

# Cancer Risk in Patients Living with HIV/AIDS: Systematic Review

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*Risco de Câncer em Pacientes que Vivem com HIV/Aids: Revisão Sistemática*

*Riesgo de Câncer en Pacientes que Viven con VIH/Sida: Revisión Sistemática*

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## ABSTRACT

**Introduction:** Cancer will affect about 50% of HIV (human immunodeficiency virus) infected individuals with a significant burden of non-AIDS-defining cancers (acquired immunodeficiency syndrome). **Objective:** To analyze different risk factors for the non-defining type in the HIV positive population through selection of cohort studies conducted in several regions of the world. **Method:** Literature review conducted from March to April 2019 using the descriptors Cancer Risk, HIV and non-AIDS-defining Cancer. **Results:** Non-defining cancers representing the greatest incidence among HIV-positive population are lung, colorectal, cervical, vaginal and uterine, gastric, Hodgkin's lymphoma, and liver. **Conclusion:** Studies demonstrate that there are increased risks for several types of non-AIDS defining cancers, leading to a new paradigm, not only for HIV control but for early detection and timely treatment, in order to minimize the morbidities and increase life expectancy of these individuals.

**Key words:** Neoplasms; HIV Infections/complications; HIV Long-Term Survivors; Systematic Review.

## RESUMO

**Introdução:** O câncer acometerá cerca de 50% dos indivíduos com infecção pelo vírus da imunodeficiência adquirida (HIV), com importante carga daqueles do tipo não definidores da síndrome da imunodeficiência adquirida (aids). **Objetivo:** Analisar diferentes fatores de risco para câncer do tipo não definidor na população HIV positiva, por meio da seleção de estudos de coorte realizados em diferentes Regiões do mundo. **Método:** Trata-se de uma revisão de literatura realizada no período de março a abril de 2019, utilizando os descritores *Cancer Risk*, HIV e *non-AIDS-defining Cancer*.

**Resultados:** Os cânceres não definidores, que representam maior incidência entre a população HIV positiva, são o de pulmão, colorretal, cervical, de vagina e útero, gástrico, linfoma de Hodgkin e de fígado. **Conclusão:** Os estudos demonstram risco aumentado para diversos tipos de câncer não definidores da aids, o que nos leva a um novo paradigma, voltado não somente para o controle do HIV, mas também para a detecção precoce e tratamento oportuno, a fim de minimizar as morbidades e aumentar a expectativa de vida desses indivíduos.

**Palavras-chave:** Neoplasias; Infecções por HIV/complicações; Sobreviventes de Longo Prazo ao HIV; Revisão Sistemática.

## RESUMEN

**Introducción:** El cáncer afectará aproximadamente al 50% de las personas con infección por virus de inmunodeficiencia adquirida (VIH) con una carga significativa de cánceres que no definen el síndrome de inmunodeficiencia adquirida (sida). **Objetivo:** Analizar diferentes factores de riesgo para el cáncer no definitorio en la población VIH positivo en estudios de cohortes realizados en diferentes regiones del mundo. **Método:** Esta es una revisión de la literatura realizada de marzo a abril de 2019 utilizando los descriptores *Cancer Risk*, *HIV non-AIDS-defining Cancer*. **Resultados:** Los cánceres no definitorios que representan el mayor riesgo e incidencia entre la población VIH positivo son de pulmón, colorrectal, cervical, vaginal y uterino, gástrico, linfoma de Hodgkin y de hígado. **Conclusión:** Los estudios muestran riesgos para varios tipos de cáncer que no definen el sida, lo que nos lleva a un nuevo paradigma, que se centra no solo en el control del VIH sino también en la detección temprana y el tratamiento oportuno.

**Palabras clave:** Neoplasias; Infecciones por VIH/complicaciones; Sobrevivientes de VIH a Largo Plazo; Revisión Sistemática.

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## INTRODUCTION

Cancer will affect nearly 50% of the HIV (human immunodeficiency virus)-infected individuals, a considerable part of the disease burden and mortality of the pathology attributed to the virus. The infection defining cancers mark the beginning of the clinically relevant immunosuppression and appear through the loss of immune control of oncogenic viral infections, very common mainly prior to the antiretroviral therapy. Among them, the most common are Kaposi sarcoma, non-Hodgkin lymphoma and cervical cancer<sup>1</sup>.

The introduction of the Highly Active Antiretroviral Therapy (HAART), also known as combined antiretroviral therapy brought the viral load control to very low levels and recovery of the CD4+CD8+ cells, modifying the epidemiologic outlook of the HIV population and promoting the increase of life expectancy<sup>2</sup>.

The increase of longevity was a gain for those who live with HIV, but, along the time, it was observed that this increase in life expectancy has also promoted an increase of cumulative exposure to the systemic inflammation and accumulation of somatic mutations as well as epigenetic alterations related to carcinogenesis, raising the incidence of neoplasms unrelated to the acquired immunodeficiency syndrome (aids) as anal, liver and lungs cancers<sup>2,3</sup>.

Some factors may be involved with a bigger risk of cancer in the HIV-infected population such as: a) increase of new cases of the disease; b) higher rates of tobacco smoking in the population; c) increase of immunosenescence ; d) residual viral replication below detectable levels; e) infection by oncogenic virus: human papilloma virus (HPV), Epstein-Barr, hepatitis B (HBV) and hepatitis C (HCV) that can multiply because of the immunodepression condition<sup>3,4</sup>.

This means that this review has the objective of analyzing different risk factors for non-defining cancers in the HIV positive population in cohort studies conducted worldwide.

## METHOD

The present systematic review was carried out according to the strategy Preferred reporting Items for Systematic Reviews and Meta-analyses (PRISMA) for the checklist and construction of the flowchart in four main stages (identification, selection, eligibility and enrollment). The current review was registered in the International Prospective Register of Systematic Reviews (PROSPERO) with number CRD42020168929.

The research question was based in the strategy PICO, with “P” for population of the study (people living with

HIV); “I” for intervention studied or variable of interest (risk factor); “C”, for control, comparison with other variable (people without HIV); “O” outcome of interest (development of cancer). Therefore, the research question for the present study was: “Which neoplasms have more risks of incidence in seropositive individuals?”

From March to April 2019 the search for articles of every year without specific period was conducted through the search engine PubMed, main tool of data retrieve of the Medical Literature Analysis and Retrieval System Online (MEDLINE). The controlled descriptors utilized for this study were Cancer Risk, HIV and Cancer non-AIDS-defining, surveyed separately and combined.

The inclusion criteria to select articles were: a) presence of the descriptors selected; b) full texts available at the Internet; c) publications in Portuguese, English or Spanish; d) studies with systematized and coherent methodological definitions. Descriptive studies that did not provide the method utilized and/or results obtained and incomplete articles, reviews and editorials were excluded.

Duplicate articles were identified and excluded for abstract reading. The articles included after this stage were critically reviewed in relation to methodology, results obtained and regions where the studies were performed.

The strategy of the synthesis of the data included the identification, selection, eligibility and inclusion. The survey in the database resulted in 260 articles, excluding 73 reviews. Titles and abstracts of 187 articles were thoroughly read, 169 of them failed to comply with the eligibility criteria of the current study, resulting in 11 articles that form the *corpus* of this review as demonstrated in the flowchart of articles survey (Figure 1).

In order to minimize possible bias of checking the studies as errors of interpretation and design, two investigators read the articles and filled the instruments separately for further comparison. In the cases where discrepancies occurred, the articles were read again, and a third independent investigator filled the instrument.

## RESULTS

It was applied the seven-levels classification system in the current review: a) level I (evidences drawn from systematic reviews or meta-analysis of relevant clinical trials); b) level II (evidences drawn from at least one randomized, controlled, well-designed clinical trial); c) level III (well-designed non-randomized clinical trials); d) level IV (well-designed cohort and case-control studies); e) level V (systematic review of descriptive and qualitative studies); f) level VI (evidences drawn from one descriptive or qualitative study); g) level VII (opinion of authorities

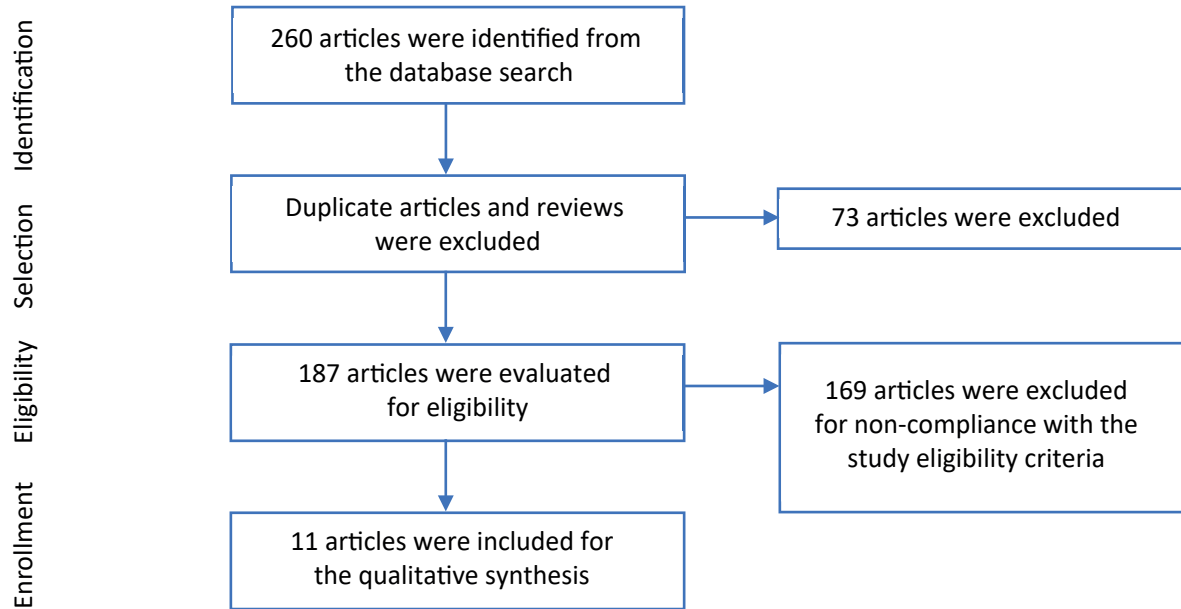


Figure 1. Flowchart of articles' survey

or experts panel reports). All the articles included in the study were classified as level of evidence IV.

The selected studies were from cohorts located in eight different European, American and Asian continents countries: Spain, France, Italy, England, Japan, United States of America, Mexico and Brazil. Figure 2 shows the geographical distribution of the studies included in this study.

Among the countries referenced, lung, colorectal, cervical, vagina and uterus, gastric, Hodgkin lymphoma and liver are the most frequent in the population living with HIV in comparison with the population non-HIV-infected. Table 1 show the articles surveyed.

## DISCUSSION

The World Health Organization (WHO)<sup>5</sup> estimated that in 2018 there were nearly 17 million new cases of cancer in the world population with approximately 9.5 million deaths by neoplastic diseases. In general, the most frequent types were lung, breast, colorectal, prostate, stomach, lung, esophagus and cervical cancer, which are also those with higher mortalities.

In a study conducted during nine years with 1,185 HIV adult patients in Japan, 49.2% of the persons diagnosed with non-defining cancer were already at an advanced stage of the tumor and mean age of 57 years.



Figure 2. Graphic representation of the distribution of cohorts per countries

Table 1. Result of the selection of articles

<b>Title</b>	<b>Country</b>	<b>N</b>	<b>Year</b>	<b>Results</b>
<i>Riesgo de cáncer en personas con VIH en España, 2004-2015. Estudio de la cohorte CoRIS</i>	Spain	12,239	2019	Hodgkin lymphoma, cervical, breast and head and neck are the non-defining cancers with higher risk in women.
<i>Risk for cancer among people living with AIDS, 1997-2012: the São Paulo AIDS – cancer linkage study</i>	São Paulo – Brazil	87,109	2018	Anal and Hodgkin lymphoma present higher risk in men and in women, liver, anal, amygdala, oropharynx, vulva and vagina.
<i>Increased risk of non-AIDS-defining cancers in Asian HIV-infected patients: a long-term cohort study</i>	Tokio – Japan	1,118	2018	Non-defining cancers with noticeable increased risk were liver, cervical and stomach.
<i>Non-AIDS defining cancer (NADC) among HIV-infected patients at an oncology tertiary-care center in Mexico</i>	Mexico	127	2018	In men, cancers who have more risk of development were non-Hodgkin lymphoma, followed by anal cancer, and in women, vulvovaginal followed by breast cancer.
<i>Risk of non-AIDS-defining cancers among HIV-1-infected individuals in France between 1997 and 2009: results from a French cohort</i>	France	84,504	2014	Lung, Hodgkin lymphoma, anal and liver were the cancers with higher risk.
<i>Trends and predictors of non-AIDS-defining cancers in men and women with HIV infection: a single-institution retrospective study before and after the introduction of HAART</i>	Milan – Italy	5,924	2013	Vulva, Hodgkin lymphoma, anal and lung were the cancers with higher risk for women and for men the risks were anal cancer, Hodgkin lymphoma, amygdala, lung and liver.
<i>HIV infection and the risk of cancers with and without a known infectious cause</i>	California – USA	20,277	2009	Overall, cancers with higher risk for the HIV population were squamous cells, anal and Hodgkin lymphoma.
<i>Cancer risk in people infected with human immunodeficiency virus in the United States</i>	USA	57,350	2008	Among aids non-defining cancers, it was noticed elevated incidence of lung cancer, Hodgkin lymphoma and oral/pharynx, anus, larynx, pancreas and penis cancer.
<i>The risk of cancer in HIV-infected people in southeast England: a cohort study</i>	United Kingdom	26,080	2005	The most frequent cancers in men were: anus and anal channels, liver, bronchial and lungs, other cells, Kaposi sarcoma, nerves and soft tissues, secondary lymph node, unknown site, Hodgkin disease, non-Hodgkin lymphoma, leukemias and other hematopoietic lymphoid.
<i>Risk of cancer in persons with AIDS in Italy, 1985-1998</i>	Italy	12,104	2003	Anus, lung, brains Hodgkin disease and leukemias were the cancers with higher risk of occurrence.
<i>Risk of cancer in patients with HIV disease. London African HIV/AIDS Study Group</i>	United Kingdom	2,048	1999	Most common non-defining cancers were Hodgkin disease and anal cancer.

Half of non-aids defining neoplasms was gastric cancer. There was a significant increase of the incidence of liver and rectum cancer in seropositive population when compared to the general population<sup>6</sup>.

The higher incidence and mortality by cancer among the world population is in Asian countries. In the Asian continent, 50.9% of the world incidence and 57.4% of the mortality by cancer are recorded, resulting in an estimate of 8.6 million new cases in 2018<sup>5</sup>.

Either in the Japanese population in general or in the HIV population, it was found a strong incidence of gastric cancer. According to Nagata et al.<sup>6</sup>, in Japan there is an elevated prevalence of *H. pylori* associated to high occurrence of the pre-cancer condition of intestinal neoplasm, which brings great risks of gastric cancer to the general population and when related to immunity reduction, raises significantly the exposure to infection and severe gastritis leading to increase of gastric cancer especially in HIV-infected individuals.

In a recent study published in Spain with 12,239 HIV-infected individuals who were followed up in a cohort for 11 years, the mean age of the participants was 41 years, of which 68.1% developed some type of non-defining cancer. In comparison with the general population, the risk of cancer was twice for HIV-infected men. Hodgkin lymphoma and lung cancer are among the higher relative risks found in the study for both genders; non-Hodgkin lymphoma higher for men and cervical cancer, head and neck cancer for women<sup>7</sup>.

Lung cancer is one of the most important causes of morbimortality and the type of cancer most prevalent among the non-defining surveyed in several studies as, for instance, García-Abellán et al.<sup>7</sup> where 50% of the participants were smokers, the double of the prevalence among the general population. In addition, the oncogenic potential of tobacco in HIV-positive individuals can be prolonged for until five years after quitting smoking which brings a great risk of lung cancer in this population<sup>7-9</sup>.

A French study evaluated 84,504 HIV-infected individuals where age at the diagnosis was significantly younger for this population for Hodgkin lymphoma and liver cancer, being nine-fold higher for Hodgkin lymphoma and 2.4-fold higher for liver cancer. The same study indicated that the risk was close to that of the general population for lung cancer<sup>10</sup>.

Two studies conducted in Italy, the first with HIV-infected 4,382 men and 1,542 women demonstrated increased risk for both genders for anal, Hodgkin lymphoma and lung cancer. For HIV-positive women, the risk was higher for vulva cancer and for men, amygdala, lung and liver<sup>9</sup>. The second demonstrated higher risk for anus, lung cancers and, Hodgkin lymphoma and

differently from the first, brain cancer incidence was identified<sup>11</sup>.

For Dal Maso et al.<sup>11</sup>, brain cancer can have high incidence due to misinterpretation during diagnostic closing. Non-neoplastic masses or attributable to non-Hodgkin lymphoma might have been misdiagnosed as brain tumors resulting in altered risk for this type of neoplasm.

In a study conducted in England there was significantly standardized increased incidence for all non-aids defining cancers in men, but not significant in women. The main types of neoplasms were: anal, liver, bronchial and lung, nerves and soft tissues, secondary lymph node, Hodgkin lymphoma and leukemias. Despite the great variety of types found, it was also one of the studies with large number of participants, 26,080 men and 7,110 women were enrolled<sup>12</sup>.

In the study of Petrukkevitch et al.<sup>13</sup>, also in England, the defining cancers were the most prevalent and non-defining were only Hodgkin lymphoma and anal cancer. One of the possible causes of other types with elevated risk in the HIV-positive population not been identified is the study period. HAART had more adherence in 1996 and only henceforward there was increase in life expectancy of the HIV patient and cure of aids, and the appearance of other diseases as different neoplasms types<sup>2</sup>.

The higher incidence of new cases of cancer and mortality rates are found in the European general population, 3.9 and 1.9 million, respectively, behind only Asian countries. The main types of neoplasm diseases affecting the European population are prostate, lung, colorectal and bladder cancer in men and breast, colorectal, lung and cervical cancer in women<sup>5,14</sup>. When prostate, bladder and breast cancers are compared, there were no significant incidence for the HIV-positive population.

After Europe, North America had 1.8 million new cases of cancer in the general population with 692 thousand deaths in 2018<sup>5</sup>. In two different USA articles with HIV patients, there was high incidence of Hodgkin lymphoma, anal and lung cancer. Engels et al.<sup>15</sup> demonstrated significant elevated risk for cervical, oral, larynx, liver, pancreas and penis cancers<sup>8,15</sup>.

South America is the fourth region with great incidence among the world general population, there were nearly 1.3 million new cases and 665 thousand deaths estimated for 2018<sup>5</sup>. In a cohort Brazilian study with HIV-positive population in São Paulo, colorectal non defining cancer had the highest risk. It is estimated that HPV infection is responsible for 93% of all the cases of squamous cells anal cancer. In a cohort in Rio de Janeiro (Brazil), with 863 seropositive women, it was identified

that 51% had anal carcinogenic HPV high risk infection and 31% presented abnormal anal cytology. In a cohort with 84,504 HIV-positive patients in France, there was a risk 79-fold higher for anal cancer in this population in comparison with the total population<sup>3,10,16</sup>.

In HIV-infected women, cervical and vulva, vagina and uterus cancers were the most frequent found in the studies. These cancers are associated to different kinds of HPV and also to low screening coverage exams as the Papanicolaou test. In Brazil, the national guidelines recommend the annual preventive exam in the population from 25 to 64 years old, but public policies to prevent HPV and early diagnosis specific for the HIV population are necessary<sup>3,11</sup>.

In a Mexican study with 1,126 HIV positive individuals, 11% developed non defining cancer, being 5% of multiple primary neoplasms. Non-defining cancers most frequent were Hodgkin lymphoma and anal cancer in men and vulvovaginal and breast cancers in women<sup>17</sup>.

Tumors associated to viral infections represented 50% of all the neoplasms in the study conducted by Cornejo-Juárez et al.<sup>17</sup>, with high incidence of Hodgkin lymphoma which is associated to the Epstein-Barr virus infection and vulvar, vaginal and colorectal cancer. In another study conducted in the state of California, USA the infections-related cancers represented 70% with relevance of Hodgkin lymphoma and colorectal cancer. A cohort in France indicated a 26-fold higher risk of Hodgkin lymphoma in the HIV population even in individuals with CD4+<sup>8,10,17</sup> cells recovery. Other works suggested that HAART induced immune reconstitution can increase the risk of Hodgkin lymphoma when stimulation of B cells and number of lymphocytes infected by the Epstein-Barr is expanded<sup>9</sup>.

Franzetti et al.<sup>9</sup> indicate there is a significant increase of the CD4+ count at the cancer diagnosis when comparing the period of immunosuppression suggesting that low CD4 does not predict the occurrence of neoplasms and justifies because many of them do not reduce its risk when CD4 count increases. In a cohort in Italy, the authors<sup>9</sup> affirmed that the immune recovery in patients with severe immunodeficiency may not reduce the risk of non-defining cancer, possibly because there is not a complete recovery, suggesting that these types of cancer do not need to be strictly associated to a high degree of immunosuppression in the moment of the diagnostic<sup>9,17</sup>.

In the articles included, all types of defining cancers and most of the non-defining cancers occurred at higher rates in the HIV-positive population. The studies also demonstrated that these patients are affected by neoplasm diseases in younger ages than in the general population. The studies demonstrated that all HPV infection

associated cancers, except tongue and penis, had increased rates in the HIV-positive population in comparison with the general population.

## CONCLUSION

The present article showed that non-defining cancers which are riskier and more frequent in HIV-positive population are lung, colorectal, cervical, vagina and uterus, gastric, Hodgkin lymphoma and liver cancers. Despite brain tumor is a risk cancer for this population, there are discrepancies among the studies in relation to the cause and can be attributed to misdiagnosis.

The articles presented in this manuscript showed higher risk of several types of cancer in the seropositive population affecting at younger ages when compared to the general population, which brings us to reflect about the necessity of specific prevention policies and early diagnosis not only about HIV defining cancer but also of other types of cancer.

Primary prevention, including strategies to encourage tobacco quitting and reduce alcohol use, vaccination against potentially oncogenic viruses as HPV and HBV, and the effective treatment of chronic infections including HAART are important tools for cancer management in HIV-infected individuals. Early cancer detection through screening and timely treatment could contribute to reduce even more the morbimortality in this population further to increasing the quality of life of these individuals.

Even if the design of the selected studies were correct to verify risks of cancer in individuals living with HIV, the development of more researches to test the associations of variables that could be involved in this process is necessary. The non-inclusion of other languages, only one investigator conducting the search regardless of two other investigators analyzing the articles and only one database for data collection are some of the limitations of the study.

The results obtained allowed to identify gaps mainly in relation to the necessity of evaluating the justification for increased risk of certain pathologies in the HIV-positive population.

## CONTRIBUTIONS

Larissa Di Leo Nogueira Costa contributed for the conception and planning of the manuscript, gathering, analysis and interpretation of the data and wording of the text. Aline Santos Kennelly contributed for the wording. Dayse Azevedo Coelho de Souza contributed for the wording and critical review with intellectual input. Uiana Regina Silva de Lima contributed for the conception and design of the study. Conceição de Maria Pedrozo Silva de

Azevedo contributed for the conception and planning of the manuscript, analysis and interpretation of the data, wording and critical review. All the authors approved the final version to be published.

#### DECLARATION OF CONFLICT OF INTERESTS

There is no conflict of interests to declare.

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