

# Breast cancer in women living with HIV

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**Abstract.** – With the introduction of HAART, the life expectancy of the patients infected with HIV almost approached that of the general population. The incidence of certain HIV-Associated cancers as Kaposi Sarcoma (KS) and Non-Hodgkin Lymphoma (NHL) decreased, while an increase in Non-AIDS-Defining cancers (NADCs) has been documented. HIV infection is a risk factor for numerous cancers in PLWH. Breast cancer is the most common cancer worldwide among all women. The association between HIV infection and breast cancer has not been thoroughly investigated: when compared to the general population, people living with HIV/AIDS (PLWHA) have a similar or slightly lower risk of breast cancer. Screening tests are essential weapons to fight cancer burden and more effective therapeutic and preventive strategies are needed, especially among PLWHA. Further and more comprehensive studies are needed to better characterize breast cancer among PLWH.

*Key Words:*

Breast Cancer, Screening, Human immunodeficiency virus (HIV), Epidemiology.

## Introduction

The introduction of ART has had a significant impact on people living with HIV/AIDS (PLWHA) survival, turning HIV infection into a chronic condition. As a consequence, long-term morbidities, including malignancies, represent a new challenge to manage<sup>1-26</sup>.

Cancer is a burden worldwide, of interest the epidemiology in PLWHA has changed in the last 20 years. In fact, the incidence of the three classically AIDS-defining cancers (Kaposi's Sarcoma, Cervical cancer and Non-Hodgkin Lymphomas) has significantly decreased, while an increase in Non-AIDS-Defining cancers (NADCs) that typi-

cally occur at older ages has been documented<sup>27-38</sup>.

Several studies suggest a synergistic carcinogenic effect of aging and HIV, as a matter of fact, beyond the "classic" risk factors such as smoking, alcohol and age, it is important to consider the HIV-related risk factors, such as immunodeficiency, chronic persistence of infection and viral infections often associated with HIV (Hepatitis B Virus (HBV), Hepatitis C Virus (HCV), Human Papilloma Virus (HPV)<sup>39-47</sup>.

Human Immunodeficiency Virus (HIV) leads to progressive immunosuppression that has been associated with an increased cancer risk. Decreased immune surveillance and increased immune activation play an important role in cancer development. Moreover, HIV may have a direct role in carcinogenesis, inhibiting tumor suppressor genes and activating cellular proto-oncogenes<sup>48,49</sup>.

Furthermore, susceptibility to the effects of carcinogens may be greater in PLWHA than in HIV-uninfected individuals, maybe due to the endothelial alterations associated with HIV infection, which may be permissive for tumor growth<sup>50</sup>. As well, HIV-associated immunosenescence may also be associated with increased cancer risk<sup>51,52</sup>.

Predictors for NADCs in HIV-infected patients include old age, lower CD4+ cell count, smoking habits and socioeconomic disadvantage<sup>28,29</sup>. On the other hand, while antiretroviral therapy has been shown to be protective against ADC it was not against NADCs. In fact, the incidence of certain NADCs in HIV patients has been reported to have increased in the combination antiretroviral therapy (ART) era<sup>50</sup>.

## Breast Cancer Epidemiology

Breast cancer is the most common cancer worldwide among all women, it represents the 12% of all new cancer cases in the world and the 25% of

all cancers<sup>53</sup>. Of note, it is the most common cause of cancer-related deaths among women, representing the 15% of total cancer deaths<sup>54</sup>. Although the relationship between HIV and certain cancers has been deeply characterized, there is little evidence about breast cancer among PLWHA. When compared to the general population, PLWHA have a similar or slightly lower risk of breast cancer<sup>55</sup>. Breast cancer has previously been described as occurring less frequently in women with AIDS compared to the general population<sup>56</sup>. Goedert et al<sup>52</sup> have shown that although HIV-infected women have a lower cancer risk, over time, it has almost approached the incidence in the general population. There are no reliable data about the role of HIV infection on the risk of breast cancer and the stage; the histological and molecular characteristics seem to be independent factors. However, more side effects occur during the treatment of the neoplasm, probably caused by the drug interactions between chemotherapy and HAART<sup>57</sup>. Hurley et al<sup>58</sup> found that chemotherapy was poorly tolerated in patients with HIV, suggesting that HIV/AIDS and ART may negatively affect chemotherapy tolerability with a greater degree of lymphocytopenia and neutropenia. Parameswaran et al<sup>53</sup> similarly reported that 56% of patients with HIV and breast cancer in New York required a dose reduction in chemotherapy, compared with 30% of uninfected patients. Breast cancer is a result of a complex interplay of genetic, metabolic, immunologic and environmental factors. Several studies suggest an accelerating or detrimental effect of HIV in the natural evolution of breast cancer. Furthermore, similar genetics, signaling pathways and common receptors to both HIV and breast cancer<sup>59,60</sup> have been suggested as the possible cause of this complex interplay. The common expression of genes and receptors does not establish a link between HIV and breast cancer, but may suggest a possible role of HIV in the natural history of this tumor. However, several data suggest that HIV infection promotes tumor growth acting on immune signaling, angiogenesis and metastasis<sup>61-65</sup>. HIV infection and ART are known to be associated with a variety of metabolic disorders, including metabolic syndrome. Several studies confirm an overall increase in the incidence of metabolic syndrome in patients with HIV receiving ART<sup>66</sup>, particularly relevant for patients with HIV and breast cancer.

### **Biomarkers**

Biomarkers are used for breast cancer and they are classified as predictive and prognostic mar-

kers<sup>67</sup>. Predictive markers provide information about the therapy and its efficacy, while prognostic markers offer information about biological characteristics that may influence the prognosis of the disease. Numerous biomarkers have been investigated for clinical applications. P53 was observed in approximately 15% of breast cancer patients, but it is not specific to breast cancer<sup>68</sup>. CA15-3 is a biomarker for advanced breast cancer with limited sensitivity for early-stage cancer. It can be applied to monitor therapy and recurrences<sup>69-71</sup>. HER2 levels were observed higher in about 30% of patients with breast cancer. It is helpful for monitoring disease relapse, cancer progression and choosing appropriate therapy. BRCA1 and BRCA2 are commonly used to evaluate breast cancer susceptibility<sup>72</sup>. They are involved in repair of DNA double-strand breaks that are responsible for breast cancer. Gene mutations lead to instability of the genome and the result is an increased risk of breast cancer<sup>73</sup>. MicroRNAs (miRNAs) such as miR-21, are new markers with high specificity and sensitivity<sup>74</sup>.

### **Screening**

Factors involved in increased cancer risk among HIV-infected people are immunosuppression, chronic inflammation, long-term exposure to antiretroviral agents<sup>75-80</sup>.

The growing burden of non-AIDS-defining cancers requires cancer prevention and early detection among PLWHA<sup>39,53</sup>. Early detection has been associated with a reduction in breast cancer mortality and breast cancer screening allows the detection of breast cancer in an asymptomatic phase and at an early stage<sup>81</sup>. PLWHA should be screened for cancer at earlier ages than HIV-uninfected individuals and screening should be performed more frequently<sup>82</sup>. Screening tests for breast cancer include clinical and self-breast examination, mammography, screening ultrasonography, magnetic resonance imaging (MRI), and breast tomosynthesis<sup>83</sup>. The importance of self-examination is usually under evaluated. In our opinion, it is worthy to spend some time during the routine medical visits of PLWHA teaching a correct self-examination and explaining its importance. Mammography, however, is the best-studied method to reduce mortality from breast cancer, with a 77-95% and 94-97% of sensitivity and specificity, respectively<sup>78-84</sup>. The false-positive and false-negative rates of mammography are relatively high and the sensitivity could be reduced in high dense breasts and

premenopausal women. However, it has many downsides: the use of ionizing radiation, relatively high false-positive and false-negative rates, and uncomfortable examination<sup>85,86</sup>. The sensitivity of mammography is related to the age, radiologist's experience and technique quality<sup>85</sup>. Breast ultrasonography is a cost-effective and widely available exam, which detects tumors by using acoustic waves. It increases cancer detection rates for subjects with high breast cancer risk and high breast density<sup>86</sup>. Breast MRI has been recommended for subjects with high breast cancer risk, but it has not been recommended for the general population due to its high false-positive rate, high cost and the need for experienced radiologists<sup>84</sup>. The aim of screening tests is to reduce the mortality of women who are at risk. When available, they represent an effective weapon in cancer prevention, together with an early onset of therapy, lifestyle changes, coinfection treatment and vaccinations<sup>39</sup>. Screening recommendations vary by country and institution. According to the European guidelines, all women between 50 and 70 years old have to perform a mammogram every two years. In some Italian regions, screening recommendations usually range between 45 and 49 years old, and every two years from 70 to 74. It is advisable to perform a mammogram to women under 40 at high risk<sup>86,87</sup>. High-risk women are those with genetic factors (Li Fraumeni syndrome, BRCA1, BRCA2), familiarity, iatrogenic factors (a history of chest irradiation between the ages of 10-30 years for lymphomas and other tumors, hormonal therapy) and individual factors (atypical hyperplasia, pregnancy in old age, premature menarche, late menopause)<sup>88</sup>. The Guidelines for general population may be applied to women living with HIV<sup>87</sup>.

## Materials and Methods

On January 7<sup>th</sup>, 2019, we performed a review of the literature to identify the possible links existing between Human Immunodeficiency Virus (HIV) infection, HAART and breast cancer.

We searched PubMed applying the keywords "Breast Cancer", "HIV infection", "Screening", "HAART" to identify potentially relevant articles.

We included only recent articles written in English, and we found 98 publications. We excluded 10 articles after reading title and abstract. At the end of the assessment, we included in our review the 88 full-text articles.

## Discussions

Highly Active Antiretroviral Therapy (HAART) has significantly increased the survival of PLWHA, turning this infection into a chronic disease. As a consequence, we assisted to an increase in the incidence of non-AIDS defining cancer, typically occurring at older ages. HIV infection is a risk factor for numerous cancers: breast cancer is one of them, representing a major worldwide public health problem. When compared to the general population, PLWHA have a similar or slightly lower risk of breast cancer, but several data suggest a role of the virus in carcinogenesis, therapy and outcomes. For this reason, the importance of a correct management of patients should not be underestimated. Screening tests are essential weapons to fight cancer burden and more effective therapeutic and preventive strategies are needed, especially among PLWHA. Infectious specialists have to persuade the patients about the importance of screening and early diagnosis. Moreover, it is worthy to spend some time during the routine medical visits of PLWHA teaching a correct self-examination and explaining its importance. PLWHA should undergo a screening for breast cancer at younger age and more often than the general population. The different screening tests showed no differences in sensitivity and specificity between PLWHA and HIV-negative subjects, so the recommended tests for the screening of breast cancer in PLWHA should be the same that we use for the general population. What should be improved are their frequency and the adherence of our patients.

## Conclusions

Cancer screening has to become an integral part of the clinical management of patients, especially if at high risk, such as PLWHA. Further and more comprehensive studies are needed to better characterize breast cancer among PLWHA and the role of HIV in the natural history of this tumor.

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## Conflict of Interest

The Authors declare that they have no conflict of interest.

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