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Putative oncogenic viruses: Some data on Brazilian subjects

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Abstract

The concepts of cancer etiology have changed over the years, mainly based on molecular epidemiology studies and bioinformatics approaches. Until relatively recently the most accepted theory of cancer etiology has dealt with the accumulation of gene mutations and the consequent cognate proteins dysfunction, but now some authors have argued against the proposed theory. The additional role of noncellular genes in the cause of malignancy, associated to environmental factors and host genetic background, has been proposed and mostly accepted by the scientific community. Some of our data from human populations in Brazil concerning cancer epidemiology, molecular and serological surveys, were conducted looking for the detection of putative oncogenic viruses, as the Human T-cell Lymphotropic virus/HTLV-1/2, Human Papillomavirus/HPV, the Mouse or Human Mammary Tumor Virus/MMTV, the Human Endogenous Retrovirus/HERVs and the Hepatitis C virus/HCV, in human, healthy and malignized, tissues. Generally, research work around the world suggests that 10 to 20 % of all human cancers are etiologically linked to oncogenic viruses, so if the presence of exogenous or endogenous virus sequences in the human DNA has any significancy in the cancer etiology, it deserves further and continuous research work and discussion.

Introduction

Despite some controversies, it is the common sense that cancer is a multifactorial event mainly determined by aging, as the cellular biochemical machinery, along the years, gathers nucleotide sequences coding for altered or non-functional proteins playing pivotal roles at different stages of the cell cycle [1]. Dysregulated cell function displays, naturally, a dynamic process intrinsically linked to DNA replication and consequent cell division, with important contributions of endogenous and exogenous factors [2]. Living organisms are continuously under the direct or indirect influence of physical, chemical and biological agents and, the closest interaction with these environmental determinants, ultimately trigger mechanisms of evolution or life termination. Cancer seems to be an unsuccessful event for the host, that winds up with abnormal cells metabolism and growth in a chaotic genomic and tissue organization [2-5]. It is understandable and well-known that isolated events do not play any significative role in cancer etiology and evolution but, integrated and orchestrated molecular events, even in distorted physiological processes, have been well-characterized and proved to participate in the tumorigenesis and cancerization. Particularly here, we explore the eventual participation of the so-called oncogenic viruses in the etiologic processes of cell transformation and malignization [6], by the detection of gene sequences of oncogenic viruses and humoral response to these agents. How do proteins coded by virus genomes could participate or contribute to the genesis of the genomic chaos in the host cell?

The Human T-cell lymphotropic virus (HTLV)

The Human T-cell lymphotropic virus, also known as the Human T-cell leukemia virus, represents a group of viruses taxonomically positioned in the *retroviridae* family, *deltaretrovirus* genus. The Primate T-cell lymphotropic viruses (PTLVs) group include deltaretroviruses infecting human and nonhuman primates, the HTLVs and STLVs respectively. There are, presently, 4 types of HTLV (HTLV-1, HTLV-2, HTLV-3 and HTLV-4) and the corresponding 4 STLV types (STLV-1, STLV-2, STLV-3 and STLV-4). The Simian T-cell lymphotropic viruses (STLVs) are closely related to the HTLVs as phylogenetic studies point out that humans were initially infected by STLVs, in Africa and Asia, and these viruses infecting human hosts evolved to HTLVs. It is claimed that hunting of simians by human beings and feeding on them, as also cohabitation of these two hosts species, such like pet animals or in zoos, have favored deltaretroviruses zoonotic transmission [7-9]. Among the PTLVs, the HTLV-1 is the most studied virus as it is etiologically linked to neuromyelopathy, the HTLV-1 associated myelopathy (HAM) also known as Tropical Spastic Paraparesis (TSP), and a leukemogenic process, the Adult T-cell leukemia/lymphoma (ATLL). HTLV-1, as its designation stands for, has tropism for T lymphocytes, being transmitted by biological fluids containing these cells, as mucosal fluids, breast milk and blood, of infected subjects, therefore, the virus is acquired by sexual intercourse, breast milk feeding and blood transfusion [10]. Neuromyelopathy is characterized by the spinal cord chronic inflammation or myelitis caused by strong immune response to HTLV-1 infected cells, in the central nervous system milieu [11], while leukemogenic processes arise from $TCD4^+$ abnormal proliferation after cell physiological dysregulation in the event of HTLV-1 infection [12]. ATL, a $CD4^+$ T cell malignancy, is rare, aggressive and a hard-to-treat hematological malignancy, differing

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its onset in Japanese subjects around 70 years, and 50 years among Americans and Europeans [13], and not well-determined among other Asians and African populations. About 4 out of 100 HTLV-1 infected subjects slowly progress to ATL, with this proportion mainly determined by ethnicity and geographical distribution. It is worthwhile to mention that, as ruled for all malignancies, the sole HTLV-1 infection is not enough to cause ATL, but comorbidities, the host genetic background and environmental factors synergize for the pathogenesis development, despite the clonal integration of HTLV-1 proviral DNA in all patients' ATL cells [14]. One of the proteins encoded by HTLV-1, the p40 tax oncoprotein, plays a pivotal role activating the canonical and non-canonical forms of the host nuclear transcription factor κB (NF-κB), leading to the expression of numerous viral genes involved in inflammation processes. The hijacking and aberrant activation of the cell ring finger protein 8 (RNF8) exert a critical role in the cell DNA repair mechanisms or cellular DNA damage response (DDR), that in later instances generates host cell genomic instability, as DNA lesions are not repaired [15]. According to Ameur et al. [16], it is not well-understood the molecular mechanisms of HTLV-1 induced splicing modifications and/or the interplay between transcription and splicing mechanisms. Physiological processes that determine cells' fate comprehends an intrinsic biochemical interaction of endogenous and exogenous factors affecting RNA processing in the transcriptome and proteome plasticity, ultimately characterizing the cells phenotype [17,18]. Besides p40tax, the negative-stranded virus encoded helix-basic-zipper-protein (HBZ) expressed in HTLV-1 chronically infected cells contrasts to the low levels of Tax and Gag proteins production. Tax and HBZ have antagonistic roles in the cell signaling pathways, as tax activates NF-κB, NFAT and AP-1 while HBZ inhibits them. Also, HBZ activates the TGF-β/Smad pathway and tax inhibits it. Therefore, to rescue HTLV-1 infected cells of tax deleterious effects, HBZ promotes cell survival and proliferation, as an essential factor for leukemogenesis and the inflammation process in HAM/TSP, and minor HTLV-1 related pathologies [19]. Another accessory protein, the p30 (tof protein), encoded by the doubly spliced Tax-ORF II mRNA, puts in place transcriptional and post-transcriptional activities blocking virus replication and preventing interferon synthesis in HTLV-1 infected myeloid cells, consequently impairing innate and adaptive host immunity. Some studies point out that the tof protein participates in the mechanisms of gene expression, cell cycle progression and DNA damage response, raising the possibility of its role in T cell transformation, being also essential for virus infection and persistence [20,21].

The Human Papillomavirus (HPV)

The members of the *Papillomaviridae* family are non-enveloped small virions of 50-60 nm in diameter. Its capsid encloses a circular double stranded DNA that extends approximately for 8 kb. Up to date, 32 genera have been described in this family, distributed in the vertebrate classes, except amphibians. Human papillomavirus (HPV) is restricted to the genera Gamma, Mupa and Nupapapillomavirus, incorporating more than 200 different HPV types [22-25]. Just about 4-5 % of all human cancers have HPV etiologic contribution, despite the majority of HPV infections shows as benign growth expressed mainly as warts of epithelial origin as also present in healthy skin, even though actinic keratosis, epidermal cysts, lichen sclerosus, psoriatic plaques, seborrheic keratosis and skin tags have also been claimed as related to HPV infection. There are evidences that the fate of HPV infection that culminates in cancer or other less serious skin condition depends on the type of HPV and epithelial cells' genes responses to the infection [26-28]. Papillomavirus has tropism for epithelial cells, in both cutaneous and mucosal environments, including the oral cavity and anogenital tract. The virus gains space through tissues' microlesions, and specifically infects the host's dividing basal stratified epithelia, spreading and remaining the viral progeny persistently and latently interacting with the host cells' biochemical machinery for years [29,30]. Depending on the environmental and host factors, most of the persistent papillomavirus infection could be cleared by the host immune system or triggers, more or less, benign skin lesions. In the worst-case scenario, it is constantly proposed the concomitant role played by the mentioned factors as the host exposure to environmental UV irradiation, tobacco smoking, alcohol consumption, HIV infection and host hormonal disbalance, particularly among women, concerning estrogen metabolites, in the evolution of papillomavirus persistent infection to neoplasia development [31-33]. Besides the interplay among these factors, papillomaviruses are grouped in the high-risk and low-risk groups according to the carcinogenic potential. Therefore, the HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58 and 59 are considered the high-risk papillomaviruses, and the others, the low-risk. Independently of high or low-risk papillomavirus infection, there are assumptions that any persistent papillomavirus infection could lead to malignization [34,35]. Papillomavirus infection is circumscribed to the wounded basal stratified epithelial layer, through initial interaction of L1 and L2 viral capsid proteins with epithelial cell membrane heparan sulfate proteoglycans and host cell factors generated by the microlesions as growth factors and cytokines [36]. The E6 and E7 papillomavirus proteins highly produced by infected cells are the major determinants of associated diseases, from relatively benign warts to aggressive malignization processes in the anogenital to head and neck body areas [37].

The Mouse/Human mammary tumor virus (MMTV/HMTV)

Human breast cancer is the second cause of mortality among women. Its etiology is multidiverse as the cancer per se, but mainly determined by hormonal factors. Apart from environmental and genetic factors, infectious agents have been investigated for their causative role in the cancerization process, e.g., the Herpes simplex virus and the Human papillomavirus [38-40]. Nevertheless, a sole viral agent, the Mouse Mammary Tumor Virus (MMTV), transmitted from lactating mice to their offsprings, also named Bittner Milk Agent, initially reported by Bittner in 1943, proved to be etiologically linked to mouse breast cancer. At that time, there were already reports concerning the above-mentioned factors involved in the etiology of breast cancer, mainly utilizing mice as a model [40]. A MMTV homologue, tentatively denominated Human Mammary Tumor Virus (HMTV) has been detected in human breast tissues, as viral particles by electron microscopy, and the viral RNA, even though it is a hot topic the role played by this virus in the etiology of human breast cancer [41-43]. A controversial data obtained in Poiesz laboratory [41] showed that human DNA samples, from healthy and breast cancer tissues, amplified for MMTV *env* primers as also mouse DNA of several species, but the authors evaluated the number of copies obtained, and concluded that the amplified DNA samples were from laboratory environment contamination, arguing also that the low number amplification copies would not explain the possible etiologic role played by MMTV in human breast cancer, according to one of the proposed mechanism of insertional mutagenesis, activating neighboring proto-oncogenes, as the fibroblast growth factor receptor 2/*Fgfr2* and the wingless/*Wnt-1*, in the MMTV proviral integration

site [44,45]. Nevertheless, a recent study by Lessi et al. [46] confirmed the pioneering studies of Bogo laboratory [43], of MMTV-like virus in human breast cancer, when finding MMTV-like sequences in the DNA of human mandibula fossils, dated back between the Copper age and the 17th century, therefore it is estimated that MMTV jumped species, from mouse to man, around 4,500 years ago [46]. One of the 7 MMTV genes, *Sag*, commonly described in the genome of certain viruses and bacteria, codes for a superantigen, a protein that strongly and excessively stimulates T cells polyclonal activation by an uncommon mechanism. This viral protein is claimed to be linked to MMTV infection and carcinogenesis [47,48]. Cells, of the immune system and of the breast epithelia, express receptors for MMTV infection, of both endogenous and exogenous origin, at least in mice, leading the retroviral integrated zygote chromosome to exhibit viral antigens which generate immunologic tolerance during T lymphocytes clonal selection in the thymus, allowing exogenous MMTV infection, host cell chromosome integration and insertional mutagenesis, that ultimately activate proto-oncogenes promoting the carcinogenic process, certainly modulated by endogenous and epigenetic factors, as also T cell polyclonal activation by Sag superantigen, which consequentially induces the expression of inflammatory cytokines. According to reports of different research groups, these mechanisms occur slowly, taking years to progress to breast cancer [39,44,47-49].

Human Endogenous retroviruses (HERVs)

Genomes of all vertebrate species have homologous sequences to genes of exogenous retroviruses. It is commonly accepted that ancient infection of multicellular organisms by exogenous viruses, particularly retroviruses, followed by its genome integration into the host cells' germ line chromosome, perpetuated the acquisition of viral nucleotide sequences by host organisms. Katsura and Asai [50] stated that "accumulation of viral sequences has created the current human genome". About 5-8% of the human genome is composed of endogenous retroviral nucleotide sequences exerting a plethora of functions by the cognate proteins expressed, some of them fundamental for the host reproduction and survival, but also, it is argued the pathological role played by these endogenous retroviral sequences, mainly in autoimmune diseases and cancer. According to Gao et al. [51], HERVs expression acts as accessory factors in the carcinogenic process activating oncogenic signaling pathways and inhibiting tumor suppressor genes. The taxonomy of the Endogenous Retroviruses is not yet defined, the present time nomenclature utilized is based on distinct features, anyway efforts to establish a rational classification is undertaken as proposed by Gifford et al. [52]. For example, one of the most important HERVs, the HERV-K, has its designation based on the usage of lysine tRNA, but the applied criteria will not cover other Endogenous Retrovirus representatives. Also, HERV-K is a recently acquired group of HERVs profusely spread in the human genome. Some of these HERV-K integrated copies displays intact open reading frames capable of transcription and translation, linking its activity to indispensable role in the embryogenesis mechanisms. Among members of HERV-K group, HML-2 is the most actively transcribed and its aberrant expression has been associated to disease pathophysiology as certain types of cancer and neurodegenerative processes [53]. The HML-2 abnormal *env* gene expression produces two viral oncogenic polypeptides, Np9 and Rec, besides their role in autoimmune diseases. Experimental therapeutic approaches target the *env* gene products with monoclonal antibodies for multiple sclerosis treatment [54]. Another HERV member, HERV-W, encodes a syncytin-1 protein, essential in the trophoblast formation, therefore playing a major role in the fetal physiology. The fine-tuning regulatory mechanisms in the expression of HERVs genes is determinant for a physiological or pathological performance in human organisms, as similarly for ERVs in other eucaryotic pluricellular species, mainly vertebrates [55].

The Hepatitis C Virus (HCV)

Hepatitis of viral etiology encompasses agents of 4 different families (*Hepadnaviridae*, *Picornaviridae*, *Hepeviridae* and *Flaviviridae*) and still one of an unsigned family (Delta virus genus), but not all claimed to be oncogenic [56]. Molecular and immunovirological studies characterize the Hepatitis C Virus infection in primates (*Homo sapiens* and *Pan troglodytes*), and also reassure its link to liver pathologies, including cancer, conclusively performed by Houghton's group, but not successfully without many years of non-A non-B hepatitis viruses' investigation by other research groups [57,58]. Classified in the *Flaviviridae* family, the enveloped HCV particles range from 30 nm to 140 nm in diameter, presenting a single-stranded RNA genome of positive polarity with 9600 nucleotides coding for a long polyprotein cleaved into structural and replicative polypeptides [59,60]. It is estimated that 0.91 % of the entire world population is chronically infected by HCV, which progress to cirrhosis leading to the most common associated pathologies as hepatocellular carcinoma, cholangiocarcinoma and B-cell non-Hodgkin lymphoma [61-63]. The continuous expression of HCV proteins resulting in simultaneous disturbed cell signaling processes, oxidative stress and chronic liver inflammation reinforced by the host and environmental factors, plays an orchestrated and long sustained activity to progression of cancerous pathologies and other life-risking diseases [64]. Oxidative stress is the main biochemical cell erosion process ubiquitous in disease mechanisms, triggered by many agents including HCV, mostly implicated in cirrhosis progression to cancer, as the hepatocellular carcinoma, the hallmark of HCV persistence. Elevated levels of superoxide and hydrogen peroxide in hepatocytes triggered by phagocytes' production of NADPH oxidase responding to HCV infection, and glutathione reduction, promote cell death and Hepatitis C virions progeny replication. Counterbalance mechanisms in the redox microenvironment contributes to persistent infection which dysregulate the MDM2-p53 axis, or MDM2 overactivation and p53 inactivation as a feedback mechanism, besides virus transformed hepatocytes protection from cellular immune response by the depletion of Kupffer cells, stellate cells and $CD4^+$T cells [65,66].

Discussion

Our previous work on HTLV-1/2 epidemiology in northern Brazil demonstrated virus circulation in both healthy and cancer patients of different ethnicities, including Amazonian Amerinds, even though our initial collaborative research work, in early years of 1985, with Maruyama's laboratory in Japan, did not distinguish HTLV-1 from HTLV-2 [67-69], but later on, we were aware that HTLV-2 was responsible for the high prevalence among Amazonia Amerinds, except our findings of HTLV-1 positivity among Waiãpi amerinds inhabiting forest areas in the border of the Brazilian Amapa state and French Guyana [70]. Cervix uterine cancer patients exhibited relatively elevated HTLV-1 prevalence [67,69], but scarce data confirmed our results, as published by Du et al. [71] assessing the potential association of HTLV-1 to endometrial carcinoma; in the Yucatan peninsula, Góngorra-Bianchi et al. [72] showed that Mexican Mayan descendants with high incidence of cervix uterine cancer, yielded HTLV-2 positivity, in both cancer and healthy women, as expected; as well, in Japan and Jamaica, HTLV-1 markers were detected among cervix uterine cancer patients [73,74]. HTLV-1/2 etiological involvement in cervix uterine

Table 1: Synopsis of HTLV-1/2, HPV, HCV, MMTV and HERV-K analysis on human groups in Central/Northern region of Brazil.

Viral Agent	Method	Primer/gene region	Number of Subjects	Positive
HTLV-1/2[1]	Immuno Assay	N.A.[7]	156 HIV/AIDS[11];35 breast cancer[11]	6 HIV
	PCR	A/B/C/D/E/F/G/H[8]	35 breast cancer[11]	0
HPV[2]	RT/PCR[6]	HPV L1 genotype-specific fragments	38 head and neck cancer[11]	1 (HPV 70)
HCV[3]	Immuno Assay	N.A.[7]	288 healthy[12]; 156 HIV[11]	3 healthy;15 HIV
MMTV[4]	PCR	brt1/brt2/brt3/brt4(*env*)[9]	20 healthy[11]/15 breast cancer[11]	0
HERV-K[5]	PCR	fwGAGherv/rwGAGherv(*gag*)[10]	35 head and neck cancer[11]	31

[1]Human T-cell Lymphotropic Virus Type ½; [2]Human Papillomavirus; [3]Hepatitis C Virus; [4]Mouse Mammary Tumor Virus; [5]Human Endogenous Retrovirus-K; [6]Real Time Polymerase Chain Reaction; [7]Not Aplicable; [8]A(5'-CTCCTTCCCCACCCAGAGA-3')/B(5'-GGGTGGGTTCCATGTATCCATT-3')/C(5'-CTCCTTCCCCACCCAGAGA-3')/D(5'-GTTGGTTC-CAGGCATCCATT-3')/E(5'-AGAACTACCCGCACCCTCAA-3')F(5'-GGTGAGCTCGAGGCAATTGTTTC-3')/

G(5'-GCAAGAAAGTGCTCGGTG-3')/H(5'-CTACTCAGTGTGGCAAAGGTG-3');[9]brt1(5'-CCTCACTGCCAGATC-3')/brt2(5'-TACATCTGCCTGCCTGTGTTAC-3')/brt3(5'-ATCTGTGGCATACCT-3')/brt4(5'-GAATCGCTTGGCTCG-3'); [10]fwGAGherv(5'-GGGGCCATCAGAGTCTAAACC-3')/rwGAGherv(5'-TGATAGGCTACTTGCGGTTGG-3'); [11]Subjects from Central region of Brazil (Brasilia); [12]Subjects from Northern Brazil (Marajó Islands).

cancer is elusive despite its high statistical probability. As commonly substantiated, cervix uterine cancer is etiologically linked to HPV persistent infection but, both HTLV-1/2 and HPV are mainly sexually transmitted, and mostly by promiscuous behavior, despite HTLV-1/2 infection be usually circumscribed to nuclear families. In addition, radiotherapy procedures represent an important variable among cancer uterine patients that could contribute to HTLV-1/2 expression [69,75,76], furthermore we still reported HTLV-1 positivity among health care workers exposed to ionizing radiation as already discussed elsewhere [77]. Based on these findings, of HTLV-1 and HTLV-2 expression, it could be reinforced the hypothesis of ionizing radiation protagonism in the activation of host cell integrated HTLV-1/2 genes [77]. In vitro and ex vivo studies aim to explain in vivo phenomena which accounts for Koch postulates [78] that is under review, so it would infer, for example, that virus associated cytopathology and related dysregulated cell signaling, not necessarily and definitively prove the etiological role played by some viruses in cancer etiology. As already stated, environmental factors and host genetic background are associated with genesis of cancer and, why not contributing to viral genes expression? Recent serological survey performed by us (Table 1), did not detect HTLV-1/2 among patients attended in hospitals in Central region of Brazil, with different histological types of neck, head and breast cancer [79], but some HIV infected subjects of this same area showed HTLV-1 positive serology (unpublished data), possibly explained by the direct and strong immunosuppression exerted by HIV infection and the usual mode of virus transmission [80,81]. Carriers, of HTLV-1/2 and of many HPV genotypes, are largely distributed in different geographical locations and among distinct ethnicities, besides the host-genetic background that somehow influences virus type as happens among Amerindian populations, more prone to express HTLV-2 viral genes [67,68,70]. In the Central region of Brazil, screening head, neck and breast cancer patients for high-risk and low-risk HPV type gene sequences, HPV type 70 (low-risk type) was detected by the Real Time PCR (Table 1), in a patient with oral cancer (head and neck cancer group) that previously yielded negative result by the hybrid capture assay [82,83]. As stated before, findings of any viral gene sequence claimed to be enrolled in the cancer etiology is not a definitive proof, as evidences reported by Ciccarese et al. [88] of HPV positivity of 51 % and 43 % among subjects with genital lesions and apparently healthy subjects, respectively; Sontakke et al. [85] found 44.23 % and 5.76 % positivity for HPV type 16 and HPV type 18 respectively, in a group of asymptomatic women with normal cervix, while women with benign cervical lesion had 38.46% and 3.84% HPV type 16 and HPV type 18 positivity respectively, and 62.5 % and 22.5% HPV type 16 and 18 positivity respectively, in a group of women with cervical malignancy. As observed, HPV positivity ratio is elevated among cancer patients, anyway healthy subjects harbor HPV genome. Some authors argue that the host competent immune system clears the virus genome, and the failure to achieve it conducts to HPV viral persistence, probabilistically linked to virus infection progressing to malignization, not solely by the virus action but synergistically with other factors as host-derived and environmental, as previously discussed. It could not also be discarded the possibility that HPV composes the normal human virome; a diversified number of host genetic and environmental factors play a fundamental role in the host homeostasis such as that any dysregulation in the fine balance of these factors could trigger pathological phenomena culminating in cancer. Various studies credit the role of E6 and E7 oncoproteins of high-risk HPV types in the steady state progression of malignization of uterine cervix by counteracting the host pro-apoptotic tumor suppressor p53 and pRb, addressing these anti-tumor proteins to ubiquitination and proteasome degradation [86-89]. Neutralization of the host cell anti-tumor proteins is not exclusively exerted by HPV oncoproteins, but by other viral and non-viral factors. Also, depending on the HPV genera and type, there are conflicting data suggesting the protective role of common skin existing HPV genus and types, including protection against UV induced cancer or even as an adjuvant factor in the oncogenic mechanism [90].

Most of the patients, mainly those diagnosed with oral squamous cell carcinoma, in the group of head and neck cancer, attending hospitals in the Central region of Brazil, displayed amplified bands corresponding to the *gag* gene by PCR of HERV-K nucleotide sequences (Table 1). Previously, these samples had negative results for low-risk and high-risk HPV and MMTV gene sequences by the hybrid capture assays and PCR, respectively [91]. Concerning our preliminary data on HCV epidemiology (Table 1) (unpublished data), healthy subjects of a small village, in the Marajó island [92], had low prevalence, of 1.04 % (3/288), comparing to a high prevalence in a group of HIV/AIDS patients in the Central region of Brazil, of 9,6% (15/156). Interesting to note the relatively high HTLV-1 prevalence in this small Marajó village, of 2.8 % (8/287), even though we could not detect dually HTLV/HCV infected subjects.

Conclusion

Our data contributes to the epidemiology of these putative oncogenic viruses, particularly in populations of diverse ethnicity in Brazil as in the Central region of Brazil inhabited by people of all regions of the country, as also in northern Brazil, specially mixed ethnicities' descendants of Amerinds, black Africans and mainly European Portuguese. Further assays and analysis in enlarged number of samples, including representants of other ethnicities and regions of the country, will be necessary to offer more robust scientific information.

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Disclosure statements

None of the authors have conflict of interests.

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