The Fred Hutchison Cancer Research Center and Uganda Cancer Institute Collaboration on Infections and Cancer

Creating a center of excellence for cancer care, prevention, research and training in Africa

Overview

To many in the developed world, cancer is often viewed as a "luxury" of those fortunate to live to older ages, and not a major problem in areas with high rates of infant mortality, malnutrition and infectious diseases. Yet research in Africa in the last fifty years has revealed that nothing could be farther from the truth: cancer is increasingly common among African children and adults alike, and not only causes an inordinate amount of individual suffering but also is an increasing burden on society. Compounded by the spread of HIV, rates of some cancers have increased more than 20,000-fold in many African regions. And yet while significant resources have been applied to combating HIV, malaria, TB, poverty and malnutrition in recent years, little is being done to explore or address the problem of cancer in Africa.

HIV increases the risk of cancer by up to 20,000-fold, leading to epidemics of cancer in areas hard-hit by the HIV pandemic

This problem is especially evident in the region of East Africa. Clinicians and epidemiologists have described extraordinary rates of cancers among the children and adults of East Africa, data which have been validated by the World Health Organization (WHO) (Figure 1). Uganda, an East African country of more than 27 million people, has among the highest rates of cancer in the world but only two practicing cancer specialists. These oncologists see patients at the Uganda Cancer Institute (UCI), which was established in the 1950s, in the capital city of Kampala. Once a vibrant facility credited with discovering new cancers and developing novel treatment regimens, the UCI is now dilapidated and without reliable electricity, clean water or medical supplies. Despite a high level of care from doctors and nurses at the facility, even patients with curable cancers go untreated due to their inability to afford diagnostic tests, basic chemotherapy or even pain-relieving medications.

East Africa has some of the highest rates of cancer in children and adults worldwide

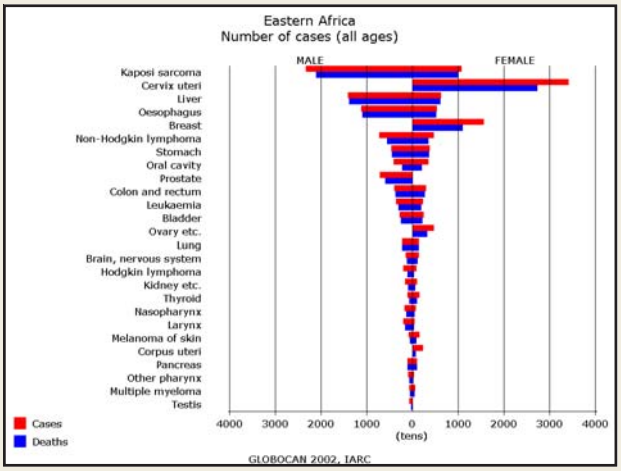


Fig. 1: Cancer frequencies and mortalities among East African men and women

Two years ago, physician-scientists from the Fred Hutchinson Cancer Research Center (FHCRC) in Seattle teamed up with Drs. Edward Mbidde and Jackson Orem from the UCI to investigate the problem of cancer in Africa. We soon discovered that the UCI is an ideal site for developing a program in global cancer research and care for several reasons. First, Uganda has enjoyed a stable political environment and increasing economic prosperity under the leader, President Yoweri Museveni. Second, an infrastructure currently exists which can support significant reforms: in Kampala, electrical power is relatively abundant, roads and telecommunications are surprisingly reliable (including high-speed satellite internet and mobile phone coverage that is often better than that found in the US). Third, the UCI is based at the largest and most prestigious academic medical center in Uganda, Mulago Hospital, and is adjacent to the campus of Makerere University, a renowned school for students of medicine, nursing and public health.

Uganda has only 2 cancer specialists and only 1 treatment facility in a country of 27 million people

Few patients can afford medications or tests, let alone mattresses

Research Agenda

The reasons for the high burden of cancer in East Africa are not known, but there is good evidence that it is due to the high prevalence of viruses that cause cancer. Chronic viral infections are thought to be the cause of one in four cancers worldwide and five viruses have been shown to cause cancer. While only the minority of persons with each of these chronic infections develop cancer, the factors which predispose to the development of cancer from chronic infection are uncharacterized. Each of these cancers are more frequent, and often more severe, in persons with HIV infection; consequently, due to the high prevalence of HIV, rates of viral-associated cancers in Uganda are among the highest in the world. The FHCRC has a long history in the study of viral-mediated cancers, making a collaboration between the UCI and FHCRC especially relevant. As Kaposi's sarcoma (KS) is both the most common cancer in Uganda and a major focus of research within the Program in Infectious Disease at FHCRC, our initial efforts have been devoted to exploring these questions within the context of this viral-associated cancer.

PROGRAMMATIC RESEARCH QUESTIONS:

1. **How are infections that cause cancer acquired?**
2. **What factors govern the progression from chronic infection to cancer?**
3. **Can molecular diagnostics predict persons at high risk for development of cancer from chronic infection?**
4. **Can therapies be developed or employed to prevent viral-associated cancers?**

A female UCI patient with Kaposi's sarcoma

Human Herpesvirus 8 (HHV-8) and Kaposi's Sarcoma: KS was initially described over 125 years ago as an unusual tumor among elderly men of Ashkenazi Jewish or Mediterranean decent. In the 1950s, pioneering work at the UCI described a high rate of KS among African children and adults. Since that time, the tumor has become one of the most common malignancies worldwide. In the early 1980s, KS became the face of AIDS in the US and Western Europe, affecting over one-third of HIV-infected patients. There are now villages in Africa where more than 80% of the population has KS.

The active virologic research that was spurred by the HIV pandemic aided in the discovery of a novel pathogen, human herpesvirus-8 (HHV-8, also known as Kaposi's sarcoma-associated herpesvirus or KSHV).Nearly one in two Ugandans is infected with HHV-8, compared with only one in ten people in the US. In Uganda, most infections occur prior to the onset of puberty. As the mode of HHV-8 transmission has not been identified, the reason for a prevalence nearly five times that seen in the US is unknown.

Even among persons with immune systems that have been devastated by HIV, only the minority of HHV-8 infections progress to cancer. This is analogous to what has been well-described with Epstein Barr virus (EBV), another human herpesvirus which is closely related to HHV-8. EBV causes infectious mononucleosis, and infects greater than 90% of people worldwide. A tiny fraction of those infected with EBV, however, go on to develop either lymphoma or nasopharyngeal carcinoma. The extraordinary rates of viral-associated cancers in East Africa offer a unique opportunity to understand the factors that govern the progression from chronic viral infection to cancer. It is our hope that if these factors

- **Adults with KS = 975 new cases / year**
- **Kids with KS = 42 new cases / year**
- **Kids with Burkitt's = 150 new cases / year**

can be uncovered, strategies to predict and prevent the development of cancer could be developed for both resource-poor and resource-rich settings.

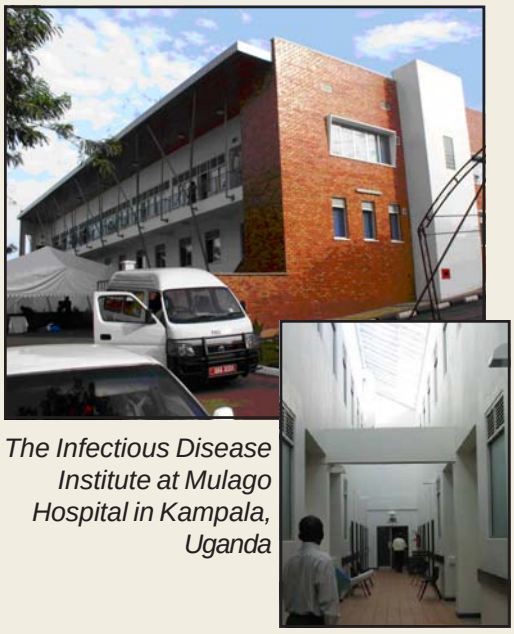
Recent work from the HHV-8 research group at FHCRC led by Dr. Corey Casper, under the direction of Dr. Lawrence Corey, head of the Program in Infectious Disease, has indicated that some people infected with HHV-8 are able to control the virus' replication in the body, while others are not. Our work in Uganda to date has been aimed at investigating the relationship between HHV-8 replication and the progression to cancer.

The initial work in Uganda was funded by a small Early Detection Initiative Grant from the FHCRC to Dr. Corey. This pilot study sought to determine the feasibility of characterizing viral replication patterns in Uganda and was conducted in collaboration with the UCI. The pilot study is anticipated to be complete in during the summer of 2006, but has proven that our research collaboration is efficient and capable of producing high-quality data. A subsequent grant was awarded from the Doris Duke Charitable Foundation (DDCF) to Dr. Casper to continue this important work. This study will begin to examine the reasons for the high rates of HHV-8 infection and progression to KS in Uganda by comparing HHV-8 infected individuals in Uganda to those in Seattle.

Nearly one in two Ugandans is infected with HHV-8 and KS is the most common cancer

We are currently initiating a number of other scientific projects in Kampala. These include a closer study of the incidence of KS in Ugandan women, children and HIV-negative persons and a characterization of trends in survival after KS diagnosis. This work will be conducted in collaboration between Dr. Casper from the Program in Infectious Disease and Dr. John Potter, Director of the Public Health Division at FHCRC. Additional projects looking at the transmission of HHV-8 among families and the response to treatment of children with KS will be conducted in collaboration with the division of Pediatric Infectious Disease at Children's Hospital in Seattle.

The Molecular Diagnostics Laboratory: A cornerstone in the diagnosis and treatment of infections and cancer is a 21st century molecular laboratory. Currently, most Ugandans admitted to the hospital can afford either a test to allow doctors to make the proper diagnosis, or the medicines to treat it, but rarely both. We would like to provide diagnostic testing free of charge to hospital patients and also have a modern laboratory available to Ugandan physicians to spark interest in medical research. In 2004, a center for the treatment of HIV, the Infectious Disease Institute, was built with money donated from US pharmaceutical companies. This building is adjacent to the UCI and features an 8,000 square foot laboratory space that rivals those of the best academic institutions in the US.



The Infectious Disease Institute at Mulago Hospital in Kampala, Uganda

The FHCRC Program in Infectious Disease has committed to supplying over $100,000 of cutting edge laboratory technology and to bringing Ugandan laboratory technicians to Seattle for training. It is our hope that this will facilitate the diagnosis and treatment of viral diseases and cancer in Uganda.

Training Opportunities

The severe shortage of cancer specialists in Uganda is another factor that makes the delivery of effective care nearly impossible. In collaboration with the Ugandan oncologists, the Dean of Makerere Medical School and the FHCRC Clinical Research Division, we have been working on a tailored training program for educating Ugandan Medical Oncologists in Seattle. This training program would provide skills in both clinical care and research and would be directed at care for

common cancers in Africa. It is envisioned that the training program be bidirectional: the variety of malignancies infrequently seen in the US, as well as the challenges in treating cancer in resource-poor settings, both would provide outstanding training opportunities for FHCRC physicians traveling to the UCI.

Improving Patient Care

Average number of annual new cancer cases seen at the UCI:

- **Adults with cancer: 1,500**
- **Childhood cancers: 300**

The collaborative research conducted by the FHCRC and UCI has enormous potential to help prevent cancer in the near future. This work, however, does little to ease the current burden of cancer in Uganda.The UCI currently cares for approximately 1,800 new cases of cancer each year. The most common cancers in adults are KS, non-Hodgkin's lymphoma and breast cancer, while children most commonly present with Burkitt's lymphoma, Kaposi's sarcoma and lymphoma. Access to inexpensive chemotherapy is limited, with most patients either not receiving any treatment, or only receiving a single course of drugs in what should be a multi-course regimen. Survival after diagnosis of the cancers in Uganda is typically dismal: less than 10% of patients with KS live five years and only about 30% of patients with lymphoma or breast cancer live five years after diagnosis.

Meetings between the FHCRC and the Director of Mulago Hospital and the Uganda Ministry of Health in April 2006 led to a series of understandings that will facilitate the importation of chemotherapy without government levies, bureaucracy or corruption. In addition, we are currently soliciting donations for chemotherapy from various sources and hope to provide medications for the treatment of the most common Ugandan cancers within the next year.

Average number of annual follow-up visits (at least a single visit) at the UCI: 5,000

A UCI patient with Burkitt's lymphoma

Breakdown of the new cancer cases seen annually at the Uganda Cancer Institute:

Cancer Type: Adult	Number of New Cases Annually	Percent of All Adult Cancer Cases
Kaposi's sarcoma	975	65
Non Hodgkin's lymphoma	105	7
Breast cancer	90	6
Soft tissue sarcoma	90	6
Liver cancer	75	5
Hodgkin's lymphoma	75	5
Colon cancer	30	2
Lung cancer	30	2
Others	30	2

Cancer Type: Childhood	Number of New Cases Annually	Percent of All Childhood Cancer Cases
Burkitt's lymphoma	150	50
Kaposi's sarcoma	42	14
Lymphomas	36	12
Leukemia	21	7
Osteosarcoma	18	6
Nephroblastoma	12	4
Rhabdomyosarcoma	6	2
Other tumors	6	2
Neuroblastoma	3	1
Hepatoblastoma	3	1
Retinoblastoma	3	1

Capacity Building

We have established an ambitious agenda to conduct research, improve clinical care and supplement training in medical oncology, infectious disease and laboratory medicine in Uganda. The current facilities in Kampala are not sufficient to support this mission and we must look to the future to identify how we can grow to accommodate these goals. In the short term (the next two years), minor renovations of the five buildings that comprise the UCI will allow for the immediate continuation of current projects. We have begun to explore basic renovations on the research unit which has recently been vacated by Case Western Reserve University. A modest fee will allow for reliable power, telecommunications and office space to house our research team and supplies.

Crumbling ceilings and broken windows at the UCI

In the long term, however, we envision a building which will jointly house research, clinical and educational activities. In discussions with the Director of Mulago Hospital and the Ministry of Health, we have been told that space behind the current UCI is available to us for such a project. Collaboration between Makerere University and Johns Hopkins University ("MU-JHU") has resulted in the construction of a building for research, clinical care and education several hundred feet away from the UCI. This building was constructed at a cost of less than $400,000 and serves as the epicenter for a renowned program in HIV care, pediatrics and maternal-child medicine. We envision a project of similar scope will be necessary for the Seattle-Uganda collaborative program.

The UCI outpatient clinic has neither running water nor electricity

The goals of the FHCRC-UCI collaboration are three-fold:

To study the intersection between infections and cancer by promoting cutting-edge research aimed at the prevention, diagnosis, pathophysiology and treatment of infectious-related cancers in Africa.

To provide first-quality cancer care in Uganda and act as a regional referral center for all of Africa.

To improve the quality of medical education in oncology so that a steady supply of cancer care providers are available to the Ugandan population.

Summary

The collaboration forged between physician-scientists in Seattle and Kampala has built a solid foundation to make important advances in the biology, treatment and prevention of virally-mediated malignancies. We stand at a moment of extraordinary opportunity, where the momentum of our current activities can launch a program that will surely lead to a lasting legacy in the global fight against cancer.

Timeline

2006

CAPACITY BUILDING

- Initiate planning for multidisciplinary building for research, clinical care and education

RESEARCH

- Complete FHCRC EDI pilot study
- Initiate DDCF study
- Initiate collaborative cancer registry research
- Initiate study of KS in children and intrafamilial transmission of HHV-8
- Embark on small renovation of research space at UCI

CLINICAL CARE

- Procure donations for chemotherapy for KS

EDUCATION

- Plan training programs for Ugandan health care providers in medical oncology
- Initiate training of Ugandan laboratory technicians in molecular virology

2007

CAPACITY BUILDING

- Initiate construction of multidisciplinary building

RESEARCH

- Obtain funding from NIH to conduct continued research activities
- Continue collaborative research projects

CLINICAL CARE

- Embark on operational and outcomes research for the treatment of common cancers in resource-poor settings

EDUCATION

- Train the first Ugandan physicians in medical oncology
- Initiate exchange program for FHCRC health care providers to teach / learn in Kampala

2008

CAPACITY BUILDING

- Complete construction of multidisciplinary building

RESEARCH

- Expand research activities to investigators from other disciplines at FHCRC

CLINICAL CARE

- Install first of US-trained health care providers at the new UCI

EDUCATION

- Continue bi-directional oncology training programs

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