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Cervical Cancer: A Global Health Crisis

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Precis for use in Table Contents: Cervical cancer is a leading cause of death worldwide. In this paper, we discuss biology, prevention, and treatment of this disease, in addition to activist efforts aimed at improving treatment and access to care.

Abstract:

Cervical cancer is the fourth most common malignancy in women worldwide. Almost all cases of cervical cancer result from infection with human papilloma virus (HPV), and prevention of cervical cancer includes screening and vaccination. Primary treatment options for cervical cancer may include surgery or a concurrent chemoradiotherapy regimen consisting of cisplatin-based chemotherapy with external beam radiation therapy and brachytherapy.

Cervical cancer causes more than a quarter of a million deaths per year, as a result of grossly deficient treatments in many developing countries. This warrants a concerted global effort to counter shocking loss of life and suffering that largely goes unreported.

This article provides a review of cervical cancer: its biology, prevention, treatment, and discusses the global cervical cancer crisis and efforts to improve the prevention and treatment of cervical cancer in underdeveloped countries.

Keywords: cervical cancer, developing world, HPV, vaccination, GCIG, CCRN, chemotherapy, brachytherapy, activism

Introduction

Cervical cancer is one of the leading causes of cancer death among women [1]. Worldwide, cervical cancer is the fourth most frequently occurring malignancy in women and results in an estimated 530,000 new cases annually with 270,000 deaths. About 85% of the worldwide deaths from cervical cancer occur in underdeveloped or developing countries, and the death rate is 18 times higher in low and middle-income countries (LMIC) compared to wealthier countries. [2]. The highest incidence rates occur in Central and South America, the Caribbean, Sub-Saharan Africa, and Southern Asia [3]. In the United States in 2016, there were an estimated 12,990 cases and 4,120 deaths from cervical cancer [4], and the median age of diagnosis is 47 years.

Standard management of early stage (IA – IB1) cervical cancer is radical hysterectomy and lymph node dissection and/or radiation +/- chemotherapy. [5-7]. Standard management of locally advanced cervical cancer includes external beam radiotherapy with concurrent cisplatin-based chemotherapy with brachytherapy [8-16]. Brachytherapy is critical for curative intent treatment of cervical cancer and when replaced by external beam radiotherapy the results are clearly inferior[17-20]. With state-of-the-art staging and treatment, 3-year local control for early stage and advanced stage cervical cancer is 87-95% and 74-85%, respectively [15,16]. For all stages combined, 3-5-year survival from cervical cancer for many underdeveloped countries is <50% [21]. Death from cervical cancer often involves local progression resulting in significant suffering including ureteral obstruction, pain, and fistulas. The purpose of this article is to thoroughly review the biology, prevention strategies, treatment, and activism regarding cervical cancer with an emphasis on the global impact of these complex issues.

Biology of Cervical Cancer

The cervix is lined by stratified squamous epithelium that covers the exocervix and mucus-secreting columnar epithelium characteristic of the endocervical canal. The transition between these two populations of cells is called the squamocolumnar junction, and it is this area that is believed to be at greatest risk of viral neoplastic transformation. Tumors arising in the ectocervix are most commonly squamous cell carcinomas, which account for 75% of invasive cervical carcinoma. In contrast, tumors arising from the endocervix are more likely to be adenocarcinomas. Adenosquamous, small cell or neuroendocrine, serous papillary, and clear cell carcinomas of the cervix are less common histological subtypes.

The majority of cases of cervical cancer result from infection with HPV, with HPV DNA identified in approximately 95% of malignant cervical lesions [22]. The majority of HPV infections are transient and will be spontaneously cleared. However, in some cases, persistent infection will result in the development of the premalignant conditions of cervical intraepithelial neoplasia or adenocarcinoma in situ. Without treatment, the transition from dysplasia to invasive carcinoma may take years to decades to develop in most women. However, in around 10% of patients this transition can occur in under a year [23]. In addition, adenocarcinoma in situ appears to be more difficult to detect on Pap smear and this is thought to be one of the reasons for the increasing incidence of this subtype of cervical cancer [24].

Various factors have been suggested to increase the likelihood of the development of persistent infection and subsequent malignant transformation including cigarette

smoking, long-term oral contraceptive use, high parity, and co-infection with type 2 herpes simplex virus or human immunodeficiency virus (HIV). HPV serotypes 16 and 18 account for approximately 70% of cases, with the most common serotypes of HPV in women with cervical cancer in descending order of frequency being 16, 18, 45, 31, 33, 52, 58, and 35.

Perhaps due to the relative rarity of locally advanced or metastatic cervical cancer in the developed world, there have been only a few published reports of profiling of cervix tumors to look for actionable driver mutations. The most common finding has been of abnormalities in the PI3Kinase pathway, as reported by Wright et al. [25] who used the Oncomap platform to interrogate 80 cervical tumors for 1250 mutations in 139 genes. They identified PIK3CA mutations in 31% of cases, with shorter survival times seen in those with a mutation [25]. However, targeting this pathway therapeutically has proven difficult. They also identified KRAS mutations in 17.5% of the adenocarcinomas but none of the squamous cell carcinomas, suggesting that these tumor subtypes will need different types of targeted therapies. Ojesina et al. [26] have recently published the findings of deep sequencing of 115 cervix cancers to look for somatic mutations. They identified several novel somatic mutations in the squamous cell carcinomas profiled including E322K substitutions in the MAPK1 gene (8%); inactivating mutations in the HLA-B gene (9%); and mutations in EP300 (16%), FBXW7 (15%), TP53 (5%), and ERBB2 (6%). Somatic mutations in ELF3 (13%) and CBFB (8%) mutations were found in 24 adenocarcinomas [26].

Prevention of Cervical Cancer

Recognition that cervical neoplasia begins as intraepithelial change, which usually takes many years to develop into invasive disease, led to the use of cervical exfoliative cytology to detect cervical intraepithelial neoplasia that can be treated to prevent the development of cervical cancer. With the discovery that cervical cancer is caused by high risk HPV infection, the development of prophylactic vaccination in the 1990s there is now the means to achieve a more global approach to prevention through prophylactic vaccination. Vaccination can be viewed as primary prevention, with screening as secondary prevention.

The pivotal role of HPV in cervical carcinogenesis means that screening with HPV testing can achieve a more accurate risk-based approach. Randomized trials [27-30] have demonstrated that HPV testing is more sensitive than cytology, and for HPV negative women, screening intervals can safely be extended [31]. HPV testing lacks specificity, which means that cytology is required to triage women for referral to colposcopy. Based on limited data, triage of high-risk (hr) HPV-positive women using a combination of genotyping for HPV 16 and 18 and reflex cytology for women positive for the 12 other hrHPV genotypes appears to be a reasonable approach to managing hrHPV-positive women [32]. A challenge for primary HPV screening is the management of women with negative cytology, but various risk-based strategies are being developed based on HPV type and persistence. Screening programs around the world are in the process of switching from primary cytology aided by visual inspection with acetic acid to primary HPV testing.

Prophylactic Vaccination Against HPV

HPV infection of the cervix, thought to occur in most women at some time in their life, is most prevalent following the onset of sexual activity. In the majority of cases, the infection is cleared by the immune system. However, in a significant minority, infection is persistent and the viral genome becomes integrated into host DNA resulting in genomic dysregulation caused largely by the HPV oncogenes E6 and E7. The concept behind prophylactic vaccination is to achieve a high level of type-specific neutralizing antibodies directed against HPV capable of preventing cervical infection. The critical discovery that led to the vaccines we have today is that the major capsid protein of HPV, L1, could self-assemble into so-called virus like particles (VLPs) [33], which were shown to be highly immunogenic. Two vaccines, both based on VLPs made from HPV types 16 and 18, were produced with each using a different adjuvant. One was bivalent (types 16 and 18), and the other was quadrivalent to include the types responsible for genital warts (types 6 and 11). Both of these vaccines have been rigorously tested, initially in phase I and II trials and then in pivotal phase III trials [34,35]. These were performed on cohorts aged 15-26, and they demonstrated very high levels of type-specific antibody, which achieved very high efficacy (greater than 95%) in preventing HPV infection and similar efficacy in preventing type-specific CIN as well as vaginal and vulvar lesions. The data from these trials showed however that the vaccines were ineffective in females who already had an established HPV infection. Additionally, vaccination of boys prior to sexual activity at age 11-12 is recommended by the American Academy of Pediatrics to prevent HPV-induced cancers of the oropharynx, anus, and penis [36]. Vaccination of both sexes will have a large impact on herd immunity.

Most developed countries have introduced vaccination programs for pre-pubescent girls, and there has been early evidence of public health benefit with reduction in the incidence of high-risk infection, reduced incidence of cervical abnormalities, and even a reduction in genital warts in males who have not been vaccinated. This provides clear evidence of herd protection achieved by vaccination.

Recent Developments in Prophylactic Vaccination

The original vaccination regimens were based on three doses, given at time 0, 2, and 6 months. Recently, two doses have been shown to be as effective as three [37], provided the second dose is given 6-12 months after the initial dose. In the United Kingdom, for example, a two-dose regimen has now replaced the three dose regimen in the publicly funded schools-based program, which is achieving 85-90% coverage. Another development has been the production of a nonavalent vaccine that adds types 31, 33, 45, 52 and 58 to the 6, 11, 16 and 18 vaccine. This vaccine has been demonstrated in phase III trials to achieve similar efficacy against types 6, 11, 16 and 18 in addition to achieving high efficacy against the new types [38,39]. The nonavalent vaccine has been licensed in some countries, including the U.S. and the U.K. [40, 41], and may well replace the bi- and quadrivalent vaccines over the next few years [42, 43]. Prophylactic vaccination has the means to save hundreds of thousands of lives, but this will require the political will to ensure that vaccination is implemented in resource poor countries.

There is also increasing interest and research into the possibility of treating established cervix cancer using immunotherapy approaches. The 2 main oncogenes associated with HPV driven cancers, E6 and E7 are considered excellent targets for immunotherapy. Promising results have been seen with clinical trials involving

therapeutic HPV vaccines, adoptive T cell therapy and checkpoint inhibitors, with ongoing trials examining various combination immunotherapy approaches with standard treatments such as radiotherapy [44].

Gynecological Cancer Intergroup (GCIG) and the Cervix Cancer Research Network (CCRN)

The Gynecologic Cancer InterGroup (GCIG), formalized in 1997, aims to promote and facilitate high quality clinical trials in order to improve outcomes for women with gynecological cancer. Currently, there are 29 member groups including representation from North America, Europe, Asia and Australia. GCIG has several standing committees including Ovarian Cancer, Endometrial Cancer, Cervix Cancer, Translational Research, Harmonization (operations & statistics), Rare Tumors, Symptom Benefit, Phase II, and Membership.

The GCIG has also developed a Cervix Cancer Research Network (CCRN) whose aim is to promote high quality clinical research for cancer of the cervix in developing countries. The purpose of CCRN is to bring research in cervical cancer to the countries where the burden is the highest and there is a lack of GCIG cooperative groups (Figure 1). Interested sites complete a pre-qualifying set of Capability questions followed by a Radiologic/Physics check (questionnaire courtesy of IROC, Houston, TX). Site visits are then performed by a review team from GCIG assessing clinical activity, site resources, clinical trial operations, radiation therapy facilities/quality assurance and treatment record, and clinical trials management information. Participation in a beam measurement

program (TLD/OSLD) every 2 years is a requirement. Ongoing QA/QC is performed according to the lead group trial protocols. CCRN currently has 4 active cervical cancer trials described below.

The success of the GCIG relates to pooled intellectual resources and collaboration, rapid and large accrual, evidence-based medicine and application of the results, and opportunity for substantial translational research. GCIG is unique in the world of cancer research and been intensively productive in collaborative trials, intellectual exchanges and learning, brainstorming and consensus conferences.

Figure 1:

[FIGURE 1]

Modern Treatment of Cervical Cancer

The treatment of cervical cancer is dictated by FIGO stage: a clinical staging system [45]. For early cervical cancers, surgery is recommended. A cone biopsy is adequate treatment for stage IA1 whereas, for patients with IA1 with lymphovascular space invasion or IA2 cancer, a cone biopsy with negative margins and pelvic lymph node dissection is recommended. Fertility sparing surgery is an option for patients with early cervical cancers. For high risk IA1 thru IB1 a radical trachelectomy and pelvic lymph node dissection can be considered. An additional option for some would be pelvic radiotherapy and brachytherapy. There are ongoing trials evaluating reduced intensity surgery for patients with early lesions. The SHAPE trial is evaluating simple versus radical hysterectomy for patients with cervical tumors less than 2 cm in size. SHAPE is a CCRN trial which has immediate application to under-resourced countries. A randomized

trial of surgery versus radiotherapy for IB1-IIA cervix cancer showed no difference in survival [5]. Notably, patients in this trial did not receive chemotherapy, and 84% of patients in the surgical arm with tumors greater than 4 cm required postoperative radiotherapy. Morbidity was greater in patients that received both modalities; hence, current recommendations are to try to use a single modality.

Advanced imaging such as CT, MRI, and PET are not permissible in FIGO staging; however, imaging (if available) should be used to appropriately guide treatment. PET scans are helpful at delineating the extent of disease. MRI is superior at showing soft tissue resolution for the extent of cervical cancer within the pelvis. This can be critical for brachytherapy treatment planning or conformal radiotherapy techniques.

An NCI Alert in 1999 demonstrated the superiority of cisplatin-containing concurrent chemoradiotherapy for women with advanced cervical cancer. The hazard rate for reduction and death was approximately 0.52 [11]. Consequently, this was rapidly adopted worldwide, and weekly cisplatin became the worldwide standard [46]. The optimization of chemotherapy is unclear, and the CCRN has 3 trials testing the optimal combination of chemotherapy and radiotherapy [47]. Extended adjuvant chemotherapy in locally advanced disease is being tested currently in the OUTBACK trial. RTOG 0724 is also evaluating extended adjuvant chemotherapy for patients treated with a radical hysterectomy who have positive nodes or positive parametria, although this currently is not a CCRN trial. Dose-intense neoadjuvant chemotherapy is being tested in the phase III INTERLACE trial. Additionally, a phase II trial showed promising results of a higher dose of cisplatin given every three weeks [48]. This is now being compared to weekly

cisplatin in the TACO trial. The TACO trial has been the most successful CCRN trial with significant accrual from Vietnam and Thailand.

In patients with advanced disease receiving curative radiation, an important quality metric is to keep the total treatment course within 8 weeks. Prolonged treatment after 8 weeks in multiple studies have documented an approximate 1% loss in local control for every day beyond 8 weeks. Adherence to a few quality metrics such as receipt of concurrent chemoradiotherapy, brachytherapy and completion of treatment within 8 weeks will markedly improve survival worldwide.

Brachytherapy

Brachytherapy is an integral component of the treatment of advanced cervical cancer and is the standard of care in combination with external beam radiation therapy in all-national guidelines. [49-51] The advantage of brachytherapy comes from its dosimetric benefits including the ability to deliver a locally high and conformal dose to the site of disease with a rapid dose fall-off, sparing adjacent structures such as the bladder, rectum, sigmoid, and small bowel. [52] Brachytherapy remains unavailable in many countries. Even in countries where brachytherapy is easily accessible, utilization is declining [53-63]. An analysis of the Surveillance, Epidemiology, and End Results (SEER) database found a decline in the use of brachytherapy from 83% in 1988 to 58% in 2009 ($p < 0.001$), though brachytherapy was independently associated with better cause-specific survival (hazard ratio [HR] 0.64; 95% confidence interval [CI], 0.57-0.71) and overall survival (OS) (HR 0.66; 95% CI, 0.60-0.74) [52]. A similar study of the National Cancer Database (NCDB) found brachytherapy utilization decreased from 97%

in 2004 to 86% in 2011 [63,64]. In one of these studies, the impact of the use of brachytherapy was greater than that seen for the use of concurrent chemotherapy. [63] Brachytherapy is a complex procedure that necessitates significant resources and infrastructure that is particularly challenging in resource limited countries. Only 20 of the 52 African countries had brachytherapy in 2010 [52,64]. Of 12 centers in Latin America, three do not perform gynecological brachytherapy [52].

One high-dose rate brachytherapy machine can treat approximately 10-12 cases a day. In Ethiopia, a country of 94.1 million people with 60,000 new cancer cases per year, there is one after-loader for the whole country. In Thailand, in one hospital, 1,000 brachytherapy procedures are done in one year by one after-loader. In Honduras, where 1,000 new cases of cervical cancer are diagnosed annually, there is no brachytherapy in the entire country. Increasing the worldwide availability of brachytherapy should be a global health priority.

Treatment of Cervical Cancer in the Developing World

The majority of cervical cancer patients in the developing world present with advanced stage disease with limited access to adequate treatment. As a result, the mortality rates are high for women in the developing world. (Fig. 2) Because of the unpredictable availability of resources, the guidelines that are used to treat cervical cancer in high-income countries are not applicable to many of the developing countries.

Figure 2:

[FIGURE 2]

Figure 2. Estimated age-standardized rates (world) of deaths, females, cervical cancer, worldwide in 2012

Data source: GLOBOCAN 2012

Graph production: IARC (<http://gco.iarc.fr/today>)

World Health Organization

Two resource-stratified guidelines were recently published by National Comprehensive Cancer Network (NCCN) and American Society of Clinical Oncology (ASCO). [45] The NCCN Guidelines provided evidence-based recommendations by the representatives from NCCN Member Institutions. ASCO established a process including mixed methods of guideline development, adaptation of the clinical practice guidelines of other organizations, and formal consensus by the international expert panels. Recommendations were made on management of cervical cancer based on four different resource stratifications (Table 1). Included in Table 1 is the four resource settings that included a basic setting where bare essential services are available to provide gynecologic cancer care. The other three settings, limited, enhanced to maximal, offer additional capacities that are essential in providing care and improving survival for cervical cancers. Both guidelines stressed that the highest level of care be provided to women whenever available.

Table 1:

[Table 1]

A Global Call to Action

It is no exaggeration to say that cancer represents an imminent and severe crisis for developing countries, with cervical cancer leading as the one of the most prevalent. A resounding call to action for this crisis is building; advocates are needed to save lives. For example, a recent report from the *Lancet Oncology* presented a body of evidence that quantifies the worldwide shortage of radiotherapy services by country. By scaling up radiotherapy departments in lower-middle- income countries, we could potentially see more than 26.9 million life-years saved in low- and middle- income countries over the lifetime of the patients who received treatment [65].

A global call to action against cancer in low- and middle-income countries is desperately needed [66]. While there are organizations attempting to make a difference [67,68], much needs to be accomplished to stem this global crisis. Seven hundred and forty woman die **per day** from cervical cancer. The majority of these deaths are in relatively young woman and the deaths result in unmeasurable pain and suffering. The world health organization (WHO) has made safer motherhood a priority [69], the same urgency needs to be directed to cervical cancer. Vaccination programs are important, but we cannot ignore women that already have HPV. We, and others, implore the global woman's health movement to make the treatment of cervical cancer a priority [70].

Conclusions/Summary

Cervical cancer is one of the leading causes of cancer death among women [1], representing the fourth most common malignancy in women worldwide [3]. In order to tackle this complex problem there needs to be action on multiple fronts, including

primary and secondary prevention, improvements in treatment and access to care. The treatment of cervical cancer is a global health crisis that needs to be a call to action for the world health community. The GCIG through CCRN is bringing relevant and important trials to low and middle income countries. Our hope is that new attention can be brought to cervical cancer, especially among governmental and philanthropic agencies.

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Figure Legends:

Figure 1. Countries around the world have many GCIG members or are interested in joining GCIG or CCRN. Reproduced with permission from Gaffney, D.K., Suneja G., Ryu S.Y., McCormick M., Plante, M., Mileshekin, L., Small, Jr., W., Bacon, M., Stuart, G., Kitchener, H. The Cervix Cancer Research Network: A Global Outreach Effort on Behalf of the Gynecologic InterGroup, International Journal of Radiation Oncology*Biophysics, 2015, 92:506-508.

Figure 2. Estimated age-standardized rates (world) of deaths, females, cervical cancer, worldwide in 2012. Reproduced with permission from Ferlay J., Soerjomataram I., Ervik M., Dikshit R., Eser S., Mathers C., Rebelo M., Parkin D.M., Forman D., Bray, F. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet]. Lyon, France: International Agency for Research on Cancer; 2013. Available from: <http://globocan.iarc.fr>, accessed on 21/12/2016.

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Table 1. Treatment capacity for different modalities based on setting. Reproduced with permission from Chuang et al., Management and Care of Women with Invasive Cervical Cancer: American Society of Clinical Oncology Resource-Stratified Clinical Practice Guideline, Journal of Global Oncology, 2(5):311-340.

Table 1 – Treatment Capacity.

Treatment	Setting			
	Basic	Limited	Enhanced	Maximal
Surgery	Simple (extrafascial) hysterectomy or more extensive hysterectomy can be performed*	Modified radical or radical hysterectomy	Capable of performing most major surgeries, including radical hysterectomy, radical trachelectomy,† pelvic and para-aortic LN sampling, and pelvic exenteration† Following are not available: PET scan, interventional radiology, sentinel node biopsy/IORT, or bevacizumab	Radical hysterectomy, radical trachelectomy, pelvic and para-aortic LN sampling, sentinel node biopsy, and pelvic exenteration; RT, chemotherapy, interventional radiology, palliative care service, and bevacizumab are all available
Chemotherapy	Availability of chemotherapy drugs is unpredictable	Chemotherapy may be available	Chemotherapy available; bevacizumab not available	Chemotherapy available; bevacizumab is available
RT	No RT available	Limited external RT with no brachytherapy available; in some areas where there is only brachytherapy and no external RT, this will be considered as basic level	RT including external beam and brachytherapy available; interventional radiology not available	RT including external beam and brachytherapy available; interventional radiology available
Pathology	Pathology services are not available; if there is a way to send pathology for review when needed, that should occur (Basic pathology may be available, but diagnosis is often delayed for more than 1 month; there are no frozen sections or pathology consultations in the region)	Pathology services in development (There are basic pathology and frozen section services; consultations are not readily available)	Pathology services in development or not always available (Pathology services including frozen sections are available; tumor registry and regular multidisciplinary conferences are not consistently available in the region)	Pathology available (Full pathology services including diagnosis, consultation, tumor registry, and multidisciplinary conferences are available)
Palliative care	Palliative care service is in development; basic palliative care, including pain and symptom management, should be provided‡	Pain and symptom management available; palliative care service is in development	Palliative care service not always available	Palliative care service available

NOTE. It is the view of the American Society of Clinical Oncology that health care providers and health care system decision makers should be guided by the recommendations for the highest stratum of resources available. This guideline is intended to complement but not replace local guidelines. Bold font indicates addition of a recommended action over a previous resource level (eg, in limited setting, a bold action is one that was not recommended in basic).

Abbreviations: IORT, intraoperative radiation therapy; LN, lymph node; PET, positron emission tomography; RT, radiotherapy.

*Where medical facilities exist to take care of women who are at high risk for postoperative complications.

†Can be performed at some enhanced levels.

‡Palliative care is multifaceted and in some contexts can be provided concurrently with tumor-directed therapy. Pain management and best supportive care are necessary but insufficient parts of palliative care in all settings. Women with advanced cervical cancer with or without access to tumor-directed therapy may have specific late-stage symptoms that require clinicians to perform or offer urogenital-specific interventions. See Special Commentary.

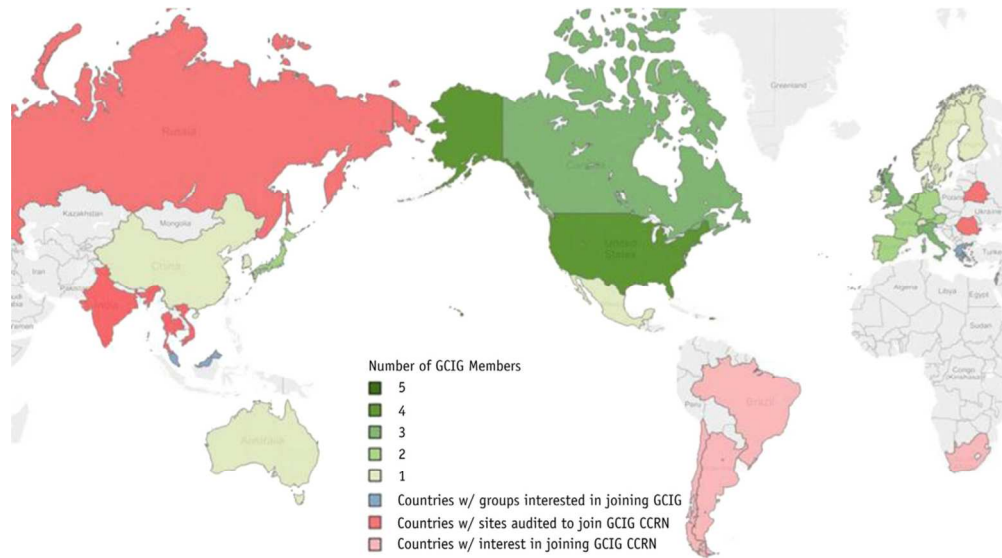


Figure 1

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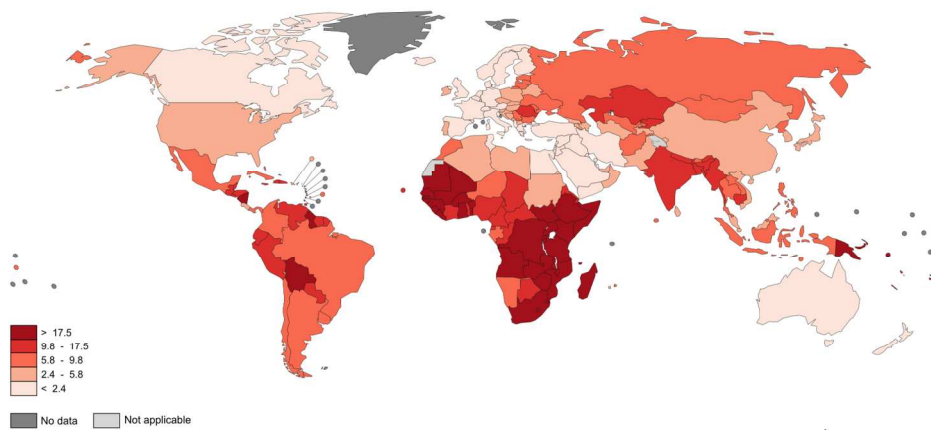


Figure 2

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