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Cervical Cancer Induced by Human Papillomaviruses in the Context of Africa: Contribution of Genomics

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Abstract

In recent years, Africa has been increasingly involved in biotechnology and genomics. However, this interest is much more accentuated in the field of agriculture. From published studies, we know that biotechnology and genomics can be of great interest in the health field. Africa would, therefore, benefit from investing in these disciplines, especially since the continent is facing several pandemics and epidemics. The objective of this chapter is to make a review of the applications in genomics already existing in Africa, particularly in Burkina Faso, to show the interest of genomics in the field of health by taking into account the context of developing countries and to specify the possible applications of genomics in the fight against papillomaviridae and their associated cancer.

Keywords: genomics, papillomaviridae infection, cancer, Africa

1. Introduction

Advances in molecular biology and genomics, combined with computer and technological development, artificial intelligence, and significant improvement in the production and processing of NGS data, will increasingly have an impact on strategic sectors such as agriculture, breeding, energy, and health. Since the advent of modern biotechnology, it is increasingly evident that the solutions to the major challenges of our world will undoubtedly come from bio-innovation. As the world understands the importance of new technologies, more and more startups are investing in specific areas of health such as oncology, infectious diseases, immunology, metabolism, etc.

While the rest of the world has understood the challenges of current innovations and tries to use them for its population, it remains a great challenge for Sub-Saharan Africa. The intellectual, scientific, and political elite understood the challenges of the biological sciences and new technologies, but this elite often faces external constraints that affect the priorities to be defined for the countries concerned. The consequence is a very low representation of African researchers in the global dynamics of biotechnological innovations. Very often, research funding is provided by external mechanisms and this is still not sufficient to take into account all research concerns. African scientists, including those from Burkina Faso, are then forced to fight for the minimum amount of capital in order to finance their own research.

Located in the heart of West Africa, Burkina Faso covers an area of 274,000 km² with a population of 20,244,080 inhabitants in 2018 [1]. Burkina Faso is a landlocked country, with neighboring countries Mali to the north and west, Niger to the east, Benin to the south-east, Togo and Ghana to the south, and Côte d'Ivoire at the south west. Burkina Faso's economic outlook remains strong; the economy has remained resilient despite difficult security and health environment. However, like many African countries, the part of the budget allocated to research remains low, at 0.9% in 2019 [2]. However, since the advent of SARS-COV2, the interest in research has increased for the population and also for political leaders. Initiatives to enhance the research activities carried out in the country and also to enhance the multidisciplinary nature of research have been started. funding from the President of Burkina Faso has been granted to researchers to conduct research on the topics of COVID-19 and infectious diseases. This constitutes a very good opportunity to promote a new dynamic and perspective for research in the country. In addition, there is today an improvement at the national level in the fight against cancer through the intensification of prevention activities and improvement of the technical platform through the construction of cancer and radiotherapy centers. Despite COVID-19 and insecurity staying the major problems, this dynamic remains. And the boost given to research in this context of the coronavirus pandemic will undoubtedly benefit cancer research.

The objective of our reflection in this chapter is to make concrete proposals on the contribution of genomics in the fight against cancers, especially cervical cancer caused by the human papillomavirus (HPV) in the context of African countries such as Burkina Faso.

The part attributable to infections in the occurrence of cancer in resource-limited countries such as Burkina Faso is around 26%, compared to 7% in developed countries. Among these infections are the human papillomavirus (HPV) and hepatitis B virus (HBV). The fight against infectious diseases would therefore constitute an important element in the cancer control strategy in African countries.

This chapter will focus on three points: a brief overview of the contribution of genomics in infectious diseases in general and HPV in particular, a review of human papillomavirus and associated cancers in Africa, and finally, a study of the contribution of genomics in the fight against papillomavirus and cervical cancer in Africa, and in Burkina Faso in particular.

2. Contribution of genomics in the fight against papillomaviridae and related cancers

2.1 Contribution of genomics in the fight against infectious diseases

Since the rediscovery of Mendel's work in 1900, the progress of science has been considerable. The discovery of DNA as a carrier of genetic information, the discovery of RNA, as well as the elucidation of the molecular mechanisms of replication, transcription, and the cell cycle, all of this combined with the rapid development of techniques of molecular biology have deeply opened the fields of application of the biological sciences. All these potentials have led researchers to move very quickly from "classical" genetics to genomics. Genomics, which appeared in the 1990s, was born out of a change in the scale of molecular genetics, from studying a single gene or a small fraction of the genome to studying the genome as a whole. Its objective is to understand the functioning of living organisms in all their complexity. An anonymous source said: "If creating human beings is only about aligning sequences of nucleotides, we geneticists would be able to create humans. Fortunately, there is the notion of epigenetics that must be taken into account. And it forces us to recognize how perfect a human is. "New scientific discipline at the crossroads of biology, new analytical techniques, robotics, computer science, and genomics requires us to take epigenetics into account in understanding the mechanisms of infectious and noninfectious diseases. Genomics has opened up new therapeutic possibilities for the treatment of certain diseases: knowledge of genes predisposing to major pathologies makes it possible to provide very specific treatments in addition to increasingly sensitive screening tests at a lower cost. Likewise, the identification of the genes responsible for various diseases offers researchers the possibility of determining the exact targets on which the drugs should act. In recent years, advances in genomics have transformed the therapeutic research and strategy of most of the major pharmaceutical groups. 'recombinant' drugs can be more effective and their development faster, and therefore it could be less expensive.

People are often exposed to viruses, bacteria, and parasites. Some of these microorganisms are sources of infection, epidemics, and even pandemics. During the previous centuries, these infectious diseases have negatively impacted the life expectancy of the population in the long term. With the discovery of microorganisms by Louis Pasteur, humans seemed to have learned to "control" infectious diseases through the enhancement of personal and public hygiene, and access to vaccines and antibiotics. Unfortunately, over the past few decades, we have seen more and more so-called "emerging or reemerging" infectious diseases. In developing countries, infectious diseases were responsible for 6 of 10 deaths between 2000 and 2019. This is in contrast to the rest of the world where it is noncommunicable diseases that cause the most health challenges. The World Health Organization estimates that nearly a quarter of deaths worldwide or nearly thirteen million persons die per year, and this is still directly linked to infectious diseases. This shows how infectious diseases remain a major public health problem in Africa. The fight against infectious diseases requires the establishment of an effective awareness and prevention strategy, reliable diagnostic tools, and a rapid response. Already, after the publication of the results of the sequencing of the whole human genome, the WHO report entitled "Genomics and World Health" indicated that a better knowledge of the genomics of pathogens and their vectors would greatly contribute to the fight against these infections [3].

Prevention of infectious diseases: Since it was understood that infectious diseases were caused by microorganisms, it became evident that to guard against

these pathologies, it was necessary to combine a healthy lifestyle and vaccination. Hygiene also involves the implementation of barrier measures and to develop these measures, it is necessary to have a good knowledge of the germ, its mode of transmission, its target in the body, and also its mode of multiplication. Providing an effective vaccine also requires a very good knowledge of the germ and its genetic material. Since the advent of sequencing and bioinformatics, much information on the genetics of microorganisms is now available in international databases and accessible to all. Likewise, nowadays, the development of sequencing tools gives researchers the ability to sequence any genome in few hours, analyze the sequencing data, and even make comparisons and classify organisms. More and more studies show that human genetic factors play a major role in susceptibility to infections. We notice, for example, that different populations, confronted with the same germ, react differently to infection. Genomic studies take into account factors related to the germ, the host, and the environment in understanding the dynamics of disease occurrence following microbial infection.

Diagnosis of infectious diseases: A good diagnosis, made early, can reduce the transmission of a disease. For a long time, the diagnosis of a disease depended on knowing the clinical signs and symptoms presented by the patient. It was quickly realized that different diseases could have almost the same symptoms; moreover, between contact with the germ and the onset of the first symptoms, a person can infect many other people. It, therefore, became evident that diagnostic tests were needed to confirm the presence of the germ as early as possible. Hence, the emergence of indirect diagnostic tests and later direct diagnostic tests, which target the pathogenic organism. But setting up these tests required very advanced knowledge of the microorganism. It, therefore, required more time for the provision of these tests. With the appearance of new molecular biology technologies and the genomic knowledge of germs, it is becoming easier and faster to make a diagnostic test accessible to populations.

The response to infectious diseases: A rapid response to a disease requires a synergy of action involving several skills at the same time. The response is different depending on whether you are dealing with a new disease or an “old disease.” The example of the COVID-19 pandemic shows us how genomics can revolutionize the management of infectious diseases. The accumulated knowledge, as well as the pooling of skills and the availability of ultra-modern technologies, have enabled the world to have diagnostic tests only a few weeks after the appearance of the virus and a vaccine less than a year later. At the same time, this made it possible to develop response mechanisms on a global and continental level against the virus. Knowledge of the molecular mechanisms of resistance of pathogens to drugs would certainly help save lives by making it possible to precisely prescribe the most effective drug to treat a specific disease. This is called pharmacogenomics. According to the European Agency for the Evaluation of Medicinal Products, pharmacogenomics can be defined as the study of the variability in the expression of different genes in relation to the response to drugs, whether this expression is assessed at the cell, tissue, individual, or population level [4]. It is a science that allows the identification of genomic expression profiles involved in the therapeutic response, whether in the expression of drug efficacy or toxicity. Genomics also allows the monitoring of different pathogen variants. Currently, the technological capacity in terms of genomics facilitates the traceability of the variants of SARS-COV2 and anticipates the availability of vaccines and also the transmission of the virus throughout the world.

In addition to infectious diseases being a major concern in terms of mortality in developing countries, some of them are also a source of cancer, such as HPV, the subject of our study.

2.2 Human papillomavirus and associated cancers in Africa

HPVs are DNA viruses, belonging to the papillomaviridae family. HPV transmission occurs primarily through direct skin-to-skin or mucous-to-mucous membrane contact, indirectly through contaminated objects or from mother to child. Sexual transmission is the most common mode. This virus is responsible for cancer of the cervix and also for other types of cancers, such as of the penis, anus, ear, nose, throat, etc.

2.2.1 HPV and cervical cancer

HPVs are further subdivided into high-risk and low-risk oncogenic types. High-risk HPVs cause high-grade lesions and invasive cervical cancers. In the mucous membranes, the onset of a high-grade lesion or cancer is usually preceded by the appearance of a low-grade lesion. If the persistence of infection by an HPV is an essential factor in the progression to cancer, infection with a high-risk HPV and the existence of cofactors linked to the field is a fundamental phenomenon in the genesis of related cancers to these viruses. The determinants of persistence are both viral and linked to environmental factors such as immune response, genetics, and carcinogens. In the cervix, the vast majority of HPV is eliminated spontaneously in 18 months on average. Cohort studies show that only 10% of genital mucosal HPV infections progress to a high-grade lesion and cancer, between 10 and 20 years. However, in some cases, the period of progression from mild dysplasia to high-grade lesion may be short, one to two years, and some lesions may turn out to be high-grade straight away, progressing very quickly to cancer [5]. The contribution of HPVs in cervical cancer depends on the genotypes of the virus. HPV16 and 18 contribute to more than 70% of all cases of cervical cancer, between 41% and 67% for high-grade cervical lesions and 16 to 32% for low-grade cervical lesions [6]. This is due to their higher carcinogenic capacity than other HPV genotypes [7]. The other six most commonly detected HPV genotypes in the world after HPV16 and 18 were HPV31, 33, 35, 45, 52, and 58 [8]. They are thought to be responsible for an additional 20% of cervical cancers worldwide [6]. However, this global distribution could vary from region to region or from study to study (study type and population). In Burkina Faso, the prevalence of HPV was estimated at 58.33% and 59.6% in two populations of HIV-positive women, with HPV50'S, HPV18, and HPV30'S as the most prevalent [9, 10]. In women with normal cytology in general populations who attended gynecological services, the prevalence of HPV infection in studies carried out in Burkina Faso was 40.4%, 25.3%, and 34.1% [11–13]. These prevalences were also variable according to the locality. In high-grade lesions and cancer cases, the prevalence was 48.8% and 72.31%, respectively [14, 15].

Cervical cancer is the most common cancer in women worldwide in 45 countries and kills more women than all other forms of cancer in 55 countries. These countries include many countries of Sub-Saharan Africa, Asia (especially India), and some countries of Central and South America. Cervical cancer accounts for over 80% of cancers attributable to HPV infection [16]. The number of cervical cancer cases worldwide is 569,847 with 311,365 deaths. It is the 3rd leading cause of death in the world, and the 2nd most common cause of cancer and death in women aged 15 to 44 [17]. In Africa, where cervical cancer is the second leading cause of cancer in women after breast cancer, 119,284 cases are diagnosed each year. It is also the leading cause of cancer death (81,687 deaths) in Africa according to 2018 estimates [6]. Among women aged 15 to 44, cervical cancer is the most common cause of cancer death (2nd rank) [6], West and East Africa are the most affected. Each year

in West Africa, there are approximately 31,955 cases of cervical cancer with 23,529 deaths. And specifically, depending on the country, the estimates are 783 cases and 652 deaths in Benin; 2517 cases and 2081 deaths in Burkina Faso (a leading cause of cancer); 1789 cases and 1448 in Côte d'Ivoire; 2206 cases and 1704 deaths in Mali (a leading cause of cancer); 543 cases and 476 deaths in Niger; 568 cases and 414 deaths in Togo [6, 18, 19].

2.2.2 Anal cancer and HPV in Africa

Similar to cervical cancer, anal cancer is associated with HPV infection in approximately 88% of cases worldwide [17, 20]. It is frequently detected in both sexes and there are differences based on sexual orientation. The prevalence of HPV in anal infections is thought to be higher in male homosexuals and HIV-positive men. In women, a decrease in the prevalence of HPV with age has been observed, unlike that of heterosexual men [21–23]. According to a meta-analysis, the prevalence of anal HPV in homosexuals (men who have sex with men) is double that of women (58.8% against 30.7%); and the prevalence of the latter is thought to be double that of men who have sex with women (14.2%) [24]. According to HPV genotypes, HPV16 is the most common genotype (73% of all HPV positive tumors) followed by HPV18 (approximately 5% of cases). In precancerous anal lesions (AIN), HPV DNA is detected in 91.5% of AIN1 cases and 93.9% of AIN2/3 cases [17, 25]. Worldwide, the different prevalence of HPV in anal infections is 80.8% in Asia, 87.6% in Europe, 95.8% in the USA, 61.9% in West Africa [26], 97.1% in Australia [27], 100% in Germany [28], and 95.4% in Ukraine [29]. We lack data in Burkina Faso on anal cancer. However, a retrospective and cross-sectional study which involved patients seen during lower gastrointestinal endoscopy from the period between 09/29/1999 and 10/04/2008 in a hospital setting in Ouagadougou showed that anorectal malignancies (6, 9%) were in fourth place after hemorrhoidal disease (45.6%), anitis (21.1%), and fissures (13.9%) [30].

2.2.3 Vulvar cancer and HPV

HPV is responsible for 43% of vulvar cancer worldwide [20]. Vulvar cancer has two distinct histologic profiles: basaloid wart types more common in young women with an infection of about 86% HPV and keratinizing types, the frequency of which in older women is about 6%. HPV infection is frequently detected among high-grade VIN (VIN2/3) cases (85.3%). HPV16 was the most common type detected, followed by HPV33 [25]. HPV infections were detected in 70.8% of vulvar cancer cases in Africa, 28.7% in Asia [31], 90.0% in Australia [32], 50.0%, in the USA, and 19.3% in Europe [31].

2.2.4 Vaginal cancer and HPV

Cancer of the vagina in women may present with a history of other anogenital cancers, such as cervical cancer, which are frequently and simultaneously diagnosed. Invasive vaginal carcinomas where DNA of HPV was detected in 70% of cases and high-grade vaginal neoplasia (VaIN2/3) in 91% of cases. HPV16 was the most common type in high-grade vaginal neoplasia and is detected in at least 70% of HPV-positive carcinomas [17, 20, 25]. Several studies and meta-analyses allow some estimation of the prevalence in some regions of the world: 68.4% of HPV infection was observed in vaginal carcinomas in Africa, 71.1% in Europe, 78.0% in America, 97.6% in VaIN2 / 3 in Europe, and 92.5% in VaIN2/3 in America, still with a predominance of HPV16 [33].

2.2.5 Penile cancer and HPV

A prevalence of 50% of HPV DNA has been detected in penile cancers [12]. HPV16 was the most common type, followed by HPV18 and HPV types 6/11 [34]. A large majority of invasive penile cancers (over 95%) is squamous cell carcinomas (SCC). Keratinization (49%), mixed wart-basaloids (17%), verrucas (8%), and basaloids (4%) are the most common histological subtypes of penile SCC. HPV is commonly detected in basaloid and verrucous tumors, but it is less common in keratinizing and verrucous tumors. Still, with a higher prevalence of the HPV16 type, the prevalence of HPV was detected in 36.8% and 87.5% of penile cancer cases in Africa [35, 36], 13.4% in Asia, 32.2% in Europe, 36.5% in Latin America and the Caribbean, 18.8% in the USA [35], and 63.2% in Brazil [37]. In the cases of PeIN2/3, the prevalence of HPV was 18.8% in the USA and 89.1% in Europe [35].

2.2.6 Oropharyngeal and HPV cancers

The origin of head and neck cancer associated with HPV is an oral HPV infection, which, in the absence of clearance, persists and progresses to a neoplastic lesion. About 25.6% of all oropharyngeal cancers is attributable to HPV infection, with HPV16 the most common type [20]. In Africa, specifically in Burkina Faso, a prevalence of 54.84% of HPV6/11 infection has been attributed to laryngeal papillomatosis, 15.4% and 25% of high-risk HPV infections (HR-HPV) to cancers of mucous cells of the throat and nose, respectively [38, 39]. Worldwide, HPV infection ranges from 22.4% (19.9–25.0) for the oropharynx, 4.4% (3.3–4.8) for the oral cavity, to 3.5% (2.4–4.8) for the larynx, with a dominance of HPV16 [40]. Two meta-analyses of healthy individuals reported an oral HPV prevalence of 4.5% (3.9–5.1) and 7.5% (6.7–8.4) [41, 42]. In the United States, an oral HPV prevalence of 6.9% (5.7–8.3) was observed, with a significant difference between 10.1% males and 3.6% females [43].

In the rest of our study, we will mainly address the case of cervical cancer, which is the cancer with the highest incidence in Africa. Over the past 30 years, the incidence and death rate of cervical cancer has declined in countries where socioeconomic levels have improved. These decreases are largely the result of the implementation of secondary prevention measures, which include effective screening, early diagnosis, and treatment of precancerous lesions. Because of this situation, the contribution of genomics in the fight against HPV infections and cervical cancer could be an alternative for developing countries such as Burkina Faso. This strategy will undoubtedly save a lot of time and use less economic resources in this struggle.

2.3 Contribution of genomics in the fight against papillomavirus and cervical cancer in Africa

The fight against cervical cancer includes three main components: primary prevention, which consists of the elimination of HPV through sensitization, socio-behavioral change, communication, and importantly vaccination; secondary prevention consists mainly of screening to detect and treat precancerous lesions; and tertiary prevention, which consists of management of cervical cancer and palliative care. Tertiary prevention requires intensive therapeutic approaches, which still produces poor outcomes, especially in our countries with limited resources. WHO, therefore, recommends focusing control strategies on primary and secondary preventions. Most of the time, a high-risk oncogenic HPV infection progresses 10 to 20 years before cancer develops. This implies that if the tools for diagnostic

strategies are put in place effectively, there would be a great chance of preventing the development of cancerous lesions. WHO recommends the use of molecular tests in combination with other techniques such as visual inspection with acetic acid or Lugol solution, cervico-vaginal smear, etc. Several screening strategies are recommended by the WHO for developing countries: the “screen-and-treat” strategy that consists of applying visual tests (IVA /IVL) and treating women who test positive without going through a viral detection diagnostic test; the “see-and-treat” strategy that consists of offering women who are screen positive by visual methods, a colposcopy examination before treatment. The diagnosis of the virus requires the use of molecular biology techniques such as the polymerase chain reaction (PCR), DNA/RNA hybridization, etc. Until fairly recent times, many people would have been said that the developing countries of the African continent are unable to utilize these molecular biology techniques nationwide. However, since the advent of COVID-19, developing countries have reorganized their testing laboratories to include PCR testing. Availability of equipment and skills should no longer be an obstacle for molecular HPV testing, but the issue of the cost of consumables and reagents remains. We will address this case in our specific analysis in Burkina Faso.

Another strategy for the use of genomics in the fight against HPV is the provision of effective vaccines at lower costs for the majority of the population. In the context of HPV, two vaccines are already available. They are: Cervarix®, which protects against HPV16 and 18, and Gardasil 9®, which protects against HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58. However, these vaccines are not yet subsidized in all African countries and they do not cover all the high-risk genotypes encountered in these countries such as HPV56, 66, 59, 39, 51, 35, 68, and 45. However, some studies show that these genotypes are part of the “Top 5” of the most common HPVs. In addition to testing for the virus, African countries would benefit from testing for HPV genotypes circulating in cancer cases. This will allow them to make a wise choice in terms of the vaccine available and also to invest strategically in the design of a specific and more effective vaccine for their population. It should also be noted that genomics will accelerate the implementation of this vaccine development. It is increasingly becoming clear that HPV, like other viruses, does not always cause disease to develop in an infected person. The influence of genetic factors of the host on the susceptibility or resistance to this infection is suspected. It would, therefore, be very interesting to understand these mechanisms of susceptibility/resistance. This will help to protect vulnerable people and elucidate possible treatment pathways against HPV and associated cancers. Likewise, some low-grade lesions spontaneously progress to clearing while others progress to cancer. In addition to viral and environmental factors, genetic and epigenetic factors of the human host are also suspected. An investigation of these mechanisms could lead to the establishment of markers for monitoring or early diagnosis of cancer. HPV sequencing would also be an asset for identifying new viral variants, for molecular epidemiological surveillance of the virus, and for understanding the biology of the pathogen. A better knowledge of the biology of the virus will also allow a good understanding of the mechanisms of carcinogenesis.

Cancer is known to be a genetic disease, for it induces mutations in the genome or epigenome level. It is also known that people with the same type of cancer can have different mutations. And these mutations can influence a person's treatment. It is, therefore, evident that without the contribution of genomics, the analysis which enables these mutations to be identified, at some point clinicians are forced to treat patients “blind.” If it is later found that the treatment is not working, it will need to be changed. And during this time, the disease physically, psychologically, and economically has a negative impact on the person. Therefore, for low-income countries, it would be more strategic to encourage pharmacogenomics, as this will reduce

costs and also improve patient survival rate, especially, since there is undoubtedly a delay in diagnosis of cancers. These delays are most often due to a lack of money, inaccessibility to medical specialists, and the refusal to accept the disease. Thus, a genomic study of cancer cells will make it possible to offer adapted and personalized therapeutic protocols to people already suffering from cancer due to HPV.

2.4 Specific case of Burkina Faso

Burkina Faso is a landlocked country and, therefore, constitutes a crossroads for the populations of certain West African countries. This position is advantageous from an economic point of view, but from a health point of view, it can be a way for rapid transmission of infectious diseases. According to estimates from the West African Economic and Monetary Union (WAEMU), 2 out of 5 people (41.4%) lived in poverty in 2018. The country was victim of several terrorist attacks, which claimed the lives of several thousands of people and caused the internal displacement of more than one million people. In addition to this insecure situation, we have the COVID-19 pandemic and its health and economic consequences. This situation of insecurity prompted the government to initiate capacity building for the defense forces in order to provide an effective response to the security issue. This puts pressure on public finances with a budget deficit of nearly 5% of GDP in 2018 against 7.5% in 2017.

In terms of health, the Burkinabè live longer now than in previous decades. Life expectancy at birth has increased from 53.8 years in 1996 to 60.4 years in 2016. This is mainly attributed to the improvement of living conditions, better access to health services, reduction of diseases preventable by vaccination, and better management and treatment of malaria and infectious diseases such as pneumonia, tuberculosis, and HIV/AIDS.

Burkina Faso has a Ministry of Health, Public Hygiene and Well-being and a Ministry of Higher Education, Research and Innovation for the implementation of its policies in health and research. We will develop below, the organization of these two ministries.

2.4.1 Organization of the health system

Burkina Faso's national health system includes the public subsector, the private subsector, and the traditional medicine/pharmacopeia. The leadership of the Ministry of Health (MoH) is reflected in the adoption of policies and standards, the adoption of laws and other conventions relating to health, the increase in resources for health through the development of the partnership, implementation of the common basket, and better structural and functional organization. The organization of the health system takes into account the organization of administrative services and the organization of care services. Administratively, Burkina's health system comprises three levels, namely the central, intermediate, and peripheral levels: the central level is made up of central structures organized around the cabinet of the Minister and the General Secretariat; the intermediate level includes 13 regional health directorates; the peripheral level is made up of 70 health districts. The health district is the operational unit of the national health system. The provision of care is provided by public and private structures. Public health care structures are organized into three levels which provide primary, secondary, and tertiary care. The first level has medical centers (CM): 71, health and social promotion centers (CSPS): 2041, isolated dispensaries and maternities: 120, infirmary: 187. The second level of care is the medical center with a surgical unit (CMA): 46. It is the reference center for health facilities at the first level of the district. The second level of care

is represented by the regional hospital center (CHR) which serves as a reference for the CMAs. There are a total of nine (09) CHR in the country. The third level consists of the university hospital center, numbering six (06) in 2020. These structures constitute the highest reference level. In addition to these structures, there are pharmacopeia, traditional medicine, and community-based health which also contribute to the provision of health services to the population. The population/health center ratio makes it possible to assess the country's health coverage. It is estimated at 9662 inhabitants for 01 CSPA in 2019 and efforts still need to be made to bring the country closer to the standard defined by WHO which recommends 01 CSPA for 5000 inhabitants. The number of nurses in public health facilities in 2019 was 8613, i.e., a ratio of 41 nurses per 100,000 inhabitants, which is higher than the WHO standard which recommends 2 nurses per 10,000 inhabitants. Malaria remains the main reason for consultation and hospitalization, and the leading cause of death in health facilities. In 2018, deaths attributed to malaria were 16.4%. Overall, the Burkinabé health system still faces enduring bottlenecks including geographic and financial accessibility, low availability of drugs and trained personnel, quality of care, and socio-cultural acceptability.

The National Institute of Health is a public health establishment created by decree No. 2018-0618/ PRES/PM/MINEFID/MS/MESRI of 06/18/2018, which depends on the Ministry of Health. It is made up of 6 technical departments namely: the Direction of the MURAZ Center (CM), the Direction of the National Center for Research and Training on Malaria (CNRFP), the Direction of the Nouna Health Research Center (CRSN), the Direction of the Health Emergency Response Operations Center (CORUS), the Directorate of the National Population Health Observatory (ONSP), and the Directorate of the Central Reference Laboratory (LCR). Both public and private medical biology laboratories are organized into a network and coordinated by the laboratory management. The network architecture is as follows: the national reference laboratories (NRLs) which report directly to the LCR; national-level laboratories (located in the CHU and research centers); intermediate or regional level laboratories (located in CHR), and peripheral level laboratories (located in CM/CMA). Each laboratory level has clear texts that specify its organization and missions, so that all laboratory activities are well coordinated.

The part of the national budget allocated to health was relatively stable between 2015 and 2016, standing at 12.15% and 12.4%, respectively. Nevertheless, we note a downward trend in 2017 and 2018, i.e., 11.89% and 10.70%, respectively, probably attributable to the security situation. The country adopted Law N° 060-2015/CNT establishing a single and compulsory universal health insurance scheme (RAMU) as part of the strengthening of inclusiveness, solidarity, and social protection. The establishment of this insurance scheme will improve the well-being of the population and help to considerably reduce the direct health costs in the household budget. Funding for health research is an area that will need to be strengthened because it is practically nonexistent.

2.4.2 Research organization

As a member country of the West African Economic and Monetary Union (WAEMU), Burkina Faso had 20.5 million inhabitants, of which 51.7% were women in 2019 according to the preliminary results of the RGPH 2019. The average annual rate of population growth remained at 2.9%. Those under 20 years represented 55.8% of the total population. The urbanization rate was 26.3%. This urbanization is concentrated between the cities of Ouagadougou (administrative capital) and Bobo-Dioulasso (economic capital), which alone absorbs 62.1% of the urban population. In 2019, Burkina Faso was ranked 182nd out of 189 countries with an HDI of

0.452 according to the 2020 UNDP Sustainable Human Development Report. This index improved from the previous year when it was 0.434. The value of the HDI in 2019 places Burkina Faso in sixth place in the WAEMU area.

From a structural point of view, research activities are mainly carried out in public and private research centers, public universities, and public hospitals. In 2019, the total number of research facilities was 45, including 15 research centers, 9 research institutes, 8 research stations, and 13 universities. All the structures have 2272 researchers and teacher-researchers, 17.1% of whom are women. The private and international sectors only account for 2.9% and 2.5% of researchers. In a population of 1,000,000 inhabitants, the number of researchers is 111. In terms of funding, 151 research projects/agreements were registered in 2019 for a total funding of 13,636,364 US dollars. The part of the national budget allocated to research represents 0.9% of all the budget and 24.3% of that of the Ministry of Higher Education, Scientific Research and Innovation (MESRSI). The contributory share of external research aid was 85.4% and that of the state 7.8%. In 2019, expenditure other than projects/programs of research structures amounted to 16,138,182 US dollars. Salary costs represented 36.8%, functionary costs 50.9%, spending on investments represented 7.7%. The budget devoted to expenditure other than projects and programs of research structures represented 33.6% and the contribution of external partners 24.7%. The expenditure on own resources is the highest and represented 41.7%. The research sector is one of the 14 planning sectors of the National Economic and Social Development Plan (PNDES). Thus, to boost this sector and improve scientific output, the government has instituted, among other things, the prize for excellence in scientific research, the International Symposium on Science and Technology (SIST). Also, to provide a secure framework for funding research and innovation activities, the government has in recent years increased the budget of the National Fund for Research and Innovation for Development (FONRID). Most of the specific research infrastructures, listed in 2019, belonged to public structures. Indeed, the public owns 78.3% of the infrastructures against 12.0% for the private sector. In 2019, all the researchers and teacher-researchers produced 1787 publications. Publications by public research structures represent 85.5%. Private and international structures respectively account for 5.4% and 9.1% of published research results. The average number of publications per researcher ratio in 2019 is less than one publication per researcher (0.8). The highest ratio is recorded in international organizations where it is nearly three publications per researcher. Scientific articles (34.4%), technical reports (29.5%), and scientific communications (13.3%) are the most common scientific publications.

Overall, it appears that research is very poorly funded in Burkina Faso. Most of the research activities done are carried out with external capital. This calls into question the country's sovereignty in the field of research. However, an effort is being made in the area of valorization of research results. This effort remains very insufficient, especially in universities where there are very few documents of vulgarization and technical reports compared to research centers and institutes.

We were unable to obtain sufficient data on the part of health research funding in the national budget or external funding. But nevertheless, given the meager part of research funding in general, we can assume that health research funding remains very low.

2.5 Possible strategy

At this point, we will make concrete proposals for Burkina Faso, and therefore, for the other countries of Sub-Saharan Africa which have similar problematic management mechanisms in terms of health and research. For efficiency in the

implementation of contribution strategies of genomics in the fight against cervical cancer induced by papillomaviruses, we will address aspects of governance, capitalization of existing structures, human resources, and equipment.

2.5.1 The governance

The fight against HPV and associated cancers will not happen without a political commitment as strong as that seen for the fight against COVID-19. One of the great strengths of the Burkina Faso Ministry of Health is that it is very well organized. And this is due to the gains made over the decades. However, in this fight against HPV and associated cancers, it will absolutely be necessary for this ministry to work in close collaboration with the Ministry of Higher Education, Research and Innovation because most of the human skills and equipment of genomics are located in research centers which work under this ministry. There is, therefore, a need for a synergy of inter-ministerial action. Let us not forget either the Ministry of Finance which is the “portfolio” of the government and therefore responsible for financing all the activities that will be initiated by the other two ministries. We propose that the government create a “cell” under the first ministry. This cell could be called “medicine and genomics” for example. It should be constituted from clinicians, researchers, and academic-researchers working in the field of genomics or teaching-hospital-university teachers, bio-ethicists (to take ethical aspects into account in decisions), and sociologists (for taking sociological aspects into account in decisions). The first ministry will then have to work to make available organizational and functional texts of this “cell” and to allocate the necessary resources to achieve its objectives. This unit should also be able to mobilize external resources to finance its activities.

2.5.2 Capitalization of healthcare and research structures and equipment

Several research structures are currently working in the field of health. These structures work under the Ministry of Health or the Ministry of Research. In addition, the structuring of the Ministry of Health has made it possible to set up national reference laboratories. Among these NRLs is the National Reference Laboratory for HPV (LNR-HPV) hosted by the Pietro Annigoni Biomolecular Research Center (CERBA). This structure could be the technical arm of the “medicine and genomics cell” in the implementation of its activities, particularly dedicated to HPV and associated cancers. CERBA also has an efficient technical platform for genotyping, sequencing, and anticancer tests in vitro. Likewise, certain structures such as the Muraz Center, the plant virology and biotechnology laboratory of the Institute for the Environment and Agricultural Research, etc., also have state-of-the-art equipment which can contribute to the fight against these diseases. Knowing that these structures have more or less developed cooperative relations, but in a sometimes informal way, it will just be necessary to strengthen and formalize the partnerships in order to make them more fruitful. Certain structures such as the IRSS and the Laboratory of Animal Physiology at Joseph KI-ZERBO University will be able to make an excellent contribution to clinical trials. The laboratories of the department of pharmacy of Joseph KI-ZERBO University and the IRSS would contribute to the pharmacology, toxicology part. Results of a study carried out by CERBA’s team have shown that essential oils of *Cymbopogon nardus*, a medicinal plant from Burkina Faso, have quite interesting properties on cervical cancer cells in culture [44].

The cell will therefore have to create diversified partnership agreements with several national structures for carrying out genomic analysis and also for the

research activities necessary to understand the mechanisms of infection and carcinogenesis. It should also be noted that this kind of partnership network could be used for any pathology other than HPV and cervical cancer.

Referral hospitals will be encouraged to set up patient cohorts for better organization of clinical and research activities. And also for better patient follow-up like has been done with HIV.

2.5.3 Capitalization of human resources

Burkina Faso has skilled human resource in the field of molecular biology, genetics, and biotechnology. Unfortunately, these human resources are not sufficient to effectively implement a large national program in genomics and medicine. However, the country could approach Burkinabès living outside even part-time. Some countries such as China and India have experimented with this approach and it has enabled them to boost research and also to draw on the skills of their compatriots living and working in developed countries.

3. Conclusions

HPVs and their associated cancers constitute a public health problem in our African countries. This is a shame since it is a preventable cancer if screening is done systematically and also on time. Burkina Faso, like many other countries in Sub-Saharan Africa, has many health and security challenges to overcome. These countries have very few financial resources and they would benefit from focusing on new sciences such as molecular biology, biotechnology, bioinformatics, and genomics. This will allow them to make a considerable leap in the fight against infectious diseases and also against cancer. Very often, there are competent human resources in these countries, advanced equipment too, but due to a lack of optimal coordination, this is not valorized. We suggest in this analysis, a pooling of skills and equipment already available and above all a common organization of research and health with a unique vision driven by political leaders. It would be a shame if African countries failed to enter the field of genomics as they did in other fields.

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