0.82-1.18	0.823
Ethnicity								
Non-Hispanic	*ref*	*ref*	*ref*		*ref*	*ref*	*ref*	
Hispanic	0.09	1.09	1.02-1.18	0.017	0.19	1.21	1.07-1.38	0.003
Residency								
Urban	*ref*	*ref*	*ref*		*ref*	*ref*	*ref*	
Rural	0.08	1.09	0.98-1.21	0.124	0.15	1.16	0.96-1.41	0.116
Age (years)								
<39	*ref*	*ref*	*ref*		*ref*	*ref*	*ref*	
39–63	0.78	2.17	2.01-2.33	< .001	0.69	2.00	1.76-2.27	< .001
>63	1.44	4.20	3.80-4.64	< .001	1.38	3.99	3.37-4.72	< .001
Income								
<$40k	*ref*	*ref*	*ref*		*ref*	*ref*	*ref*	
$40k–100k	0.01	1.01	0.76-1.34	0.993	0.00	1.00	0.54-1.81	0.995
>$100k	-0.04	0.96	0.71-1.29	0.775	-0.19	0.83	0.44-1.52	0.551

Notes: aOR= adjusted odds ratio, 95% CI= 95% confidence interval for the odds ratio, ref= reference level

Table 4.4 Predicted (Logistic regression) versus observed proportion of late-stage diagnosis overall and by demographic factors for the first (2020) and second (2021) years of the COVID-19 pandemic

Proportion of late-stage diagnoses	**2020 SEER Data**				**2021 SEER Data**			
Group	**Predicted**	**Observed**	**O/P Ratio**	**95% CI**	**Predicted**	**Observed**	**O/P Ratio**	**95% CI**
Overall	0.598	0.609	1.020	1.000-1.040*	0.606	0.615	1.010	0.996-1.030
Race								
White	0.588	0.601	1.020	1.000-1.040*	0.598	0.611	1.020	1.000-1.040*
Black	0.656	0.661	1.010	0.964-1.050	0.665	0.659	0.991	0.945-1.040
Other	0.584	0.594	1.020	0.962-1.070	0.588	0.584	0.992	0.939-1.050
Ethnicity								
Non-Hispanic	0.603	0.609	1.010	0.989-1.030	0.611	0.610	0.997	0.976-1.020
Hispanic	0.584	0.609	1.040	1.010-1.070*	0.596	0.625	1.050	1.020-1.080*
Residency								
Rural	0.596	0.603	1.010	0.995-1.030	0.606	0.614	1.010	0.995-1.030
Urban	0.615	0.655	1.060	1.010-1.120*	0.614	0.621	1.010	0.957-1.070
Age (years)								
< 39 years	0.423	0.439	1.040	1.000-1.080*	0.432	0.470	1.090	1.050-1.130*
39-63 years	0.613	0.627	1.020	1.000-1.050*	0.623	0.617	0.989	0.965-1.010
> 63 years	0.752	0.751	0.998	0.965-1.030	0.759	0.773	1.020	0.984-1.050
Income								
<40 k	0.646	0.594	0.919	0.749-1.090	0.578	0.714	1.240	1.040-1.430*
40-100k	0.600	0.614	1.020	1.000-1.040*	0.608	0.623	1.020	1.010-1.040*
>100k	0.584	0.586	1.000	0.960-1.040	0.599	0.567	0.947	0.904-0.991

Notes: O/P= ratio of observed proportion late-stage diagnosis divided by predicted proportion, 95% CI= 95% confidence interval for the O/P ratio

Table 4.5. Two-part model results predicting time to treatment during the five-year period preceding the COVID-19 pandemic (2015-2019)

	Pre-Covid Logistic Regression (2015 - 2019)				Pre-Covid GLM (2015 – 2019)			
Variable	**Estimate (β)**	**aOR**	**95% CI**	***p*-value**	**Estimate (β)**	**SE**	***t*-value**	***p*-value**
Race								
White	*ref*	*ref*	*ref*		*ref*	*ref*	*ref*	
Black	0.106	1.11	0.99-1.24	0.065	0.160	0.023	7.056	<0.001
Others	0.031	1.03	0.91-1.17	0.636	0.063	0.027	2.303	0.021
Ethnicity								
Non-Hispanic	*ref*	*ref*	*ref*		*ref*	*ref*	*ref*	
Hispanic	0.167	1.18	1.08-1.29	<0.001	0.203	0.019	10.859	<0.001
Residency								
Urban	*ref*	*ref*	*ref*		*ref*	*ref*	*ref*	
Rural	-0.019	0.98	0.86-1.11	0.770	-0.084	0.027	-3.111	0.002
Age (years)								
<39	*ref*	*ref*	*ref*		*ref*	*ref*	*ref*	
39–63	0.212	1.24	1.14-1.35	<0.001	0.010	0.020	0.490	0.624
>63	0.575	1.78	1.57-2.01	<0.001	0.032	0.024	1.318	0.187
Income								
<$40k	*ref*	*ref*	*ref*		*ref*	*ref*	*ref*	
$40k–100k	0.059	1.06	0.76-1.49	0.729	0.077	0.072	1.073	0.283
>$100k	0.043	1.04	0.73-1.49	0.811	0.025	0.075	0.332	0.740
Late-stage diagnosis								
No	*ref*	*ref*	*ref*		*ref*	*ref*	*ref*	
Yes	1.927	6.87	6.34-7.44	<0.001	-0.128	0.017	-7.414	<0.001

Notes: GLM= generalized linear model with gamma function, aOR= adjusted odds ratio, 95% CI= 95% confidence interval for the odds ratio, SE= standard error, ref= reference level

Table 4.6. Two-part model results predicting time to treatment during the first two years of the COVID-19 pandemic (2020-2021)

	Logistic Regression (2020-2021)				**GLM (2020-2021)**			
Variable	**Estimate (β)**	**OR**	**95% CI**	***p*-value**	**Estimate (β)**	**SE**	***t*-value**	***p*-value**
Race								
White	*ref*	*ref*	*ref*		*ref*	*ref*	*ref*	
Black	0.064	1.07	0.87-1.3	0.528	0.093	0.036	2.617	0.009
Others	0.123	1.13	0.91-1.41	0.278	0.054	0.041	1.318	0.188
Ethnicity								
Non-Hispanic	*ref*	*ref*	*ref*		*ref*	*ref*	*ref*	
Hispanic	0.166	1.13	1.01-1.38	0.036	0.199	0.028	7.037	<0.001
Residency								
Urban	*ref*	*ref*	*ref*		*ref*	*ref*	*ref*	
Rural	-0.068	0.93	0.74-1.17	0.560	0.002	0.042	0.047	0.962
Age								
<39	*ref*	*ref*	*ref*		*ref*	*ref*	*ref*	
39–63	0.214	1.24	1.06-1.44	0.006	0.025	0.031	0.802	0.423
>63	0.341	1.41	1.15-1.72	0.001	0.012	0.037	0.331	0.741
Income								
<$40k	*ref*	*ref*	*ref*		*ref*	*ref*	*ref*	
$40k–100k	0.281	1.32	0.66-2.64	0.425	0.160	0.135	1.180	0.238
>$100k	0.279	1.32	0.65-2.7	0.442	0.073	0.139	0.527	0.598
Late-stage diagnosis								
No	*ref*	*ref*	*ref*		*ref*	*ref*	*ref*	
Yes	2.043	7.71	6.72-8.85	<0.001	-0.128	0.028	-4.647	<0.001

Notes: GLM= generalized linear model with gamma function, aOR= adjusted odds ratio, 95% CI= 95% confidence interval for the odds ratio, SE= standard error, ref= reference level

Table 4.7. Predicted (two-part regression model) versus observed average time to treatment (in days) overall and by demographic factors for the first (2020) and second (2021) years of the COVID-19 pandemic

Mean N days to treatment	**2020 SEER Data**				**2021 SEER Data**			
Group	**Predicted**	**Observed**	**O/P Ratio**	**95% CI**	**Predicted**	**Observed**	**O/P Ratio**	**95% CI**
Overall	36.712	36.576	0.996	0.96-1.04	36.999	40.123	1.084	1.04-1.13*
Race								
White	35.962	36.267	1.008	0.96-1.06	36.475	40.089	1.099	1.05-1.15*
Black	41.298	38.204	0.925	0.83-1.02	41.135	41.928	1.019	0.92-1.12
Other	35.532	36.462	1.026	0.91-1.14	35.240	38.070	1.080	0.96-1.20
Ethnicity								
Non-Hispanic	34.552	34.123	0.988	0.94-1.03	34.662	37.671	1.087	1.04-1.14*
Hispanic	42.074	42.664	1.014	0.94-1.09	42.141	45.517	1.080	1.00-1.16*
Residency								
Rural	37.215	36.554	0.982	0.94-1.02	37.528	40.653	1.083	1.04-1.13*
Urban	32.538	36.753	1.130	0.99-1.27	32.345	35.463	1.096	0.96-1.23
Age (years)								
< 39	32.590	32.794	1.006	0.91-1.1	33.060	35.762	1.082	0.98-1.18
39-63	36.805	36.886	1.002	0.95-1.06	37.098	41.463	1.118	1.06-1.18*
> 63	41.006	39.972	0.975	0.91-1.04	41.208	41.524	1.008	0.94-1.08
Income								
<40 k	30.440	32.625	1.072	0.72-1.42	30.842	25.762	0.835	0.37-1.30
40-100k	37.288	37.310	1.001	0.96-1.05	37.552	41.021	1.092	1.05-1.14*
>100k	34.424	33.407	0.970	0.88-1.06	34.599	36.407	1.052	0.94-1.16
Late-stage diagnosis								
No	28.187	27.611	0.980	0.89-1.07	28.297	30.189	1.067	0.97-1.16
Yes	42.185	42.331	1.003	0.96-1.05	42.458	46.355	1.092	1.05-1.14*

Notes: N= count of number of days, O/P= ratio of observed mean number of days to treatment divided by predicted mean number of days to treatment, 95% CI= 95% confidence interval for the O/P ratio

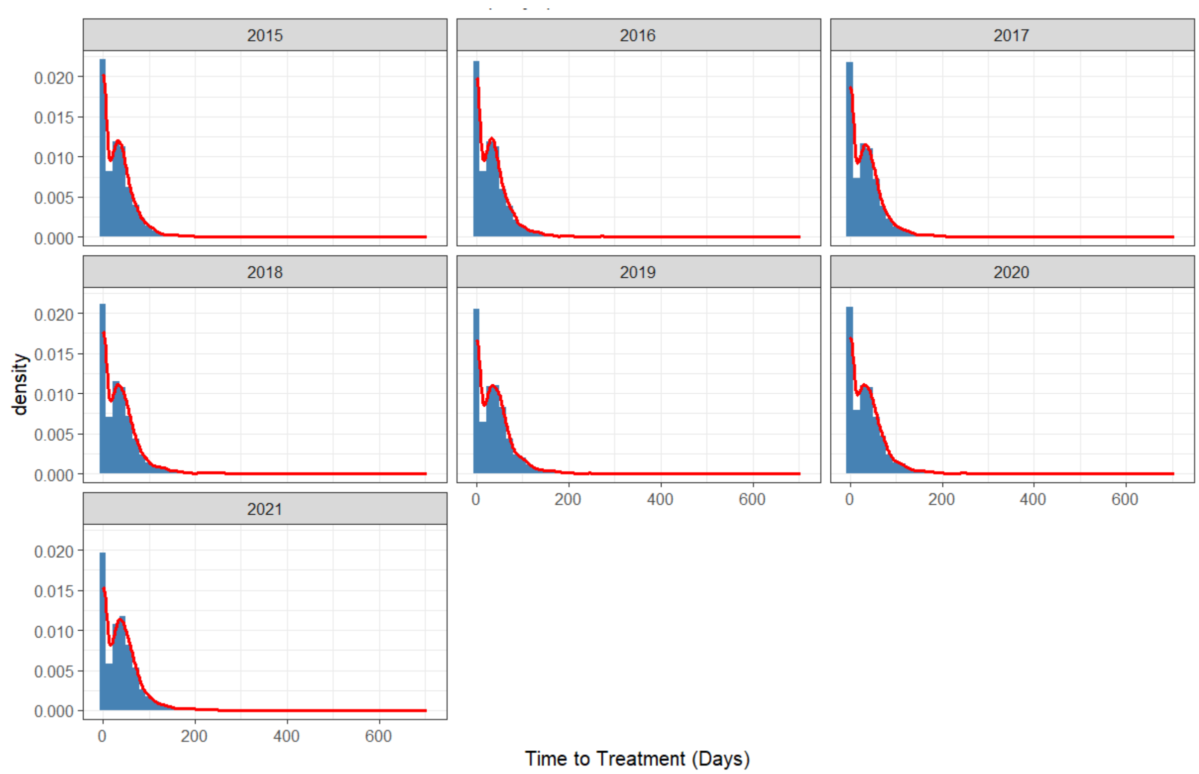

Figure 4.1. Distribution of values for time in number of days from cervical cancer diagnosis to treatment across study period (2015-2021)

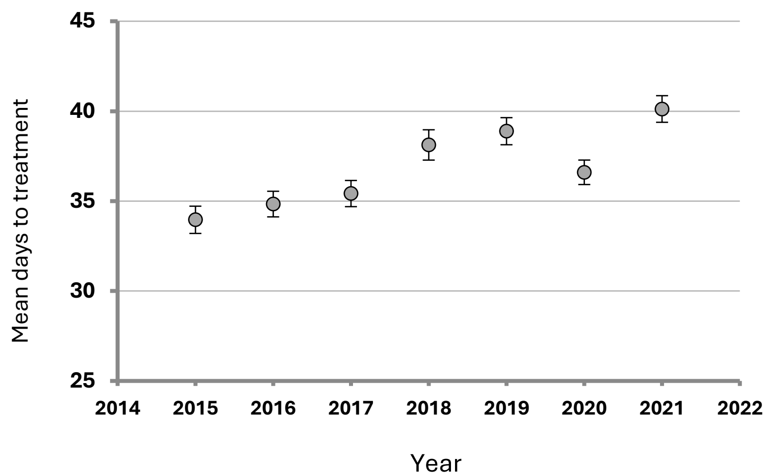

Figure 4.2. Average annual number of days from diagnosis to treatment

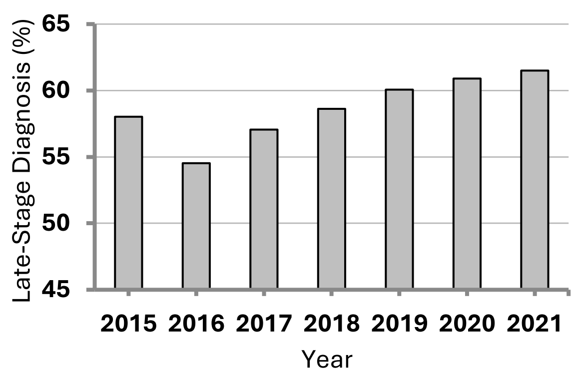

Figure 4.3. Average annual percentage of subjects with late-stage diagnosis (error bars show standard error of mean)

Chapter 5. Conclusion

The central aim of this dissertation was to better inform public health efforts for cervical cancer prevention, screening, and treatment. It synthesizes emerging literature on cervical cancer screening behavior for a novel exposure (childhood sexual abuse, CSA), provides novel information about the individual and interactive impacts of two widespread exposures (obesity and adverse childhood experiences, ACE) on HPV vaccination, as well as sheds new light on how known disparities in cervical cancer outcomes were impacted by the COVID-19 pandemic. These are important areas for public health research because cervical cancer remains one of the most common cancers among women and causes thousands of deaths each year in the US alone (Cecilia et al. 2017, CDC 2024), despite the fact that cervical cancer is now highly preventable given HPV vaccination, timely cervical cancer screening, and early treatment for incident cases (Schaefer et al. 2025).

Cervical Cancer Prevention & Childhood Trauma

A systematic review, quantitative meta-analysis, and nationally representative survey were used to elucidate new information about the relationships between ACEs, such as CSA, and cervical cancer prevention. We did not find evidence that adherence to cervical cancer screening guidelines was related to CSA but did find that ACEs were positively related to HPV vaccination status among young (18-36 year old) women. The former is consistent with one previous report (Kelly 2018) but contrary to other reports of lower adherence to screening guidelines among women with higher levels of childhood trauma (Alcalá et al., 2017; Farley et al., 2002; Olesen et al., 2012; Kohler et al., 2021) while others have found no difference (Alcalá et al., 2018; Brandford et al., 2023;

Ramasamy et al., 2011). ACEs have been associated with 52.6% higher risk of HPV-related cancer, and it's possible that people with ACEs are becoming aware of the higher risk, either though healthcare provider education or through survivors of abuse realizing independently they are at higher risk. It's also likely that individuals who have higher resilience are more likely to identify and be willing to report childhood abuse on phone surveys which may be related to our finding that ACE were positively related to HPV vaccination.

The overall results found in this work suggest that public health efforts to improve cervical cancer screening and HPV vaccination rates would benefit more by focusing on intervening in known at risk-groups than implementing ACE screening and ACE-informed care initiatives at this time. However, only a small number of these types of studies exist at this point and more work is still needed to draw more definitive conclusions regarding the impacts of CSA and other forms of childhood trauma on cervical cancer prevention in the USA.

A few key limitations exist related to our work on ACE, CSA, and cervical cancer prevention outcomes. First, the systematic review showed that data on CSA and cervical cancer screening is still limited both in number (only eight studies were eligible for inclusion in the synthesis) and by reliance on self-reported data (six of the eight studies from the synthesis). Because the data on HPV vaccination in this study was from the Behavioral Risk Factor Surveillance System (BRFSS), it is also limited by probable self-reporting bias. For exposures like ACE and CSA it's likely that self-reporting results in underreporting of the exposure due to embarrassment or shame, suppressed memories, and in some cases the inability to distinguish abuse/neglect from acceptable behavior (Langeland et al., 2015; Katzenstein & Fontes, 2017; Chandran et al., 2018). Underreporting biases results towards the null hypothesis. Therefore, more work is needed on these topics, and future studies should aim to use medical/legal records to determine ACE exposures and/or work to estimate the frequency of unreported CSA among women of different demographic groups to better help estimate the impact of CSA on healthcare and health outcomes.

Cervical Cancer Prevention & Race/Ethnicity

A consistent finding in this dissertation was that sociodemographic factors continue to have strong influences on cervical cancer prevention, treatment, and disease outcomes. Race and ethnicity are known to have strong relationships with cervical cancer screening behaviors (Musselwhite et al., 2016) but our results add novel information on how variability in the strength of association found in the existing literature is related to factors like the race of study cohorts. We also found that HPV vaccination rates were 44-52% for 18–26 year-old white women but only 29-46% for their Hispanic counterparts, which is consistent with other studies (Rincon et al., 202). Using the 2022 SEER dataset, we found evidence consistent with other studies that Black and non-Hispanic women experienced higher late-stage diagnosis and longer treatment wait times relative to their White and non-Hispanic counterparts in the five years leading up to COVID-19, and also find novel evidence that disparities were worsened disproportionately for Hispanic women during the pandemic.

The results of this dissertation combined with the existing literature highlights the importance of public health efforts to reduce racial and ethnic disparities in cervical cancer prevention, detection, and treatment. These public health efforts should focus on possible intervention areas such as addressing historical legacies/race-related distrust of institutions, differences in provider offering of screening/vaccination services based on race (explicit and implicit), and challenges regarding low-SES neighborhoods relationships with race/ethnicity and healthcare access (Harrington et al., 2021; Schaefer et al. 2025; Rincon et al., 2021). Specifically, systemic racism in cervical cancer care may be reduced if healthcare institutions obtain leadership buy-in and commitment with dedicated resources to support training and education for staff, policy and organizational interventions to increase accountability, and maintain partnerships with leaders and community members from impacted groups (Hassen et al., 2021). National programs aimed at delivering services to low-income women in areas traditionally underserved would also help alleviate disparities, especially if these programs engage community health workers and from the area which are known and trusted community members to increase participation (Attipoe-Dorcoo et al. 2021) and patient navigators who can help connect patients to screening, vaccination, and treatment services (Nelson et al., 2020).

Conclusion

Through HPV vaccination, timely cervical cancer screening, and prompt treatment, virtually all cervical cancer mortality could be prevented (Schaefer et al. 2025). Although cervical cancer incidence and mortality has been declining since the introduction of PAP smears in the 1970s (CDC 2024), there are still over 4,000 deaths per year in the USA and 300,000 deaths worldwide annually (Cohen et al., 2019) and certain racial/ethnic demographic groups are continually having lower cervical cancer screening and HPV vaccination rates, and experiencing longer wait times for treatment (Musselwhite et al., 2016; Rincon et al., 2021; Schaefer et al. 2025). Our results underscore that improving cervical cancer screening rates and HPV vaccination uptake remain important public health priorities, given that most diagnoses in this study were late-stage and that levels of adherence to screening and vaccination remain lower than desired.

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