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ONCOLOGY

CONTENT

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Clearly there are important differences between oncology in high income countries (HICs) and low-and-middle income countries (LMICs), both from a public health perspective (different epidemiology and risk factors), as well as from a clinical perspective (limited diagnostic and therapeutic options). The best example is the impact of the HIV epidemic that hit Africa hard in the 1990s and overwhelmed the already stretched health services. It brought with it not only a large burden of seriously ill patients but also a spectrum of malignancies that were either new, more serious or both. Kaposi's sarcoma (KS) is and was the most frequently occurring cancer; while not new, the HIV associated type is much more common and more aggressive.

In addition to well known risk factors such as smoking, cancer may be caused by microbial agents (viruses, bacteria, and parasites); some of these agents exert an increased effect in HIV infection (HHV-8, EBV, hepatitis B and C virus), but for other agents this is not the case, such as in *Schistosomiasis haematobium* infection; bladder carcinoma occurs after years of chronic infection that started in early childhood. *S. haematobium* is restricted to Africa. In Asia, cholangiocarcinoma (cancer of the biliary tract) is common – and associated with two common parasites in this region (*Opisthorchus viverrini* and *Clonorchis sinensis*) as a risk factor, indicating that worldwide and regional differences exist because of environmental and other epidemiological factors that are not always well understood. Indeed, HTLV-1 infection as a cause of adult-T-cell leukaemia/lymphoma is well reported, with high prevalence in South America (Peru, Ecuador) and also in Japan; the reason for this is unclear.

A well-known pathogen in HICs is *Helicobacter pylori*, that is well-recognized as a causative agent in upper gastrointestinal tract malignancies; research in LMICs is limited but it has been shown to be common; e.g. in Rwanda which offers options for prevention by treatment. Less well known are special pathogens, such as aflatoxin causing liver cancer, and cancers that may be caused by contagion.

In terms of management, making a proper diagnosis is essential. Whereas for KS in the skin or oral mucosa this is usually a clinical diagnosis, for gastrointestinal malignancies (including KS) gastroscopy is required. This requires the establishment of a gastroscopy service that needs training and sustaining; it also requires a critical number of medical doctors who are interested in being trained. The diagnosis of *H. pylori* can already be done with a rapid diagnostic test; the diagnosis of cervical carcinoma may also become easier using vaginal swab for early detection of Human Papilloma virus (HPV) by PCR, with may lead to a better outcome. Also here, it takes several motivated people to take things further; based on their experience, a number of doctors explain why they became interested in gyne-oncology with a focus on LMICs. Clearly, prevention is key and there are vaccines for HBV and HPV. Mass (targeted) drug treatment is applied for Schistosomiasis.

In addition to research, training of local staff in LMICs is essential, not only in the home country but also through fellowships in HICs to experience oncology services at the highest level to be transferred to the home country, a perfect example for a global collaboration.

In conclusion, oncology in a tropical environment has specific characteristics in terms of risk factors that include microbiological agents; while this means that targeted interventions may reduce the risk for the individual and the population, differences in epidemiology require different approaches in each region.

Patient care has improved over the years, which is in many cases the result of locally performed research and successful bilateral collaborations.

Ed Zijlstra
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Pathogens causing cancer - an overview

Cancer can be caused by both physiological and environmental conditions. Infections with certain viruses, bacteria and parasites have been associated with carcinogenic activity in humans and play an etiologic role in approximately 20% of the cancer cases worldwide.[1]

There are currently seven known viruses, one bacterium and three parasites identified as cancer-related pathogens.[1] This article aims to give a short overview of these pathogens and their corresponding cancer types (Table 1).

Pathogen	Associated cancer types
VIRUSES	
Hepatitis B (HBV)	Hepatocellular carcinoma (HCC)
Hepatitis C (HCV)	Hepatocellular carcinoma
Human Papillomavirus (HPV)	Carcinoma of the cervix, oropharynx, vulva, vagina, penis, anus and anogenital tract
Epstein-Barr virus (EBV) / human herpes virus 4 (HHV-4)	Nasopharyngeal carcinoma, gastric carcinoma, Hodgkin's lymphoma, Burkitt lymphoma, diffuse large B-cell lymphoma and extra nodal NK/T-cell lymphoma, nasal type (ENKTL-NT)
Kaposi's sarcoma associated herpes virus (KSVH) / human herpes virus 8 (HHV-8)	Kaposi's sarcoma (KS)
Human T-lymphotropic virus (HTLV-1)	Adult T-cell leukaemia/lymphoma
Merkel cell polyomavirus (MCPyV)	Merkel cell carcinoma (MCC)
BACTERIUM	
Helicobacter pylori	Gastric adenocarcinoma, gastric mucosa-associated lymphoid tissue (MALT) lymphoma, hepatobiliary tumours
PARASITES	
Schistosoma hematobium	Squamous cell carcinoma, urothelial carcinoma of the bladder
Opistorchis viverrini	Cholangiocarcinoma
Clonorchis sinensis	Cholangiocarcinoma

Table 1. An overview of pathogens that cause cancer and corresponding cancer types.

Five viruses (HPV, EBV, KSVH, HTLV-1, and MCPyV) are identified as direct carcinogens, which express their protein products. A portion of the viral genome can be detected in each cancer cell, which results in the expression of viral oncogenes that affect several cellular pathways, including DNA repair, proliferation, and apoptosis.[1,2] The indirect carcinogenic pathogens (HBV, HCV, *H. pylori, S. haematobium, O. viverrini, and C. sinensis*) do not induce expression of oncogenes but cause chronic inflammation leading to the release of cytokines, chemokines, and prostaglandins. This can result in deregulation of the immune system and promotion of neovascularization.[2]

VIRUSES

HEPATITIS B AND C VIRUS

HBV and HCV are different types of hepatitis viruses. In highly endemic areas, hepatitis B is most commonly spread through perinatal transmission, but it can also be horizontally transmitted through bodily fluids. HCV is mainly transmitted through blood transfusion and intravenous drug use. Both HBV and HCV cause liver disease, including hepatocellular carcinoma (HCC). The exact molecular mechanisms of how they cause cancer are unknown, although chronic inflammation and DNA damage have been shown to contribute.[2]

The global burden of HCC is high. It is the third leading fatal cancer worldwide, and its incidence continues to increase. According to the WHO, about 296 million people live with HBV infection and 58 million with HCV infection.[3,4] This leads to about 661,000 cases of cancer every year.

The worldwide incidence of HCC is heterogeneous because of the variable prevalence of other underlying risk factors. It is estimated that 72% of cases occur in Asia (more than 50% in China), 10% in Europe, 7.8% in Africa, 5.1% in North America, 4.6% in Latin America and 0.5% in Oceania.[5]

HUMAN PAPILLOMAVIRUS (HPV)

HPV is a DNA virus that belongs to the papillomaviridae family. It is associated with cancers of the cervix, oropharynx, vulva, vagina, penis, anus and anogenital tract. The route of transmission is through skin-to-skin, skin-to-mucosa, and mucosa-to-mucosa contact. A difference was found between high-risk and lower-risk subtypes of HPV. HPV-16 and -18 are two of those high-risk subtypes and are associated with cervical carcinoma.

HPV is believed to cause cancer by integration of its DNA into the host genome, altering cellular functions and promoting transformation, and the expression of viral genes acting as oncogenes.[2]

EPSTEIN-BARR VIRUS AND KAPOSI'S SARCOMA-ASSOCIATED HERPESVIRUS

Epstein–Barr Virus (EBV) or human gamma herpesvirus 4 (HHV-4) is a DNA virus. It mainly spreads through bodily fluids, especially saliva. Other minor but significant routes of transmission are through blood and semen, and using objects recently used by an infected person. All this makes EBV extremely widespread, with more than 90% of people getting infected.[6] Although EBV is a poor and inefficient carcinogenic agent, it is associated with a number of malignancies and contributes to about 1.5% of cancer worldwide.[3]

The types of cancer with the highest EBV-related case burden are nasopharyngeal carcinoma (NPC), gastric carcinoma (GC), Hodgkin's lymphoma (HL), Burkitt lymphoma (BL), diffuse large B-cell lymphoma (DLBCL), and extra nodal NK/T-cell lymphoma, nasal type (ENKTL-NT).[6]

Another DNA virus belonging to the gamma herpesvirus family is Human herpesvirus 8 (HHV-8) or Kaposi's sarcoma-associated herpesvirus (KSHV), which causes Kaposi's sarcoma.

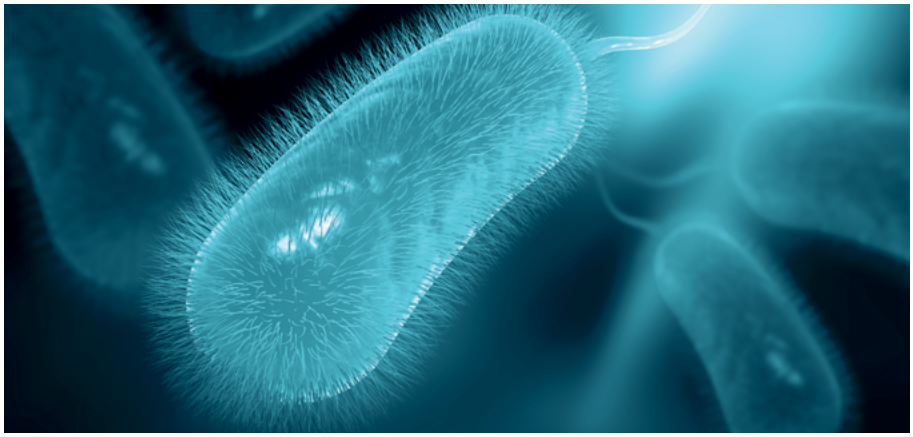
The prevalence of KSHV varies greatly, ranging from about 3% in the UK up to almost 80% in some areas of sub-Saharan Africa.[7] It is strongly associated with advanced HIV/AIDS. It is thought to spread by mother-child transmission and through saliva. Various environmental factors, such as co-infection with malaria, seem to increase the replication of KSHV and thus lead to enhanced transmission.[7] KSHV is rarely associated with cancer, except in immunocompromised patients.

HUMAN T-LYMPHOTROPIC VIRUS 1 (HTLV-1)

The human T-lymphotropic virus type 1 (HTLV-1) is a retro virus that can cause adult T-cell leukaemia/lymphoma (ATL) and a progressive nervous system condition known as HTLV-1-associated myelopathy or tropical spastic paraparesis (HAM/TSP). HTLV-2 has virological and pathological similarity to HTLV-1 and is mainly associated with HAM/TSP. Both infect CD4 cells and thus stimulate cell proliferation leading to ATL. HTLV-3 causes death of CD4 cells and was later renamed as the human immunodeficiency virus (HIV).

HTLV-1 is transmitted primarily through direct contact via cell-containing bodily fluids including blood, breast milk and semen. While breast feeding is associated with ATL, HAM/TSP is related to transmission by blood transfusion.

The WHO estimates that the total number of people living with HTLV-1 infection range from 5 to 10 million, although this is likely an underestimation due to a scarcity of reliable data.[8] Seroprevalence of HTLV-1 in Europe and the USA is low (1%), while in certain areas in Japan it is as high as 30%.[9]



Helicobacter pylori bacterium (photo Shutterstock)

Although most people do not develop conditions that can be linked to the infection, there are several serious diseases thought to be caused by or strongly associated with the virus. The lifetime risk of developing ATL among people with an HTLV-1 infection is about 5%, although this again may be an underestimation. There is currently no vaccine or recommended treatment for asymptomatic HTLV-1. Treatment should instead focus on the symptoms of associated diseases.

MERKEL CELL POLYOMAVIRUS (MCPYV)

Merkel cell polyomavirus is a DNA virus that is widely prevalent and can be detected on the skin of most healthy adults. It usually causes asymptomatic infection in the skin, but occasionally leads to an aggressive type of neuroendocrine skin cancer called Merkel cell carcinoma (MCC), also known as trabecular carcinoma of the skin. More than 80% of MCC tumours can be related to MCPyV[10], although the exact mechanism that leads to carcinogenesis is not yet fully understood.

The prognosis of MCC is poor, with a 5-year overall survival of around 51% for patients presenting with local disease at the time of diagnosis, and worse prognoses for those with more advanced stages of disease.[10] The incidence of MCC varies according to geographic regions but has tripled over the last 20 years and is expected to increase further in the future.[10] Risk factors associated with MCC are advanced age, immunosuppression, fair skin, and exposure to ultraviolet light. Skin pigmentation appears to protect against MCC.[11]

BACTERIUM

HELICOBACTER PYLORI

H. pylori is a spiral shaped, Gram-negative bacterium that selectively colonies the epithelial layer of the stomach. *H. pylori* colonization is very common, with the Centers for Disease Control and Prevention (CDC) in the United States estimating that approximately two-thirds of the world's population is infected.[12] In most people, *H. pylori* colonization does not cause any symptoms. However, long-term infection causes chronic inflammation and significantly increases the risk of developing duodenal and gastric ulcer disease and gastric cancer. Infection with *H. pylori* is the strongest known risk factor for gastric cancer, which is the second leading cause of cancer-related deaths worldwide. Approximately 1-3% of carriers develop gastric adenocarcinoma.[13]

Other malignancies that *H. pylori* is thought to contribute to are gastric mucosa-associated lymphoid tissue (MALT) lymphoma and hepatobiliary tumours.

MALT lymphoma is a rare type of non-Hodgkin lymphoma in the stomach lining. Normally, the lining of the stomach lacks lymphoid tissue, but as a response to colonization with *H. pylori* this tissue is stimulated. Nearly all patients with MALT lymphoma show signs of *H. pylori* infection, and the risk of developing this tumour is more than six times higher in infected people than in uninfected people.[12]

Although there are multiple studies that show a positive association between *H.*

pylori infection and the development of HCC and biliary tumours, this evidence is limited, and a causal relationship has not yet been confirmed.[14]

H. pylori infection can be treated with antibiotics and eradication has been shown to greatly decrease the risk of developing gastric cancer, with a decreased incidence of almost 40%.[12] However, due to the development of antibiotic resistance, treatment is becoming a challenge.

PARASITES

SCHISTOSOMA HAEMATOBIUM

S. haematobium is a trematode parasite and one of the schistosomiasis species that causes schistosomiasis. People can get infected via contact with infested water, where the larval form of the parasite is excreted by freshwater snails and can penetrate the skin.

Schistosomiasis is a public health problem in certain areas and has been reported in 78 countries, mainly in sub-Saharan Africa. It affects around 240 million people worldwide, and more than 90% of all cases occur in Africa.[15]

There are 2 major forms of schistosomiasis – the intestinal and urogenital form. *S. haematobium* causes the urogenital type and is known to cause squamous cell carcinoma and urothelial carcinoma of the bladder if it remains untreated. Tumours are mostly found in a young age group (reflecting exposure since early childhood) and have a poor prognosis. The WHO strategy for control is implementing mass drug administration (MDA) with praziquantel in endemic areas as preventive chemotherapy.[15]

OPISTORCHIS VIVERRINI AND CLONORCHIS SINENSIS

O. viverrini and *C. sinensis* are trematodes that can be contracted by eating raw or undercooked fish, crabs or crayfish, and can infect the liver, gallbladder, and bile ducts. Most infections are asymptomatic but if untreated can cause severe diseases of the liver, including cancer of the bile duct (cholangiocarcinoma, CCA).[16] CCA is found in the epithelial lining of the bile ducts and is untreatable in most cases.[16]

C. sinensis is mostly found in rural areas of Korea and China and therefore known as the oriental liver fluke. *O. viverrini* is found in Thailand, Laos, Cambodia, Vietnam, Germany, Italy, Belarus, Russia, Kazakhstan, and Ukraine and is especially common in the north-east of Thailand, where at least 70% of people are infected. This leads to a high number of CCA. Worldwide, bile duct cancers make up 15% of the primary liver cancers, compared to 90% in Khon Kaen province, Thailand.[16]

HYMENOLEPIS NANA

There is one case report on malignant transformation of infection with *H. nana*, a tape worm, in an HIV infected individual.[17]

CONCLUSION

Infections are an important source of human malignancies. It is important to note epidemiological differences; while *S. haematobium* infection is restricted to Africa, liver flukes such as *O. viverrini* and *C. sinensis* are mainly found in South-East Asia. HIV/AIDS related cancers such as KS and non-Hodgkin lymphoma reflect the endemicity of HIV infection, particularly in Africa, while HTLV-1 prevalence is highest in Japan.

Reducing the incidence of pathogen-driven cancers can be done by prevention or early treatment. For instance, HBV can be prevented by vaccination which is becoming widely available. *S. haematobium* infection prevention requires mass drug administration and early treatment with praziquantel. However, although infectious agents contribute significantly to the overall global cancer burden, it is important to realize that most infected people will not develop malignancies. Most at risk are people in underserved communities in LMICs and immunosuppressed patients.

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ARTICLE

Aflatoxin, food toxin that causes liver cancer

Figure 1. Aspergillus growing on ground nuts that may be contaminated by aflatoxin (photo Shutterstock)

Liver cancer, also known as hepatocellular carcinoma (HCC) is one of the leading causes of cancer related deaths. It accounts for up to 8.2% of all reported cancer deaths and is among the top four common causes of cancer mortality worldwide.[1] Underlying conditions such as chronic hepatitis B (HBV) or C (HCV) infection are, at present, still the most common risk factors for HCC, although their attribution will most likely decline in the coming years. Unfortunately, the prevalence of other risk factors like alcohol abuse, diabetes mellitus, and non-alcoholic fatty liver disease (NAFLD) is increasing. Moreover, much research has highlighted the - not to be underestimated - role of aflatoxins in inducing HCC.[2]

Aflatoxins are highly toxic and carcinogenic compounds produced by certain strains of *Aspergillus* fungi, including *A. flavus* and *A. parasiticus*. These fungi are commonly found in warm and humid regions and are able to contaminate a variety of food products, including grains, maize, nuts, and spices (Figure 1).

Aflatoxins are classified as mycotoxins, which are toxic compounds produced by fungi that can have negative impacts on human and animal health. These impacts can be either acute illness directly after consumption of contaminated food products, or long-term effects like immune deficiency and induction of cancers.[3,4] Around 4.5 billion people worldwide are exposed to dietary aflatoxins. The majority lives in (sub)tropical regions, where maize and nuts are dietary staples and storage conditions are suboptimal.[5] Due to globalized trade, dietary aflatoxins are a worldwide concern.

CONTAMINATION OF CROPS

Worldwide, around 25% of all crops are contaminated with mycotoxin.[6] Crops get contaminated either during the growth and development phase, or during the transport and storage while exposed to warm and humid conditions, or severe drought. Some of the products at risk of contamination are maize, peanuts, rice, cassava, chili pepper, sunflower seed, sesame, and many more. Animals fed on contaminated food products can also pass aflatoxin into eggs, milk products and meat.[6]

AFLATOXIN AND LIVER CANCER

Aspergillus species produce four principal aflatoxins; B_1, B_2, G_1 and G_2, of which aflatoxin B_1 (AFB_1) is the most potent one.

Aflatoxins are highly toxic to the liver and there is strong evidence linking aflatoxins to the development of liver cancer. Acute exposure to high levels (acute aflatoxicosis) can cause acute hepatic necrosis, which can eventually lead to cirrhosis and HCC. Symptoms of acute liver failure are - among others - fever, jaundice, vomiting, abdominal pain, bleeding, and mental changes.[6] Additionally, chronic exposure to aflatoxin increases the risk of developing liver cancer. This is because aflatoxin can cause DNA damage and mutations in the P53 tumour suppressor gene, which is an essential gene in preventing cell cycle progression in case of mutated DNA.[6] As AFB1 biomarkers were developed – which made it possible to demonstrate a relationship between AFB1 and HCC – the International Agency for Research on Cancer (IARC) decided to classify AFB1 as a group 1 human carcinogen.[2,7]

Research showed that 4.6% to 28.2% of all global cases of HCC can be caused by aflatoxin.[6] Concomitant exposure to aflatoxin and HBV is quite common in low- and middle-income countries and greatly increases the risk of developing HCC. A meta-analysis by Liu et al. (2012) showed that AFB1 causes a 6-fold increase in HCC risk, HBV alone a 11-fold increase, and the two combined a 54-fold increase.[5]

Sadly, despite comprehensive research over the past decades, the five-year life expectancy of a person with liver cancer is less than 20%. Upon initial diagnosis of liver cancer, up to 95% of the liver has already been functionally destroyed. Even after liver transplantation, the survival rates of HCC patients with advanced disease are poor.[8] Moreover, a recently published study by scientist from the IARC predicts that the annual number of new cases and deaths will increase by more than 55% by 2040.[9] This is why strategies to reduce risk factors for HCC, like aflatoxin, are so important to decrease the incidence of HCC.

PREVENTION AND CONTROL

To reduce the risk of aflatoxin exposure and the development of liver cancer, it is important to implement measures to prevent the growth of mould on food and to properly store and handle food to minimize the risk of contamination. This includes storing food in dry, cool conditions, avoiding the use of damaged or rotting food, and cooking food thoroughly. In addition, individuals can reduce their risk by eating a varied and balanced diet and avoiding high-risk foods, such as mouldy grains or nuts. The World Health Organization (WHO) recommends that governments and the food industry take steps to reduce the risk of aflatoxin contamination through measures such as improving food storage and handling practices, implementing food safety regulations, and providing education and training to food producers and handlers.[4]

In 2015, the IARC convened a working group to review health effects of aflatoxins and to evaluate intervention measures with the aim of reducing exposure. A few of these interventions were suitable for implementation. One of these interventions was increasing dietary diversity, which could have a dose effect reduction of hepatocellular carcinoma.[10] This is quite challenging, as there are still many countries who are dealing with food-, arable land- and water-insecurities. Other strategies include post-harvest measures like improved storage and sorting of the crop.

Over the years, several aflatoxin-specific biomarkers have been developed and validated. With these biomarkers, it is possible to define human exposure and risk, and they have been used in preventive intervention trials. In China, this has led to a reduction of aflatoxin exposure and a 50% reduction of liver cancer incidence as a result.[11]

CONCLUSION

In conclusion, aflatoxins are toxic compounds produced by certain species of Aspergillus that have been linked to the development of liver cancer and other health problems. To reduce the risk of aflatoxin exposure and the development of liver cancer, it is important to implement measures to prevent the growth of mould on food and to eat a varied and balanced diet.

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Close-up of Aspergillus flavus and A. parasiticus producer of aflatoxins in corn used for food and animal feed (photo Shutterstock)

Cancer by contagion

Figure 1

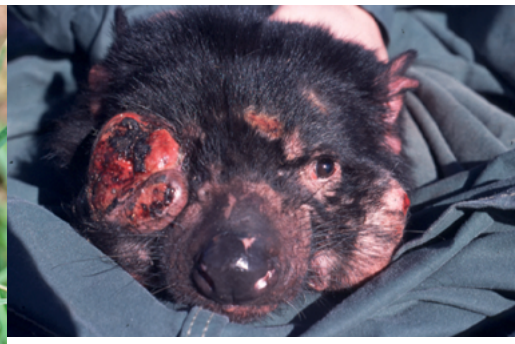

Figure 2

While risk factors for cancer normally include smoking, dietary factors, exposure to chemicals and (UV) radiation, hereditary predisposition, microorganisms (particularly viruses), or combinations hereof, transmission by contagion may also occur. This is not uncommon in animals but less well known in humans.[1]

The best-known transmissible cancer is the Devil Facial Tumour Disease (DFTD) that occurs in Tasmanian devils, a carnivorous marsupial (*Sarcophilus harrasii*), so-called because when threatened it may go into a rage, producing guttural, spine-chilling growling sounds with teeth baring.[2] (Figure 1,2) It is estimated that 4 out of 5 animals are affected by DFTD, and this animal species is therefore at risk of extinction. The tumour is transmitted by fighting and biting, hence the involvement of the face, mainly around the mouth, which interferes with ability to eat. Eventually, the animal dies of starvation. There is no immune response. The lesion ulcerates and becomes friable; it can be easily dislodged and may enter the new host by implantation (as in an allograft).[3] The tumour is remarkably uniform in all cases sampled, showing the same chromosomal rearrangement that is characterized by the absence of X and Y chromosomes in both male and female animals. This and other chromosomal abnormalities suggest that the tumour does not originate from the individual animal's own tissues.[3] While DFTD is a relatively new cancer (detected in 1996), the Canine Transmissible Venereal Tumour probably has been colonizing dogs for thousands of years and is thought to have reached its current state after millions of mutations.[1,4] The living cancer cells transplant themselves, even long after the death of the original animal. It affects the genitalia in both sexes; in male dogs, lesions on nose and mouth are more common, probably as the result of sniffing at female genitalia.[5]

Another intriguing example is the occurrence in soft shell clams (*Mya arenaria*) of a transmissible neoplasm of the hemolymphatic system behaving as a form of leukaemia. Transmission of this clonal cancer has occurred between clam beds that are hundreds of miles apart suggesting a thus far unidentified agent.[6]

In humans, cancer by contagion is rare, with the best-known example being the development of Kaposi's sarcoma in a transplanted organ. Here it is thought that the KS occurs because of outgrowth of virus-infected tumour cells rather than by free virus.[7] There also is an example of a surgeon who cut himself while operating on a patient with a giant cell tumour and developed the same tumour afterwards.[8]

Another example is the occurrence of metastatic breast cancer in four recipients of donor organs from a female donor who was thought to be medically free of disease.[9]

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A man with a swelling of the wrist

SETTING

This case is from Masanga hospital, a rural training hospital located in the jungle of central Sierra Leone. The hospital has four physicians Global Health and Tropical Medicine, six community health officers (of which two are surgically trained), two midwives, sixty nurses and around ten clinical health officers who follow the local surgical or paediatric training programme. The hospital has 120 beds and provides healthcare for about 12,500 patients every year (inpatient and outpatient department). It is one of the few hospitals that provides trauma care on a large scale in the rural area and therefore receives a lot of referrals from other hospitals. The local infrastructure is very poor, while around 440,000 people in the widespread area are dependent on this hospital for healthcare.

SPECIALIST ADVICE

The specialists of the Consult Online panel thought of a giant cell carcinoma. Other potential diagnoses could be a bone cyst or fibrous dysplasia. It should be noted that the differential diagnosis, in a case like this with little information and without additional diagnostic tests, can be broad. The panel agreed that the clinical findings, course of the disease and X-ray were not suspect for an osteosarcoma (in which faster growth and a sunburst aspect and spiculae on the X-ray would be expected). The process on the X-ray was described as benign (at most low grade malign) and the panel advised a biopsy with a sharp spoon and histological analysis. The therapy advice for a benign tumor like this would be to scrape out the bone and fill it with autologous spongiosa bone (for instance from the pelvis), and then place an external fixator to prevent fractures. The panel advised this operation to be performed by an experienced surgeon to spare the ulnar and median nerves and thereby the function of the hand.

CASE

A 23-year-old man presents at the hospital with a swelling of the right wrist (Figure 1). It originated a few months earlier and slowly increased in size. It was not preceded by any trauma. On clinical examination a round, hard swelling with varying surface is palpable on the ulnar side of the right wrist. No enlarged lymph nodes can be palpated.

An X-ray of the wrist shows an expansive lytic lesion of the distal ulnar bone of the right wrist (Figure 2). A chest X-ray was performed and showed no abnormalities.

A biopsy was not performed right away because of lack of the patient's financial means and because there is only one pathologist in the whole country. Based on the clinical findings and x-ray the medical team made a differential diagnosis of an osteosarcoma or benign bone cyst and consulted the Consult Online panel for help. On clinical examination a round, hard swelling with varying surface is palpable on the ulnar side of the right wrist. The swelling does not feel warm, and the function of the hand is normal.

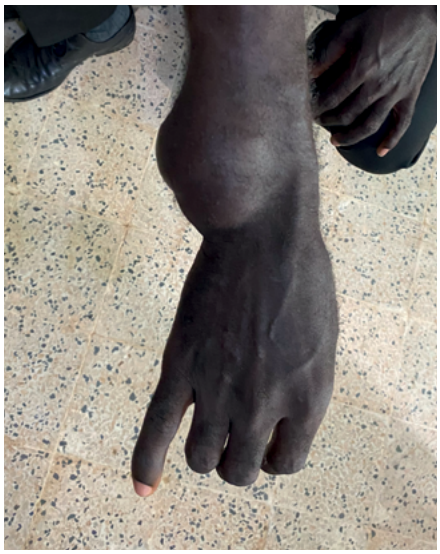

Figure 1 The patient at presentation with a large swelling at the ulnar side of the right wrist

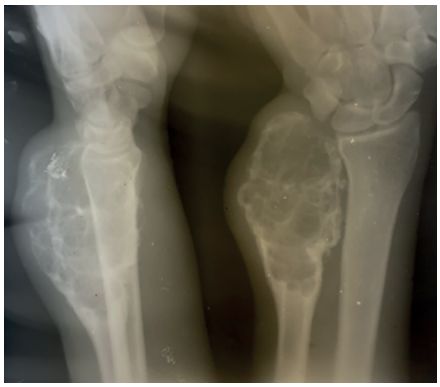

Figure 2 The X-ray of the right wrist

GIANT CELL TUMOR OF THE BONE

A giant cell tumor of the bone (GCTB) is a rare, often benign, osteolytic skeletal neoplasm characterized by a myriad of giant osteoclast-type cells. Although it is non-cancerous it can be locally aggressive and lead to destruction of surrounding tissue.[1,2]

GCTB represents 3-5% of primary bone tumors and 15-20% of benign tumors in the 'western' world.[1,3] Studies estimate an incidence rate of 1.03-1.7 per million persons per year.[2,3] The frequency of occurrence of GCTB seems to be higher in the Chinese population, where GCTB represents roughly 20% of all primary bone tumors.[1]

GCTB usually occurs after the closing of the epiphyseal plates and mostly affects young adults between the age of 20-40.[1,3] Described by the radiologist of the consult online panel as: An expansive bone lesion of (unknown) cm in the distal ulna, with a predominantly osteolytic matrix, some ground glass areas and no obvious calcifications. Some thin septae and cortical thinning is seen. Females are slightly more often affected than males.[1,2,3] An occurrence of the disease before the age of 20 is

GRADE I	Intraosseous lesions with well-marginated borders and an intact cortex.
GRADE II	More extensive intraosseous lesions having a thin cortex without loss of cortical continuity. IIa: without pathologic fracture IIb: with pathologic fracture
GRADE III	Extraosseous lesions that break through the cortex and extend into soft tissue.

Table 1: The Campanacci grading system for giant cell tumor of the bone. [1]

uncommon. The disease most often presents solitary, although multicentric GCTB has been seen in younger individuals.[1] Risk factors of the disease and the exact pathogenesis is not yet fully understood.[1]

GCTB is a relatively slow growing tumor that most commonly affects the meta-epiphysis of the long bones. It is often seen around the knee (proximal tibia, distal femur) and wrist (distal radius) but can present in almost all bony parts of the body.[1,3,4] Patients frequently present with pain, swelling and reduced joint movement leading to mechanical difficulty.[3,4] Destruction and thereby thinning and weakening of bone can often lead to pathologic fractures.[1,4] Distant metastases of GCTB can occur and are seen in less than 5% of cases and most frequent to the lungs.[1,3] The clinical behavior of these metastases is different from metastases derived from malignant tumors and does not often lead to death of the patients.[1] A primary malignant form and malignant transformation, although very rare, exist and have poor prognosis.[1,3]

The diagnosis is based on clinical findings in combination with medical imaging (X-ray, CT or MRI) to assess the extent of the disease and a biopsy for histopathologic evaluation.[1,2] The Campanacci grading system (table 1) can be used to categorize the extent of the lesion based on radiographic imaging, and could be helpful in determining definitive treatment.[1,4]

Surgery is the treatment of choice.[1,4] Surgical treatment options depend on localization and extent (size of the tumor, extent to surrounding tissue and the existence of a pathologic fracture) and range from local intralesional (extended) curettage to en-bloc resection with or without reconstruction.[1] Risk of recurrence in benign GCTB varies in the literature (6-42%) en is more often seen with simple curettage.[1,2] This risk, in combination with morbidity and postoperative functional outcomes, should be considered before surgical treatment.[1] For patients with a contraindication to surgery, non-surgical treatment options include radiotherapy, arterial embolization or systemic therapy with denosumab, but have shown limited success.[1,3] The latter is often not possible in low-resource settings.

FOLLOW UP

A short while after the first consultation, the patient returned to the hospital with a pathology report. It turned out he had been to a hospital in the capital Freetown a few months earlier, where a biopsy of the swelling was performed and sent to India for analysis. The report showed a biopsy result of a giant cell tumor. A conservative approach was agreed upon and the patient was sent home. When an experienced trauma- orthopaedic- or plastic surgeon will visit the hospital the plan for an operation as advised by the panel will be further discussed. It must be noted that an operation with autologous spongiosa transplantation can be very challenging in a low-resource setting like this. After this last consultation the patient was not yet seen again.

Described by the radiologist of the consult online panel as: An expansive bone lesion of (unknown) cm in the distal ulna, with a predominantly osteolytic matrix, some ground glass areas and no obvious calcifications. Some thin septae and cortical thinning is seen.

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Gastrointestinal endoscopy in Rwanda

The 5th Rwandan Endoscopy Week 2022

All over the world many patients are suffering from conditions requiring gastrointestinal endoscopy. But endoscopy facilities in many African countries are rare, as is the case in Rwanda, with about 2.5 million inhabitants. This leads to high numbers of late consultations, if any, to prolonging of suffering, and to undertreatment of diseases. In the case of gastrointestinal malignancies, this results in advanced disease and high mortality rates. For long periods, gastrointestinal endoscopies in Rwanda were performed only occasionally. The need for far more endoscopy facilities and expertise is evident. At this moment the number of gastroenterologists and internists with some expertise in gastroenterology and endoscopy is very limited, and less than 30 doctors perform endoscopies at various locations.

ESTABLISHING AND SUSTAINING AN ENDOSCOPY SERVICE

In 2015, within the University Teaching Hospital of Kigali (Centre Hospitalier et Universitaire de Kigali - CHUK), the Department of Gastroenterology and Hepatology was established including an endoscopy unit to provide specialized consultations for patients with gastrointestinal conditions. In 2017, Rwandan health professionals interested in gastroenterology, and hepatology founded the Rwandan Endoscopy Society (RSE). This was done with the support of international and local partners, especially the King Faisal University Hospital in Kigali.

In the same year, the RSE, in collaboration with GI-specialists from Dartmouth Hitchcock Medical Center (Hanover, New Jersey, USA) and Brigham & Women's Hospital (Boston, USA) and later also with partners from Australia, the Netherlands, and the World Endoscopy Organization (WEO), launched the first Rwandan Endoscopy Week. This proved a great success and stimulated a now yearly recurring academic and clinical event. The clinical activities throughout this week are conducted at seven hospitals countrywide, including public, private, urban and rural facilities, with increasing numbers of endoscopies. Endoscopy, alongside *Helicobacter pylori* identification and eradication, aids in GI cancer prevention and diagnosis. This microorganism is highly prevalent in Rwanda. About 85% of the procedures performed are gastroscopies. The teaching program includes lectures and hands-on training for fellows, residents, general practitioners, and endoscopy unit nurses. In addition, biomedical engineers from the US assess the functional status of and repair the endoscopy equipment available in the country, if necessary. During the recent 5th Rwandan Endoscopy week from 24 October to 4 November, 2022, over 900 upper, lower, and advanced GI endoscopies were performed. GI awareness and endoscopies are on the rise.

In 2020, the US non-governmental organization GI Rising (cooperation between Dartmouth and Brigham & Women's) was founded to further GI education and care in Rwanda. This resulted in Rwanda's first post-graduate GI training program, a self-sustaining fellowship in gastroenterology and hepatology. Two university hospitals in Kigali have jointly been recognized in 2021 by the World Endoscopy Organization as centres of a formal 2-year fellowship training program in GI endoscopy: CHUK and King Faisal University Hospital. This program is open not only to Rwandans but to medical doctors from other African regions as well.

CHALLENGES

Despite all these favourable developments within a very short period of time, the lack of endoscopic equipment, coupled with a lack of training and expertise in therapeutic endoscopy, hinders specialized gastrointestinal care. The equipment is often donated, namely used endoscopes from abroad, and maintenance of this equipment is a challenge. Also, consumables such as balloon dilators, varices band ligators, and biopsy forceps are in short supply.

The value of exposure to GI practice and training in high-income countries cannot be overestimated. Such global health experience enables the trainee from a low- and middle-income country (LMIC) to acquire a deeper understanding of the entire spectrum of GI disease including cultural differences (for example in risk factors). In addition, the trainee will experience GI care at the highest level and may be able develop a similar framework at home in a bilateral long-term collaboration with the host institute in the HIC, in which leadership skills should also be strengthened. This training and exposure may reduce inequities in global health care. Some residency training programs and medical schools in HICs have developed global health electives for that purpose, but the number of fellowships is limited. Another challenge is the (permanent) scheduling of such electives in educational programs.

In conclusion, in the field of endoscopy in Rwanda, considerable progress has been made in terms of training in GI endoscopy and patient care; sustaining and further developing this initiative are important challenges for the future.

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Feasibility of cervical cancer screening methods in low-resource settings

ELIMINATION STRATEGY OF CERVICAL CANCER

Cervical cancer is globally the fourth leading cause of death among women.[1] Worldwide, in 2020, there were an estimated 604,127 new cases and 341,831 deaths, mainly among poorer women in society[2] An infection with high-risk human papilloma virus (hrHPV) can cause precancerous lesions of the cervix. Generally, the immune system can clear the virus. If not, the precancerous lesions can over time develop into cervical cancer. Before hrHPV was identified as the cause of precancerous lesions, cytology (Pap smear) was used to classify the risks of developing cancer. In many Western countries, the Pap smear is still used as the primary screening tool. Low-risk HPV causes genital warts. HPV infection of the cervix is a sexually transmitted disease, which can effectively be prevented by HPV vaccination.

In 2020, the World Health Organization (WHO) launched the Global Strategy to eliminate cervical cancer as a public health problem. The strategy includes the following global targets: 1) 90% of girls have received full doses of HPV vaccination by age 15 years, 2) 70% of women are screened at least twice in their life with a high-performance test, and 3) 90% of women identified with (pre)cancer receive adequate treatment.[3] This combination of HPV vaccination, cervical cancer screening, and treatment will fully achieve the cervical cancer elimination targets in the next century and can already reduce mortality by half in 2040 (figure 1).[4]

At the moment, HPV vaccination campaigns have not yet been introduced or widely implemented in low- and middle-income (LMICs) countries, and in the absence of HPV vaccination, millions of women are at risk of cervical cancer.[5] This means that accessible and affordable screening programmes are crucial to early detection of hrHPV and treatment of precancerous lesions.

INNOVATION IN SCREENING FOR CERVICAL CANCER

The WHO guidelines for cervical cancer prevention recommend hrHPV testing of vaginal fluid as the primary screening test. HrHPV positive women are offered either direct treatment with thermal ablation or cryotherapy of the cervix in a screen-and-treat approach, or a second triage test is applied whereby women are treated when precancerous lesions are identified.[6] However, up to now, visual inspection with acetic acid (VIA) is the most commonly used screening method in LMICS, and only a limited number of LMICs are implementing hrHPV testing. The costs of high-quality PCR testing are generally high (around US$ 50 per test), and the

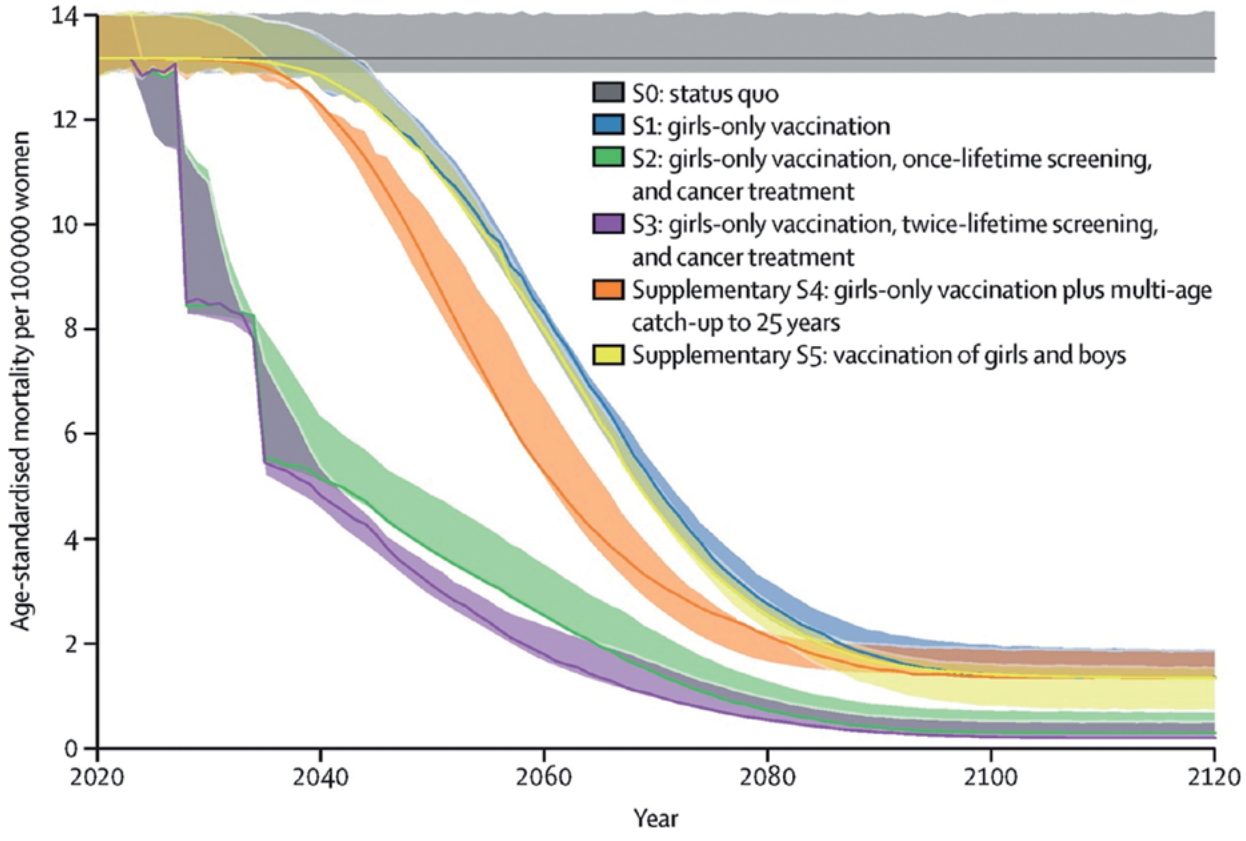

Figure 1 WHO cervical cancer elimination strategy [3]

technology of testing is too advanced for clinics in remote areas. The laboratory procedure is comparable to TB testing, often using the same equipment. VIA is cheap and relatively easy to establish. However, both the sensitivity and specificity of VIA are variable and dependent on the skills of healthcare providers performing VIA. The inter- and intra-observational variations result in variation in the quality of screening services, particularly in resource-poor settings.[7] HrHPV testing offers higher sensitivity compared to VIA and cytology[8] Self-sampling of vaginal fluids for hrHPV testing has the potential to further increase uptake of cervical cancer screening by reducing socioeconomic, cultural, and logistical barriers to participation in screening.[9] Innovative financing models for HPV testing, including self-sampling, are needed to allow accessibility for all women.[10]

TESTING FEASIBILITY OF THE WHO STRATEGY

While the WHO strategy targets both high- and low- and middle-income countries, most research concerning the elimination of cervical cancer comes from high-income countries. HPV vaccination and cervical cancer screening are mentioned more and more in national health strategy plans in LMICs in the context of universal health coverage, but actual implementation is challenging.

The PREvention and SCReening Innovation Project Toward Elimination of Cervical Cancer (PRESCRIP-TEC) project studies the feasibility of the WHO strategy in LMICs (Bangladesh, India and Uganda) and vulnerable populations, like ethnic minorities, in Europe (Slovak Republic). These countries have screening and treatment strategies in place but have not yet implemented HPV testing as a primary screening strategy.

Preliminary results of a baseline study conducted among women and decision-makers in the family (e.g. husbands, mothers in law) in these countries showed considerable variation in awareness of cervical cancer, its symptoms and risk factors. Intensive community mobilisation was therefore initiated to convince women and their family members to participate in HPV self-testing (either at home or in a healthcare facility), using not only classical methods of posters and radio messages, but also new approaches like social media. Home-based distribution of HPV self-tests, with personal information from community workers, helped in all countries to achieve an uptake of 80% to 95% among eligible women. Tests were analysed in laboratories in nearby health facilities, and results were then communicated to women, often by text message (if negative) or by community volunteer (if positive).

Preliminary results of our study show substantial differences in prevalence of hrHPV infection between countries and populations. In rural areas in India and Bangladesh, prevalence ranges between 2% and 3% in rural areas and between 6% and 8% in urban areas. In India, HIV-positive women and sex workers are included in the target population, with their hrHPV prevalence being around 30% and 40% respectively. In the Roma population in Slovakia, hrHPV prevalence is between 10% and 12%, and in rural areas in Uganda, around 21%. HIV and HPV multimorbidity is a frequent phenomenon, and therefore all HIV-positive women in Uganda are tested for HPV infection as part of HIV treatment.[11]

Women with an hrHPV positive test result were invited for gynaecological examination in a nearby clinic. When hrHPV testing is done as primary screening, the number of women who need VIA is dramatically lower than when VIA is used as primary screening, since hrHPV-negative women do not need gynaecological examination. This saves much time for women and health workers and saves costs.

Unfortunately, as long as no instant Point of Care (POC) hrHPV test exists, women must wait until the laboratory results are known before travelling to the nearby clinic for follow-up examination. Waiting creates a risk for drop-out of participants, which we try to address by personal support by community volunteers. Drop-out in our project is less than 10% at the moment, while others report higher drop-out rates.[12]

When health workers conduct VIA in the clinics in the PRECRIP-TEC project in Bangladesh, India, and Uganda, they use an Artificial Intelligence Decisions Support System (AI-DSS), which was developed by the Manipal Academy of Higher Education, School of Information Sciences, India.[13] The AI-DSS was developed to reduce intra- and inter-observer variation of the VIA assessment and to allow for task shifting of VIA screening in the future.[14] It is one of the first AI-DSS systems that can be used offline in remote clinics and is built into a smartphone. The first experiences in the project are that the AI-DSS is very user-friendly, but it is too early to conclude that it can replace a health worker's VIA assessment. A qualified nurse is still needed to recognise full-blown cancers, cervical infections, or other conditions that are not precancerous lesions.

By the end of the project in 2024, we will review the coverage and uptake of the adjusted WHO screening strategy and analyse the cost-effectiveness of the new approach. From our first preliminary data analysis, we can conclude that it is important that cheaper point-of-care tests for hrHPV become available, for example using photonics (lab on a chip) for urine testing. Such tests are expected within 5 to 10 years and have the potential to revolutionise cervical cancer screening worldwide.[15]

INTERNATIONAL COORDINATION OF RESEARCH

The Global Alliance for Chronic Diseases coordinates five big multi-country research projects into strategies of cervical cancer screening in LMICs, including the PRESCRIP-TEC project. These projects provide new evidence regarding HPV self-testing, community mobilisation strategies, and screen-and-treat approaches. In the coming years, there will be much more knowledge available regarding strategies to increase uptake, the use of artificial intelligence, and the cost-effectiveness and budget impact of potential screening policies in the LMICs in line with the WHO's elimination strategy. Most LMICs intend to start or scale-up HPV vaccination and cervical cancer screening programmes, and scientific evidence will help make this a reality. In short, reducing global cervical cancer prevalence by half in 2040 may become feasible.

The PRESCRIP-TEC research project is a collaboration between UMCG, LUMC, Female Cancer Foundation, and universities and NGOs in Bangladesh, India, Uganda and the Slovak Republic. It is funded by the European Union and the Indian Ministry of Science and Technology, and coordinated by the Global Alliance of Chronic Diseases.

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A career after the 'Global health and Tropical Medicine' training?

A gynaecology-oncology perspective

"Is it possible to become a specialist after the 'physician of Global Health and Tropical Medicine' (GH&TM, in Dutch: AIGT) training and after having worked abroad?" This is a question that medical students often ask me. The short answer is YES! This year I graduated as a sub-specialist gynae-oncology after six years of working as a physician in the refugee camps on the Thai-Myanmar border, with subsequent gynae-cology specialisation. Often the subsequent question is: *"How does your experience have an impact on your work in the Netherlands?"*. As a recently graduated sub-specialist, I decided to ask respected colleagues, some who followed the same path as I did, how they have integrated their experiences into their daily work. I received such motivating stories that I would like to share them. After a brief introduction about their professional life, we talked about the relation between their working experience in a low-income country, global health, and the sub-specialisation gynae-oncology.

THE FIRST QUESTION I ASKED THEM WAS: CAN YOU SHARE SOMETHING ABOUT THE EXPERIENCE YOU HAD IN LOW-RESOURCE SETTINGS?

Heleen van Beekhuizen, gyne-oncologist in Rotterdam, worked more than three

PRESCRIP-TEC project in Uganda. (photo Freek van Slooten)

years in Papua New Guinea (PNG) as a physician GH&TM and four years in Tanzania as a gynaecologist. "In Tanzania, my focus was on fistula surgery and oncology, besides the obstetric work." **Luc van Lonkhuijzen**, gyne-oncologist in Amsterdam, was a medical officer in a district hospital in Botswana (two years) and Malawi (two years): "Apart from being able to care for many patients in need, this experience influenced my own career as well. In Botswana, I worked in a truly multicultural setting with colleagues from all over Africa. Having a lot of responsibilities as a young doctor helped me to develop a certain surgical confidence which is still useful in my current practice." **Lawrencia Dsane**, gynaecologist in Zwolle, was born in Ghana. After secondary school, she studied medicine in Russia. She graduated as a gynaecologist in the Netherlands. During her study, she continued her work with a breast cancer clinic in Ghana through short-stay visits. Lawrencia explains: "There are so many women who present with advanced stages of cancer that we often can't do anything for them anymore. This stimulates me to make a difference in oncology care for women." Also **Jogchum Beltman**, gynae-oncologist in Leiden, lived in Malawi: "I worked from 2005-2007 in Thyolo, a large district hospital in the South. That experience had a huge impact on me in terms of responsibility and coping with few resources. It helped me to develop clinical skills which I currently still use." **Marlieke de Fouw**, OBGYN resident/ PhD student in Leiden, was a "Doctors without Borders" doctor for four years in various projects in PNG, Sierra Leone, Ethiopia and South Sudan. Marlieke added: "Although all projects were different, obstetrical care and care for survivors of sexual violence was an important issue." A few years ago she joined the Female Cancer Foundation (FCF, a Dutch foundation which strives to eradicate cervical cancer) and contributed to cervical cancer projects in Uganda, Gambia, Malawi and Ethiopia.[1]

HOW DO YOUR EXPERIENCES IN LOW-RESOURCE SETTINGS HAVE AN IMPACT ON YOUR WORK IN THE NETHERLANDS?

Marlieke: "I discovered my strengths and limitations, which proved to be extremely valuable during my OBGYN training- I have gotten to know what I needed to learn. Furthermore, I learned that all people share a common desire, which is respectful care. Listening and being interested in people is really important, anywhere in the world." **Heleen** agrees: "The impact is obvious in my communication with women from another culture: I feel connected. But also, technically – I learned to be creative and that still helps in solving surgical problems." **Jogchum** adds another important issue: "My daily motivation for work comes from the enormous burden of cervical cancer in the world. As a gyne-oncologist, I would like to make a difference in quality of care."

CANCER PROJECTS IN POOR-RESOURCE SETTINGS

Jogchum explains: "Cancer is a rising problem in low- and middle-income countries (LMICs). Life expectancy is improving, and there is a change in lifestyle. The speed of this transition necessitates training local health workers." **Luc**: "Yes I totally agree. The gynae-oncology training in Eldoret, Kenia, which I was involved in, is a perfect example of global health training. It is important that subspecialist training is being recognised locally. It leads to quality improvement because local doctors can perform advanced surgeries as they are now adequately trained in gynae-oncology." **Heleen**: "I spend the most time on research and care for women with gynaecological cancer in the Netherlands, especially on screening and vaccination for HPV. Globally, every year half a million women die from cervical cancer. Therefore I started the website www.HPVkankervrij.nl and I am very active in the International Gynaecologic Cancer Society."[2] Lawrencia participates in the Breast Care International (BCI Ghana) screening and prevention programmes. During the 'walk for cure' breast cancer awareness campaigns we address taboos, myths and disinformation about (breast) cancer. In May 2022, we organised the launch of the Lancet Oncology Commission on cancer in sub–Saharan Africa.[3] **Marlieke**: "Palliative care does not exist in many places in Africa, but I hope good examples such as 'Hospice Africa' will inspire oncologists in the world to include palliative care."[4]

TRAINING AND RESEARCH

It is striking how much this group of dedicated sub-specialists is involved in training and research next to their clinical tasks. Examples include hands-on emergency obstetric and surgical skill training for doctors in Berekum, Ghana and training for the Female Cancer Foundation (FCF). The FCF received a large European grant for an innovative implementation project on cervical cancer screening in Asia, Africa and Eastern Europe (including focusing on artificial intelligence, social media and HPV tests).[5] **Marlieke** is one of the PhD students of this project: "Being involved in global health projects gives me a lot of energy. As described in the book Afrika is besmettelijk[6] [Dutch book about a doctors' experience working in Africa, translated meaning something like 'Africa is catching'], I am infected with the global health virus. That motivation helps me to combine my resident training and PhD work."

WHAT ARE POTENTIAL BARRIERS FOR SUCCESS OF GLOBAL GYNAE-ONCOLOGY PROJECTS?

Luc: "Such projects should always be embedded within the local situation to

ensure adequate support. For example, treatment for cervical cancer is complicated. In early stages, a radical hysterectomy can be life-saving. However, this requires specific skills of the surgeon and quality care of the hospital staff as well as good anaesthesia, electrocoagulation, and post-operative-care. Therefore, just training a surgeon is not enough. Global surgery projects should involve the whole continuum of care. All screening programmes should also facilitate treatment for women who have been diagnosed with cervical cancer. But I recognize that radiotherapy may not be available in many settings. Maybe the most affordable gynaecological cancer to cure is gestational trophoblastic disease, but women need to be motivated to come for follow up." **All**: "Yes, we agree. Oncological care is a multidisciplinary team work and complex to organise. This is often not the case in resource-poor settings, but with more attention for global surgery projects, there will be more collaboration and, if we work together, oncology teams may be able to make a difference."

DRIVERS TO STAY MOTIVATED AND PASSIONATE

Lawrencia and **Marieke**: "During our projects in LMICs, we saw and heard of women who died from cervical cancer on a daily basis. When we tell our colleagues in the Netherlands, they often cannot believe this. This is so unfair. This drives us in our motivation to make cancer prevention programmes accessible for everybody." **Luc**: "It is a must for every doctor: do not accept injustice in this world, and care for all patients irrespective of their background, ethnicity or culture". **Jogchum** recommends reading the book The power of women written by Denis Mukwege, a gynaecologist from Congo.[7] "Widen your scope, open your mind to the world, make a difference." **Heleen** congratulates me on my new position and concludes: "As a gyne-oncologist you will perform long surgeries and hard work, so please continue doing things which provide you lots of positive energy. Let's work together in fighting gynaecological cancer".

READY TO TAKE OFF

In January 2023, I will start as a consultant gynae-oncology in the Antoni van Leeuwenhoek Hospital in Amsterdam. I feel privileged to have such an inspiring group of people around me in the Netherlands. In order to boost each other with positive energy and collaborate in medical care, research and education, we started the global gyne-oncology group within the working party International Safe Motherhood and Reproductive Health (WP-ISM&RH). Several projects are planned to improve access to a high quality of gyne-oncology care on a global scale, education and research.[8] And all these projects are in close collaboration with our partners from LMICs.

If you are interested in the work of our group or for other questions, do not hesitate to contact us. On behalf of the global gyne-onco group,

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The changing spectrum of HIV and cancer: risk factors and principles of management

People who are HIV-infected have a higher risk of developing cancer.[1] In the early days of the HIV epidemic, the presence of cancers such as Kaposi's sarcoma (KS), non-Hodgkin lymphoma (NHL), primary central nervous system lymphoma (PCNSL), and invasive cervical carcinoma were designated as AIDS-defining cancers (ADC). After the introduction of anti-retroviral therapy (ART), the spectrum changed; the incidence of KS and NHL decreased while other cancers, referred to as non-AIDS -defining cancers (NADCs), became more common in HIV infected individuals, with a considerable contribution to mortality.[1]

While immunosuppression was the most common risk factor for ADC before the introduction of antiretroviral therapy (ART), other risk factors included co-infection with oncogenic viruses, smoking, substance use, medication use, and HIV-associated metabolic disturbances. Ageing became a more important risk factor, as life expectancy increased considerably after successful ART became available. ART may also be a risk factor as there is a high incidence of KS and NHL shortly after starting ART, possibly in the context of the immune reconstitution inflammatory syndrome (IRIS). However, those patients who do not respond well to ART also have an increased risk of NADCs; these risk factors include the presence of an AIDS diagnosis, a persistent low CD4 count (< 200 cells/μL), and a low nadir CD4 count.[2,3] HIV itself is not oncogenic, but the virus integrates in the host genome as a provirus in the reservoir of infected cells. Co-infection with other oncogenic

Box 1 Most important Aids defining and non-Aids defining cancers[5]

AIDS-defining cancers

- **Kaposi's sarcoma** – caused by human herpesvirus (HHV)-8, also known as Kaposi sarcoma-associated herpes virus (KSHV); spectrum varies from indolent to explosive growth; in high-income countries mainly affecting men who have sex with men (MSM). Frequently arises in extra-nodal sites such as oesophagus and stomach. This type of KS is different from other forms of KS (see Box 2).
- **Non-Hodgkin lymphoma** – Epstein-Barr virus (EBV) related. This includes diffuse large B cell lymphoma, Burkitt's lymphoma, immunoblastic lymphoma, plasmablastic lymphoma, and primary effusion lymphoma.
- **Primary central nervous system lymphoma (PCNSL)** – strongly related to EBV; there may be focal or non-focal symptoms and signs: confusion, lethargy, memory loss, hemiparesis, aphasia, and seizures
- Invasive cervical carcinoma – human papilloma virus (HPV).

(Most important) non-AIDS defining cancers

1. Non-virally mediated

- **Lung cancer** – 3x increased risk, even when correcting for smoking status. In smokers, sensitization by HIV infection to tobacco has been suggested.[6]
- **Prostate** – no increased risk, incidence increases with ageing; outcome worse in HIV/AIDS.
- **Breast** – slightly increased risk, worse outcome.
- **Colorectal** – occurs at younger age and more aggressive.

2. Virally mediated
Human Papilloma Virus (HPV)

- Squamous cell carcinoma of the anus – most common in MSM
- Squamous cell carcinoma of oropharynx
- Squamous cell carcinoma of vagina, vulva, penis, conjunctiva
- Non-melanoma skin cancer: squamous cell carcinoma, basal cell carcinoma.

In general, there is an increased risk of squamous cell carcinomas in HIV infection with worse outcome compared to non-HIV infected individuals. The incidence increased after the introduction of ART.

Hepatitis B virus (HBV) and hepatitis C virus (HCV)

- Hepatocellular carcinoma: low CD4 counts are risk factor; 24% increased mortality in HIV/AIDS.[7]

Merkel cell polyoma virus

- Causes Merkel cell carcinoma; poorly differentiated neuroendocrine carcinoma arising in the skin. The incidence increases more than 10-fold in persons with HIV/AIDS.

3. Other microorganisms

- Hymenolepis nana: Malignant transformation of this tapeworm has been described in an HIV infected individual. (8) This is a novel mechanism that needs to be explored further.[8]

viruses and severe immunosuppression are important risk factors.[4]

CONSIDERATIONS FOR PREVENTION AND MANAGEMENT

PREVENTION

Malignancies in HIV infected individuals occur at an earlier age, with a rapidly progressive clinical course because of high tumour grade and late presentation with advanced disease. There are opportunities for prevention such as smoking cessation, vaccination for HPV and HBV, and treatment of HBV and HCV disease.

There is a need for sensitive and specific biomarkers for early detection and thus better outcome, particularly since the NADCs became more important. Identification of risk groups is important such as HIV patients with HBV or HCV related cirrhosis, and MSM for risk of anal

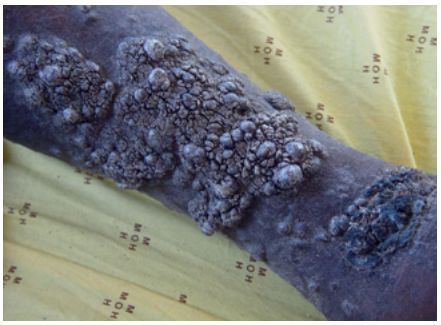


Figure 1. Verrucous lesions on the lower leg – AIDS-related Kaposi sarcoma

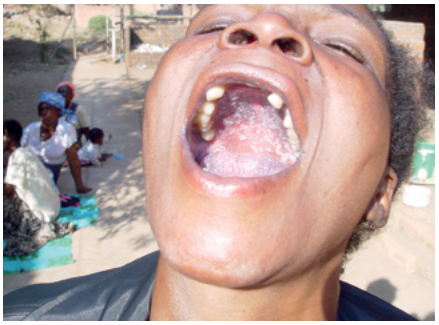


Figure 2. Prominent oral thrush, and in the background on the palate and laterally, multiple blueish flat lesions of Kaposi's sarcoma

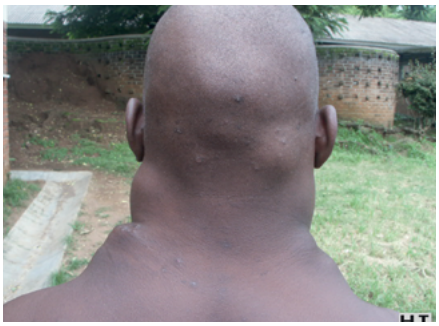


Figure 3. Multiple lymph node swelling in the neck in HIV/AIDS; a biopsy showed non-Hodgkin lymphoma

Box 2. Types of Kaposi's sarcoma (KS)

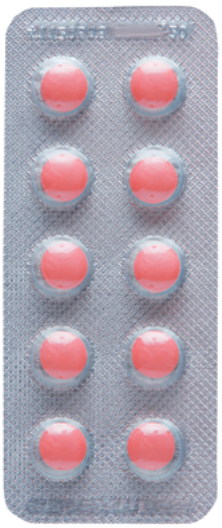
TYPE	CHARACTERISTICS	CLINICAL	COURSE
Classic (sporadic)	Age > 60 yrs Mediterranean, Eastern/central Europe, Middle East	Lower legs, feet	Indolent usually
AIDS associated	HIC: MSM LMICs: heterosexual males and females (Africa); low CD4 counts Co-morbidity, ART start and use of corticosteroids may unmask KS	Common in legs, feet; oral cavity; visceralization common: frequent manifestations: pleural effusion, pericardial effusion, ascites, lymphadenopathy, intrapulmonary	Indolent or aggressive; may respond to ART and chemotherapy
Endemic (African)	Male adults, in children male and female Equatorial Africa Common before HIV era	Variable, lymphoedema legs	Indolent to aggressive (children)
Iatrogenic	Older patients with transplants or other immunosuppression	Lower legs, feet; may disseminate	

ART antiretroviral therapy / LMICs low- and middle-income countries / MSM men who have sex with men

carcinoma. All these factors have implications for outcome including poor response to treatment and recurrent disease.

MANAGEMENT

As HIV-infected patients often use multiple drugs, chemotherapy may lead to drug-drug interactions including increased immunosuppression. Depending on the treatment that needs to be given for a certain malignancy, ART may have to be stopped temporarily. Newer ART drugs such as integrase inhibitors may be more suitable for combined administration with other drugs. A multidisciplinary approach is needed (infectious disease specialist, HIV/aids specialist, oncologist).



Other factors to be considered in outcome are the presence of co-morbidities that are common in HIV/AIDS. In addition, as reactive lymphadenopathy is common in HIV/AIDS, this may complicate accurate staging of the cancer and decision making on the best approach. Patients with advanced AIDS may be at risk of post-operative complications in case surgery is needed in the treatment of cancer.

Treatment consists of two pillars: adequate treatment for the malignancy (that should be confirmed by biopsy) and therapy. Successful anticancer therapy necessitates the elimination of all cells with tumour regenerating potential. In parallel to cancer therapy, all the infected cells that can regenerate new infectious HIV-1 particles need to be removed.

RESEARCH AND TREATMENT CAPACITY

While in the past, HIV infected individuals were excluded from most clinical trials, there is a pressing need for such trials specifically directed towards this group of individuals. In addition, there is a need for trial sites and availability of treatment modalities, such as chemotherapy and radiotherapy, in LMICs.

©

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Physician watch thyself!

Witty lessons on shitty ailments of a Dutch GP by Pieter van den Hombergh

Published by Yes!press, available from Amazon.

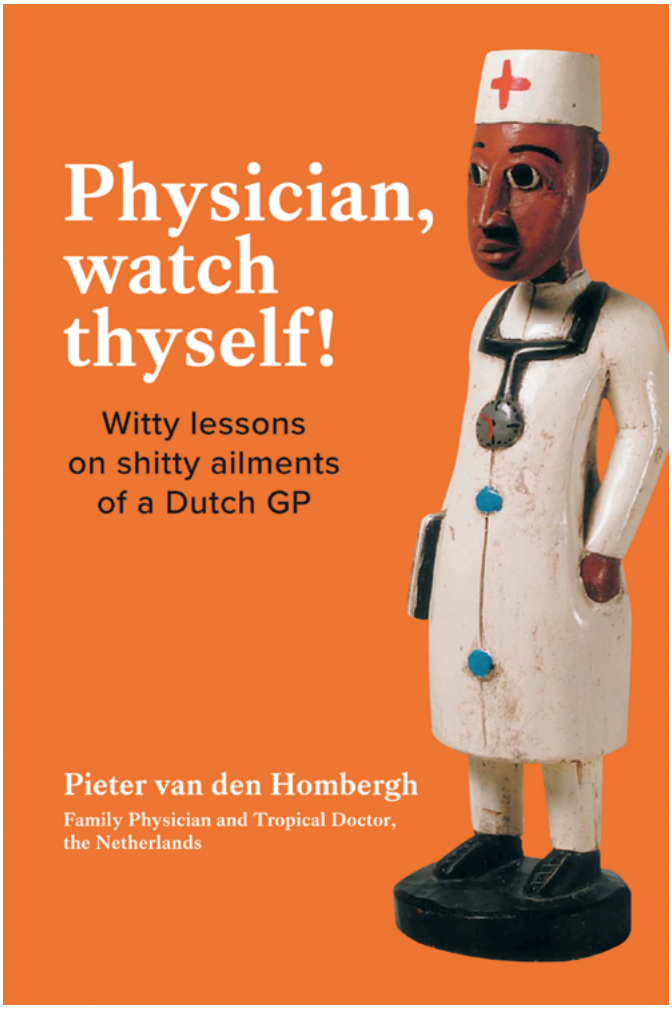
In Dutch: Van eigen kwalen word je wijzer. Uitgeverij Belvedere, 2021. ISBN 978-90-804345-8-5. Available at www.uitgeverijbelvedere.nl

When I met Pieter van den Hombergh during the Netherlands Society of Tropical Medicine (NVTG) annual symposium in November 2022, he was as friendly as ever and apparently in good health, which in retrospect was a pleasant surprise. You may find this a somewhat unusual introduction. Let me explain.

Pieter (Venray, the Netherlands, 1950) is a (now retired) general practitioner by training who worked as a Tropical Doctor in Kilgoris, Kenya (1980-1984) and also served as chairman of the NVTG. He gave me a copy of his recently published book, in which he describes numerous serious and less serious conditions, diseases, and ailments which he suffered from during his life. In a pleasantly light and optimistic way, he writes about his life and career and how he dealt with his medical problems over the years, ranging from pulmonary tuberculosis to jiggers and from gastritis to prostate hypertrophy as well as a wide spectrum of orthopaedic conditions. In addition, the skin problems he encountered include most of what any medical student should know about (tropical) dermatology. Mind you, this list is not exhaustive.

Far from being a hypochondriac (he asked himself this question and discusses this), it seems that most of his ailments were coincidental, apart perhaps from a positive family history for e.g. migraine; other were a sign of the times (persistent gastritis before H2-blockers became available) or a result of exposure to the tropics (jiggers, tuberculosis, traffic accident) or a hobby (running – spondylarthrosis; cycling – orchitis). There were also intriguing less well-known ailments such as moccasin feet and proctalgia fugax.

What I appreciate in this book is that he had the courage to actually write and publish it, and in such a way that it is never about complaining about the bad luck encountered, or about a show of self-pity or self-importance. He describes, with honesty and transparency, what young (and in fact also older) doctors experience when they encounter an illness and sometimes struggle to understand it, or do not exactly know what to do. In the end, the solution comes from medical knowledge and science, but common sense also helps. He learned from his conditions as he went along and wished that he had all this knowledge during his working life, particularly while working as a general practitioner, which has always been his passion.



A tremendously entertaining and informative book.

Ed Zijlstra

The Clinical Book

of the Department of Medicine, Kamuzu University of Health Sciences (Blantyre, Malawi)
By T Phiri and EE Zijlstra

2022 (third edition), 447 pages
ISBN / EAN 9789081571975

For inquiries: info@roctm.com

The Clinical Book is a very instructive and practical white coat pocketbook for doctors and medical students in Malawi. The first part serves as a guide to history taking and physical examination; these clinical skills are even more important in settings where options for additional diagnostics (like laboratory and radiological tests) are limited (Figure). The second part contains some of the most common medical emergencies, including differential diagnosis and treatment. The next part of this book, section 3, might even be the most useful. It gives a practical approach to common clinical presentations, such as anaemia, ascites, or abdominal pain. This is extremely helpful as patients seldom present with a clear diagnosis, and quite often a specific diagnosis is not even made. With the help of specific points in physical examination, differential diagnosis, and details on investigation results, the book guides you to a diagnosis.

The last sections of the book contain to-the-point information about several diseases and treatments, such as HIV/aids, general infectious diseases, and non-communicable diseases. Although the book is written for a Malawian hospital setting, it can be used in many other countries with similar settings and resources. I would highly recommend that doctors and medical students who (prepare to) work in low-resource settings put this practical blue book in their white coat pockets!

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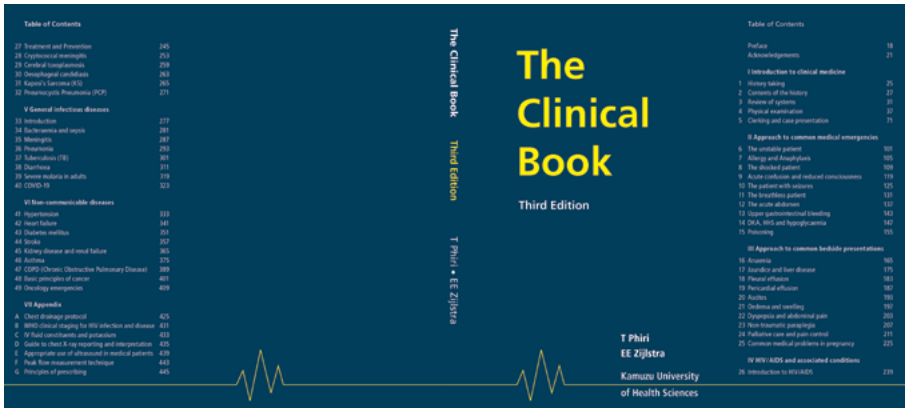
Olga Knaven



The Clinical Book cover with Table of Contents

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