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PROSTATE CANCER IN HIV-POSITIVE PATIENTS: A REVIEW OF THE LITERATURE

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Abstract – *Objective:* *Highly Active Antiretroviral Therapy (HAART) has significantly increased the survival of people living with HIV/AIDS (PLWHA) and reduced the incidence of AIDS-related diseases. The incidence of certain HIV-associated cancers such as Kaposi sarcoma (KS) and non-Hodgkin lymphoma (NHL) decreased after the widespread introduction of HAART in 1996, but more recent data show that HIV-infection is a risk factor for numerous cancers in PLWHA. Despite the increased prevalence of prostate cancer in general and in the HIV/AIDS population, the exact incidence of this malignancy in HIV-positive men is still unknown, due to the relative poor number of publications on this topic.*

Materials and Methods: *We considered the studies published about the incidence of prostate cancer in PLWHA by a systematic research on PUBMED (Bethesda MD, USA).*

Results: *The analyzed studies showed conflicting results, with a reported increase of prostate cancer incidence in PLWHA compared to the general population in some of them, while others reported a decrease.*

Conclusions: *Further studies are required to clarify the real association between prostate cancer and HIV/AIDS. Increasing the knowledge about this association is necessary to improve the outcomes for this unique population.*

KEYWORDS: *HIV, Prostate cancer, PLWH.*

INTRODUCTION

Antiretroviral Therapy (ART) has extremely modified the natural history of the Human Immunodeficiency Virus (HIV) infection, increasing survival and reducing the incidence of AIDS-related diseases[1]. However, despite its efficacy, ART has turned this infection in a chronic disease with the virus persistently present in the organism[2-13]. This latent infection is burdened with a high rate of morbidity

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and mortality caused by cardiovascular disorders, neurological disease, renal failure, bone diseases and malignancies[14-47].

As a consequence of the ART success, the number of elderly patients infected by HIV has significantly increased and it is estimated that the proportion of HIV patients aged ≥ 60 years old will increase from 8% to 39% in 2030, with a high percentage of late diagnosis[48-50]. This delay exposes HIV-infected people to the risk of reaching a very low CD4+ T-cell count with a quicker progression to AIDS than that occurring in younger People Living with HIV/AIDS (PLWHA)[51-54].

Despite the incidence classic AIDS-defining cancers decreased after the widespread introduction of ART in 1996, recent data show that HIV infection has to be considered a risk factor for numerous cancers[55-59]. Because of the lengthening of the average life expectation of PLWHA, it appears extremely important to evaluate cancer risk in this population, including the effects of age and time from HIV diagnosis. The increased cancer risk in PLWHA could be due especially to HIV-associated immune-dysregulation, presence of co-infections with oncogenic viruses and high prevalence of other behavioural cancer risk factors such as smoking[58,60-67]. Moreover, concomitant viral infections due to human herpes virus 8 (HHV-8), Epstein-Barr virus (EBV) and the human papillomavirus (HPV) play an important role in the pathogenesis of AIDS-defining cancers (ADCs). PLWHA also have an increased risk to develop some non-AIDS defining cancers (NADCs), such as Hodgkin lymphoma (HL), lung cancer, hepatocellular carcinoma (HCC), anal cancer, head and neck squamous cell carcinoma (HNSCC) and prostate cancer[54,58,63-70].

In industrialized countries, the majority of HIV-infected subjects are men[71,72]. This is why testis cancer, the most frequent tumour in HIV-negative men aged 20-40 years, and prostate cancer, the most common cancer in HIV-negative men overall, may have an even higher prevalence in the setting of HIV-positive individuals[73]. The aim of this paper was to review the literature about the epidemiology of prostate cancer in PLWHA.

Epidemiology of prostate cancer

Prostate cancer is the second most frequently diagnosed cancer worldwide and the fifth cause of cancer death among men, with 1.1 million of new cases diagnosed and 307,000 deaths in 2012[74]. It was estimated that, during his lifetime, a man has a probability of developing a prostate cancer equal to one out of seven[75]. Due to the increase and aging of population worldwide, it is expected that the global burden of prostate cancer will raise to 1.7 million of new cases, leading to 499,000 deaths by 2030[76]. The incidence of this malignancy changes considerably according to the geographical location and the ethnic origin. Particularly, Afro-American and French West Indian populations show the highest incidence rates (> 170 new cases per 100,000 people), whereas Asians show the lowest (< 20 new cases per 100,000 people). Despite this racial distribution, the highest rates of prostate cancer are observed in Australia and New Zealand (111.6 per 100 000), northern and Western Europe, and North America[74]. The majority of western countries have incidence rates ranging between 60 and 100 new cases per 100,000 people[77]. Mortality rates follow the ethnic origin more than the geographical distribution, ranging from 26.5% in East and Central Asia to 0.4% in Oceania. Europe and North America show an intermediate mortality rate[74].

The aetiology of prostate cancer remains largely unknown but age, ethnicity and a positive family history are well-established risk factors[78,79]. Current evidence on prostate cancer aetiology hasfocused on the environmental role, chronic inflammation, hormones and metabolism, diet and genetic factors. Interestingly, all these factors could interact with each other in a complex interrelationship. Prostate cancer incidence rates changed through the years in high-income countries, increasing accordingly with the increased use of transurethral resections of prostate (TURPs) and later to use of Prostate-Specific Antigen (PSA) testing in patients with benign prostatic hyperplasia (BPH)[80].

Prostate cancer in PLWHA

The incidence rates of this cancer have been rising over time even among HIV-infected men following the introduction of ART[81]. Prostate cancer in HIV-infected people is burdened with higher mortality rates compared to HIV-negative people and lower rates of PSA screening[82]. In the general population, constitutive risk factors are represented by older age, African American race and positive family history, whereas androgen supplement use and obesity are its modifiable risk factors[83-86]. However, the influence of HIV-related factors on prostate cancer incidence in HIV-positive men remains poorly defined[87-96].

Some studies reported a higher incidence of prostate cancer in PLWHA when compared to the general population. On the other hand, there are also reports of the opposite evidence.

Before the introduction of ART, evidence showed that rapid progression of prostate cancer in HIV-positive patients was associated to a severely depressed immune system. Moreover, probably because of a hypogonadal status, androgen deprivation therapy (ADT) had poor outcomes[97-99]. Supposedly, reasons for the increased rate of progression in HIV infected patients include suppressed cell-mediated immune responses, impaired immune surveillance, increased angiogenesis and reduced apoptosis[100-114].

As shown in *Table 1*, the majority of reported studies have identified a low or similar prostate cancer risk associated with HIV/AIDS compared to general population, during both the pre-ART and ART eras. However, other studies reported higher incidences of this malignancy in these patients compared with general population.

Similarly, some investigations have reported a decrease of breast cancer incidence in HIV-positive patients and immunosuppressed transplant recipients[115-117]. This interesting finding could be explained by different mechanisms known for a long time, as the hypothetic protective role of immunodeficiency, the capacity of HIV to infect, replicate in and damage the proliferation of cancer cells, endocrine effects or direct antineoplastic activity of the ART[118-123].

Among studies reporting a higher incidence rate of prostate cancer in PLWHA there are variable findings. Dal Maso et al[102] conducted a large population survey (n=12,104) to estimate the cancer burden among PLWHA in Italy during the period 1985-1998. As expected, the authors found high Standardized Incidence Ratios (SIRs) for Kaposi's Sarcoma (KS; 1749; 95% CI: 1602-1905), Non-Hodgkin Lymphoma (NHL; 352; 95% CI: 320-386), and, to a lesser extent, invasive cervical cancer (ICC; 22; 95% CI: 13-35), of which all were squamous-cell carcinomas. The combination of NADCs showed a SIR of 2.3 (95% CI: 2.0-2.7). Moreover, significantly elevated SIRs were found for cancer of anus (34; 95% CI: 12-74), HL (16; 95% CI: 12-22), leukaemias (5.3; 95% CI: 2.8-9.2), brain (4.4; 95% CI: 2.2-8.0) and lung (2.4; 95% CI: 1.5-3.7). The SIR of prostate cancer resulted slightly higher compared to other malignancies, accounting for 1.2 (95% CI: 0.1-4.3).

Crum et al[101] evaluated the incidence of prostate cancer in a relatively large cohort (n=269) and investigated the usefulness of prostate carcinoma screening in this population. Among men with HIV infection, the reported SIR of neoplastic prostate disease was equal to 3.1 cases per 1000 person-years. The authors reported that prostate cancer occurred in greater than one-third of 60-70 years old men in the studied cohort, a rate far higher than that found

TABLE 1. Published studies reporting the Standardized Incidence Rates (SIRs) of prostate cancer in PLWHA.

Study	*Year*	*Country*	*Total population, n*	*Study period*	*SIR (95% CI)*
Frisch et al[91]	2001	USA	302,834	1978-1990	0.7 (0.6–0.8)
Gallagher et al[93]	2001	USA	122,993	1981–1994	0.6 (0.5–0.9)
Dal Maso et al[102]	2003	Italy	12,104	1985–1998	1.2 (0.1–4.3)
Crum et al[101]	2004	USA	269	2002-2003	3.1 (//-//)
Newnham et al[103]	2005	UK	33,190	1985–2001	0.9 (0.3–2.1)
Clifford et al[100]	2005	Switzerland	7,304	1985–2002	1.43 (0.29–4.17)
Engels et al[56]	2006	USA	375,933	1980–1989	0.9 (0.4–1.8)
				1990–1995	0.5 (0.4–0.7)
				1996–2002	0.5 (0.4–0.7)
Hessol et al[88]	2007	USA	14,210	1990-2000	1.4 (1.0–2.0)
Grulich et al[104]	2007	Australia	13,067	1985–1999	1.06 (0.53–1.89)
Patel et al[89]	2008	USA	54,780	1992–1995	0.3 (0.1–0.3)
				1996–1999	0.7 (0.4–1.3)
				2000–2003	0.7 (0.4–1.0)
Crum-Cianflone et al[96]	2009	USA	4,498	1984-1990	(0-0.4)
				1991-1995	0.1 (0-0.2)
				1996-2000	0.2 (0-0.5)
				2001-2006	0.6 (0-1.1)
van Leeuwen et al[92]	2009	Australia	20,232	1982–1995	1.19 (0.57–2.18)
				1996–1999	0.63 (0.23–1.38)
				2000–2004	0.27 (0.11–0.52)
Powles et al[105]	2009	UK	11,112	1983-1995	0.00 (0.00-6.33)
				1996-2001	0.00 (0.00-1.91)
				2002-2007	0.88 (0.24-2.26)
Shiels et al[106]	2010	USA	287,247	1992-2007	0.5 (0.4–0.6)
Seaberg et al[107]	2010	USA	6,972	1984-2007	0.9 (0.5–1.6)
Franceschi et al[108]	2010	Swiss	9,429	1985-1996	0.00
				1997-2001	1.8 (0.6–4.1)
				2002-2006	1.3 (0.4–3.1)
Silverberg et al[109]	2011	USA	235,933	1996-2008	0.8 (0.6–0.9)
Raffetti et al[110]	2015	Italy	16,268	1986-2012	0.5 (0.3–1.0)
Godbole et al[111]	2015	India	32,575	1996-2008	4.4 (0.9-12.8)
Yanik et al[112]	2016	USA	142,940	2004-2011	0.78 (0.63-0.98)
Coghill et al[113]	2018	USA	2,923	1996–2012	0.48 (0.46-0.51)
Mahale et al[114]	2018	USA	183,542	1996-2012	0.47 (0.45 - 0.50)

in general population. These findings suggest that old age and/or duration of HIV infection can increase significantly the prostate cancer risk in these men. Finally, a very recent investigation carried out by Godbole et al[111] reported a higher incidence rate (4.4) compared to other studies. The authors estimate the SIRs of various types of AIDS- and non-AIDS-defining cancers. They reported that PLWHA may contribute to about 1.9% of cancers in general population and that SIRs of cancers in PLWHA are elevated about 11.5-fold compared with general population. While relatively few articles describe a more elevated SIR of prostate cancer in PLWHA compared to general population, the majority of published investigations about this topic report similar or lower SIRs. Particularly, one of the largest analysis of cancer incidence trends in HIV-positive patients in the USA compared the SIRs of all types of cancers in 54,780 PLWHA in two multicentre prospective observational cohorts: the "Adult and Adolescent Spectrum of HIV Disease (ASD) Project" and the "HIV Outpatient Study (HOPS)." The authors identified 3,550 incidences of cancer, of which 20% were non-AIDS-defining. Between 1992 and 2003, incidence rates in HIV-positive individuals decreased significantly for Kaposi sarcoma and non-Hodgkin lymphoma, and increased significantly for anal, colorectal and prostate cancer (14.7 cases per 100,000 person-years during 1992-1995 to 37.5 per 100,000 person-years during 2000-2003; p <0.01)[89]. Similarly, a retrospective analysis of a multicentre observational study enrolling 4,498 HIV-positive US military beneficiaries carried out between 1984 and 2006 revealed a decline in AIDS-defining malignancies between the pre-HAART and post-HAART eras but a parallel increase in the rates of non-AIDS-defining malignancies. However, a non-significant trend towards an increased prostate cancer event rate was found (0.1-0.6 per 1,000 person-years)[96].

Two very recent investigations confirmed the lower incidence rates of prostate cancers in PLWHA compared to general population. Coghill et al[113] found that HIV-infected men were more than 50% less likely to be diagnosed with prostate cancer (SIR 0.48, 95% CI: 0.46 to 0.51, p<0.001) and they demonstrated that this category has similarly lower SIRs of breast and colorectal cancer compared to general population. Moreover, the authors have demonstrated that HIV-infected patients with history of severe immunosuppression and a prior AIDS diagnosis had lower risks for prostate, proximal colon and rectum cancers compared with individuals with only HIV infection. A previous study showed that HIV-infected men with CD4 T-cell counts of less than 50 cells/mm3 have the lowest prostate cancer risk[106]. These findings, concordant with similar low rates of breast and prostate cancers in immunosuppressed transplant recipients[124], suggest that the severity of immunosuppression can play an important role in cancer risk.

Like Coghill et al[113], Mahale et al[114] found a low SIR for prostate cancer in PLWHA (0.47, 95% CI: 0.45-0.50) and confirmed that this category has a risk to develop prostate, breast and colorectal cancer lower that general population.

CONCLUSIONS

The real incidence of prostate cancer in PLWHA is still unclear, due to the conflicting published reports on this topic. The increased incidence of prostate cancer in PLWHA reported by some studies is likely due to the spread of PSA screening worldwide and a similar rise in incidence of this cancer in general population. Conversely, the lower incidence might be secondary to the ability of HIV to impair the proliferation of cancer cells or to changes associated with ART. Moreover, according to some authors, the observed lower rates of this cancer have been hypothesized to be due to a lower administration of PSA screening test in PLWHA compared with the general population. This condition could result in less frequent tumour detection at the early stage, leading to a decrease of local stage tumours compared to a population receiving screening (i.e., screening effect). However, there is not a lower cancer rates for larger tumours, which are generally clinically detected. In fact, the lack of frequent screening, could lead to a higher proportion of cancers diagnosed at advanced stages, which could result in an elevation in risk for distant-stage disease. An aspect that deserves further attention, due to the nature of prostate cancers, is whether HIV infection could modify cancer risk through causing hypogonadism and altering hormone levels. Further studies on this cancer epidemiology in PLWHA are required to clarify the real association between prostate cancer and HIV/AIDS. This is necessary to lead to the development of strategies improving outcomes for this unique population.

Conflict of Interest:

The Authors declare that they have no conflict of interests.

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