Received: 18 January 2022 | Revised: 15 April 2022 | Accepted: 27 April 2022

DOI: 10.1002/cncr.34487

REVIEW ARTICLE

Current gaps and opportunities in screening, prevention, and treatment of cervical cancer

Bobbie J. Rimel MD[1] | Charles A. Kunos MD, PHD[2] | Nikeya Macioce PhD[3] | Sarah M. Temkin MD[3]

[1]Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, Cedars-Sinai Medical Center, Los Angeles, California, USA

[2]Department of Radiation Medicine, University of Kentucky, Lexington, Kentucky, USA

[3]Office of Research on Women's Health, National Institutes of Health, Bethesda, Maryland, USA

Correspondence
Bobbie J. Rimel, Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, Cedars-Sinai Medical Center, 8700 Beverly Blvd. Suite 290 W Los Angeles, CA 90048, USA.
Email: bobbie.rimel@cshs.org

Abstract

In their fiscal year 2021 reports, the US House and Senate Appropriations Committees requested that the National Institutes of Health (NIH) evaluate current research related to women's health and topics that include stagnant cervical cancer survival. In response, the NIH Office of Research on Women's Health, with input from women's health experts; members of the public; representatives from NIH institutes, centers, and offices; and members of the NIH Advisory Committee on Research on Women's Health, reviewed the public health needs and current NIH activities on cervical cancer. The *Advancing NIH Research on the Health of Women: A 2021 Conference* held in October 2021 reviewed these findings and allowed the identification of opportunities to strengthen research. In this review, the authors summarize public health needs related to cervical cancer and NIH activities in this realm. Cervical cancer has become a rare disease in the United States, yet significant portions of the US population remain under screened or unscreened for cervical cancer, human papillomavirus vaccination rates remain low, access to high-quality treatment remains a challenge for many, and large inequities by race and ethnicity persist. Novel, inclusive, and intentional research is needed to produce improvements in cervical cancer survival within the United States.

KEYWORDS
cancer mortality, cancer prevention, cervical cancer, clinical research, social determinants of health

INTRODUCTION

In their fiscal year (FY) 2021 reports, the US House and Senate Appropriations Committees requested that the National Institutes of Health (NIH) evaluate research currently underway related to women's health, specifically regarding the following three topics: (1) maternal morbidity and mortality; (2) rising rates of chronic, debilitating conditions in women; and (3) stagnant cervical cancer survival. In response to the Congressional request, the NIH Office of Research on Women's Health obtained input on the three priority areas from experts in women's health; members of the public; representatives from NIH institutes, centers, and offices; and members of the NIH Advisory Committee on Research on Women's Health. After a review of the NIH portfolios and activities, on October 20, 2021, a concerning meeting entitled *Advancing NIH Research on the Health of Women: A 2021 Conference* was held. This

See commentary on pages 4041–6 and referenced review article on pages 4074–84, this issue.

 © 2022 American Cancer Society.

article provides a summary of the public health concerns and a review of current and past NIH-sponsored research related to invasive cervical cancer. In addition, gaps and opportunities related to improving cervical cancer survival for all women identified through the process of responding to the Senate inquiry and preparing the conference are discussed.

In the United States, an estimated 14,480 new cases of cervical cancer were diagnosed in 2021, with over 4000 patients dying of disease.[1] Globally, cervical cancer is the second most common cancer among women. Cervical cancer is the fourth leading cause of cancer death among females in the world, behind breast, lung, and colon cancers.[2] Despite the global burden of disease, cervical cancer incidence is inversely related to social and economic development, life expectancy, education, and gross national income.[3,4]

Human papillomavirus (HPV) is the established cause of nearly all cervical cancers. The natural history of HPV-related carcinogenesis is well understood and widely accepted.[5] The predicable and lengthy latent period—from 12 to 15 years—between HPV infection and its progression to cervical cancer from preinvasive disease has allowed for the development of successful cancer prevention and screening interventions.[6] A rapid decline in incidence in the United States occurred in the decades after the introduction of widespread cancer screening programs with the Papanicolaou (Pap) test in the 1950s. Declining incidence has not been universal; and, for those women living in the lowest income counties, cervical cancer incidence has recently increased.[7] In the last 2 decades, both liquid-based cytology and high-risk HPV testing have improved the test characteristics of cervical cancer screening.[8] Screening rates in the United States remain high, with >80% of persons eligible for cervical cancer screening in the United States up to date.[9] Safe and effective HPV vaccines have been available in the United States to be administered as cervical cancer prevention since 2006.[10]

Despite these advancements in screening and prevention, improvements in survival from cervical cancer have stagnated.[11] The age-adjusted death rate from cervical cancer in the nation fell by only 0.7% annually between 2009 and 2018.[12] This reduction in mortality is far less pronounced than recent survival benefits observed in other cancers affecting women (e.g., breast, ovary, lung).[11,12] The proportion of cervical cancers diagnosed at locally advanced or distant disease increased from 2001 to 2009 in most states. There are substantial variations in survival by state—survival has recently declined in 22 states while increasing in 13.[11]

Notable inequities exist in this disease site. Cervical cancer has one of the largest Black/White mortality gaps of all disease sites.[13] Black women remain 30% more likely to be diagnosed with cervical cancer and more likely to be diagnosed with advanced-stage disease compared with non-Hispanic White women and are 75% more likely to die of cervical cancer compared with White women.[13] Racial inequities in mortality are likely driven by stage at diagnosis, the most important prognostic factor in cervical cancer, because Black women are more likely to be diagnosed with advanced or metastatic disease compared with White women.[11] Inequity extends to geographic location as well. Women who live in rural census tracts are disproportionality burdened with cervical cancer compared with those living in nonrural census tracts.[14] Intersectionality, defined by Kimberle Crenshaw, explains the overlapping dimensions of social categorization, such as race, gender, class, sexuality, language fluency, and others, on humans in the context of discrimination.[15] This concept is most starkly realized in cervical cancer mortality, where the health outcomes of patients are compounded by interconnected disadvantages (Figure 1).

GAPS IN SCREENING AND PREVENTION

In the United States, nearly all cases of invasive cervical cancer result from a lack of screening, underscreening, or failure to follow-up on abnormal screen results. More than one half of patients diagnosed with cervical cancer in the United States have never been screened or have been inadequately screened, and underscreening is associated with advancing stage at diagnosis.[16,17] Several groups remain at risk of underscreening, thereby increasing the risk of cervical cancer mortality. Risks for being unscreened or under screened include living below the federal poverty threshold, being underinsured or uninsured, persons without usual sources of care, those living in rural communities, and individuals with low English-language proficiency.[18,19] English proficiency tracks with immigration status, which is another risk factor for underscreening.[20]

Although routine cervical cancer screening is recommended and covered under the Affordable Care Act, a recent survey of 702 low-income women who were uninsured or publicly insured demonstrated multiple perceived barriers to engaging in this crucial preventive service—with 72% citing financial barriers.[21] Persons without health insurance are less likely to be screened or vaccinated against HPV.[22]

Population characteristics, such as poverty and underinsurance or uninsurance, that place women at greater risk for cervical cancer are disproportionally concentrated in the less populated, rural areas of the United States. Health care facilities that provide screening and diagnostic interventions for cervical cancer are limited for patients living in rural communities.[23] State-level variability in screening quality exists with co-testing rates lowest in Midwestern and Southern states.[19] Sociodemographic characteristics accounted for some, but not all, state-level variation. As a result of many of these factors, there are significant geographic variations in cervical cancer incidence by state, with incidence rates two to three times higher in states like Arkansas and Kentucky compared with Vermont and New Hampshire.[1]

Underscreening in postmenopausal women has been of recent concern because current guidelines recommend discontinuation of screening after age 65 years.[16] Only one third of patients currently meet exit criteria to discontinue screening, most commonly due to a lack of adequate testing data.[24] Women aged 65 years and older account for one fifth of new cervical cancer cases and are more likely to be diagnosed with advanced and/or metastatic disease.[25,26]

Challenges remain for those patients who have abnormal screen results. Significant out-of-pocket costs for colposcopy are common

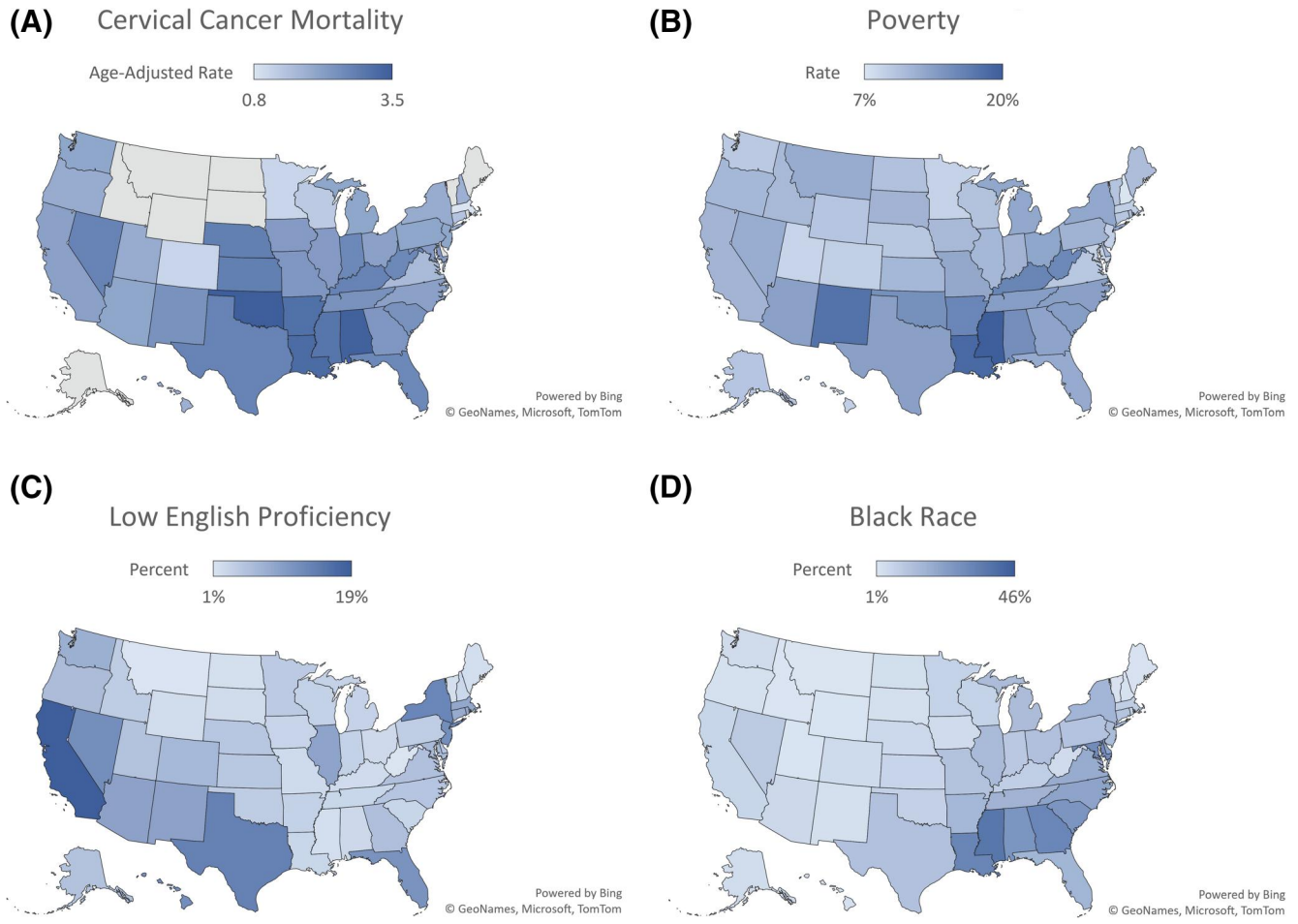


FIGURE 1 US rates of (A) cervical cancer mortality (https://www.cdc.gov/cancer/cervical/statistics/index.htm), (B) poverty (https://www.census.gov), (C) low English proficiency (https://www.lep.gov/maps), and (D) Black race (https://www.census.gov)

and have increased over time.[27] Nearly one quarter of women with an abnormal screen test do not receive diagnostic follow-up.[28] Overall, an estimated 9% of cancers are diagnosed in patients who did not receive recommended follow-up with biopsy or treatment after positive screening tests.[17]

Uptake of the HPV vaccine in the United States continues to be generally lower than that of other childhood vaccines, with only 40% of eligible people (70% of adolescents) vaccinated in 2018 (Figure 2).[29,30] Large geographic variations in vaccination exist with individuals who live in the South and in some Western states at highest risk for not being vaccinated against HPV.[30] US HPV vaccination rates lag behind those of other high-income countries, such as Canada and Australia.[31]

GAPS IN TREATMENT

Access to specialty care remains a challenge for many patients with cervical cancer. Nearly one half (44%) of patients are diagnosed with early stage cervical cancer that can be treated with surgery with or without postoperative radiation therapy.[34,35] However, less than one half of patients (47%) with early stage disease receive guideline-adherent care, and <20% receive treatment in high-volume centers.[36] Fewer than 1200 gynecologic oncologists—the specialists with the training and expertise in treatment of gynecologic malignancies, including cervical cancer—practice in the United States.[37] Access to a gynecologic oncologist is not included in the network adequacy standard specified by Center for Medicare Services. Remarkably, as many as 27% of health insurance marketplace plans in the United States lack a gynecologic oncologist specialist within their networks.[38] One half of rural residents travel >60 miles to reach the nearest gynecologic oncologist, and >10% of rural residents travel at least 2 hours to see a surgeon.[39]

For those women diagnosed with locally advanced disease (regional disease beyond the cervix), pelvic external-beam radiation therapy with intracavitary brachytherapy and concurrent chemotherapy is the standard-of-care treatment.[40] Despite the strong association between receipt of brachytherapy, decreased recurrence rates, and improved survival, recent surveillance data demonstrate that nearly one half of women with locally advanced cervical cancer in the United States do not receive brachytherapy.[33,40]

Chemotherapy is the mainstay of therapy in patients with metastatic and recurrent disease. Published in 2017, the results of a National Cancer Institute (NCI)-supported clinical trial, Gynecologic

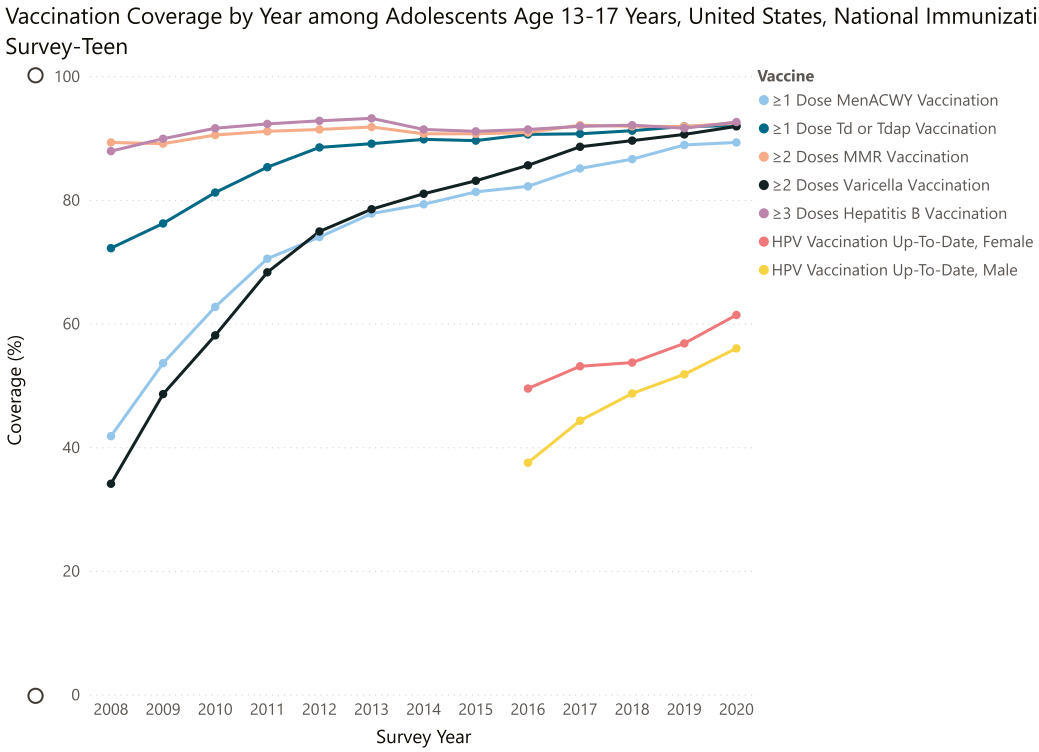


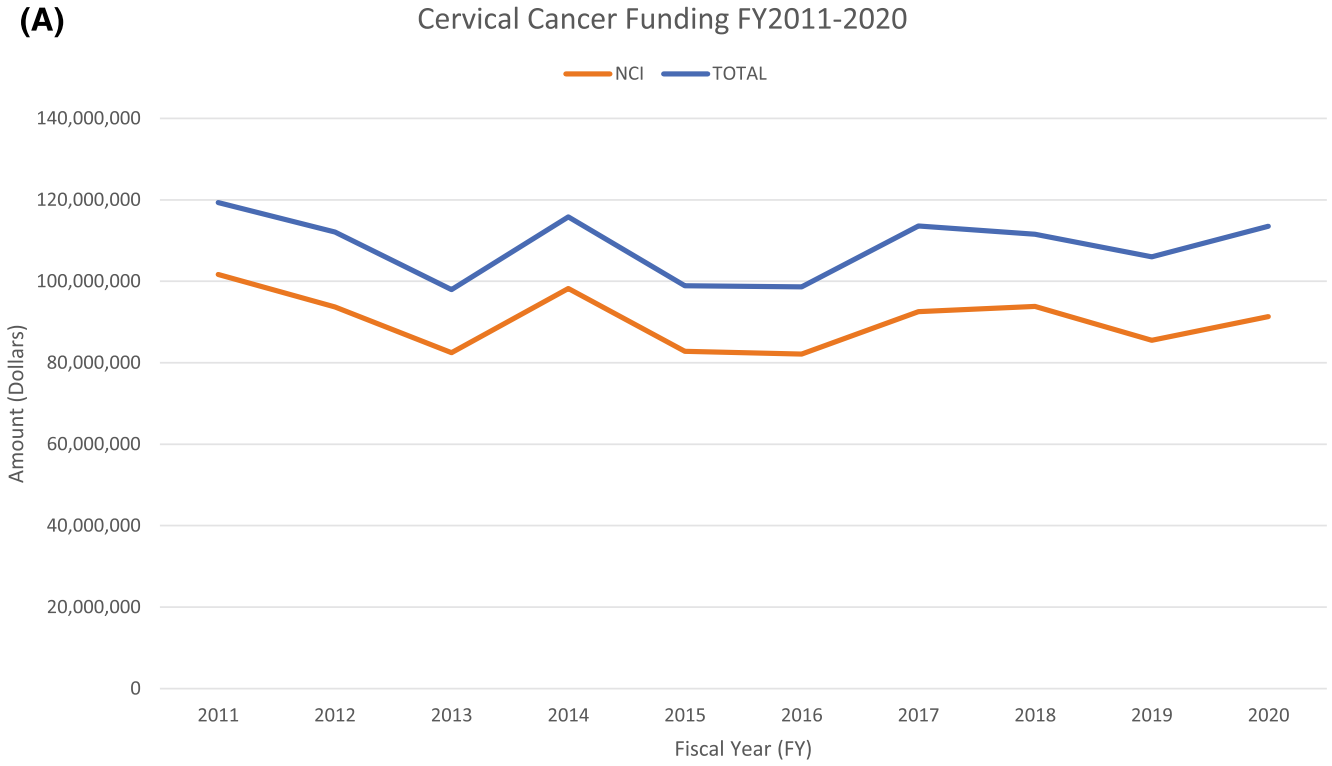
FIGURE 2 Recent trends in childhood vaccination coverage (https://www.cdc.gov/vaccines/imz-managers/coverage/teenvaxview/data-reports/index.html). HPV indicates human papillomavirus; MenACWY, meningococcal conjugate; MMR, measles, mumps, and rubella; Td, tetanus-diphtheria toxoids; Tdap, tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis

Oncology Group-0240 (ClinicalTrials.gov identifier NCT00803062), demonstrated a 3-month improved survival for patients who received bevacizumab in addition to chemotherapy, making the three-drug regimen (carboplatin, paclitaxel, and bevacizumab) the new standard of care.[41] Despite these improved outcomes, cost-effectiveness studies have consistently suggested that bevacizumab is not a cost-effective therapy.[42] Furthermore, the toxicity profile of the three-drug regimen limits its use in many older patients as well as patients who have comorbidities, such as hypertension or renal disease.[43] Additional novel agents, including cemiplimab, tisotumab vedotin, and pembrolizumab, have recently been approved for use in metastatic and recurrent cervical cancer; however, the impact of these drugs on the US population of patients with cervical cancer is not yet known. Recently, the addition of a fourth drug to the Gynecologic Oncology Group-0240 regimen, pembrolizumab, resulted in improved overall survival in the European phase 3 study KEYNOTE 826 (ClinicalTrials.gov identifier NT03635567).[44] Pembrolizumab combined with chemotherapy and bevacizumab resulted in 2.2 months of improved progression-free survival in the intention-to-treat population (median, 10.4 months [95% CI, 9.1–12.1 months] vs. 8.2 months [95% CI, 6.4–8.4 months]; hazard ratio, 0.65; 95% CI, 0.53–0.79; $p < .001$).[41] Although these data are exciting, the increasing health care costs and treatment time for patients are likely to further intersect with the difficulties faced by many women with cervical cancer.

There are notable disparities in the receipt of care provided to Black patients with cervical cancer. That Black patients with cervical cancer are diagnosed at advanced stage, despite similar rates of screening compared with White patients, suggests that a disproportionate number of Black patients are not receiving timely follow-up for abnormal screen results. Even when adjusted for stage at diagnosis, Black women are less likely to receive surgery compared with White women and receive external-beam radiation therapy without brachytherapy more frequently than White women.[32,33] These findings point to the need for targeted interventions to improve the timeliness of treatment for and follow-up care, particularly among Black women.[11]

CURRENT NIH-SUPPORTED RESEARCH

In FY 2020, the NIH invested $113 million in cervical cancer research—with the majority of projects funded by the NCI (Figure 3A). Cervical cancer research represents 1.4% of the overall NCI budget. The National Institute of Allergy and Infectious Diseases, the National Institute on Minority Health and Health Disparities, and the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development also fund research on cervical cancer, primarily focused on HPV biology, screening and prevention of preinvasive cervical disease, and reducing disparities in screening and prevention in historically underrepresented communities. States with the most NIH-supported research in cervical cancer do not map onto states with the highest burden of disease (Appalachia and Mississippi Delta) (Figure 3B). Disproportionate NIH funding for diseases that are female-predominant,



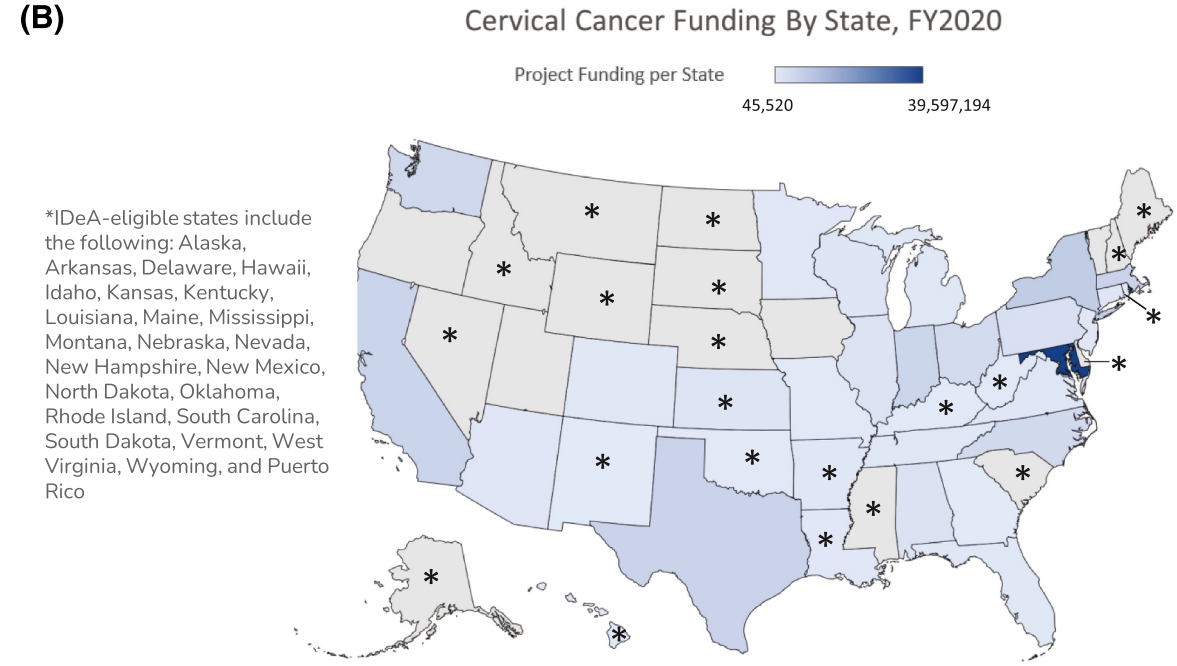


FIGURE 3 (A) Funding trends for cervical cancer for fiscal years (FY) 2011–2020 (data from Research, Condition, and Disease Categorization [RCDC] Categorical Spending Reporting; https://reporter.nih.gov/). NCI indicates National Cancer Institute. (B) National Institutes of Health (NIH) funding for cervical cancer by state for FY 2020 (https://reporter.nih.gov/)

including gynecologic cancers and cervical cancer, has been described.[45,46]

The Research, Condition, and Disease Categorization system is the NIH system of categorization and publicly reporting funding in each of more than 280 reported categories of disease, condition, or research area.[47] The Research, Condition, and Disease Categorization report for cervical cancer includes basic research, translation and clinical studies, premalignant and invasive

cervical diseases, HPV biology, prevention, screening, vaccination, treatment, and related health services. NCI cervical cancer projects further classified by Common Scientific Outline codes demonstrate investments in early detection, etiology, prevention, cancer control, treatment, and biology (from the greatest to the least number of projects).

BASIC AND TRANSLATIONAL SCIENCE

Basic science is the foundation of scientific discovery, whereas translational science moves discoveries into clinical practices. A scientific challenge relevant to viral-mediated malignancies like cervical cancer is discovering ways to elicit robust, tumor-specific immune responses. Mechanistic studies are needed to understand the recruitment of immune-suppressive cells to the tumor microenvironment and develop ways to generate robust, tumor-specific immune responses that target the tissue site.[48] Research is ongoing to exploit two viral oncoproteins that drive HPV cancers—E6 and E7—as tumor-specific immune therapy.

Notable specific programs include the cervical cancer Specialized Programs of Research Excellence (SPORE) program, which currently supports three projects to develop novel HPV vaccines. The Cancer Genome Atlas, a landmark cancer genomics program and collaboration between the NCI and the National Human Genome Research Institute, has molecularly characterized more than 20,000 primary cancer and matched normal samples—generating a wealth of publicly available genomic, epigenomic, transcriptomic, and proteomic data on 33 cancer types, including cervical cancer. Discoveries from The Cancer Genome Atlas hold great promise for improving cervical cancer treatment as new molecular alterations are identified and made available to be exploited as therapeutic targets.[49]

SCREENING AND PREVENTION RESEARCH

The NCI has a robust portfolio of studies to improve test characteristics of cervical cancer screening in the United States. The Improvement of Risk-Informed Screening cohort study will evaluate the performance of several promising biomarkers head-to-head in 70,000 women screened for cervical cancer (storing *discard* cytology and HPV test specimens).[50] The cohort will be a resource for ongoing and future etiologic work on HPV-related cancers—particularly the work on HPV viral and host genetics, epigenetics, and the cervicovaginal microbiome. A partnership among the NCI, the University of Mississippi Medical Center, and the Mississippi State Department of Health (the STRIDES [STudying Risk to Improve DisparitiES of cervical cancer in Mississippi] study) evaluates the risk of cervical dysplasia and studies novel biomarkers in women undergoing cervical cancer screening in a state with a high burden of disease.[51] The NCI's Study to Understand Cervical Cancer Early Endpoints and Determinants (SUCCEED; ClinicalTrials.gov identifier NCT00339989) aims to assess biomarkers of risk for progressive cervical dysplasia with the goal of developing biomarkers that can distinguish women at highest risk of progression to cervical cancer. SUCCEED investigators will prospectively validate the most promising biomarkers by assessing their predictive values for key outcomes related to progression (HPV persistence, intraepithelial neoplasia) or nonprogression (HPV clearance).[52]

Improving cervical cancer screening strategies using self-collected specimens has the potential to expand access to women in both high-resource and low-resource settings. The feasibility of testing self-collected samples for HPV DNA methylation on specific genes is under investigation. The NCI's Last Mile Initiative is a public–private partnership to examine cervical screening self-sampling and inform the relevant regulatory approvals.[53]

The NIH has supported the New Mexico HPV Pap Registry, a novel model for public health surveillance and prevention established in 2006 as the first population-based, statewide cervical screening registry in the United States.[54] The New Mexico HPV Pap Registry includes address-level data on health care facilities that provided cervical screening (Pap and/or HPV testing), diagnostic testing (colposcopy), excisional precancer treatment (loop electrosurgical excision procedure or cone biopsy), and linkages to HPV vaccine administrative data. Data can inform statewide progress as well as unanticipated or adverse events related to changes in screening and HPV vaccination practices.

The NCI clinical trials portfolio includes secondary prevention approaches using investigational agents to treat HPV-related precancerous lesions, thereby reversing HPV-driven malignant transformation. Ongoing trials of immunologic agents include a phase 1 single-arm trial on the safety and tolerability in women with and without HIV with biopsy-confirmed high-grade cervical pre-cancers (ClinicalTrials.gov identifier NCT04131413), a phase 2B clinical trial of a therapeutic HPV E6 peptide vaccine with or without a Candida skin testing reagent to treat high-grade premalignant cervical lesions (ClinicalTrials.gov identifier NCT02481414), and a phase 3 trial of HPV vaccine therapy to reduce high-grade cervical lesions in patients with HIV and HPV(ClinicalTrials.gov identifier NCT03284866). An additional clinical trial of secondary prevention is a phase 1 trial assessing self-applied 5-fluorouracil with clinician-applied, once-weekly imiquimod as a topical agent for women with high-grade cervical precancers before excisional biopsy (ClinicalTrials.gov identifier NCT03196180). Additional trials of topical, intralesional, or immunologic agents are targeting men and women with HIV and HPV in other disease sites (anus and vulva).

Efforts continue to improve HPV vaccination rates include the ESCUDDO (Estudio de Comparacion de Una y Dos Dosis de Vacunas Contra el Virus de Papiloma Humano [Comparing One or Two Doses of the Human Papillomavirus Vaccine for the Prevention of Human Papillomavirus Infection] Study; ClinicalTrials.gov identifier NCT03180034). This prospective trial is co-funded by the NCI and the Bill & Melinda Gates Foundation, with support from the International Agency for Research on Cancer, to study whether one dose of the HPV vaccine is as effective at preventing infection as two doses.[55] If one dose of an HPV vaccine is sufficient to reduce cervical cancer burden,

the feasibility of operating vaccination programs will increase as overall cost will decrease. Low-cost, simpler vaccination programs could improve vaccine uptake in the United States and worldwide.

CLINICAL RESEARCH

The NCI funds multiple clinical research networks, including the NCI National Clinical Trials Network, the NCI Community Oncology Research Program, the Experimental Therapeutics Clinical Trials Network, and the Cancer Prevention Clinical Trials Network (formerly, the Early Phase Consortia Program), that provide extramural investigators with research infrastructure within which clinical trials in all cancer disease sites can be performed. Therapeutic clinical trials specific to gynecologic malignancies were disadvantaged by the consolidation of NCI clinical research networks that followed the 2010 Institute of Medicine report *A National Cancer Clinical Trials System for the 21st Century: Reinvigorating the NCI Cooperative Group Program*.[56] In the subsequent cancer cooperative group reorganization, the legacy Gynecologic Oncology Group joined the Radiation Therapy Oncology Group and the National Surgical Adjuvant Breast and Bowel Project Foundation to form NRG Oncology. Decreases in participation in gynecologic cancer clinical trials followed this merger.[57] Currently, there are few clinical trials specific to innovative, novel therapeutic for patients with invasive cervical cancer within these research networks. In the advanced and/or metastatic setting, where mortality is highest, an NCI-supported trial has not been open since the practice-changing Gynecologic Oncology Group GOG-240 trial (ClinicalTrials.gov identifier NCT00803062) demonstrating a survival benefit from the addition of bevacizumab to chemotherapy closed to patient accrual in 2010. Current ongoing trials in cervical cancer are listed in Table 1.

Intramural NCI investigators have pioneered the use of tumor-infiltrating lymphocyte therapy for HPV-related malignancies, which have demonstrated encouraging response rates in patients treated to date.[48] Additional clinical research includes an NCI-sponsored clinical trial demonstrating that, among patients who received tumor-infiltrating lymphocyte therapy (i.e., a lymphocyte-depleting conditioning regimen followed by an infusion of immune cells and then systemic, high-dose aldesleukin), individuals with cervical cancer had a higher percentage of tumor regression (28%) than those with other types of malignancies (18%).[48] Therapeutic HPV vaccines are under investigation in a range of patients—from individuals with preinvasive, intraepithelial disease to those with end-stage cancers.[58]

HEALTH SERVICES RESEARCH

The NCI leverages diverse data resources—such as various Surveillance, Epidemiology, and End Results Program linkages, the National Survey of Precision Medicine in Cancer Treatment, the Health Information National Trends Survey, household surveys, and information on cancer care in community settings—to examine care delivery. The NCI's Population-based Research to Optimize the Screening Process Project aims to understand ways to improve the cancer screening process (including recruitment, diagnosis, and referral for treatment) in community health care settings.[59] These efforts are intended to expand access to cervical cancer screening and ensure that the service is available to underserved populations and in low-resource settings. The NCI's Cancer Moonshot supplements are accelerating cervical cancer control by helping federally qualified health centers in North Carolina implement self-collection. In another Moonshot project, the Cancer Intervention and Surveillance Modeling Network (a consortium of NCI-sponsored investigators) is modeling older women's risks to determine when to stop cervical cancer screening. Four NCI-designated cancer centers are examining HPV vaccine hesitancy, with the intent of increasing uptake.

RESEARCH OPPORTUNITIES AND SOLUTIONS

Despite advances in screening, prevention, and treatment for cervical cancer, little change in survival from this disease has been seen over the last 2 decades in the United States. In 2018, the World Health Organization set an ambitious goal for the worldwide eradication of this disease.[50] Models project that cervical cancer elimination in the

TABLE 1 Ongoing clinical trials on the treatment of invasive cervical cancer open to accrual

Trial ID	Research network	Description
NCT02595879	ETCTN	A phase 1 bioavailability study of oral triapine combined with concurrent chemoradiation for locally advanced cervical cancer and vaginal cancer
NCT01101451	NCTN	An evaluation of radiation therapy with and without chemotherapy in patients with stage I–IIA cervical cancer who previously underwent surgery
NCT02466971	NCTN	An evaluation of the addition triapine to the usual chemotherapy treatment (cisplatin) during radiation therapy for advanced-stage cervical and vaginal cancer
NCT00980954	NCTN	An evaluation of postoperative chemotherapy in treating patients with high-risk, early stage cervical cancer after hysterectomy
NCT01649089	NCORP	A study of physical functioning and quality of life before and after surgery in patients with stage I cervical cancer

Abbreviations: ETCTN, Experimental Therapeutics Clinical Trials Network; NCTN, National Clinical Trials Network; NCORP, National Cancer Institute Community Oncology Research Program.

United States will occur 10–18 years later than in Australia, a peer nation in which high-coverage vaccination has been achieved and primary screening transitioned earlier to HPV-based methods.[60]

Opportunities for primary and secondary prevention research relate primarily to the implementation of best practices. Vaccination and screening rates remain less than ideal within many US communities, particularly in geographic regions with high burdens of HPV infection and cervical cancer.[29,30] Specifically, research is needed to help improve HPV vaccination rates among US adolescents (e.g., by better understanding vaccine hesitancy). Lessons learned from the COVID-19 pandemic may be instrumental in achieving higher vaccine coverage.

The majority of patients with cervical cancer who were unscreened before their diagnosis have seen a physician for a physical or routine check-up within the past 5 years, indicating missed opportunities for screening and/or vaccination.[22] Research on self-sampling and ways to enhance the screening process may help reduce disparities in screening rates but also may only alleviate barriers for patients already receiving current screening and prevention interventions without expanding the reach of this intervention. Implementation research scaling up effective screening and prevention interventions at the population and community levels will require novel approaches. The feasibility of implementing cervical cancer screening in alternate and new locations (e.g., emergency departments, primary care offices, schools where screening could occur with vaccination of children) can be investigated. Programs like the CDC's Prescription Drug Monitoring Program, COVID vaccination data collection, and the New Mexico Pap Registry can provide templates for linkage systems to track and monitor individual and patient-level adherence to cervical cancer screening and prevention interventions. Database solutions to identify in real-time whether patients have or need vaccination, HPV testing, or cytology could facilitate access for patients across multiple health care settings.

Research on how to improve linkages to care for people who have positive screening results would fill one of the largest gaps in cervical cancer care. Cervical cancer survival is defined most by stage at diagnosis, thus interventions that improve treatment of pre-invasive lesions have a dramatic impact on the population ultimately diagnosed with cervical cancer. Research on prevention and screening efforts can be focused on how to move beyond office-based interventions toward community-based interventions to better serve populations with historically low uptake. Innovative models of service delivery (e.g., nontraditional provider delivery, see-and-treat clinics, telehealth) should be investigated in the United States.

Specific attention to enhanced basic and translational cancer research in this disease site can produce survival benefits. Increasing the availability of in vivo models and biospecimens for studies of HPV-related, premalignant lesions as well as invasive cervical cancer would enhance the advancement of molecular and genetic discovery. Further study of HPV genotypes, gene expression, and proteomics might be translated into better outcome prediction and targeted treatments that may benefit patients with all HPV-related malignancies. Knowledge of subtype-specific molecular or genetic drivers that might direct responses to therapy would allow for subtype-specific treatment algorithms rather than our current one-size-fits-all therapies. Results from projects like The Cancer Genome Atlas could be leveraged to study HPV genotypes and HPV gene expression as well as the role of messenger RNAs, microRNAs, and long noncoding RNAs. Facilitating access to biobanking and augmented real-time data, allowing specimens from clinical research to be used secondarily for novel basic and translational discovery, is of particular importance for rare diseases such as cervical cancer. Single-institution or multiple-institution cohorts often do not have adequate numbers of banked samples to meaningfully assess predictive and prognostic biomarkers.

Quality of care for women receiving treatment for cervical cancer must be assessed and tracked to improve adherence to best practices. Targeted queries within the Surveillance, Epidemiology, and End Results database specific to cervical cancer and an investment in building information systems (at the state, regional, and national levels) would bolster research in this area. Metrics like brachytherapy receipt should be defined and measured, with incentives provided for high-quality care.

Current Medicare reimbursement policy may disincentivize specialized care. Reimbursement for hysterectomy and brachytherapy for cervical cancer, especially in free-standing centers, has declined over time.[40,61] Because physician reimbursement is often linked to annual relative value units, this presents a potential financial disincentive against brachytherapy delivery as brachytherapy becomes increasingly more complex and time-consuming in the era of individualized, image-guided treatment, without a commensurate increase in recognition of the increased complexity.[40]

The increasing complexity of chemotherapy regimens for advanced and metastatic disease leaves many patients ineligible for clinical trials and subsequently at risk for limited benefit or toxicity from novel therapeutics. Pragmatic clinical research to alleviate many of the social and structural barriers that are faced by patients with cervical cancer are needed. Hypofractionated radiation regimens and oral chemotherapeutics, for example, would help alleviate many of the housing and transportation barriers facing the majority of patients with this disease.

Structural factors that drive stagnant cervical cancer survival rates require additional investments in health services research to improve survival in this disease site. High-volume, specialized cancer centers can be encouraged and incentivized to promote linkages to care and access to treatment and clinical trials to patients who have been historically underserved within their catchment areas through increased infrastructure funding or reimbursement. Extending relationships between cancer centers and minority-serving and safety-net hospitals would extend the reach of and diversify the patient population enrolling onto clinical trials in cervical cancer, making clinical research results more applicable to the population with the burden of disease. Interventions that reduce health inequities and multilevel approaches to achieving equitable representation of historically understudied populations in cancer-related clinical trials will be of benefit to patients with cervical cancer.

The clinical and research workforce providing the complex multidisciplinary care required to treat gynecologic cancer remains small. The number of gynecologic oncologists in the United States remains small (<1200 physicians), as does the number of radiation and medical oncologists trained in the management of cervical cancer. Training opportunities could be targeted toward oncologists with this expertise to expand. Ensuring that gynecologic oncologists and radiation oncologists with cervical cancer expertise contribute to funding decisions for oncologic research would help prioritize this and other research on gynecologic malignancies.

CONCLUSION

Cervical cancer presents a unique prevention opportunity through vaccination and early detection of precancerous lesions. However, for women who have invasive disease, access to timely, specialized care is critical to obtain a cure. Metastatic cervical cancer is rarely curable, and complex, multiagent treatment continues to widen the gap in access. Mortality from cervical cancer is a direct reflection of resource distribution. To decrease mortality, future research must incorporate approaches that overcome systemic barriers to care and eradicate structural inequities in addition to identifying novel agents and therapies to treat this disease.

AUTHOR CONTRIBUTIONS

Bobbie J. Rimel and **Sarah M. Temkin** developed the concept and format for the article. **Bobbie J. Rimel**, **Sarah M. Temkin**, **Charles A. Kunos**, and **Nikeya Macioce** wrote the article.

CONFLICT OF INTEREST

Bobbie J. Rimel reports honoraria from Genentech, and participation on Advisory Boards for Tesaro/GlaxoSmithKline, Merck, Clovis, AstraZeneca, and Immunogen; and personal fees from Deep6AI and Tempus outside the submitted work. Sarah M. Temkin, Charles A. Kunos, and Nikeya Macioce had no disclosures.

ORCID

Bobbie J. Rimel https://orcid.org/0000-0003-4808-3805
Sarah M. Temkin https://orcid.org/0000-0002-6472-2745

REFERENCES

1. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2021. *CA A Cancer J Clin*. 2021;71(1):7-33. https://doi.org/10.3322/caac.21654
2. Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA A Cancer J Clin*. 2021;71(3):209-249. https://doi.org/10.3322/caac.21660
3. International Agency for Research and Cancer, World Health Organization. *Global Cancer Observatory*. Accessed December 29, 2021. International Agency for Research on Cancer; 2022. https://gco.iarc.fr/
4. Lin S, Gao K, Gu S, et al. Worldwide trends in cervical cancer incidence and mortality, with predictions for the next 15 years. *Cancer*. 2021;127(21):4030-4039. https://doi.org/10.1002/cncr.33795
5. Crosbie EJ, Einstein MH, Franceschi S, Kitchener HC. Human papillomavirus and cervical cancer. *Lancet*. 2013;382(9895):889-899. https://doi.org/10.1016/s0140-6736(13)60022-7
6. Schiffman M, Castle PE. The promise of global cervical-cancer prevention. *N Engl J Med*. 2005;353(20):2101-2104. https://doi.org/10.1056/nejmp058171
7. Lin Y-Y, Damgacioglu H, Suk R, et al. Trends in the incidence of human papillomavirus-associated cancers by county-level income and smoking prevalence in the United States, 2000-2018. *JNCI Cancer Spectr*. 2022;6(2):pkac004. https://doi.org/10.1093/jncics/pkac004
8. US Preventive Services Task Force, Curry SJ, Krist AH, et al. Screening for cervical cancer: US Preventive Services Task Force Recommendation Statement. *JAMA*. 2018;320(7):674-686. https://doi.org/10.1001/jama.2018.10897
9. Sabatino SA, Thompson TD, White MC, et al. Cancer screening test receipt—United States, 2018. *MMWR Morb Mortal Wkly Rep*. 2021;70(2):29-35. https://doi.org/10.15585/mmwr.mm7002a1
10. Markowitz LE, Dunne EF, Saraiya M, et al. Human papillomavirus vaccination: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep*. 2014;63(RR-05):1-30.
11. Benard VB, Watson M, Saraiya M, et al. Cervical cancer survival in the United States by race and stage (2001-2009): findings from the CONCORD-2 study. *Cancer*. 2017;123:5119-5137. https://doi.org/10.1002/cncr.30906
12. Surveillance, Epidemiology, and End Results Program, National Cancer Institute, National Institutes of Health. Annual Report to the Nation 2021: Overall Cancer Statistics. Accessed December 29, 2021. https://seer.cancer.gov/report_to_nation/statistics.html
13. DeSantis CE, Miller KD, Goding Sauer A, Jemal A, Siegel RL. Cancer statistics for African Americans, 2019. *CA A Cancer J Clin*. 2019;69(3):211-233. https://doi.org/10.3322/caac.21555
14. Yu L, Sabatino SA, White MC. Rural-urban and racial/ethnic disparities in invasive cervical cancer incidence in the United States, 2010-2014. *Prev Chronic Dis*. 2019;16:180447. https://doi.org/10.5888/pcd16.180447
15. Bauer GR. Incorporating intersectionality theory into population health research methodology: challenges and the potential to advance health equity. *Soc Sci Med*. 2014;110:10-17. https://doi.org/10.1016/j.socscimed.2014.03.022
16. Fontham ETH, Wolf AMD, Church TR, et al. Cervical cancer screening for individuals at average risk: 2020 guideline update from the American Cancer Society. *Cancer J Clin*. 2020;70:321-346. https://doi.org/10.3322/caac.21628
17. Landy R, Mathews C, Robertson M, et al. A state-wide population-based evaluation of cervical cancers arising during opportunistic screening in the United States. *Gynecol Oncol*. 2020;159(2):344-353. https://doi.org/10.1016/j.ygyno.2020.08.033
18. Fuzzell LN, Perkins RB, Christy SM, Lake PW, Vadaparampil ST. Cervical cancer screening in the United States: challenges and potential solutions for underscreened groups. *Prev Med*. 2021;144:106400. https://doi.org/10.1016/j.ypmed.2020.106400
19. Goding Sauer A, Bandi P, Saslow D, Islami F, Jemal A, Fedewa SA. Geographic and sociodemographic differences in cervical cancer screening modalities. *Prev Med*. 2020;133:106014. https://doi.org/10.1016/j.ypmed.2020.106014
20. Goel MS, Wee CC, McCarthy EP, Davis RB, Ngo-Metzger Q, Phillips RS. Racial and ethnic disparities in cancer screening: the importance of foreign birth as a barrier to care. *J Gen Intern Med*. 2003;18(12):1028-1035. https://doi.org/10.1111/j.1525-1497.2003.20807.x
21. Biddell CB, Spees LP, Smith JS, et al. Perceived financial barriers to cervical cancer screening and associated cost burden among low-income, under-screened women. *J Womens Health*. 2021;30(9):1243-1252. https://doi.org/10.1089/jwh.2020.8807

22. Silver MI, Kobrin S. Exacerbating disparities? Cervical cancer screening and HPV vaccination. *Prev Med*. 2020;130:105902. https://doi.org/10.1016/j.ypmed.2019.105902
23. McDonald YJ, Goldberg DW, Scarinci IC, et al. Health service accessibility and risk in cervical cancer prevention: comparing rural versus nonrural residence in New Mexico. *J Rural Health*. 2017;33(4):382-392. https://doi.org/10.1111/jrh.12202
24. Mills JM, Morgan JR, Dhaliwal A, Perkins RB. Eligibility for cervical cancer screening exit: comparison of a national and safety net cohort. *Gynecol Oncol*. 2021;162(2):308-314. https://doi.org/10.1016/j.ygyno.2021.05.035
25. Surveillance, Epidemiology, and End Results Program; National Cancer Institute, National Institutes of Health. *SEER*Explorer: an interactive website for SEER cancer statistics*. National Cancer Institute; 2021. Accessed October 6, 2021. https://seer.cancer.gov/statistics-network/explorer/overview.html
26. Dilley S, Huh W, Blechter B, Rositch AF. It's time to re-evaluate cervical cancer screening after age 65. *Gynecol Oncol*. 2021;162(1):200-202. https://doi.org/10.1016/j.ygyno.2021.04.027
27. Fendrick AM, Dalton VK, Tilea A, Malone AM, Moniz MH. Out-of-pocket costs for colposcopy among commercially insured women from 2006 to 2019. *Obst Gynecol*. 2021;10(1):1097-1115. https://doi.org/10.1097/aog.0000000000004582
28. Barlow WE, Beaber EF, Geller BM, et al. Evaluating screening participation, follow-up, and outcomes for breast, cervical, and colorectal cancer in the PROSPR Consortium. *J Natl Cancer Inst*. 2020;112(3):238-246. https://doi.org/10.1093/jnci/djz137
29. Ghebre R, Berry-Lawhorn JM, D'Souza G. State of the science: screening, surveillance, and epidemiology of HPV-related malignancies. *Am Soc Clin Oncol Educ Book*. 2021;41:377-388. https://doi.org/10.1200/edbk_325319
30. Centers for Disease Control and Prevention (CDC). TeenVaxView. *Vaccination Coverage Among Adolescents (13-17 Years)*. CDC; 2020.
31. Loke AY, Kwan ML, Wong Y-T, Wong AKY. The uptake of human papillomavirus vaccination and its associated factors among adolescents: a systematic review. *J Primary Care Commun Health*. 2017;8(4):349-362. https://doi.org/10.1177/2150131917742299
32. Fleming S, Schluterman NH, Tracy JK, Temkin SM. Black and white women in Maryland receive different treatment for cervical cancer. *PLoS One*. 2014;9(8):e104344. https://doi.org/10.1371/journal.pone.0104344
33. Boyce-Fappiano D, Nguyen KA, Gjyshi O, et al. Socioeconomic and racial determinants of brachytherapy utilization for cervical cancer: concerns for widening disparities. *JCO Oncol Pract*. 2021;17(12):e1958-e1967. https://doi.org/10.1200/op.21.00291
34. Koh W-J, Abu-Rustum NR, Bean S, et al. Cervical Cancer, Version 3.2019, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Cancer Netw*. 2019;17(1):64-84. https://doi.org/10.6004/jnccn.2019.0001
35. Surveillance, Epidemiology, and End Results Program; National Cancer Institute; National Institutes of Health. *Cancer Stat Facts: Cervical Cancer*. National Cancer Institute. Accessed October 6, 2021. https://seer.cancer.gov/statfacts/html/cervix.html
36. Pfaendler KS, Chang J, Ziogas A, Bristow RE, Penner KR. Disparities in adherence to National Comprehensive Cancer Network treatment guidelines and survival for stage IB-IIA cervical cancer in California. *Obst Gynecol*. 2018;131(5):899-908. https://doi.org/10.1097/AOG.0000000000002591
37. Hicks-Courant K, Kanter GP, Giuntoli RL, et al. An increase in multisite practices: the shifting paradigm for gynecologic cancer care delivery. *Gynecol Oncol*. 2021;160(1):3-9. https://doi.org/10.1016/j.ygyno.2020.10.030
38. Shalowitz DI, Huh WK. Access to gynecologic oncology care and the network adequacy standard. *Cancer*. 2018;124(13):2677-2679. https://doi.org/10.1002/cncr.31392
39. Hung P, Deng S, Zahnd WE, et al. Geographic disparities in residential proximity to colorectal and cervical cancer care providers. *Cancer*. 2020;126(5):1068-1076. https://doi.org/10.1002/cncr.32594
40. Holschneider CH, Petereit DG, Chu C, et al. Brachytherapy: a critical component of primary radiation therapy for cervical cancer: from the Society of Gynecologic Oncology (SGO) and the American Brachytherapy Society (ABS). *Brachytherapy*. 2019;18(2):123-132. https://doi.org/10.1016/j.brachy.2018.11.009
41. Tewari KS, Sill MW, Penson RT, et al. Bevacizumab for advanced cervical cancer: final overall survival and adverse event analysis of a randomised, controlled, open-label, phase 3 trial (Gynecologic Oncology Group 240). *Lancet*. 2017;390(10103):1654-1663. https://doi.org/10.1016/s0140-6736(17)31607-0
42. Phippen NT, Leath CA III, Havrilesky LJ, Barnett JC. Bevacizumab in recurrent, persistent, or advanced stage carcinoma of the cervix: is it cost-effective? *Gynecol Oncol*. 2015;136(1):43-47. https://doi.org/10.1016/j.ygyno.2014.11.003
43. Sagae S, Monk BJ, Pujade-Lauraine E, et al. Advances and concepts in cervical cancer trials: a road map for the future. *Int J Gynecol Cancer*. 2016;26(1):199-207. https://doi.org/10.1097/igc.0000000000000587
44. Colombo N, Dubot C, Lorusso D, et al. Pembrolizumab for persistent, recurrent, or metastatic cervical cancer. *N Engl J Med*. 2021;385(20):1856-1867. https://doi.org/10.1056/nejmoa2112435
45. Spencer RJ, Rice LW, Ye C, Woo K, Uppal S. Disparities in the allocation of research funding to gynecologic cancers by Funding to Lethality scores. *Gynecol Oncol*. 2019;152(1):106-111. https://doi.org/10.1016/j.ygyno.2018.10.021
46. Mirin AA. Gender disparity in the funding of diseases by the US National Institutes of Health. *J Womens Health*. 2021;30(7):956-963. https://doi.org/10.1089/jwh.2020.8682
47. National Institutes of Health, Research Portfolio Online Reporting Tools. The Research, Condition, and Disease Categorization Process. Accessed January 3, 2022. https://report.nih.gov/funding/categorical-spending/rcdc
48. Stevanovic S, Helman SR, Wunderlich JR, et al. A phase II study of tumor-infiltrating lymphocyte therapy for human papillomavirus-associated epithelial cancers. *Clin Cancer Res*. 2019;25(5):1486-1493. https://doi.org/10.1158/1078-0432.Ccr-18-2722
49. The Cancer Genome Atlas Research Network, Burk RD, Chen Z, et al. Integrated genomic and molecular characterization of cervical cancer. *Nature*. 2017;543(7645):378-384. https://doi.org/10.1038/nature21386
50. World Health Organization (WHO). Cervical Cancer Elimination Initiative. Accessed January 2, 2022. who.int/initiatives/cervical-cancer-elimination-initiative
51. Division of Cancer Epidemiology & Genetics, National Cancer Institute, National Institutes of Health. STRIDES: Studying Risk and Improving Disparities of Cervical Cancer in Mississippi. Accessed January 5, 2022. https://dceg.cancer.gov/research/cancer-types/cervix/cervix-mississippi
52. Division of Cancer Epidemiology & Genetics, National Cancer Institute, National Institutes of Health. Study to Understand Cervical Cancer Early Endpoints and Determinants (SUCCEED). Accessed January 5, 2022. https://dceg.cancer.gov/research/cancer-types/cervix/cervical-cancer-early-endpoints-determinants-succeed
53. Division of Cancer Prevention, National Cancer Institute, National Institutes of Health. NCI Cervical Cancer 'Last Mile' Initiative. Accessed January 5, 2022. https://prevention.cancer.gov/major-programs/nci-cervical-cancer-last-mile-initiative
54. University of New Mexico Comprehensive Cancer Center. New Mexico HPV Pap Registry. Accessed January 5, 2022. https://unmhealth.org/cancer/research/hpv-prev-ctr/pap-registry.html

55. Division of Cancer Epidemiology & Genetics, National Cancer Institute, National Institutes of Health. Scientific Evaluation of One or Two Doses of the Bivalent or Nonavalent Prophylactic HPV Vaccines—The ESCUDDO Study. Accessed January 5, 2022. https://dceg.cancer.gov/research/cancer-types/cervix/escuddo
56. Mendelsohn J, Moses HL, Nass SJ, *A National Cancer Clinical Trials System for the 21st Century: Reinvigorating the NCI Cooperative Group Program*. National Academies Press; 2010.
57. Rice LW, Cedars MI, Sadovsky Y, et al. Increasing NIH funding for academic departments of obstetrics and gynecology: a call to action. *Am J Obstet Gynecol*. 2020;223(1):79.e1-79.e8. https://doi.org/10.1016/j.ajog.2020.03.022
58. Clark KT, Trimble CL. Current status of therapeutic HPV vaccines. *Gynecol Oncol*. 2020;156(2):503-510. https://doi.org/10.1016/j.ygyno.2019.12.017
59. Division of Cancer Control & Population Sciences, National Cancer Institute, National Institutes of Health. Population-Based Research to Optimize the Screening Process (PROSPR). Accessed January 5, 2022. https://healthcaredelivery.cancer.gov/prospr/
60. Burger EA, Smith MA, Killen J, et al. Projected time to elimination of cervical cancer in the USA: a comparative modelling study. *Lancet Public Health*. 2020;5(4):e213-e222. https://doi.org/10.1016/S2468-2667(20)30006-2
61. Uppal S, Shahin MS, Rathbun JA, Goff BA. Since surgery isn't getting any easier, why is reimbursement going down? An update from the SGO Taskforce on Coding and Reimbursement. *Gynecol Oncol*. 2017;144(2):235-237. https://doi.org/10.1016/j.ygyno.2016.06.008

How to cite this article: Rimel BJ, Kunos CA, Macioce N, Temkin SM. Current gaps and opportunities in screening, prevention, and treatment of cervical cancer. *Cancer*. 2022;128(23):4063-4073. https://doi.org/10.1002/cncr.34487