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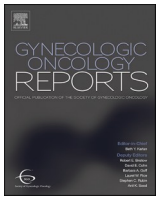

# Characterization of Cervical Cancer Screening History Among Patients with Invasive Cervical Cancer: A Population-Based Approach

Savanah Russ *, RaeAnne Kurtz, Nancy Bennett, Christina Felsen, Erica Bostick

*Rochester, NY Emerging Infections Program, Center for Community Health & Prevention at the University of Rochester Medical Center, 46 Prince Street, Suite 1001, Rochester, NY 14607, United States*

## 1. Introduction

Timely cervical cancer screening facilitates the prevention of cervical disease morbidity and mortality; however, historic, and current studies have identified a high proportion of patients diagnosed with cervical cancer who were not screened in the years preceding diagnosis (Benard et al., 2021; Leyden et al., 2005; Landy et al., 2020). Further characterization of missed opportunities and gaps in cervical cancer screening is critical to inform public health and clinical practice response to address them. Prior studies have leveraged cervical cancer screening history among patients diagnosed belonging to managed health care plans or identified via convenience sampling, however, population-based studies remain limited. Our study utilizes the preceding 5-year medical history of patients diagnosed with cervical cancer, identified via population-based surveillance, to 1) delineate gaps in screening or detection among patients diagnosed with cervical cancer, 2) elucidate demographic and clinical characteristics associated with gaps in screening, and 3) explore healthcare utilization and history for potential targeted health maintenance among patients with inadequate screening history.

## 2. Methods

Residents of Monroe County, NY aged $\geq$ 18 years diagnosed with histologically confirmed incident cervical carcinoma (cervical cancer) between January 1, 2015 through December 31, 2022 were included in this analysis. These patients were identified via the HPV Vaccine Impact Monitoring Project (HPV-IMPACT) at the New York Emerging Infections Program (NY EIP) for which methods have been previously described (Gargano et al., 2019). In brief, in 2008 the Centers for Disease Control and Prevention began to monitor the impact of HPV vaccination on cervical intraepithelial neoplasia grades 2, 2/3, 3 and adenocarcinoma in situ (CIN2+) as well as cervical cancer through active, population and laboratory-based surveillance at 5 sites across the U.S, capturing all patients meeting respective case definitions within each site's catchment area (Gargano et al., 2019). At the NY EIP, patients meeting the HPV-IMPACT case definition were identified via New York State Tumor Registry or centralized pathology software applications utilized among the two main health systems in the county. Trained abstractors utilized natural language searches of surgical tissue type and procedures within the pathology software to identify and report on all patients diagnosed in the catchment area. Enhanced medical record review was performed for patients with cervical cancer to obtain each patient's age, race, ethnicity, health insurance, date and result of most and second most recent Pap smear and HPV co-test preceding initial diagnosis, presence of cervical cancer symptoms, cancer histology and staging.

To address our study objectives, additional medical record review was performed to collect each patient's 5-year cervical cancer screening history, as well as healthcare use and history preceding diagnosis. This included exploration of each patient's gynecologic cytology and HPV testing laboratory results, clinician-reported cervical disease history, and notes pertaining to the circumstances of each patient's presentation for diagnosis (path to diagnosis). Review of healthcare use and history included evaluation of frequency of engagement with catchment area healthcare systems, types of providers seen and in what settings (inpatient/outpatient/emergent), history of non-adherence for treatment of non-cervical disease, and breast and/or colon cancer screening history, if age eligible. Quality-control measures for this enhanced review included robust training in standardized data collection procedures, followed by independent medical record review of 5 % of charts at all catchment area health systems of all patients included in this study to ensure consistency across trained medical record abstractors. This work was deemed exempt by institutional review boards at all health systems in the catchment area (STUDY00008939).

Following this additional review, patients were classified by the presence or absence of a cervical cancer screening test (Pap smear and/or HPV test) in the 6–60 months preceding diagnosis. Tests performed in the 6 months immediately prior to diagnosis were excluded, as they may

* Corresponding author.
*E-mail addresses:* savanah_russ@urmc.rochester.edu (S. Russ), raeanne_kurtz@urmc.rochester.edu (R. Kurtz), nancy_bennett@urmc.rochester.edu (N. Bennett), christina_felsen@urmc.rochester.edu (C. Felsen), erica_bostick@urmc.rochester.edu (E. Bostick).

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represent a patient's cancer workup rather than historic screening (Benard et al., 2021; Castle et al., 2017). Patients with no screening tests during the 6–60 months preceding diagnosis were classified as "Not Screened", while patients with a screening test were further sub-categorized by their cytology and HPV test results. Patients with normal cytology results alone, or normal cytology and an HPV negative test were classified as "Screened: Normal Results". In contrast, patients with abnormal cytology or HPV positive results were classified as "Screened: Abnormal Results". These patients were further classified based on the duration of time elapsed between their first abnormal result and a subsequent Pap smear, colposcopy or cervical biopsy. For our study, a duration of $\leq$ 12 months represented timely follow-up as one year encompasses what would be deemed a reasonable minimum follow-up time on abnormal cytology or HPV positive test results, per clinical guidelines (Benard et al., 2021; Saslow et al., 2012). In addition to cervical cancer screening history, patients were classified into one of three categories based on their path to diagnosis: 1) symptomatic trigger event in which they sought care solely based on the occurrence of potential cervical cancer symptoms (symptomatic); 2) routine cervical cancer screening (routine screening); or 3) incidental diagnosis that occurred as the result of treatment for non-cervical disease (incidental). Potential cervical cancer symptoms reported on for this analysis included: vaginal bleeding; pelvic, abdominal, back, flank or hip pain; pain with intercourse; urinary symptoms; fatigue, weakness or dizziness; and weight loss/loss of appetite.

To identify missed opportunities to reinforce health maintenance

**Table 1**
Association between Clinical and Sociodemographic Patient Characteristics and Cervical Cancer Screening History (N=139).

| Characteristic | N=139 N (%) | Not Screened (N=71) N (%) | Screened: Normal Results (N=27) N (%) | Screened: Abnormal Results (N=41)[c] N (%) | p-value[a] |
|---|---|---|---|---|---|
| Median Age at Diagnosis (SD) | 55.0 (15.7) | 60.0 (15.1) | 58 (13.1) | 44 (15.2) | <0.0001* |
| Age at Diagnosis | | | | | |
| <65 years | 102 (73.4) | 44 (61.9) | 21 (77.8) | 37 (90.2) | 0.003* |
| ≥65 years | 37 (26.6) | 27 (38.1) | 6 (22.2) | 4 (9.8) | |
| Year of Diagnosis | | | | | |
| 2015–2016 | 40 (28.8) | 19 (26.7) | 10 (37.1) | 11 (26.8) | 0.939 |
| 2017–2018 | 41 (29.5) | 21 (29.6) | 6 (22.2) | 14 (34.2) | |
| 2019–2020 | 28 (20.1) | 15 (21.1) | 5 (18.5) | 8 (19.5) | |
| 2021–2022 | 30 (21.6) | 16 (22.5) | 6 (22.2) | 8 (19.5) | |
| Race | | | | | |
| White | 93 (66.9) | 48 (67.6) | 21 (77.8) | 24 (58.5) | 0.325 |
| Black | 34 (24.5) | 15 (21.1) | 5 (18.5) | 14 (34.2) | |
| Asian | 3 (2.2) | 2 (2.8) | 1 (3.7) | 0 (0.0) | |
| Other/Not Available | 9 (6.5) | 6 (8.5) | 0 (0.0) | 3 (7.3) | |
| Ethnicity | | | | | |
| Hispanic | 12 (8.6) | 5 (7.0) | 0 (0.0) | 7 (17.1) | 0.065 |
| Non-Hispanic | 115 (82.7) | 57 (80.3) | 26 (96.3) | 32 (78.1) | |
| Not Available | 12 (8.6) | 9 (12.7) | 1 (3.7) | 2 (4.8) | |
| Health Insurance | | | | | |
| Private | 110 (79.1) | 57 (80.3) | 19 (70.3) | 34 (82.9) | 0.910 |
| Public | 14 (10.1) | 8 (11.3) | 2 (7.4) | 4 (9.8) | |
| Other | 3 (2.2) | 1 (1.4) | 1 (3.7) | 1 (2.4) | |
| Not Available | 12 (8.6) | 5 (7.0) | 5 (18.5) | 2 (4.9) | |
| Cancer Stage | | | | | |
| I | 58 (41.7) | 22 (31.0) | 16 (59.3) | 20 (48.8) | 0.073 |
| II | 24 (17.3) | 14 (19.7) | 4 (14.8) | 6 (14.6) | |
| III | 29 (20.9) | 15 (21.1) | 3 (11.1) | 11 (26.8) | |
| IV | 28 (20.1) | 20 (28.2) | 4 (14.8) | 4 (9.8) | |
| Cancer Histology | | | | | |
| Squamous Cell | 89 (64.0) | 50 (70.4) | 10 (37.0) | 29 (70.7) | 0.016* |
| Adenocarcinoma | 28 (20.1) | 14 (19.7) | 7 (25.9) | 7 (17.1) | |
| Adenosquamous | 4 (2.9) | 2 (2.8) | 1 (3.7) | 1 (2.4) | |
| Other[b] | 15 (10.8) | 4 (5.6) | 8 (29.7) | 3 (7.3) | |
| Not Available | 3 (2.2) | 1 (1.4) | 1 (3.7) | 1 (2.5) | |
| Path to Diagnosis | | | | | |
| Symptomatic | 81 (58.3) | 46 (64.8) | 14 (51.9) | 21 (51.2) | 0.035* |
| Routine Screening | 49 (35.2) | 18 (25.3) | 11 (40.7) | 20 (4.8) | |
| Incidental | 9 (6.5) | 7 (9.9) | 2 (7.4) | 0 (0.0) | |

* p-value of $\leq$ 0.05.
[a] Statistical tests performed to exclude values "Not Available"; statistical tests included unpaired *t*-test, chi-square or fisher's exact test.
[b] Other cervical cancer histology included: adenocarcinoma endometrioid type; adenocarcinoma gastrointestinal type mucinous; clear cell carcinoma; carcinosarcoma; mullerian adenosarcoma cervical primary; small cell carcinoma; clear cell cervical adenocarcinoma; serious carcinoma.
[c] Abnormal cytology results included: ASCUS/ACS; ASC-H; AGUS/AGC; LSIL and HSIL.

and for earlier diagnosis of cervical cancer, patients categorized as "Not Screened" were further sub-classified by their historic healthcare utilization behaviors. Patients were classified as having actively engaged with routine healthcare if they had been seen by either a primary care provider or a specialist in an outpatient setting during the 5 years preceding their diagnosis at any catchment area health system. Alternatively, patients who solely utilized urgent care or emergency departments for healthcare or had an absence of encounters within catchment area healthcare systems with a documented note by a provider that they infrequently sought care or had not seen a clinician in multiple years were classified as inactively engaging with routine healthcare.

Data were summarized descriptively, and bivariate statistical tests were utilized to examine the associations between relevant clinical and sociodemographic factors, and classification into one of the three cervical cancer screening history categories described above.

## 3. Results

Between January 1, 2015 and December 31, 2022, 153 patients diagnosed with cervical cancer while residing in Monroe County, NY were included in surveillance for the New York site of the HPV-IMPACT project. Of these, 14 were excluded from this analysis due to missing cervical cancer screening history during the 6–60 months preceding diagnosis, resulting in a final study population of 139. Among patients included in this study, their median age at diagnosis was 55 years (SD: 15.7), and the majority were White (66.9 %), non-Hispanic (82.7 %), and had private health insurance at diagnosis (79.1 %). Most patient's cervical cancer diagnoses were found to be Stage I (41.7 %), have squamous cell histology (64.0 %), and were identified via a symptom-driven path to diagnosis (58.3 %) (Table 1).

Approximately half of patients were classified into the "Not Screened" category (51.0 %), followed by a third into the "Screened: Abnormal Results" category (29.5 %), and finally, 19.4 % into the "Screened: Normal Results" category (Fig. 1). Bivariate statistical tests revealed age at diagnosis, cancer histology and path to diagnosis to be significantly associated with classification of cervical cancer screening history, with marginal significance for cancer stage and ethnicity (Table 1). Patients classified as "Not Screened" had the highest median age at diagnosis (60.1 years; SD: 15.1), as well as the highest proportion of patients who were diagnosed via a symptomatic trigger event (64.8 %) and patients diagnosed with stage IV cancer (28.2 %), as compared to patients in the other two screening categories. Of note, patients classified as "Screened: Normal Results" had the highest proportion of non-squamous cell carcinoma diagnoses (Table 1).

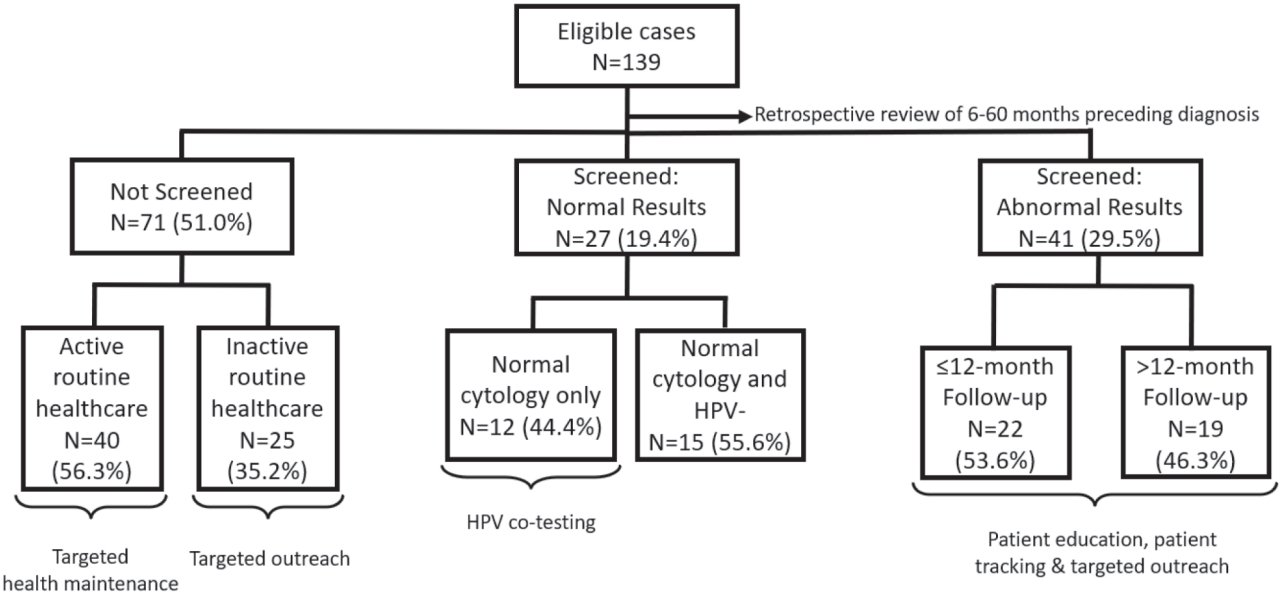
Of the 71 patients found to not have been recently screened, 56.3 % were classified as actively engaged in routine healthcare preceding their diagnosis while 35.2 % classified as inactively engaged in routine healthcare. Of note, there was insufficient information available to determine healthcare engagement for 6 patients (Fig. 1). Of the 40 patients who were not screened but actively engaged in routine care, 85 % had an outpatient visit with a primary care provider or an obstetrician or gynecologist (OB/GYN) during the 6–60 months preceding their diagnosis, with 37.5 % and 16.6 % found to be up to date on breast and colon cancer screening respectively, among those age-eligible at diagnosis.

Among the 27 patients classified as "Screened: Normal Results", 55.6 % were found to have both normal cytology and HPV negative test results, while 44.4 % were found to only have record of normal cytology results with no HPV test performed. Of the 41 patients classified as "Screened: Abnormal Results", 56.1 % had both an abnormal cytology and HPV positive test result prior to their diagnosis, with 36.6 % and 7.3 % respectively having only abnormal cytology or HPV positive results. In addition, 46.3 % were found to have a $>$ 12-month lag between their first abnormal result and a subsequent follow-up procedure.

## 4. Discussion

Our findings reinforce the need for adherence to cervical cancer screening recommendations. Examination of screening history within our study population represents a unique contribution given our exhaustive review of the 5-year medical history of all patients diagnosed within our study catchment area. We identified a number of gaps, as well as targeted points of intervention, in the cervical cancer screening continuum that need to be addressed to reduce the burden of preventable cervical cancer disease.

The identification of a high proportion of patients in our population-




*Bottoms row depicts potential intervention strategies for public health and clinical response to address missed opportunities and gaps in screening, as identified in our study.*

**Fig. 1.** Classification of Patients Diagnosed with Cervical Cancer 2015–2022 According to Cervical Cancer Screening History (N=139). Bottoms row depicts potential intervention strategies for public health and clinical response to address missed opportunities and gaps in screening, as identified in our study.

based analysis who were not screened in the 5 years preceding diagnosis is consistent with prior studies conducted among cervical cancer survivors, women belonging to managed healthcare plans, and state-wide evaluations (Benard et al., 2021; Leyden et al., 2005; Landy et al., 2020). Of note, ~40 % of patients in our study who had not been screened in the prior 5 years were over the age of 65, when diagnosed. This finding emphasizes the salient need for clinicians to ensure that those aging out of routine screening recommendations have previously been adherent to screening guidelines and had solely normal cytology and HPV co-test results. Additionally, the high proportion of patients not up to date on cervical cancer screening despite active engagement in routine healthcare with primary care providers or OB/GYNs suggests targeted health maintenance will be critical for preventing cervical cancer morbidity among this sub-group. Furthermore, community outreach will be an important tool for capturing patients who are inactively engaging with routine healthcare providers.

A third of patients in our study had an abnormal result detected prior to their cervical cancer diagnosis, with 46 % having more than a year between this result and a follow-up procedure, highlighting the need for identification of factors associated with screening compliance and recommendations. In addition, despite significant improvements in screening technology, 19 % of patients in our study presented with normal cytology results prior to their cancer workup that prompted diagnosis. High prevalence of non-squamous cell carcinoma among this sub-group may account for the lack of earlier detection given that cytology-based screening has been identified to be less effective at detecting adenocarcinoma of the cervix, as compared to squamous carcinoma (Castanon et al., 2016). Further investigation is warranted to identify missed opportunities for earlier detection among patients with solely normal cytology and HPV negative results preceding cancer diagnosis, particularly among those experiencing symptoms prior to diagnosis. Continued efforts in patient education and diligent tracking by primary care providers will be critical to ensure timely adherence to both cytology and HPV co-testing recommendations for early detection and prevention of disease progression.

Our study was limited to a singular U.S county which may hinder the generalizability of these findings to larger populations in the U.S including those more racially and ethnically diverse than our sample. In addition, our data sources don't facilitate exhaustive access to medical records outside of catchment which may affect the internal validity of study results. Study strengths include exploration of exhaustive 5-year medical history of all patients diagnosed with cervical cancer in catchment identified via robust, population-based surveillance.

## 5. Conclusion

Addressing gaps in cervical cancer screening is a critical objective to reduce preventable morbidity and mortality. Actionable items for public health and clinical practice response, as identified in our study, include: 1) adherence to age-dependent screening guidelines; 2) targeted in-reach and outreach among screening-eligible patients by clinicians and community-based efforts; and 3) utilization of cytology-based testing in combination with HPV co-testing for routine screening.

## CRediT authorship contribution statement

**Savanah Russ:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **RaeAnne Kurtz:** Writing – review & editing, Project administration, Methodology, Formal analysis, Data curation, Conceptualization. **Nancy Bennett:** Writing – review & editing, Funding acquisition, Conceptualization. **Christina Felsen:** Writing – review & editing, Project administration, Funding acquisition. **Erica Bostick:** Writing – review & editing, Methodology, Conceptualization.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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