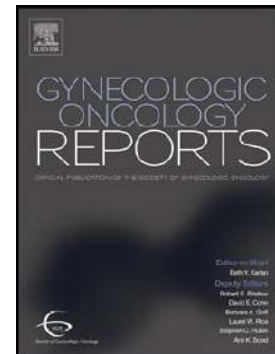


## Accepted Manuscript

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**Strengthening Care and Research for Women's Cancers in Sub-Saharan Africa**

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## Introduction

Until recently, medical care in sub-Saharan Africa (SSA) has addressed the immediate demands of Human Immunodeficiency Virus (HIV), Tuberculosis, Malaria and Maternal–Child Health. Though these challenges remain, the region has had a degree of success in these efforts, and sufficient urbanization and economic development that an epidemiologic transformation, in which people live long enough to develop cancer and other non-communicable diseases, is well underway in SSA.(1)

The care of patients with cancer is one of the great challenges and achievements of modern society. It requires specific, coordinated multidisciplinary care from highly trained specialists, extensive infrastructure and a detailed and nuanced understanding of both the individual patient and the population at hand. In high-income countries (HICs), the care of patients with cancer is costly and highly resource intense, and often based on a specific molecular or genetic defect.

The treatment of cancer in the resource-limited context of SSA, therefore, presents a tremendous challenge. A simple transposition of protocols and technologies from HICs would be impractical and inhumane; resources would rapidly be depleted and many patients would remain without care. Other models have been developed that better match their setting, and this is as it should be. The challenges of biology, resources and human capacity found in SSA are such that effective solutions should

be and, in fact, can only be developed in SSA. For this reason it is imperative that multifaceted research be developed in step with clinical cancer care in SSA. (2) Here we review some of those challenges and opportunities.

The reader should note that the region of SSA is a huge and vastly diverse one, containing multiple sub-regions, 47 countries and approximately one billion people. To discuss cancer care and research in SSA is to broadly generalize as much as it might be to discuss cancer care in other WHO designated regions. Despite this significant limitation, however, we believe that some common challenges exist across the region, and that by exploring them we may be ready to more effectively address them.

### **What is the burden of women's cancers in SSA?**

Cervical and breast cancers are consistently the two most common cancers in women across SSA.(3-5) The incidence and mortality of cervical cancer are both far higher in SSA than is seen in more developed regions, while breast cancer has been observed to present in more advanced stage and to carry a far higher case fatality rate than that seen in other regions. The mortality from cervical cancer in Eastern and Southern Africa for example is 18 times higher than that seen in Western Asia and Western Europe. Similarly, though the rate of breast cancer is lower in SSA than in more developed regions, the mortality is still high: in Western Asia the age adjusted breast cancer mortality is 6 per 100,000 women, while in Western Africa it

is 20 per 100,000. Though ovarian and endometrial cancers seem to be less common in LMICs than in more developed countries, these diseases are regularly encountered and create considerable burdens and challenges for patients and practitioners.(6)

### **What is the capacity for care of patients with cancer in SSA?**

Farmer has observed that effective health care delivery requires space, staff, staff and systems.(7) To this one might add a fifth 's': \$ (or funding). The delivery of cancer care in SSA is challenged by shortages of physical infrastructure, human resources, equipment, validated standard operating procedures, and funding. Though most nations in SSA have pledged to commit 10% of their budgets to healthcare, current budget allocations are generally significantly lower (8), and ministers of health must manage these limited funds to address a broad range of diseases. The WHO has documented the severe shortages of nurses and physicians across SSA, and the findings are concerning.(9) Kinfu and colleagues evaluated the number of physicians in 12 SSA countries and compared the number being trained to two estimates of attrition.(10) They found that these countries on average had 0.09 physicians per 1000 population, compared to the U.S which has over 26 times as many physicians at 2.4 per 1000 population. The number of nurses and midwives in SSA is 0.55 per 1000 population, compared to 9.8 in the U.S. Of more concern is the fact that most countries studied had an inflow of doctors and nurses that was either at or actually below estimated outflow of health personnel from the

workforce. Figures 1 and 2 show pictographically that the rates of cervical cancer mortality in SSA are among the highest in the world, while the supply of physicians is among the world's lowest. These levels are far below recommendations, let alone the numbers found in HICs. Holmer and colleagues recently evaluated the global distribution of surgical specialists and found that LMICs, with 48% of the world's global population, have only 20% of the world's surgical specialists. This includes 19% of the world's surgeons, 15% of the anesthesiologists and 29% of the world's obstetricians. (11) Disparities also exist within LMICs, with SSA having some of the lowest densities of specialists seen. In Uganda, for example, there are 0.6 surgeons and 0.3 obstetricians per 100,000 people, while in Nicaragua these numbers 8.7 and 4.5 and in the U.S they are 36.1 and 12.6. Medical staff in SSA are therefore both overburdened clinically and less available for specialty training.

Freestanding cancer centers are uncommon in SSA and therefore often face an overwhelming volume of patients. Stefan reviewed the published literature and the internet and found only 102 cancer programs across Africa, despite an expected annual cancer related mortality of nearly 600,000 in the region.(12) Outside of these facilities, practitioners must balance the demands of more acute patient needs against the ongoing needs of cancer patients. For example, general surgeons may commonly be forced to delay a woman's mastectomy to attend to another patient with an appendiceal abscess, while women needing a radical hysterectomy for cervical cancer may be delayed due to obstetric or gynecological emergencies. There are shortages of chemotherapy, operating theaters and surgical equipment. Perhaps

the starkest example of equipment shortage in SSA in radiotherapy: while the International Atomic Energy Commission recommends a radiotherapy facility for every 250,000 to 500,000 people, in Africa there are 140 facilities for a population of over 1.2 billion. Zubizaretta and colleagues estimate that 407 facilities, running 12 hours a day, would be needed to meet the current needs for radiotherapy in Africa.<sup>(13)</sup> In North America, by contrast, there are 2787 radiotherapy facilities while only 1200 would be needed to meet current demand. Abdel-Wahab surveyed radiotherapy needs in Africa and noted that out of 52 countries assessed, 23 had teletherapy and only 20 had brachytherapy.<sup>(14)</sup> Thus, few people in Africa have access to standard radiotherapy for diseases such as cervical cancer that require treatment with both teletherapy and brachytherapy.

This deficit of equipment and facilities further compounds the challenge of building human capacity; there are many specialized personnel, such as radiation physicists, radiotherapy technicians, and pharmacy staff qualified to work with chemotherapy, who have no training opportunities or job prospects in such a setting. The initiation and scale up of programs therefore requires a carefully coordinated development of physical resources, human resources and effective medical systems, such as record keeping and standard operating procedures for specific services.

**Why must research be an integral component of capacity building in SSA?**

We believe that research can and must be developed in step with clinical cancer care in Africa for several reasons. First, the biology of common cancers may arguably be significantly different in SSA. Due to both geography and levels of human development, people may more commonly have significant co-infections, such as parasitic infections, that might affect their clinical course. Second, what we know from clinical experience and from clinical trials is based on very specific and rarified care delivery models in high-income settings; it is important to study how differences in delivery models and settings alter the effectiveness of therapy. Third, while models of care delivery in HICs has largely developed as a sort of ‘natural experiment’ over time, studies are needed of implementation, quality improvement, patient experience and other areas, to accelerate the development of optimal care given specific settings and resources.

### **Cancer research in SSA**

The African Organization for Research and Training in Cancer (AORTIC) has performed an inventory of cancer research and clinical care centers in Africa.<sup>(15)</sup> We recommend that investigators exploring possible projects in SSA search the AORTIC handbook for ongoing projects and existing investigators with whom they might collaborate. A significant challenge to both research and clinical care in SSA is the ‘silo’ effect, in which multiple parties both from within and outside SSA have parallel, non-coordinated and potentially competing efforts. To address this the U.S. National Cancer Institute and the non-profit ‘Global Oncology!’ collaborated to create the Global Cancer Project Map (GCPM): <http://globalonc.org/Projects/global->



cancer-project-map/ The GCPM includes data gathered by the African Organization for Research and Training in Cancer (see below). We encourage investigators to enter their work on the GCPM and to utilize this resource in their searches for collaborators and to determine what work is ongoing before initiating an isolated project.

Cancer research in SSA faces the same challenges as clinical care. Investigators are largely left to look to HICs for funding. Most oncology specialists face greater patient demands than are seen in HICs, leaving limited time for research. For the most part, investigators must work with lesser facilities, in terms of physical space, administrative support such institutional review boards, and equipment when compared to their HIC counterparts, with whom they are competing for funding.

### **Partnerships can strengthen research and clinical capacity**

Many cancer centers and universities in SSA have been able to more effectively develop programs and obtain funding through leveraging the expertise of partners at HIC universities. These partnerships have often developed utilizing infrastructure built from funding and collaborations to combat HIV in SSA.

The Uganda Cancer Institute and the Fred Hutchinson Cancer Institute of the University of Washington developed a highly productive collaboration.<sup>(16)</sup> They have developed a clinical oncology fellowship. The fellows are trained

predominantly in Uganda but travel to the Fred Hutchinson Center for additional training in clinical oncology and research methods. Utilizing this collaboration, the Uganda Cancer Institute has fully trained eight Ugandan clinical oncologists, as well as providing oncology education to over 200 Ugandan scientists and 50 Ugandan physicians. Through this collaboration, key findings in infection-related malignancy as well as the clinical manifestations of malignancy in this environment have been published. (17)

A similar collaboration developed at the Academic Model of Providing Access to Healthcare (AMPATH), at Moi University in Eldoret, Kenya. This program is of particular interest to gynecologic cancer specialists. Here, the Obstetrics and Gynecology faculty worked with the University of Toronto's Gynecologic Oncology faculty to develop a gynecologic oncology fellowship on site. Similar to the clinical oncology program at UCI, the gynecologic oncology fellows were trained by their senior faculty at Moi and by regular visits from the University of Toronto faculty to teach in the clinic, on the wards and in the operating theater. When the outside faculty were not on site, they continued to give lectures, hold tumor boards and review the patients on service on a daily to weekly basis.(18)

The International Gynecologic Cancer Society (IGCS) currently has an initiative to support such partnership-based gynecologic oncology fellowships. (19) The IGCS has worked with collaborators to create a modifiable curriculum, suggesting areas of study and the roles of the partners, faculty and trainees. The goal is to create

metrics by which the success of the programs and trainees may be assessed, including the creation of examinations leading to a certificate of competence. As mentioned, cancer care in Africa, must compete with a multitude of other, often more acute, conditions, the IGCS recommends that these partnerships meet with their respective policy makers, professional societies and other stakeholders to plan the roles and career paths of graduates from these partnership based programs. The University of Michigan Department of Obstetrics and Gynecology and their partners in Ghana and Ethiopia have described a robust framework for partners to work to advance the interests of all parties through and explicit and open discussion and exploration. (20)

The Republic of Rwanda engaged Partners in Health to create a partnership, or 'accompaniment' on a grand scale to combat HIV, TB and malaria. (21) As successes were gained and the 'epidemiologic transition' from infectious to non-communicable diseases affected Rwanda, the partners expanded their collaboration to create national cancer hospital in Butaro, Rwanda. Faced with the challenge of delivering specialty care in a setting with few trained oncologists and no established clinical oncology training, the partners chose to 'task-shift': evidence based guidelines were rigorously developed and followed as medical officers and nurses made clinical assessments and gave chemotherapy while in close contact with cancer specialists from the Dana Farber Cancer Center and other collaborating centers in the U.S. Importantly, medical records were meticulously kept and outcomes have been measured and published. (22)

The American Society of Clinical Oncology (ASCO) supports a variety of international programs, many of them focused on care delivery and capacity building in severely under resourced areas such as SSA.(23) These programs such as the IDEA (International Development and Education) awards, support mentoring and education of oncologists in LMICs by HIC leaders. Other initiatives support travel-based outreach, such as direct care and teaching or through lectures. The ASCO also supports academics and research in LMICS through the journal 'Global Oncology', through mentoring, international fellowship opportunities and through the 'International Innovation Grant' funding mechanism. Lastly, the ASCO has partnered with the European Society of Medical Oncology to support the Global Curriculum in Medical Oncology, providing opportunities to harmonize and enhance oncology practice globally.(24)

The AIDS Malignancy Consortium is a clinical trials consortium sponsored by the U.S. National Cancer Institute's Office of HIV AIDS malignancy. (25) The consortium's International Resource Committee has been charged to conduct trials in SSA, and has established several new sites. Through the standards and oversight inherent in this process both the clinical capacity and the research output of these sites have been enhanced. Similarly the AIDS Clinical Trials Group sponsors multiple sites in SSA and has been instrumental in establishing standards of treatment for HIV associated malignancies.(26)

The International Atomic Energy Agency (IAEA) supports capacity building in radiotherapy through its Human Health Programme. (27) Particularly through the Program of Action for Cancer Therapy (PACT) program, the IAEA partners with low- and middle-income countries to perform assessments of cancer needs and treatment capacity, often working with countries to draft national cancer control strategies, and also supports targeted capacity building projects in both diagnostic and therapeutic radiology.

### **Initiatives From the U.S. National Cancer Institute's Center for Global Health**

The U.S. National Cancer Institute, in response to the growing challenge of cancer in low- and middle-income countries, established the Center for Global Health (CGH) in 2011. (2) The CGH strives to reduce the global burden of cancer through strengthening global cancer research and resource-appropriate cancer control strategies, building a cancer research community and through translating research results into practice.(28) This mission has led to several initiatives that either include or are specifically focused on SSA. Through a partnership with the National Institute for Biomedical Engineering and Biomedical Imaging and other U.S. government agencies, the CGH supports the funding for projects in cancer detection, diagnosis and treatment technologies for global health.(29) The P20 Regional Centers for Research Excellence opportunity seeks to support the development of cancer research infrastructure and to encourage collaboration among both HIC and LMIC universities and programs. The CGH and AORTIC collaborate to support the

Beginning Investigator Grant for Catalytic Research (Big CAT) small grant program, which supports pilot investigations by new investigators in African Universities partnering with established investigators from either HICs or LMICs.

The CGH has led two African Cancer Leadership forums, in partnership with the International Union for Cancer Control (UICC).(30) In this program leaders from Ministries of Health and other advocates can make use of technical assistance from the NCI and UICC and collaborate with peers from other SSA nations to draft national strategic plans for cancer control. Such plans can lead to concrete steps and milestones for progress in cancer control.

### **The African Cancer Registry Network**

One of the most important steps in cancer control planning is the development of a population based cancer registry. As discussed, there are multiple social and environmental factors that may affect the distribution and burden of cancer locally and nationally. An accurate and complete registry enables stakeholders to set priorities, rationally make investments, and monitor outcomes of programs and investments. Through the African Cancer Registry Network (AFCRN), Parkin and colleagues provide training, mentorship and logistical support to new and established registries.(31) Through this program 30 population-based registries are now maintained in 22 African countries.

### **AORTIC**

The African Organization for Research and Training in Cancer (AORTIC) is an African based multinational non-governmental organization dedicated to the control and palliation of cancer throughout Africa.(8, 32) AORTIC has formalized its cancer-related mission in the Dakar Declaration regarding AORTIC's role in cancer advocacy, cancer care, cancer education, and cancer research. AORTIC fosters research through the AORTIC Research Committee. This group has fostered research activities by developing the African Cancer Leaders Institute (ACLI), which is aimed at identifying and mentoring future cancer leaders in SSA. AORTIC has also fostered research activities through its co-sponsorship with the NIH of the BigCAT grant funding program, the Africa Research Project Map, the Khayelitsha Cervical Cancer Screening Project (KCCSP), and many other Africa-centric initiatives. AORTIC holds biennial research conferences and more frequent targeted regional conferences and workshops to support the growing community of cancer researchers working in Africa.

### **ASAP**

Limited pathology capacity has been identified as one of the major barriers to effective cancer research and cancer control in SSA (32, 33). These limitations not only include pathology needs for clinical (diagnostic) purposes, but also for research, confirmation of diagnoses that are required to establish valid cancer incidence and mortality rates, and a host of other cancer-related needs. To address this limitation, the African Strategies for Advancing Pathology (ASAP) network has created a set of resources, training modules, data, and protocols to promote

improved pathology capacity in SSA (<http://www.pathologyinafrica.org>). ASAP has undertaken a systematic evaluation of pathology and related clinical pathology resources in SSA. These data are freely available to researchers at the ASAP web site (<http://www.pathologyinafrica.org/data>), and could be useful for planning and evaluation purposes by researchers, ministries of health, and others.

## Conclusion

A major epidemiologic transformation is taking place in SSA as more people survive into adulthood and older age, and as more people move into cities and live more sedentary lives. This, combined with challenges in infrastructure and human resources, places people at an increasing risk for cancer. The obstacles faced are significant, but a growing international community is working together to face them. We exhort those inspired to join the fight against cancer in Africa to join these existing efforts. This community can find inspiration in the transformational work of the inspired few who battled HIV and other infectious diseases in similarly daunting circumstances.

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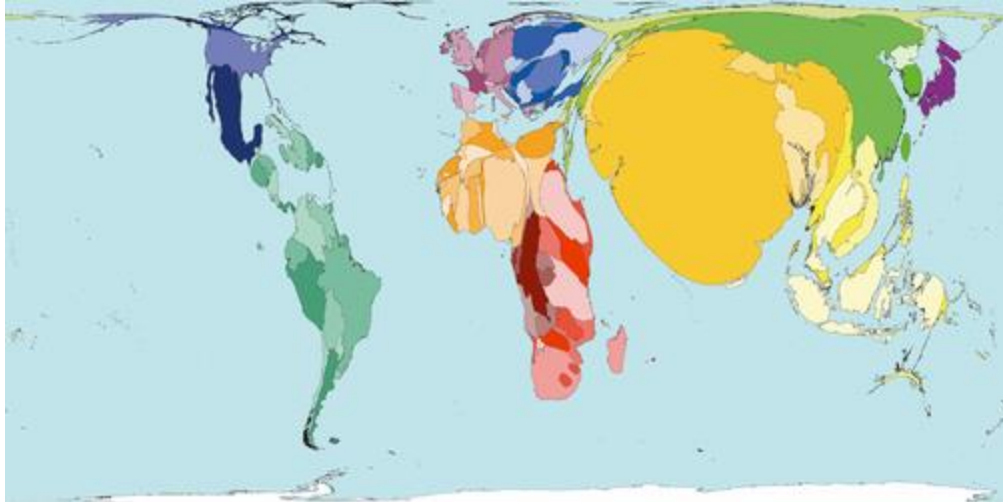


Figure 1. Pictograph of deaths from cervical cancer mapped as land area of affected countries. Low- and middle-income countries are disproportionately affected.

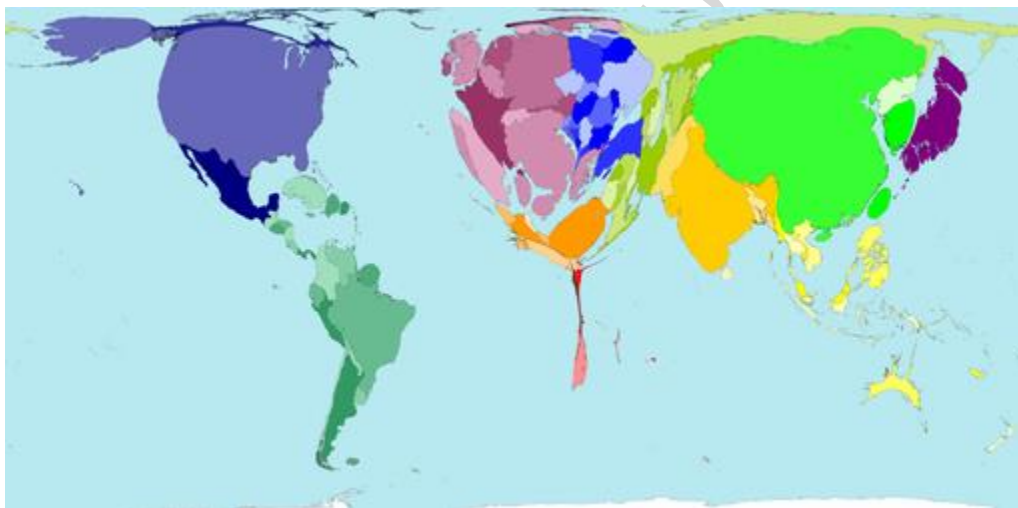


Figure 2. Pictograph of physicians working depicted as land area of the respective nations. Sub-Saharan Africa, with the highest rates of cervical cancer deaths in the world, has the fewest physicians.

Both images reproduced from Worldmapper.org with permission

### Highlights

- The burden of gynecologic cancers in low resource settings is overwhelming.
- Areas with the highest needs have few human resources and limited infrastructure.
- Cancer specialists can best help by leveraging ongoing work to assist local leaders.

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