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Review

Virus-associated human cancers in Moroccan population: From epidemiology to prospective research

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ABSTRACT

Eight human viruses have been classified by the International Agency for Research on Cancer as carcinogenic or probably carcinogenic for humans. Infection with high risk human papillomaviruses, hepatitis B and C viruses, Epstein-Barr virus (EBV), human T-Cell Lymphotropic Virus Type 1 (HTLV-1), Human herpesvirus 8 (HHV-8), Merkel cell polyomavirus and human immunodeficiency virus-1 (HIV1) alone or in combination with other agents are the main etiologic factors of many cancers. This review highlights some aspects of virus-associated human cancers, potentially responsible for > 14,000 malignancies per year in Morocco. Given that not all individuals infected with these viruses develop cancer, somatic alterations, genetic predisposition, and lifestyle or environmental factors obviously play potentializing roles modulating viral activity. These viral, host genetic signatures and lifestyle interactions may represent a reservoir of biomarkers for early detection, prevention of cancer and rationale-based therapy.

1. Introduction

Human cancer is a global health burden worldwide. According to the GLOBOCAN 2018, 18.1 million new cases (17.0 million excluding non-melanoma skin cancer) and 9.6 million cancer deaths (9.5 million excluding non-melanoma skin cancer) are expected to occur this year (Bray et al., 2018). Approximately 15% of human cancers *ie* 1.3 million new cases are attributable to tumorigenic viral infections (Plummer et al., 2016). Viral infection is one of the main drivers of cancer development but is generally considered as not sufficient for carcinogenesis. Additional co-factors including environmental/lifestyle agents, and features depending on host genetic architecture such as immune response, chronic inflammation, and metabolism also play an important role in the cell transformation process (Grivennikov et al., 2010; McLaughlin-Drubin and Munger, 2008). In persistently infected cells, direct and indirect effectors including viral proteins and immune system response disrupt cell homeostasis and drive cell proliferation to cancer development (Moore and Chang, 2017). Currently, eight human viruses have been classified by the International Agency for Research on Cancer (IARC) as “carcinogenic to humans” (Group 1) based on sufficient evidence supporting their etiologic association with human cancer: hepatitis B virus (HBV), hepatitis C virus (HCV), Human papillomavirus (HPV) with 12 oncogenic types, Epstein Barr virus (EBV), human T-cell lymphotropic virus type 1 (HTLV-1), Kaposi's sarcoma-

Abbreviations: HBV, Hepatitis B virus; HCV, hepatitis C virus; HPV, Human papillomavirus; EBV, Epstein Barr virus; HTLV-1, human T-cell lymphotropic virus type 1; KSHV, Kaposi's sarcoma-associated herpesvirus; HHV-8, human herpesvirus 8; MCV, Merkel cell polyomavirus; HIV1, Human immunodeficiency virus-1; IARC, International Agency for Research on Cancer; CC, Cervical cancer; HR-HPV, High-risk HPV; HCC, Hepatocellular cancer; HDV, Hepatitis Delta virus; NHL, non-Hodgkin lymphomas; BL, Burkitt lymphoma; NPC, Nasopharyngeal carcinoma; AIDS, acquired immunodeficiency syndrome; ATL, adult T-cell leukemia; MCC, Merkel cell carcinoma

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Table 1
Viruses associated with human cancers.

Virus	Family	Genome	Cancer types	Mechanism	References
Hepatitis B virus	*Hepadnaviridae*	DNA	Hepatocellular carcinoma, Non-Hodgkin Lymphoma	Chronic inflammation	(Ganem and Prince, 2004; Huang et al., 2017)
Hepatitis C virus	*Flaviviridae*	RNA	Hepatocellular carcinoma, Non-Hodgkin Lymphoma	Chronic inflammation	(Matsuzaki et al., 2007; Aghemo and Colombo, 2013; Gill et al., 2016)
Human papillomavirus	*Papillomaviridae*	DNA	Cervical cancer, Anal cancer, Penis cancer, Head and neck carcinoma	Oncogenic	(Burd, 2003; Crosbie et al., 2013; de Martel et al., 2017)
Epstein Barr virus	*Herpesviridae*	DNA	Burkit's lymphoma, Hodgkin's lymphoma, Nosopharyngal carcinoma	Oncogenic	(Crombie and LaCasce, 2019; Elgui de Oliveira et al., 2016)
Kaposi's sarcoma-associated herpesvirus	*Herpesviridae*	DNA	Kaposi's sarcoma	Oncogenic	(Cesarman et al., 2019; Gramolelli and Schulz, 2015)
Human T-cell lymphotropic virus type 1	*Retroviridae*	RNA	Adult T-cell leukemia	Oncogenic	(Mahieux and Gessain, 2007; Watanabe, 2017)
Merkel cell polyomavirus	*Polyomaviridae*	DNA	Merkel cell carcinoma	Oncogenic	(Liu et al., 2016; DeCaprio, 2017)
Human immunodeficiency virus-1	*Retroviridae*	RNA	Non-Hodgkin Lymphoma, Kaposi Sarcoma, Leukemia, Cervical cancer, Anal cancer, Penis cancer, Liver cancer	Immune suppression	(Goedert et al., 1998; Frisch et al., 2001; Engels et al., 2006)

associated herpesvirus (KSHV, also known as human herpesvirus 8, HHV-8), Merkel cell polyomavirus (MCV), and human immunodeficiency virus-1 (HIV1) (Table 1) (Javier and Butel, 2008).

The pattern of diseases and descriptive epidemiological data of tumor-associated viruses are not well defined in Morocco. We decided, therefore, to review the body of available data so far about the epidemiology of cancer-associated viral infections in Morocco to summarize the current knowledge and suggest some directions both for future research in the field and orientation of Public Health strategy.

2. Methods

We conducted our review in line with Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (Moher et al., 2009). All data were retrieved from relevant online databases (Medline, PubMed, Google Scholar, WHO, EMBASE, GLOBOCAN 2018, and Cancer registry of the Grand Casablanca region) collected until the end of March 2019.

3. The burden of cancers attributable to viral infections in Morocco

Viral infections are an important cause of cancer in Morocco. Out of the 52,783 cancer cases that occurred in Morocco in 2018, 26.6% were potentially linked to infection (Table 2). Thus, we considered the seven viral agents other than HIV and the associated cancer types in this review.

3.1. Papillomavirus and cervical cancer

Worldwide, HPVs are the main aetiological agents for cervical

Table 2
Incidence of virus-associated tumors in Morocco in 2018 according to Globocan 2018.

Tissue	Agent	Class	n	Crude rate	ASR	References
Non-Hodgkin Lymphoma, Leukemia	EBV	I	3504	9.7	9.4	(Bray et al., 2018)
	HIV1	I				
	HCV	I				
	KSHV	I				
	HTLVI	I				
	HBV	II				
Hodgkin Lymphoma	EBV	I	723	2.0	1.9	(Bray et al., 2018)
Non-melanoma Skin Carcinoma	HIV1	II	686	1.9	2.0	(Bray et al., 2018)
	HPV	II				
	MCV	II				
Kaposi Sarcoma	KSHV	I	83	0.23	0.21	(Bray et al., 2018)
	HIV1	I				
Larynx, Hypopharynx, Oropharynx Carcinomas	HPV	I	1379	3.8	3.6	(Bray et al., 2018)
Carcinoma of the Nasopharynx	EBV	I	844	2.3	2.2	(Bray et al., 2018)
Lip & Oral Cavity Carcinomas	HPV	I	667	1.8	1.7	(Bray et al., 2018)
Gastric Carcinoma	EBV	II	1761	4.9	4.7	
Liver Carcinoma	HBV	I	428	1.2	1.1	(Bray et al., 2018)
	HCV	I				
	HIV1	II				
Cervix Uteri Carcinoma	HPV	I	3388	22.3	22.7	(Bray et al., 2018)
Carcinomas of the Vulva & the Vagina	HPV	I	304	1.65	1.51	(Bray et al., 2018)
	HIV1	II				
Carcinoma of the Anus	HPV	I	289	0.80	0.80	
	HIV1	I				
Carcinoma of the Penis	HPV	I	9	0.05	0.05	(Bray et al., 2018)
	HIV1	II				
Total			14,065	52.6	51.9	

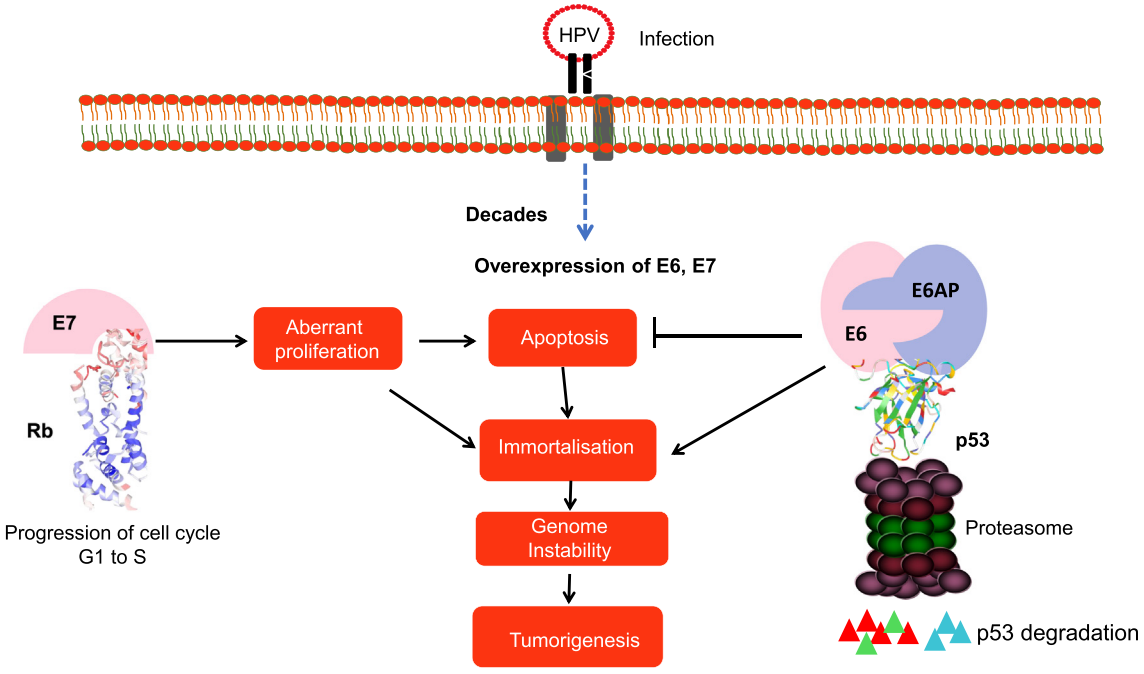

Fig. 1. A schematic diagram of high-risk human papilloma virus E6 and E7 proteins in the development of HPV-associated cancers. E6 stimulates p53 degradation through a cellular ubiquitin ligase E6AP, resulting in the induction of genomic instability and cellular proliferation. E7 inhibited retinoblastoma (Rb) family members and constitutive activation of E2F responsive genes, inducing hyperproliferation.

lesions and the persistence of high-risk HPV infection is closely associated with the development of cervical cancer (Schiffman et al., 2007). HPV is a small, non-enveloped (DNA) virus belonging to the *Papillomaviridae* family that infects skin or mucosal cells. The circular HPV genome is a double-stranded DNA approximately 8 kb in length. It encodes for 6 early proteins responsible for virus replication and 2 late proteins, L1 and L2, which are the viral structural proteins. At least, 13 of > 100 known HPV genotypes can cause cancer of the cervix and are associated with other anogenital cancers as well as head and neck cancers (de Villiers et al., 2004; Feng et al., 2007; Zur Hausen, 2009). Globally, the two most common « high-risk » genotypes (HPV 16 and 18) cause approximately 90% of all cervical cancer (CC) (Fig. 1) (World Health Organization, 2019).

In Morocco, published data showed that CC represents a significant public health concern. In the absence of a national cancer registry, data are limited to the number of cases reported in some medical centers and regional registry. However, according to the cancer registry of the grand Casablanca region, CC is the second most common cancer among Moroccan women after breast cancer (ASR: 14.8 per 100,000) with approximately 1504 new cases (Benider et al., 2016) and 3388 according to GLOBOCAN 2018 in the whole Kingdom (Cancer, 2019). Furthermore, previous reports have found inconsistent prevalence rates of HPV infection from healthy Moroccan women with 15.7% (Alhamany et al., 2010) in Rabat and 42.5–43.1% in Fez region (Bennani et al., 2012; Souho et al., 2016). However, HPV prevalence was much more important, ranging from 62% to 92%, among women with CC (Amrani et al., 2003; Birrou et al., 2015; Chaouki et al., 1998; Khair et al., 2009; Lalaoui et al., 2003; Zouheir et al., 2016). High-risk HPV (HR-HPV) DNA was detected in CC samples with a higher prevalence of HPV16 (≈36–82%) and HPV18 types (≈6–20%) (Amrani et al., 2003; Berraho et al., 2017; Birrou et al., 2015; Chaouki et al., 1998; El Hamdani et al., 2010; Khair et al., 2009; Zouheir et al., 2016). Moreover, sequencing of HPV16 isolates for E6 intra-typic variation showed the predominance of European lineage (E) strains in CC cases. These analyses also revealed that HPV16 variants might play an important role in progression to malignancy (Qmichou et al., 2013). Another study carried out on patients from Fez observed the presence of other HPV genotypes (eg 35, 51, 53, and 56) (Souho et al., 2016). This latter report suggests that a significant geographical heterogeneity of HPV genotypes distribution exists throughout Morocco, an observation that warrants obviously further studies. Interestingly, expressions of EGFR, p16INK4a, and E-cadherin were detected in most CC cases and p16-INK4a protein expression is correlated with HR-HPV status (El Hamdani et al., 2010; Zouheir et al., 2016). In addition, hypermethylation of the 5' CpG island of the p16(INK4a) and E-cadherin genes were found in half of CC samples (Attaleb et al., 2009). Genes commonly affected with somatic mutations in CC (*PIK3CA, KRAS, TP53, STK11, etc…*) have not been explored so far in Morocco.

3.2. Papillomavirus and other cancers

HPV is the major cause of cervical cancer and various types of anogenital cancers. A single survey conducted in Casablanca reported the presence of HPV in a large subset of vulvar lesions (35%). Several cases of squamous cell carcinoma were reported in this occasion but without indicating the prevalence of HPV in the tumors (Zouhair et al., 2002). Amazingly, despite rare case reports mentioning the presence of HPV, there is an almost complete lack of publications about HPV-associated head and neck cancer that concerns potentially > 2000 patients each year in Morocco. The importance taken by this disease (especially carcinoma of the tonsils) in many developed countries represent a warning that should stimulate research on this field in Morocco (El Ghelbazouri et al., 2007). By contrast, tumors for which HPV is not usually considered as bona fide risk factors have been studied in Morocco. A study reports that 52.4% of bladder cancer cases were positive for HPV with the presence of HPV16 in 95.5% of bladder tumor samples pointing out that this virus might play a causative role in bladder cancer (Berrada et al., 2013). Moreover, HPV DNA was found in 34% of nasopharyngeal carcinoma cases normally associated with EBV with 20.8% of cases sheltering HPV31. Finally, a recent study showed that DNA of beta and gamma HPV types was found in 25% of breast tumors but none was one of the high-risk types HPV16 and 18 were found (ElAmrani et al., 2018). Overall, HPV DNA is prevalent in many types of tumors in Morocco, but some of the most important target sites are still

expecting their initial publication.

3.3. Viral hepatitis and hepatocellular carcinoma

Hepatitis B virus (HBV) is a member of the *Hepadnaviridae family* and the *Orthohepadnavirus* genus. HBV is a small DNA virus with a spherical viral DNA genome, double-shelled structure, 40 nm in diameter, consisting of a proteo-lipidic envelope surrounding a capsid (Ezzikouri et al., 2014b; Liang, 2009). HBV is considered as a major global health concern with > 257 million chronic carriers and 887,000 death annually mostly from complications (including cirrhosis and hepatocellular carcinoma) (World Health Organization, 2018a). In the absence of a national seroprevalence survey, previous studies estimate that the prevalence of HBsAg in the Moroccan population ranges between 1.6 and 2% (Ezzikouri et al., 2013b).

Hepatitis virus C, a positive single-stranded RNA agent, belongs to the "*Flaviviridae*" family, and to *Hepacivirus* genus. Globally, an estimated 71 million people suffer from chronic hepatitis C infection (World Health Organization, 2018b). The most affected regions are Eastern Mediterranean and European Regions, with a prevalence of 2.3% and 1.5% respectively (World Health Organization, 2018b). Around 399,000 people die each year from hepatitis C, mostly from cirrhosis and hepatocellular carcinoma (World Health Organization, 2018b). In other regions of the world, prevalence of HCV infection varies from 0.5% to 1.0%. Estimates obtained from modeling suggest that worldwide, in 2015, there were 1.75 million new HCV infections [1]. In Morocco, < 1% of the population is infected by HCV (Ezzikouri et al., 2013c).

Hepatocellular cancer (HCC), the main type of primary liver cancer, is the fourth leading cause of cancer worldwide and approximately 841,080 new cases are diagnosed annually and 781,631 death (Bray et al., 2018). Chronic infection with HBV and HCV, aflatoxin, alcohol intake, and obesity are a major risk factor for HCC (Fig. 2). Furthermore, it remains a tumor of poor prognosis with overall 5-year survival rates that does not exceed 5–8% (Capocaccia et al., 2007). HCC, as other human malignancies, is a multifactorial disease that develops when pro-tumorigenic environmental or lifestyle circumstances meet within a susceptible individual (Balmain et al., 2003). In Morocco, the incidence of liver cancer is around 428 and 411 deaths (Cancer, 2019) with higher incidence in male (0.9% vs 0.6% in female) (Benider et al., 2016). A multicenter study conduct in North African countries showed that viral markers for HBsAg (a marker of chronic hepatitis B infection) and anti-HCV (marker of contact with hepatitis C virus) were found in > 70% of HCC cases (Bahri et al., 2011). In HCC cases of Moroccan patients, anti-HCV was found in 58.5% with the predominance of genotype 1b whereas the HBsAg was found in 12.8% with the dominance of genotype D (Bahri et al., 2011; Brahim et al., 2012; Ezzikouri et al., 2007; Kitab et al., 2011). The importance of Occult hepatitis B virus infection (OBI), characterized by the lack of circulating HBV surface antigen in patients, is considered to be as high as 62.5% in HCV-related Moroccan HCC cases. This substantial prevalence of OBI in Morocco further extends the deleterious impact of HBV persistence in liver malignancies (Kitab et al., 2014).

In Morocco, most studies on HCC susceptibility are conducted on genetic variations occurring in pathways historically considered as instrumental for liver tumorigenesis. Likewise, polymorphisms in genes operating in oxidative stress were also found associated with HCC occurrence in hepatitis C virus-infected patients (Ezzikouri et al., 2010; Ezzikouri et al., 2008). Moreover, variants in transcriptional coactivator and immune reponse genes conferring resistance against HCV have been shown to influence HCC risk in populations whose tumors are characterized by low rates of mutations or chromosome instability (Akil et al., 2012; Ezzikouri et al., 2013a; Fakhir et al., 2018; Pineau et al., 2007). In addition, we may speculate that the current high fat/carbohydrates regimen of Moroccan populations associated with a high rate of consanguinity and some degree of inherited susceptibility may potentialize in the long run the deleterious impact of chronic hepatitis C and increase substantially local HCC incidence. In this context, a recent study showed that a variant in the *adiponutrin/patatin-like phospholipase domain-containing 3* and *SOCS3* were associated with HCC progression in HCV-infected patients (Ezzikouri et al., 2014a; Jadid et al., 2018).

The impact of hepatitis Delta virus (HDV), an obligatory parasite of HBV is considered as rather low in Morocco, a situation at odds with that of the neighboring Mauritania (Lunel-Fabiani et al., 2013; Mansour et al., 2012). Infection with HDV is known to worsen liver pathology and to substantially accelerate liver tumorigenesis. A renewed appraisal of the epidemiological situation, in a context of increased human migrations, appears, thus, as advisable especially for the Southern provinces of the Kingdom (Khyatti et al., 2014).

Infections with HBV or HCV have been consistently associated with an increased risk of non-Hodgkin lymphomas (NHL). Despite sporadic case reports associating NHL and hepatitis, the overall impact of these viruses on NHL is currently poorly known in Morocco. However, a recent survey conducted in Fez observed that 9.6% and 3.2% of NHL were either associated with a HBV or a HCV infection. Such alarming infection rates are thus well above those of the general population. The author observed that NHL in hepatitis virus-infected patients were mostly of B type, of high grade with a predilection for lymph node location (Lamquami, 2010). Further studies are now warranted to determine the true prevalence of hepatitis-associated NHL that might represent several hundred incident cases each year in Morocco.

3.4. Epstein-Barr virus associated cancers

3.4.1. Nasopharyngeal carcinoma

Epstein-Barr Virus (EBV), also called human herpesvirus 4 (HHV-4), is a lymphotropic gamma-herpes virus infecting approximately 90% of adults worldwide (Thompson and Kurzrock, 2004). EBV belongs to the *Herpesviridae* family, and the *Lymphocryptovirus* genus. The EBV genome consists of linear double-stranded DNA, with the length of 172 kb and > 80 genes coding for > 85 proteins. EBV infection is typically asymptomatic and does not cause disease. In specific circumstances, EBV may cause human B cell lymphomas, including Burkitt lymphoma (BL), Hodgkin lymphoma (HL), diffuse large B cell lymphoma, and lymphoproliferative disease in immunocompromised hosts (Fig. 3A) (Thompson and Kurzrock, 2004; Vereide and Sugden, 2010; Vereide and Sugden, 2011). EBV is also associated with solid tumors such as nasopharyngeal carcinoma, or stomach cancer. The role of EBV in the pathogenesis of nasopharyngeal carcinoma (NPC) remains unclear (Fig. 3B) (Young et al., 2016). In the high incidence area of NPC, in China and southern Asia, EBV presence is predominantly associated with the non-keratinizing NPC subtype (Petersson, 2015). Globally, 120,000 new cancer cases were attributable to EBV infection in, 2012 (Plummer et al., 2016).

NPC has a distinct geographical pattern of incidence. It is most prevalent in the Arctic among Inuits and Aleuts, North Africa, and Southern Asia (Petersson, 2015). Worldwide, 87,000 new cases of NPC were reported and 83,000 (95.5%) of them were attributable to EBV (Plummer et al., 2016). NPC is a multi-stage process involving multiple risk factors, including genetic predisposition, dietary factors and EBV infection (Jia et al., 2005; Tsao et al., 2014).

Morocco is considered an endemic region with intermediate incidence for NPC. The age-standardized incidence of NPC ranges distinctly from 3.1 per 100,000 males and 1.5 per 100,000 females, respectively and accounted for 1.8% of cancer cases registered between 2008 and 2012 (Benider et al., 2016). In a retrospective study, the overall survival of NPC patients was 66.2% (Raissouni et al., 2013). Previous studies showed that some dietary factors including rancid butter, rancid sheep fat, preserved meat (*Quaddid, Khlii*), tobacco, cannabis and domestic cooking fumes intake are the main risk factors for NPC in Morocco (Belbaraka et al., 2013; Feng et al., 2007; Zur Hausen, 2009). Meanwhile consumption of cooked vegetables and

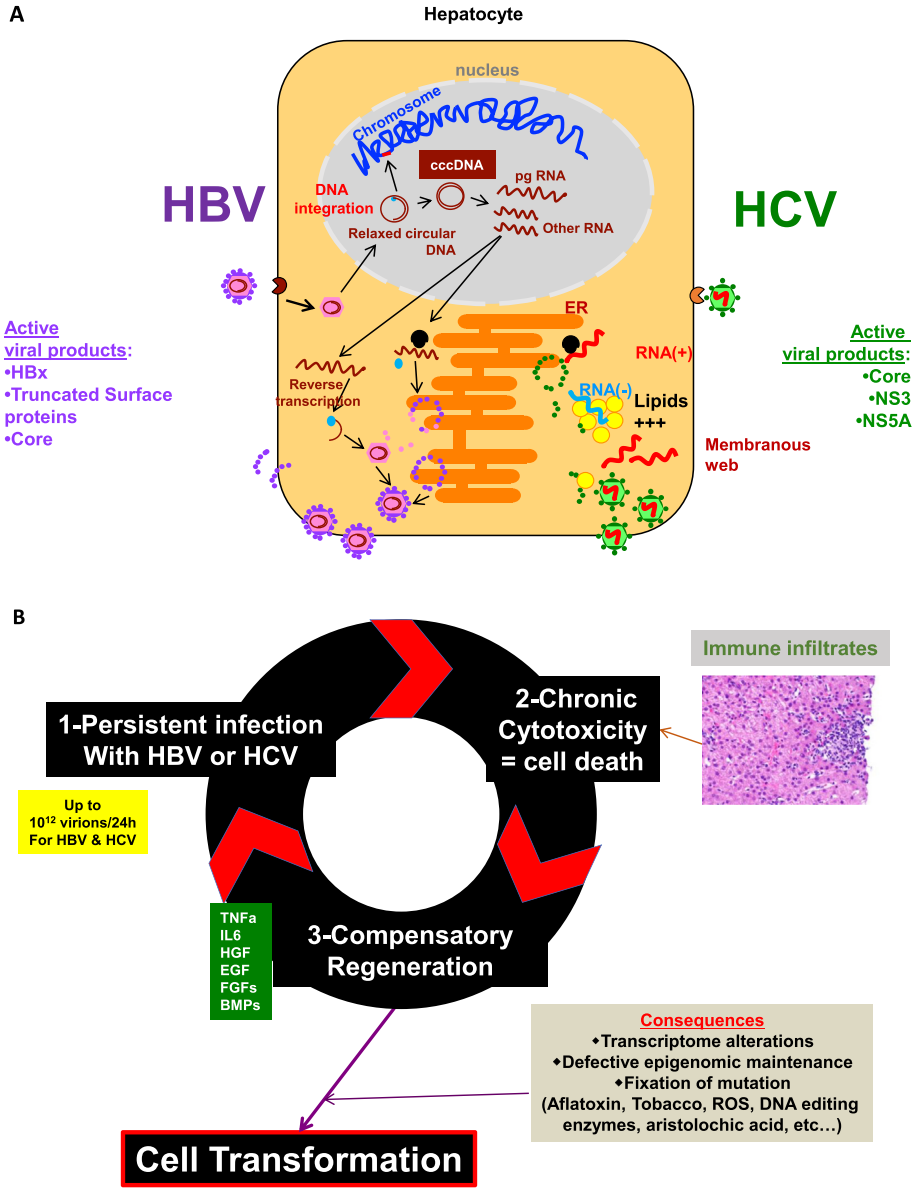

Fig. 2. Schematic representation of mechanisms of hepatitis B virus and hepatitis C virus in hepatocarcinogenesis. A) The life cycle of HCV and HBV. B) Direct and indirect roles of HBV and HCV in HCC pathogenesis.

industrial canned fish was associated with reduced risk (Feng et al., 2007).

The prevalence of infection by EBV in Moroccan NPC cases is 50% with a predominance of EBV type A (98.2%) and this infection is associated with age, smoking, and suffering a malignant process (El-Amrani-Joutey et al., 2018). Interestingly, previous data showed that EBV was detected in all NPC tumors (Laantri et al., 2011). Moreover, 82% of NPC cases were positive for EBNA1 (Nawaz et al., 2015b). These Moroccan NPC cases were different from data reported in Southern China, where the common type of undifferentiated NPC is strongly associated with EBV (Chang et al., 1990; Chen et al., 1993). Various studies indicate that antibodies against EBV are suitable markers for early diagnosis of NPC, and can be used to monitor the recurrence and progression of this malignant disease (Gu et al., 2008; Li et al., 2016). The analysis of antibody patterns in patients with NPC indicates that IgG-ZEBRA had better prognostic value in children with NPC, who showed very low titers of IgA -VCA and -EA (Dardari et al., 2008). Additionally, promising DNA methylation markers could be used to identify nasopharyngeal carcinoma patients with high specificity (90%) (Nawaz et al., 2015a; Nawaz et al., 2015b). Previous study has found that latent membrane protein-1 (LMP-1) 30-bp deletion (del) variant is present in 84% of Moroccan NPC patients (Dardari et al., 2006). Moreover, del-LMP-1 has lower immunogenicity than the non-del variant, which may give rise to tumor development via escaping immune surveillance (Hu et al., 2000).

A stepwise accumulation of genetic and epigenetic alterations results in the transformation of normal cells to cancer cells. Little is known, however, about the somatic changes affecting NPC genomes in Morocco. An early report showed that Mediterranean NPCs (Tunisia, Algeria, and Morocco) have higher frequencies of gains at 1q and losses at 13q than their Asian counterparts (Rodriguez et al., 2005). The mutation rates affecting common gene targets (*TP53, CDKN2A, PIK3CA, TERT*, etc.) including some druggable ones are currently unknown in Morocco. Nawaz et al. reported that integrin α9 gene promoter is hypermethylated and might be involved in the tumourigenesis of Moroccan patients (Nawaz et al., 2015a).

Since NPC has been linked to EBV, association of immune-related genes, especially HLA and NPC, has been intensively studied. The

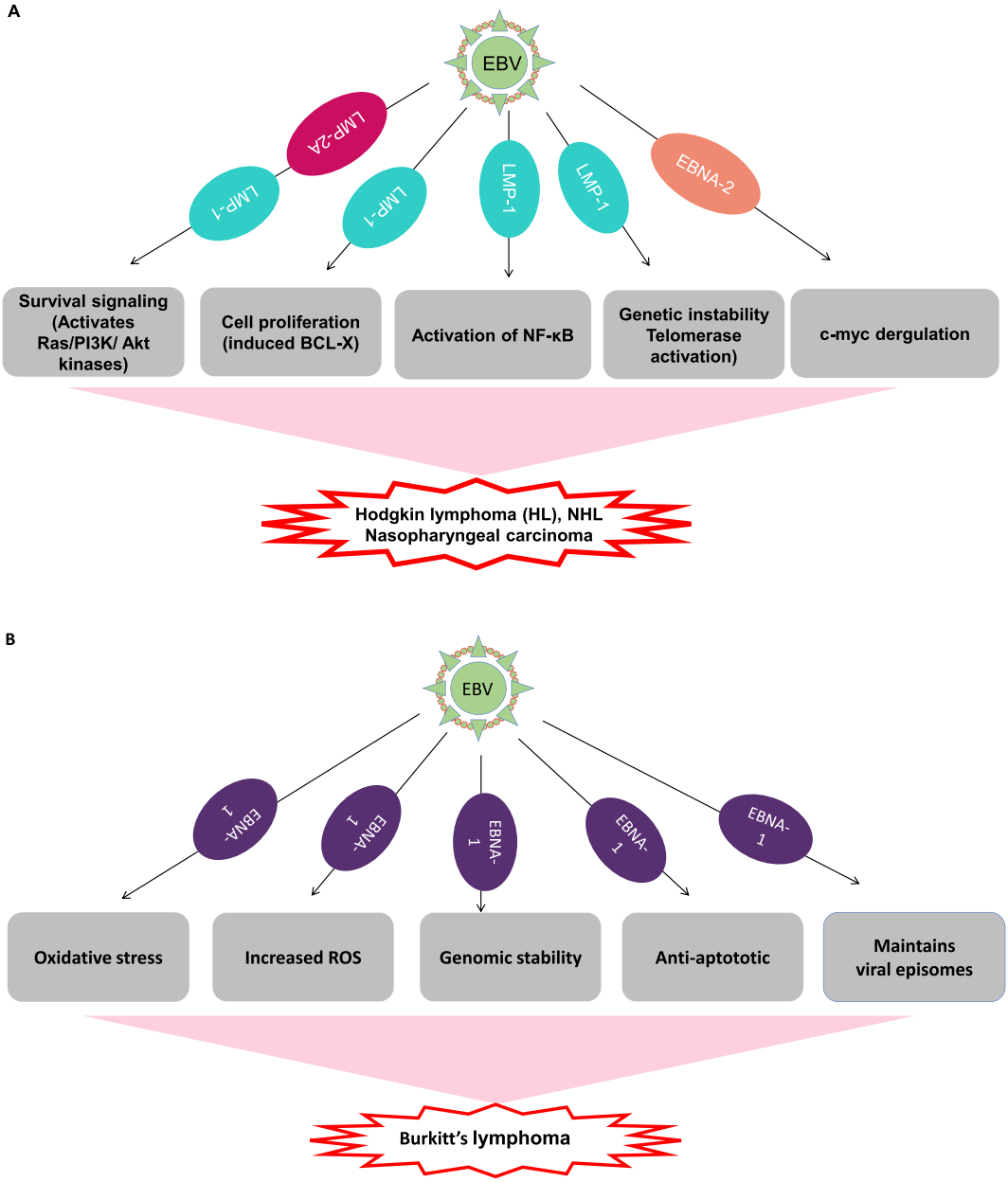

Fig. 3. Epstein–Barr Virus and cancerogenesis. A) EBV-encoded oncoproteins and their modulation of cancer-inducing pathways leading to Hodgkin lymphoma, non-Hodgkin's lymphoma, and nasopharyngeal carcinoma. B) EBV-encoded oncoproteins and their modulation of cancer-inducing pathways leading to Burkitt's lymphoma. LMP-1 mimics CD40 leads to activation of NF-kB, JNK, PI3K/Akt, and MAPK pathways to promote cellular proliferation. EBNA2 deregulates expression of c-myc. EBNA1 induces genomic instability by regulating RAG-1 and RAG-2 and increasing reactive oxygen species (ROS).
EBNA1: Epstein–Barr virus nuclear antigen 1; EBNA2: Epstein–Barr virus nuclear antigen 2; LMP-1: Latent membrane protein-1.

association of *HLA* with NPC risk in Moroccan subjects showed that *HLA-A10*, *HLA-B13* and *HLA-B18* were associated with an increased risk. However, the *HLA-A9* was identified as a protective factor against NPC (Dardari et al., 2001). These data are consistent with previous association studies on *HLA* alleles and NPC in southern Chinese (Bei et al., 2010; Hildesheim et al., 2002; Lu et al., 2003; Tse et al., 2009). In addition, association studies between candidate genes, such as those related to the immune regulation, DNA damage repair, oxidative stress pathways, and NPC risk have been conducted. *NQO1* polymorphism was associated with a significantly higher risk of NPC among smokers while it did not affect the risk among non-smokers (Moumad et al., 2018). Additionally, the rs377529 polymorphism of *TLR3* contributed to the increased of NPC risk in Moroccan population whereas *CD209* rs7248637 and *DDX58* rs56309110 polymorphisms were associated with decreased risk of NPC (Moumad et al., 2013). Plasma EBV DNA has been shown to be a powerful biomarker in the screening, diagnosing, surveillance, and treatment of NPC but it was not investigated in Moroccan NPC so far (Lam and Chan, 2018).

3.4.2. *Burkitt's lymphoma*

EBV was first identified in association with a Burkitt's lymphoma (BL) cell line (Epstein et al., 1964). BL is a rare, aggressive subtype of B-cell non-Hodgkin lymphoma (NHL) and consists of three distinct variants. BL affects > 1500 patients per year (Casulo and Friedberg, 2018). In Morocco, it was found that oral Burkitt-type lymphomas account for 8% of total childhood NHL (Otmani and Khattab, 2008).

In addition, a retrospective study reported thirty-seven children with Burkitt's lymphoma between 1998 and 2005, including 31 boys

and 6 girls with a mean age at diagnosis of 6.6 years (range 2–15 years), and a predominance of maxillary over mandibular involvement. The pattern observed in this study falls between that of the endemic (sub Saharan Africa) and the sporadic (Europe) types. In terms of clinical outcome, BL patients undergoing intensive chemotherapy, maintained a poor prognosis (Otmani and Khattab, 2008). Other cases of BL have been reported throughout the Kingdom (Akhaddar et al., 2012; Allaoui et al., 2016; Chbicheb et al., 2012) but unfortunately, due to a lack of available diagnostic tests, investigations to assess the presence of EBV were not conducted.

3.4.3. Gastric cancer

EBV is consistently associated with gastric cancer worldwide. A recent but single study, conducted in Fez, is available from Morocco (Alaoui Boukhris et al., 2018). The authors analyzed a series of 287 gastric biopsies and detected EBV DNA in 29% of cases. In 9%, EBV was found alone, in absence of *Helicobacter pylori*, the major cause of gastric cancer worldwide. Here again, further studies will be necessary to provide a fair appraisal of the role of EBV in gastric cancer cases from Morocco.

3.5. Kaposi's sarcoma-associated herpesvirus (KSHV) and Kaposi's sarcoma

Kaposi's sarcoma-associated herpesvirus (KSHV), also known as human herpesvirus 8 (HHV-8), is the etiological agent of Kaposi's sarcoma (KS) (Fig. 4). KSHV is an enveloped, double-stranded DNA virus originally identified in a tumor biopsy sample from a patient with acquired immunodeficiency syndrome (AIDS) (Chang et al., 1994). KSHV belongs to *Gammaherpesvirinae*, a sub-family of the *Herpesviridae* family, and the genus *rhadinovirus*, which is also known as *Rhadinoviridae* or gamma-2 *herpesviruses* (Hussein et al., 2019). KSHV is highly prevalent in sub-Saharan Africa (> 50% seroprevalence rates), moderately common around the Mediterranean basin and in some countries in South America (3–20%), but less frequent in most other parts of the world (< 10%) (Humans, 2012; Mariggio et al., 2017). Early studies of seroprevalence were conducted in 2 groups of HIV negative Moroccan patients, 26 patients with KS and 26 healthy blood donors. The results showed that anti-HHV-8 was positive in 92% of KS patients, whereas the 26 healthy blood donors were all seronegative for anti-HHV-8 (El Kassimi et al., 2003). Furthermore, molecular testing 26 KS tumors showed that all cases were positives for HHV-8 DNA (Hbid et al., 2005).

Kaposi's sarcoma (KS) represents a complex angioproliferative disease characterized by the appearance of spindle-shaped cells. KS was first described as a skin lesion a in 1872 by the dermatologist Moritz Kaposi but it gained a public attention as an AIDS-defining malignancy as it is more commonly associated with HIV infection (Cesarman et al., 2019). KS is causally associated with KSHV infection, and progress has been made in our understanding of the role of this virus in KS pathogenesis (Cesarman et al., 2019). The incidence of KS varies greatly with ethnic and geographic factors. In Morocco, KS is a rare cancer ranked as the 32th cancer with 84 new cases and 50 deaths per year (Cancer, 2019; Lamchahab et al., 2011). The clinical pattern of KS in Moroccan patients was characterized by its extreme variability including nodular lesions as first clinical symptoms, a more frequent association with lymphedema, disseminated skin lesions at diagnosis, unusual visceral or lymph node involvement and rare coexistence of second primary neoplasm (Errihani et al., 2011). There was predominance of males (male/female ratio: 4:1) and the mean age at diagnosis was 61.7 years. Moreover, in this study KSHV serology was done only in five patients among 56 patients in which the results were positive (Errihani et al., 2011). In addition, a retrospective study of a cohort of HIV positive patients followed at the infectious diseases unit of Casablanca under antiretroviral therapy reported that 6% of death was related to KS (Sodqi et al., 2012). Furthermore, genetic variation and polymorphism of the complete K1 gene of HHV-8 of a series of 35 viral strains, originating from 28 Moroccan patients with classic, AIDS-associated or iatrogenic Kaposi's sarcoma lesions showed that only the large C molecular subtype was identified (Renan Duprez, 2006).

3.6. Human immunodeficiency virus type 1 (HIV-1) and human cancer

HIV1 was classified by the International Agency for Research on Cancer (IARC) Working Group in 1996 as carcinogenic in humans (Group 1) (1996; Bouvard et al., 2009). HIV-1 infection causes cancer indirectly through immune suppression, leads to increased expression of the effects of oncogenic infections such as those with EBV, KSHV but

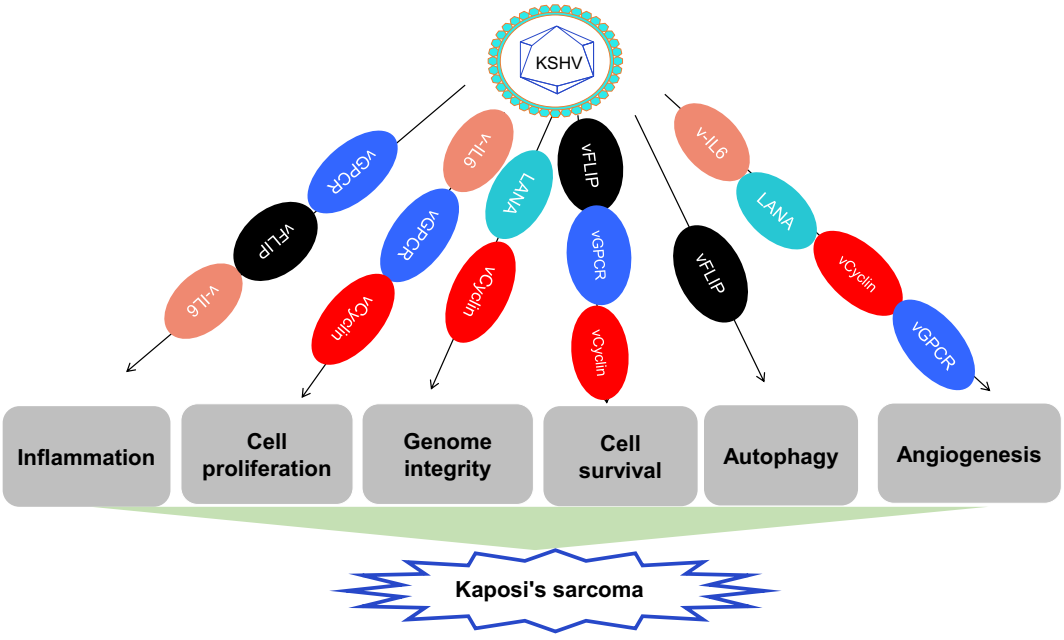

Fig. 4. Molecular mechanisms of KSHV-driven cell cycle progression and oncogenesis. KSHV-encoded oncoproteins modulate several pathways including proliferation, apoptosis, immune evasion, angiogenesis and inflammation leading to tumorigenesis. LANA: The latency-associated nuclear antigen; vCyclin: viral cyclin; vFLIP: viral FADD-like interleukin-1-converting enzyme inhibitory protein; vIL-6: viral IL-6; vGPCR: G protein-coupled receptor.

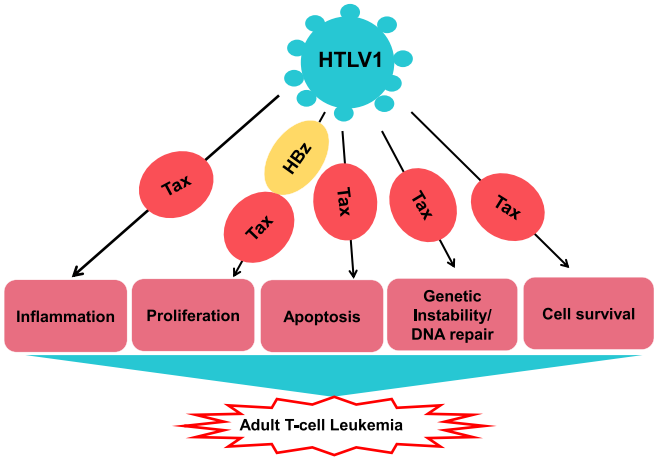

Fig. 5. A schematic diagram of human T-cell leukemia virus type-1 mechanisms involved adult T-cell Leukemia. Tax: Transactivator of pX HBz: Basic leucine zipper factor.

also HBV. However, cancer incidence among HIV-infected individuals is lacking in Morocco. There is 22,000 people living with HIV1 in Morocco (UNAIDS, 2012). Previous studies demonstrated the occurence of Kaposi's sarcoma (Chakib et al., 2003), Non-Hodgkin Lymphoma, including brain location (Sodqi et al., 2012), and advanced liver disease (Tahiri et al., 2013) among HIV1-infected patients.

3.7. Human T-cell leukemia virus type-1 and T-cell leukemia

Human T-cell leukemia virus type-1 (HTLV-1) was the first oncogenic retrovirus identified in humans and the first demonstrable cause of cancer by an infectious agent (Tagaya et al., 2019). HTLV-1 is classified as a complex type C retrovirus and belongs to the *Retroviridae* family, the *Orthoretrovirinae* subfamily and to the *deltaretrovirus* genus (Gessain and Mahieux, 2012). HTLV-1 is known to be etiologically associated with adult T-cell leukemia/lymphoma (ATL) and HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP) (Fig. 5). The HTLV-1 is highly endemic in the Southwestern part of Japan, sub-Saharan Africa and South America, the Caribbean islands, with foci of endemicity in Middle East and Australo-Melanesia (Gessain and Cassar, 2012). In Morocco, no epidemiological studies were conducted so far, but the HTLV-1 seroprevalence appears to be very low or even absent (Gessain and Cassar, 2012). However, a seroprevalence of HTLV infection among immigrant pregnant women living in Spain showed that HTLV-1 infection was present in one Moroccan woman (Trevino et al., 2011).

ATL is a rare and highly aggressive T cell malignancy and was first reported in Japan, where it has a high incidence in the southwestern region. ATL is now categorized into four types: chronic, smoldering, acute, and lymphoma (Takatsuki, 1995). Very few cases of ATL have been reported in Morocco (Thyss et al., 1990). In this study, the authors confirmed the presence of HTLV-1 in Moroccan patients with ATL (Thyss et al., 1990). Thus, based on these scarce available data, Morocco currently appears as the only country that can be considered as an endemic area for HTLV-1 in North Africa (Gessain and Cassar, 2012; Trevino et al., 2011). Overall, similar to the situation of several other oncogenic viruses, a significant effort should be made to clarify the current epidemiological status of HTLV-1 infection and its role on ATL development in Morocco.

3.8. Merkel cell polyomavirus and Merkel cell carcinoma

Merkel cell polyomavirus (MCV or MCPyV) is the last oncogenic virus discovered. It is a small circular double-stranded DNA genome of 5387 bp of genera *Orthopolyomavirus* and family *Polyomaviridae*. MCV is common in the general population with > 80% of carriers (Tolstov et al., 2009).

In 2008, MCV was identified in Merkel cell carcinoma (MCC) tumor specimens (Feng et al., 2008). MCV has been classified by the IARC as carcinogenic to humans (Group 2A) (Bouvard et al., 2012). MCC is a rare but an aggressive neuroectodermal skin tumor with a disease-associated mortality reaching 46% (Lemos et al., 2010). MCC occurs mostly in fair-skinned population but little is known about the global epidemiology of MCC. The estimated annual incidence in 2006 was 0.6 per 100,000 persons (Albores-Saavedra et al., 2010). In Morocco, the exact number of incidence and mortality of MCC is not available. However, a case report about secondary location of MCC indicates that MCV is present and associated with disease in the Moroccan population (Azami et al., 2017).

4. Conclusions and Pledge for future research

With several thousand new cases each year, human virus-associated cancers remain a virtually important societal burden in Morocco. The trends of infection-related cancers are similar to North African countries (excluding Egypt). Egypt had a unique pattern of liver cancer, with a high proportion of HCV-attributable HCC. However, the burden is different to Eastern Africa, Asia, and European countries (Bray et al., 2018).

One of the most striking features of the situation in the country is the lack of evidence-based knowledge about the role of oncogenic viruses in different forms of tumors for which they represent bona fide risk factors. This situation concerns notably all HPV-associated neoplasia to the exclusion of cervix (head and neck tumors, genital tumors), hepatitis-viruses associated lymphomas, EBV-associated stomach cancer, or the real status of HTLV1 in the country. In such circumstances, the implementation of efficient Public Health policies remains somewhat illusory.

Fortunately, for some tumors at least, primary prevention is possible. It is the case of the vaccinations against HBV and HPV that are the most effective approach to prevent HBV-related HCC and the multiple forms of HPV-associated cancers. Universal anti-hepatitis B immunization was implemented in Morocco in 1999. Since that year all infants are supposedly immunized by the administration of 3–4 doses of vaccine. After two decades, the lack of sero-epidemiological survey in the young Moroccans prevent any documented assessment of the real vaccination coverage in Morocco (Haban et al., 2017). The apparent lack of motivation exhibited by Moroccan health professionals and their employers to seek/provide for a proper anti-hepatitis B immunization for themselves (only 51% are protected) cast some doubts about the efficiency of the protection at the general population level (Djeriri et al., 2008). However, the optimal combination of vaccination and HPV infection screening strategies (including HPV testing and cytology) will require careful implementation because in many cases women are not compliant with screening recommendations. The choice of the vaccine proposed to the Moroccan population will be crucial as well. The presence of High-risk HPV genotypes different from the classical HPV-16/18 implies that the use of a vaccine of second generation with a large number of antiviral valences, such as Gardasil 9, should be preferred (Ouladlahsen et al., 2018). In addition, as in other countries, the extension of anti-HPV vaccination to males should be considered despite the absence of data about HPV in head and neck cancers (Crosignani et al., 2013).

With regard to secondary prevention, access to effective and affordable hepatitis C treatments with the new approved direct acting antivirals against HCV may interrupt the progression to HCC, reduce the reservoir of infected patients and hopefully help, on a longer term, in the elimination of this virus. A major barrier to this achievement lies in the facts that HCV infection remains incipient for a long period and that most patients are unaware of their infection (McGowan and Fried,

2012). Examples drawn from the situation in neighboring countries suggest that large and comprehensive sero-epidemiological surveys are still needed to discover the niches (geographical, social, lifestyle, and occupational) in which HCV tends to be more prevalent (Bensalem et al., 2016; Zahraoui-Mehadji et al., 2004). Furthermore, other studies linking HCV (or HBV) to the development of both indolent and aggressive B-cell non-Hodgkin lymphoma are still warranted in our country.

To date, most studies of KS reported in Morocco are descriptive and epidemiological. However, the transmission routes of HHV8, known to vary widely according to the populations considered, are not well known in Morocco and deserve further exploration. In addition, it would be of great interest to perform studies to figure out to which extent each of the immune, genetic and environmental components of the disease are capable to modulate KS presentation in Morocco especially in its classical non-AIDS-associated form (Akasbi et al., 2012). Similarly, the reasons explaining the endemic status of NPC in Morocco are poorly known. A wealth of genetic survey was conducted in South China to uncover allelic variants associated with NPC risk (Bei et al., 2012). Equivalent works produced in Morocco or North Africa are now expected to impulse a significant progress to the field.

Based on published evidence presented above, it is obvious that viruses-associated cancers are complex diseases with multifactorial contributions of viral infections, genetic predisposition and environmental exposures. There is evidence that several genetic polymorphisms and sometimes controlling epigenetic variations might be associated with a modulation of human viruses-associated cancers predisposition in Moroccan populations. A better understanding the molecular biology of cancer-associated viruses at a fine scale would offer North African oncologists a deeper insight into the etiological and management aspects of viruses-associated cancers. In addition, such surveys enabling the identification of populations at risk will allow better allocations of resources in a middle-income country. Further studies will be, of course, required thereafter to assess the clinical values of these additional data. Therefore, a multidisciplinary research is highly warranted to achieve a deep understanding of these deadly diseases, to define the key mechanistic features at work in North African populations. Such understanding could help us develop a precision medicine and rationale-targeted therapy and also protect high-risk populations from infection and may identify additional targets for developing a protective vaccine or treatment to eliminate viral infectious agents. However, access to sustainable funding of research program will be an inevitable challenge that requires concerted support from the national and international communities.

Overall, as underlined in many places of the current work, well-designed epidemiological studies aiming to identify the responsible agents, to measure the exact impact of oncogenic viruses in local form of tumors, to locate the viral reservoirs, and to define transmission routes are still needed to improve national Public Health.

Ethics approval and consent to participate

Not applicable. Only published primary studies were included in this review.

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Declaration of Competing Interest

The authors declare no conflict of interest in this study.

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