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Too Many Women are Dying from Cervix Cancer: Problems and Solutions

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Abstract

One woman dies from cervix cancer every 2 minutes, adding up to over 270,000 deaths globally per year. This cancer affects a young population, and hence, the loss of life is staggering. There are many aspects of prevention, screening, and care that are suboptimal. A great deal is known about HPV induced carcinogenesis, yet clinical outcomes have been stagnant over decades. There has been no improvement in cervix cancer survival in the US since the mid-1970s (1). With increased knowledge of the disease and greater worldwide resources including prevention, screening, and improved therapeutics, there is significant promise for fewer women to die from this virally induced cancer. We focus here on the major problems in prevention, screening, and delivery of care for cervix cancer and provide concrete solutions. With appropriate focus, a major improvement in survival from cervix cancer could be achieved in a short time span.

Summary

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Author Contributions

All authors contributed equally to the implementation of the research, the analysis of the results and to the writing of the manuscript.

Conflict of Interest

The authors confirm that there are no known conflicts of interest associated with this publication.

There is significant promise to turn the tide against the high incidence and mortality of cervix cancer. Optimistically, great change can be affected with a united effort. Increased screening programs and adherence will reduce morbidity. The HPV vaccine is one of the great medical breakthroughs of the modern era. Rapid global implementation is of paramount importance. Significant advances in surgery, chemotherapy and radiotherapy have been realized. The primary challenge is wide implementation. Together we need to promote health systems that will provide high quality gynecologic care for all women.

Keywords

cervix cancer; disparities; chemotherapy; radiation; implementation

Screening

Traditional screening methods with annual provider-based cervical collection and cytology drastically lowered the incidence of cervical cancer in the United States and other developed nations. Over the last 20 years, understanding of the pathogenesis of HPV infection in causing cervical cancer as well as the increased availability of commercial HPV tests has led to changes in screening recommendations. For decades, women were told they needed annual Pap smear testing; however, as of 2012 the U.S. Preventive Services Task Force, the American Society for Colposcopy and Cervical Pathology (ASCCP), and the American College of Obstetrics and Gynecology (ACOG) all agreed on consistent recommendations based on what trials had shown us regarding the natural history of cervical cancer: cytology screening every three years for women aged 21–65, with the option for women aged 30–65 to add the HPV test with the Pap test (co-test) and extend screening intervals to every five years (2).

However, in 2012, 8 million US women ages 21 to 65 reported they had not been screened for cervical cancer in the last 5 years (3). In 2015, an estimated 14 million US women had not been screened in the last 3 years (4). Using 2015 National Health Interview Survey (NHIS) data, Watson et al. further showed that US women had not attained the Healthy People 2020 objective of 93% of eligible women (aged 21–65) receiving cervical cancer screening with only 81.1% of women in accordance with the current recommendations. Screening was particularly low among uninsured women, immigrant women, and women without a usual source of healthcare. Most concerning, there was a statistically significant decline in Pap testing among women aged 21–65 from 2000–2015 (−5.8%) (4). This finding was further substantiated using healthcare claims data and again showed a decline from 2003–2014 for all age groups (5). Clearly efforts are needed to reach rarely or never-screened women as well as understand this declining trend in screening.

Researchers in this country and abroad have been tackling the issue of unscreened and underscreened populations and multiple approaches have emerged. Most notable is the idea of replacement of cytology-based programs with HPV primary screening. A number of randomized controlled trials (RCTs) have emerged that compared primary cytology screening to either HPV screening alone or HPV screening combined with cytology. In these

RCTs, HPV screening resulted in higher detection of CIN lesions, improved protection against cervical cancer, but lower specificity for preinvasive disease (6). Many countries are in various stages of adopting HPV primary screening with the Netherlands being the first nation to announce a nationwide shift to primary HPV screening and Australia following in December of 2017. Importantly, these national primary HPV screening programs have been designed for superior clinical effectiveness and cost-effectiveness(7).

While details such as age group, interval, and triage of positive results (given the decreased specificity of primary HPV testing) can be argued, the concept of a simple molecular-based test for use in at the very least those currently not participating in or having access to regular screening programs has many potential benefits. In addition to being much more sensitive (sensitivity of a single Pap test is only slightly higher than 50% whereas for a single HPV test it is approximately 95% (8), HPV testing is automated, making it less prone to human error and more reproducible compared with cytology which relies on cytotechnologists and pathologists for smear evaluation (9). It may also be centralized to ensure quality control and allow for high specimen throughput, which would improve efficiency and decrease costs. In this country, the ATHENA trial (10) led to the 2014 FDA approval of the Roche Cobas HPV test (Roche Inc., Pleasanton, CA, USA) as the only HPV assay approved for primary cervical cancer screening for women >25 years old. Since this approval, an interim guidance was issued by SGO, ASCCP, ACOG with information regarding the use of primary HPV testing but the guidelines have not been adjusted at this time (11). These agencies have previously called for clinical trials with primary HPV testing alone with more than 1 round of screening to further inform us regarding the implementation of primary HPV screening. Very recently, the results of the HPV FOCAL RCT, a Canadian screening trial looking at primary HPV testing versus liquid-based pap smear, were published and followed patients for multiple rounds of screening. This showed a significantly lower likelihood of CIN3+ at 48 months with primary HPV testing with a risk ratio of 0.42 (95% CI 0.25–0.69)(12). This adds to the body of literature showing the safety and efficacy of primary HPV testing for all patients and therefore, most compellingly, for underscreened and unscreened patients. We look forward to further publications from this trial including the cost-effectiveness data.

Additionally, stepping outside of the traditional provider-based health care visit for cervical cancer screening becomes possible with the use of a highly sensitive screening test. HPV primary screening offers the opportunity for self-sampling (13, 14). In a recent meta-analysis, the performance of HPV testing for self-collected versus clinician-collected specimens was found to be only slightly lower (15, 16). Novel technologies including solid media transport of HPV specimens have furthered the adaptability of HPV based self-sampling (17–20). The use of self-collection, solid transport media, and low-cost high throughput high risk human papillomavirus (HR–HPV) PCR DNA testing have given researchers the ability to implement large whole population screening programs for cervical cancer among the medically underserved (19). In this country, there are multiple small feasibility trials investigating at home HPV testing with high acceptability and compliance (21–24).

Pap screening is one of the impressive success stories of cancer screening; however, there continue to be women that are rarely or never screened. It is time to use the technologies we have and invest in future technologies to address these nonattendants.

Solutions:

1. Patient education regarding pap smears and HPV testing: Local, statewide, and national campaigns.
2. Expansion of nontraditional screening programs for unscreened and underscreened populations with acceptance by national guidelines.
3. Fund research into novel technologies for nontraditional screening.

Vaccination

The HPV vaccine has been available for a dozen years, yet its penetration is highly variable. Globally, for women, more than 50% of all cancers attributed to infection are caused by HPV.[1] High percentages of coinfections and low levels of access to health care resources influence the disproportionate incidence of many preventable cancers in low-income countries, HPV-related cancers included. The greater incidence and mortality due to cervical cancer in low-income countries is due to high rates of co-infection with HIV and poor access to timely cervical cancer screening, as well as receipt of recommended treatment procedures for precancerous cervical lesions (25).

For more than a decade, the HPV vaccine has provided protection against several types of HPV infection, which cause the majority of HPV-related cancers. The World Health Organization (WHO) recommends that girls ages 9 to 13 years receive 2 doses of the HPV vaccine (at 0, 6 months) to prevent infection with the virus types responsible for the majority of cervical cancer cases (26). As a result, girls in more than 71 countries (37% of all nations) routinely receive the HPV vaccine (27). Furthermore, women in low- and middle-income countries are increasingly introduced to the vaccine with support from Gavi, the Vaccine Alliance.[2] Established in 2000, Gavi is a global vaccine alliance that partners private and public sectors, with the shared mission of creating equal access to both underused and new vaccines for children in the poorest regions of the world (28). Expansion of Gavi's reach and increased implementation of subsidized HPV vaccination programs for low to middle income countries are strongly needed to raise HPV vaccination rates among adolescents and young adults in Africa and Asia.

Unfortunately, access to and receipt of HPV vaccination continues to be highest in countries where incidence and mortality related to HPV infection remain the lowest (27). From 2006–2014, an estimated 118 million individuals were targeted by HPV vaccination programs. Only 1% of these individuals were from low-income and lower- to middle-income countries (29). In higher income regions, 34% of women ages 10 to 20 years meet HPV vaccination series completion guidelines whereas only 3% of similar-aged women in lower-income nations meet these guidelines (29). For receipt of the first dose of the HPV vaccine, the differences between higher income and lower income regions are great (43% vs. 3%, respectively) (29). Africa (at 1%) and Asia (at 1%) have the lowest rates of HPV vaccine

receipt among girls, and these regions have the highest incidence and mortality due to cervical cancer (29). Furthermore, even when available, the HPV vaccine has not been widely accepted in the United States, in other high income countries, and globally. HPV vaccination hesitancy is often due to views that the vaccine is unnecessary, misperceptions around possible adverse side effects, and lack of knowledge/information about the vaccine (30–33). In the United States, one of the strongest determinants of HPV vaccination receipt is where you live. In 2016, 73% of female teens were up to date with HPV vaccine receipt in Rhode Island vs. 31% in South Carolina; for males, it was 69% in Rhode Island vs. 20% in Wyoming (34). In conservative regions of the U.S., religious affiliation may impact knowledge of, provider recommendation for, and actual receipt of the HPV vaccine (35).

Despite inequalities in access to and acceptance of the HPV vaccine, in regions where introduction of HPV vaccination programs have been widely adopted, we are already observing a reduction in HPV-related infections and cervical pre-cancers (36). Vaccinating boys has been shown to lower the risk of HPV transmission to sexual partners (36). The United Kingdom, Denmark, and Scotland had at least 90% of eligible girls receiving the first dose of the HPV vaccine by 2014/2015 and have seen a significant reduction in HPV types 16/18 and/or genital warts at the population level (36). Australia, with 77% of boys and 86% of girls receiving the first dose of the HPV vaccine, has seen a 92% reduction in genital warts and an 86% reduction in vaccine-type HPV infection among 18–26 year olds (36). Even with the lower rates of HPV vaccination in the U.S.at 50% first dose receipt among boys and 63% among girls, the U.S. has seen a 35% decline in genital warts among those under age 21 and a 64% decline in vaccine-type among those ages 14–19 years (36).

Solutions for Vaccine implementation:

1. Continued reduction in cost.
2. Government health program adoption.
3. Local solutions such as school based programs.

Disparities in care

In the United States, cervical cancer mortality rates are higher among women in rural areas compared to metropolitan areas (37) and among black women compared to white women (38), suggesting that there are disparities in care for cervical cancer patients. Based on cancer registry data from the CDC and SEER registries covering 97% of the US population, the age-adjusted death rate was 2.7 per 100,000 among women in rural areas in 2011–2015, compared to 2.2 per 100,000 among women living in metropolitan counties with populations of over 1 million people (37). Although the rates were higher among rural residents, the overall trend in the average annual percentage change over the period of 2004 to 2013 were similar among nonmetropolitan residents (−1.5%) and metropolitan residents (1.4%). A study in Alabama of 390 cervical cancer patients reported that living >100 miles away from a comprehensive cancer center was associated with a higher risk of death (1.68, 95%CI=1.11–2.54) (39).

The cervical cancer mortality rate disparity difference is even greater by race/ethnicity. A recent study estimated mortality rates corrected for rates of hysterectomy and reported that the disparity between black and white women was underestimated by 44% (38). Over the 2000–2012 period, the uncorrected cervical cancer mortality rate was 5.7 (95%CI=5.5, 6.0) while the corrected rate was 10.1 (95%CI=9.6, 10.6). For the same time period, the uncorrected rate among white women was 3.2 (95%CI=3.1, 3.2) while the corrected rate was 4.7 (95%CI-=4.6–4.8). The difference in the rates due to the correction among black women became more dramatic among older women with the corrected rates among black women increasing to 29.7 per 100,000 among 75–79 year olds, 33.4 among 80–84 year olds and 37.2 among 85+ year olds. The corresponding corrected cervical cancer mortality rates for white women were 11.0 per 100,000 among 75–79 year olds, 11.8 among 80–84 year olds and 11.6 among 85+ year olds.

The reasons for the race disparity have been widely argued, with potential explanations including differences in treatment adherence and access to care. Several recent studies have investigated the differences in adherence to treatment guidelines for cervical cancer patients. In an analysis of 28,482 cervical cancer patients with stage IAI-IIA tumors in the National Cancer Database (NCDB), black women were less likely to receive indicated surgery or chemo-radiotherapy in 2004–2007, but this disparity was no longer present in the next time period of 2011–2014 (40). However, among 28,013 women with later stage cervical cancer (stage IIB-IVA), black women were less likely to receive chemo-radiotherapy throughout the time period of 2004–2014. Another study of 15,194 stage IIB2-IVA cervical cancer patients based on the NCDB reported that black women were less likely to receive standard of care therapy including external beam radiotherapy with concurrent chemotherapy and a brachytherapy boost, even after adjustment for stage, insurance status, household income and hospital volume (41). Cervical cancer patients who were older, had larger tumor size, and had lower median household incomes were also less likely to receive standard of care therapy.

State-level studies have reported on treatment adherence for cervical cancer patients by race/ethnicity as well. In a study of 6,063 stage IB-IIA cervical cancer patients diagnosed between 19952009 in the California Cancer Registry, 47% received National Comprehensive Cancer Network (NCCN) guideline adherence care (42). Cervical cancer patients who had lower socioeconomic status, higher Charlson comorbidity scores, were older at cancer diagnosis, had larger tumors and were treated at small volume hospitals were less likely to receive guideline adherent care. Black race/ethnicity was not associated with whether a cervical cancer patient received guideline adherent care or not. A study based in Florida on 5,367 cervical cancer patients diagnosed between 1998 to 2003, reported that late stage diagnosis and under-treatment were the main factors that explained the race, ethnic and socioeconomic disparities in cervical cancer survival rates (43). A higher proportion of African-American women did not have insurance, were diagnosed at late stage, had poorly differentiated cancer, and did not receive surgery or chemotherapy.

Although a few studies reported that treatment adherence does not differ by race, most studies did report lower adherence for black women. Additional studies further investigated the issue of whether access to care impacted the lower treatment adherence. Another study

based on the NCDB of 16,195 stage IB2-IVA cervical cancer patients reported that race/ethnic disparities in guideline based care was the highest in high-volume hospitals, suggesting that access to care is not the main issue (44). The investigators reported that the disparity in care was not due to income or stage or histology. The previously mentioned study in Alabama had reported that a higher proportion of black cervical cancer patients lived closer to a cancer center (<100 miles) than white cervical cancer patients (78.9% of black patients vs. 75.9% of white patients; (39). On the other hand, a study of 1,553 cervical cancer patients in the United States Military Health Care system reported that equal access to care resulted in similar survival rates (45). Differences in the distribution of age at diagnosis, stage, grade or histology were not observed between white and black cervical cancer patients.

Solutions to reduce disparities:

1. Adhere to established guidelines for all patients.
2. Ensure access to healthcare.
3. Develop an oncology physician workforce that better reflects the race/ethnicity distribution of the U. S. population.

Radiation therapy delivery

High rates of local control for large tumors are achieved with a combination of external beam radiotherapy (EBRT) and brachytherapy (BT) in cancer of the cervix. Well before the megavotage era, respectable cure rates were being reported from the best centers. Henri Coutard together with colleagues from Paris described 5 year cure rates from 1930 of 75%, 56% and 37% for stage I, II, and III cervix cancers, respectively (46). With chemoradiotherapy, central pelvic control rates > 95% have been documented before and after the era of image guided brachytherapy (47, 48). The survival improvement with brachytherapy is well established. Han et al documented in a SEER database study that BT declined from 83% in 1988 to 58% in 2009 with a resulting overall survival decrement hazard ratio of 0.66 (49). This is almost exactly the survival decrement seen when chemotherapy is omitted in advanced cervix cancer (50). Gill et al in a NCDB study of 7654 patients showed that an IMRT or SBRT boost rather than BT resulted in inferior OS with a HR of 1.86 (95% CI, 1.33–2.55), which was a larger effect then not receiving chemotherapy (HR 1.61; 95% CI 1.27–2.0, (51). A second NCDB study demonstrated that only 44 percent of patients with advanced cervix cancer received the standard of care modalities: EBRT, BT and chemotherapy (41).

Brachytherapy's successful track record is due to the high central dose and conformality achieved. In one planning study evaluating target dose coverage and sparing of pelvic organs, BT was superior to both intensity modulated photon and proton treatment (52). With three dimensional treatment planning using CT, or better, MRI, brachytherapy is even more effective and safe (53). Yet brachytherapy usage is declining (54). The reasons for underutilization of brachytherapy include insufficient training of residents in radiation oncology with isolation from gynecologic oncologists, intensive requirement for physics

support, poor access to BT, and relatively inadequate reimbursement rates compared to other radiation modalities.

Radiation Oncology residents exposure to BT is declining (55). The American Board of Radiology requires radiation oncology residents to participate in 5 interstitial cases and 15 intracavitary cases. The interstitial cases include prostate BT and intracavitary cases include vaginal vault BT: both of these are markedly different than a case requiring placement of a uterine tandem. More specific brachytherapy requirements for trainees would likely be helpful such as a precise number of tandem-based brachytherapy applications. The shift toward “out-patient care” has resulted in isolation of radiation therapy departments in some centers away from gynecologic oncologists. In many academic centers there is a laudable shared approach to staging, triaging of care, treatment planning, and operative management. This is more difficult or impossible to replicate in many private settings. Survey reports have documented that non-academic centers are less likely to deliver BT and more likely to have protracted treatments: both which negatively impact survival (56).

The shift to high dose rate (HDR) has been dramatic: 15% in 1992 to 1994 compared to 69% in a 2005 to 2007 (56, 57). The number of insertions with HDR is typically double or more: 2 for LDR and 4 or 5 for HDR. This shift from in-patient to out-patient care while importantly keeping patients out of the hospital has resulted in increased workloads on physicians, physicists and departments. Coupled with relatively poor reimbursement and the fact that most private centers see 3 or fewer cervix patients annually may lead many practices to reduce access to BT and omit this life saving therapy(57) (58). A recent time-activity study documented the heightened work load on physicians performing BT with reimbursement 4 fold lower for brachytherapy compared to EBRT (59). The American Brachytherapy Society recognized that poor reimbursement was resulting in a decrease in brachytherapy; hence, in 2013 a Socio-Economic Committee was developed to work with other medical societies, industry and government to rectify the reimbursement discrepancy.

An important quality parameter in advanced cervix cancer treatment is overall treatment time. Multiple studies have documented over the past 2 decades that for every day over 8 weeks there is an approximate 1% per day loss in local control (60). A recent report for GOG trials indicated that the median treatment length was 57 days and 25% of patients had a treatment length of 66 days or longer (61). This indicates that 25% of patients have a loss of local control of approximately 10% due to lack of adherence to quality parameters. This is particularly notable since quality parameters are typical followed more attentively for clinical trial patients.

Solutions for care delivery in radiation therapy:

1. Improve training: consider specialized brachytherapy training.
2. Improve work efficiencies: utilize centers of excellence.
3. Payment reform: improve reimbursement for BT and don’t pay for inappropriate boost techniques.

4. Adhere and implement established quality metrics: chemotherapy, brachytherapy and completion of treatment within 8 weeks.

Chemotherapy and precision medicine/current global trials

Utilization of cisplatin-based chemotherapy with radiation therapy in women with advanced disease dramatically improved survival (50). The optimal timing, schedule, and dose of chemotherapy is the subject of several on-going clinical trials; as well as maintenance chemotherapy or immunotherapy in patients with advanced disease. Patients with metastatic or recurrent cervical cancer have poor prognosis with limited treatment options. Unfortunately, there have not been many advances in the use of systemic treatment in this disease. Combination chemotherapy was studied in GOG 204 trial for those with advanced or metastatic disease and showed no difference in response rates for cisplatin plus paclitaxel (control arm) with cisplatin plus vinorelbine, cisplatin plus gemcitabine, or cisplatin plus topotecan (62). Because of the toxicity seen with cisplatin chemotherapy, carboplatin has been shown to be a reasonable substitute for cisplatin per the JCOG 0505 trial (63).

Bevacizumab was the first drug approved for advanced stage cervical cancer since 2006. This approval was based on the GOG 240 trial for cervical cancer patients with recurrent, persistent, or metastatic disease in combination with Cisplatin and Paclitaxel or Topotecan and Paclitaxel (64) with the addition of bevacizumab to chemotherapy resulting in a 3.7 month improvement in overall survival compared to chemotherapy alone. No validated treatment options exist beyond this first-line treatment regimen. Chemotherapy regimens in this situation are associated with substantial toxicity and poor efficacy with a median overall survival of 7 months (65). In several published phase II studies, evaluating single chemotherapy agents in the second-line setting, including topotecan, vinorelbine, gemcitabine, docetaxel and pemetrexed, the response rate ranged between 4.5% and 18%, with a median progression-free survival (PFS) and overall survival (OS) ranging approximately between 2–5 and 5–16 months, respectively (66, 67).The response rates and improvements in survival with cytotoxic chemotherapy are low.

Due to these poor outcomes, novel cytotoxics, biologics, and combinations need to be explored (68). Pathways that are potentially important in cervical cancer include VEGF, EGFR, PI3K/Akt/mTOR, and DNA repair. The Cancer Genome Atlas project in cervix cancer showed that greater than 70% of cervical cancers exhibited genomic alterations in one or both of the PI3K–MAPK and TGFβ signaling pathways (69). Amplifications were seen in PD-L1 and PD-L2, genes that encode immunotherapy targets; and Her3 was identified as a potential immediate target. Also, Endometrial-like cervical cancers comprised predominantly of HPV-negative tumors with mutations in *KRAS*, *ARID1A* and *PTEN* (69). A large study of different cancer types demonstrated that cervix cancer had the highest mutational burden of any gynecologic cancer (70). Cervix cancer had the seventh highest mutational burden of 30 different cancers, just greater than head and neck cancers. Cervix cancers also can display mismatch repair deficiency. Approximately 4% of cervix cancers have mismatch repair deficiency which was the fifth highest of 24 separate malignancies (71).

There are currently several ongoing clinical trials of systemic therapy in recurrent or metastatic cervical cancer (clinicaltrials.gov, Table 1). Because HPV infection is associated with the majority of cervical cancers and may elicit an immune response, the use of immunotherapy is actively being studied in cervical cancer. Nivolumab, a programmed death (PD)-1 inhibitor has shown promise in the treatment of recurrent cervical cancer. CheckMate 358 (NCT02488759), a trial of Nivolumab in five virus associated cancers included 19 cervical cancer patients and 5 vaginal/vulvar cancer patients, showed an overall response rate (ORR) of 20.8% and disease control rate of 70.8% with median PFS of 5.5 months. Side effects were tolerable in this patient population (72).These results are encouraging and have led to numerous ongoing trials with checkpoint inhibitors, including combinations of immunotherapy with targeted therapy, like atezolizumab (PD-L1 inhibitor) and bevacizumab. On June 12, 2018 pembrolizumab was approved for patients with recurrent or metastatic cervical cancer with disease progression on or after chemotherapy whose tumors express PD-L1. Expression of PDL1 was observed in 79% of patients and the overall response rate was 14.3% (73).

Solutions for improving chemotherapy:

1. Ensure widespread use of chemoradiation in advanced disease.
2. Identify the optimal dose and extent of chemotherapy in curative patients.
3. Identify targets.
4. Develop mutation-specific trials.

Global medicine

Cervical cancer is the fourth most common cancer in women worldwide with greater than 85% of cervical cancer deaths occurring in less-developed regions of the world, corresponding to an 18-fold disparity in mortality rates (74). Much of the world's population has little to no access to cervical cancer care. The issues facing middle-low income countries are large and numerous including manpower, training, funding, facilities, and outreach. Radiotherapy resources are vastly deficient in Africa, South and Central America, large parts of the Asia and much of the Caribbean (74). In one analysis, the introduction of adequate radiotherapy facilities increased survival in cancer of the cervix more so than any other neoplasm (74). This is due to the fact that cervix cancer is radiosensitive and many women present with non-metastatic disease. Economic analyses have concluded that an immense improved survival can be gained with a reasonable investment. Multiple societies have developed resource stratified guidelines including the American Society of Clinical Oncology, the National Comprehensive Cancer Network and the American Brachytherapy Society that can help provide a framework for local care pathways (75–77).

Significant efforts have been employed in attempting to improve cervix cancer globally. The Gynecologic Cancer InterGroup (GCIG) recognized that a vast disparity existed between the High-Income countries that were attempting to do clinical cervical cancer research where incidence rates of cervix cancer were low, and Low and Middle-Income Countries (LMIC) where there was a high incidence of cervix cancer, yet little or no research. Hence, in 2013

the GCIG developed the Cervix Cancer Research Network (CCRN) to promote cervix cancer clinical research by partnering with developed cooperative groups and hospitals and sites where cervix cancer was endemic (Figure 1). Significant obstacles have been encountered including financial support, insurance and indemnification, drug availability and regulatory complexities of performing international trials. In the 2017 CCRN symposium held in Mexico city, 38% of participants reported insufficient numbers of radiation machines as the most common barrier to the treatment of cervical cancer with curative intent. Other common barriers included advanced disease at presentation (77%), long wait times (40%), and social issues (33%), emphasizing the complex challenges faced by Latin American providers. Approximately two-thirds of participants had never enrolled a cervical cancer patient on a clinical trial. The most common cited barriers were the lack of available open trials (66%), limited funding (58%), limited research support staff (39%), and lack of infrastructure (34%).

Despite these significant challenges, six CCRN clinical trials have been developed with recruitment underway in 5 and accrual completed for the OUTBACK trial. Five of these trials have obtained public funding. The CCRN trial with the highest number of CCRN accruals to date is the TACO Trial (Tri-weekly Administration of Cisplatin in Locally Advanced Cervical Cancer), developed by investigators from the Korean Gynecologic Oncology Group (KGOG) and Thai Cooperative Group. Based upon promising phase II data, eligible locally advanced cervical cancer patients receiving concurrent chemoradiation in this phase III study are randomized between 6 cycles of standard 40 mg/m^2 weekly cisplatin versus 3 cycles of 75 mg/m^2 cisplatin every 3 weeks (78). If found to be equivalent, administration of cisplatin every 3 weeks could result in significant cost savings for health systems, thereby increasing accessibility for patients. This trial remains open to accrual and has accrued patients from Asia.

In an effort to address high rates of distant failure in advanced cervical cancer patients, two CCRN trials are focusing on potential benefits from neoadjuvant and adjuvant chemotherapy, respectively. The INTERLACE Trial (Induction Chemotherapy Plus Chemoradiation as First Line Treatment for Locally Advanced Cervical Cancer) is a phase III randomized trial directed by the National Cancer Research Institute (NCRI) in the United Kingdom seeking to improve outcomes with neoadjuvant weekly carboplatin and paclitaxel followed by standard concurrent chemoradiation. This trial continues to accrue across the United Kingdom, Mexico, and Italy with 20% of patients enrolled from Mexico as of January 2018. The OUTBACK Trial (Cisplatin and Radiation Therapy With or Without Carboplatin and Paclitaxel in Patients with Locally Advanced Cervical Cancer), led by investigators from the Australia/New Zealand Gynecologic Oncology Group (ANZGOG), is a randomized phase III trial evaluating adjuvant chemotherapy with carboplatin and paclitaxel after standard definitive concurrent cisplatinbased chemoradiation for locally advanced cervical cancer. As of June 2017, this trial met its accrual goal with the majority of patients being accrued thru NRG Oncology.

The SHAPE Trial (Simple Hysterectomy and Pelvic Node Dissection in Patients with Low Risk Early Stage Cervical Cancer), led by the Canadian Cancer Trials Group (CCTG, formerly known as NCIC), addresses potentially avoidable morbidities from

parametrectomy in standard radical hysterectomy by randomizing patients with stage IA2 – IB1 < 2 cm cervical cancer between radical and simple hysterectomy. This trial is currently accruing with patients enrolled from North America, Europe, Russia, and Asia, and hopes to add patients from new CCRN sites in Brazil in 2018. The Senticol III study, an international prospective validation trial of sentinel lymph node biopsy in cervical cancer will randomize patients after a negative frozen section to sentinel lymph node biopsy alone versus sentinel lymph node biopsy and lymphadenectomy.

An appealing concept for LMIC where there is intense pressure for access to radiotherapy is hypofractionation. Hypofractionation, where an equivalent biologic radiation dose is administered in fewer fractions, is more convenient for patients. A phase II trial was proposed at the 2017 CCRN symposium and has been activated in sites in Mexico City and Honduras. This trial randomizes patients with pelvic only FIGO stage IB2 – IIB disease to 50 Gy in 25 fractions versus 40 Gy in 16 fractions of neoadjuvant chemoradiation with weekly concurrent cisplatin followed by definitive radical hysterectomy. Brachytherapy is omitted from the trial due to lack of access to brachytherapy.

Clinical trials can save the lives of individuals with cervix cancer, and also facilitate state-of-theart care in hospitals, regions and countries. TACO, one of the CCRN trials from Korea, has quarterly quality assurance meetings for radiotherapy fields. After the first meeting, a noted reduction in radiotherapy errors were noted from sites in Vietnam and Thailand. These CCRN trials not only seek to answer fundamental questions in cervical cancer, but also represent opportunities for LMIC patients to receive low cost, modernized treatment approaches while stimulating a local culture of research and clinical trial support. There are many important on-going cervix cancer trials. The success of these will depend on applicability to local populations, researchers and care givers. The global impact of these efforts are not certain.

Global Medicine Solutions:

1. Vaccine availability on a global scale and screening programs that are locally relevant.
2. Adherence to resource stratified guidelines that optimize local care.
3. Cost effective investments in radiation, medical and surgical oncology.
4. Development of locally relevant clinical trials.
5. Participation in trials can improve care in centers, regions, and for individual women.

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Highlights

- Patient education and expansion of nontraditional screening programs for unscreened and underscreened populations.
- Implement reduction in costs, government health programs, and school based programs for vaccinations.
- Adhere to guidelines, ensure access to healthcare, and establish an ethnically similar physician workforce for all patients.
- Improve training, work efficiencies, payment reform, and quality metrics.
- Ensure widespread use of chemoradiation, identify targets, and develop mutation-specific trials.

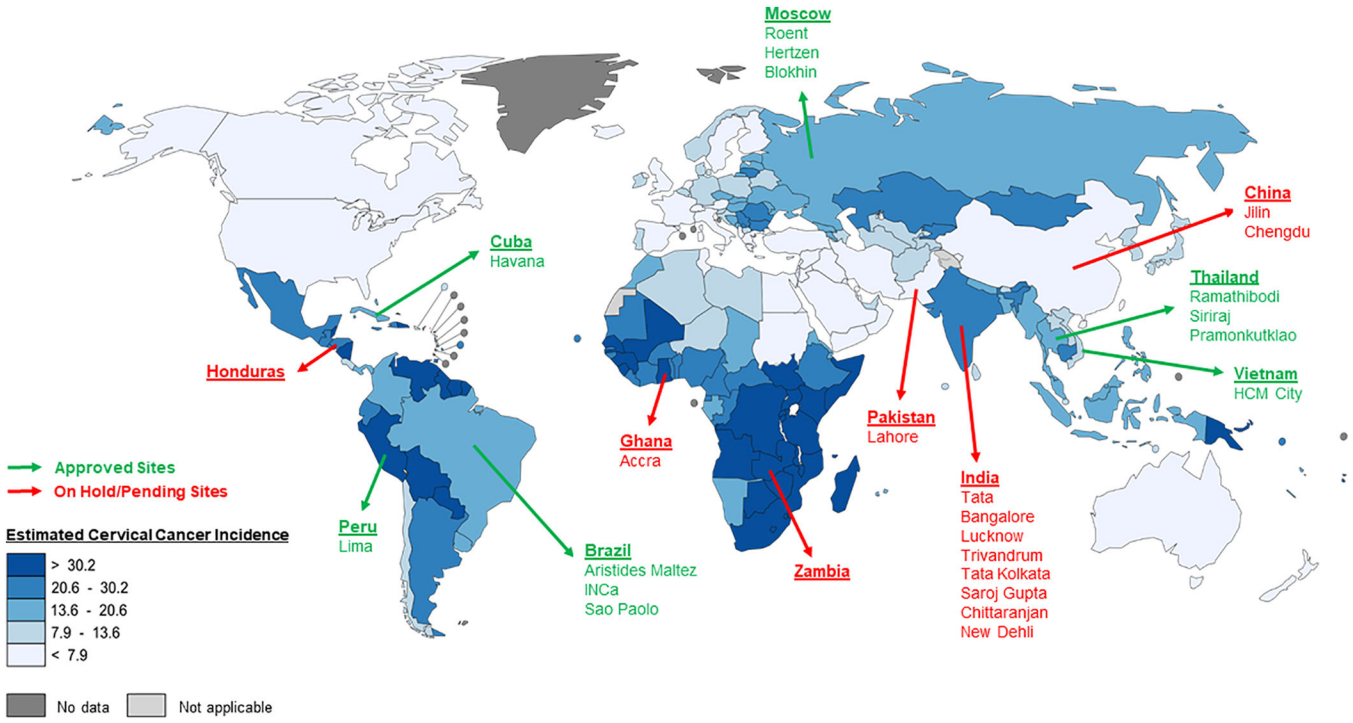

Figure 1.

Current CCRN sites and worldwide incidences of cervical cancer per 100,000 females (all ages), age standardized to the WHO standard population, 2012 (79).

Table 1.

Ongoing clinical trials of systemic therapy in recurrent or metastatic cervical cancer (clinicaltrials.gov).

Chemotherapy Trials	Biologics/Targeted Therapy Trials	Immunotherapy Trials	Vaccine Trials
Capecitabine and Docetaxel USA	Celecoxib (COX-2) Canada	Nivolumab (PD-1) USA	INO-3112 (targeting HPV 16/18 combined with a DNA plasmid for IL-12 as an immune activator) USA
Weekly Paclitaxel USA	Nimotuzumab (EGFR) China, Mexico	Pembrolizumab (PD-1) and Paclitaxel and Cisplatin USA	GX-188E DNA-based Therapeutic Vaccine) and Pembrolizumab (PD-1) Korea
Docetaxel USA	Cetuximab (EGFR) USA	Atezolizumab (PD-L1) and Doxorubicin Belgium	ADXS11–001 (Listeria monocytogenes cancer vaccine) USA
Eribulin USA	Cetuximab (EGFR) and Chemotherapy Italy, USA	Atezolizumab (PD-L1) and Bevacizumab (VEGF) USA	
Ixabepilone USA	Erlotinib (EGFR) USA	AGEN2034 (PD-1) USA	
Oxaliplatin USA	Gefitnib (EGFR) USA	REGN2810 (PD-1) USA	
Pemetrexed and Cisplatin USA	Sunitinib (VEGF) USA	Ipilumimab (CTLA4) USA	
Capecitabine USA	Apatanib (VEGF) and Chemotherapy Sequentially China	Ipilumimab (CTLA4) and chemoradiation and USA	
Pemetrexed USA	Brivanib (VEGF) USA	IL-12 USA	
Oxaliplatin and Paclitaxel USA	Cediranib (VEGF) and Carboplatin and Paclitaxel UK	LN-145 (Autologous TILs) USA	
Carboplatin and Topotecan France	Bevacizumab (VEGF) and Carboplatin and Paclitaxel Argentina and Brazil	CAR-T cells phase I/II China	
Irinotecan Taiwan	Pazopanib (VEGF) and Lapatanib (HER2) versus single agent USA		
DX-8951f (exatecan) USA	Bevacizumab (VEGF) and Rucaparib (PARP) USA		
	Veliparib (PARP) Paclitaxel Cisplatin USA		
	Veliparib (PARP) Topotecan USA		
	Everolimus (mTOR) Brazil		
	Temsiroliums (mTOR) Canada		
	Bryostatin-1 (Protein Kinase C) and Cisplatin USA		
	Tisotumab Vedotin (ADC to Tissue Factor) USA and Belgium		
	Mapatumumab (TRAIL-R1) Cisplatin Radiotherapy Netherlands		

Chemotherapy Trials	Biologics/Targeted Therapy Trials	Immunotherapy Trials	Vaccine Trials
	Pembrolizumab (USA)		