



# CANCER SCREENING IN HIV-INFECTED PATIENTS: EARLY DIAGNOSIS IN A HIGH-RISK POPULATION

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**Abstract – Objective:** *With the introduction of the antiretroviral therapy (ART) in 1996, life expectancy of the patients infected with HIV almost approached that of the general population. Immune dis-regulation increases not only the risk of developing a neoplasm, but also its progression rate and aggressiveness. Several recent studies suggest a synergistic carcinogenic effect of aging and the HIV virus. The aim of this study was to obtain data about cancer screening of the HIV-positive patients followed in our center.*

**Patients and Methods:** *Patients and controls were asked to reply to a survey after signing an informed consent. Data were registered into an electronic database in Excel format and analyzed using the IBM Statistical Package for Social Science software (Chicago, IL, USA) for Windows, version 25.0.*

**Results:** *One hundred and nine individuals (53 HIV-positive cases, 48.6%, and 56 HIV-negative controls, 51.4%) were included in the study. Ninety-four (86.2%) were males. Fourteen cases and 14 controls received a proposal to undergo a screening test during their lifetime. Of these, only ten cases and 10 controls underwent them, with an overall adherence of 18.9% both in cases and controls. Seventeen cases and 20 controls met the criteria for prostate cancer screening, 2 cases and 5 controls should have been proposed the breast cancer screening, 32 cases and 10 controls were eligible for colorectal cancer screening, 11 cases and 4 controls should have undergone lung cancer screening, 5 cases and 8 controls should have undergone PAP test at least once in their life, 27 cases and 4 controls were eligible for anal cancer screening.*

**Conclusions:** *A low percentage of patients underwent any screening test for cancers, as well as a very low percentage of controls, not only in the HIV positive population, but also in the control group. General practitioners and the infectious specialists hold the opportunity to propose and promote cancer screening tests as an integral part of the clinical management of patients, especially if at high risk, such as PLWH.*

**KEYWORDS:** *Cancer, HIV, Screening, Screening test, Adherence, Screening program.*



## INTRODUCTION

With the introduction of the antiretroviral therapy (ART) therapy in 1996, life expectancy of the patients living with HIV (PLWH) almost approached that of the general population<sup>1,2</sup>. This lengthening brought to an increase in the incidence of chronic diseases such as cancers, which epidemiology, however, has changed in the last twenty years<sup>3-24</sup>. The incidence of AIDS-defining cancers, such as Kaposi's Sarcoma (KS), Cervical cancer and Non-Hodgkin Lymphomas (NHL) has significantly decreased, while an increase in Non-AIDS-Defining cancers (NADCs) has been documented<sup>25-43</sup>. Several recent studies suggest a synergistic carcinogenic effect of aging and the HIV virus: in addition to the "classic" risk factors such as smoking, alcohol and aging, HIV-related risk factors such as immunodeficiency, chronic persistence of inflammation and viral infections often associated with HIV for similar modes of transmission (HBV, HCV, HPV) have to be considered<sup>44,45</sup>. As a matter of fact, immune dis-regulation increases not only the risk of developing a neoplasm, but also its progression rate and aggressiveness<sup>34</sup>. Therefore, it is of utmost importance preventing and early recognizing cancers in PLWH to ensure them better outcomes. The aim of this study was to obtain data about cancer screening of the HIV patients followed in our center, and to compare them with the general population to find the most recurrent risk factors needing a greater attention.

## MATERIALS AND METHODS

From October 3<sup>rd</sup>, 2017, to January 31<sup>st</sup>, 2018, patients coming to the outpatient clinic of the Infectious Diseases Unit of the University Hospital "G. Martino" in Messina, Italy, were asked to reply to a survey after signing an informed consent. The survey was a two-parts questionnaire: the first part asked for information about the patients' general health status, HIV serological status, familiar pathologies, drugs taken, past pathologies, while the second one looked into risk factors for cancers and the patients' adherence to screening tests, as defined by the "Italian Guidelines for the use of the Antiretroviral Therapy and diagnostic-clinical management of people living with HIV-1 infection – 2017 edition"<sup>46</sup>. Participation to the survey did not require the execution of additional diagnostic tests or treatments; moreover, we guaranteed anonymity and there was an opt-out chance not leading to any repercussions on medical-care continuity. No inclusion or exclusion criteria were used. Patients' and controls' were identified using their HIV serological status (positive for patients and negative for controls). Data were reg-

istered into an electronic database in Excel format and analyzed using the IBM Statistical Package for Social Science software (SPSS Inc., Chicago, IL, USA) for Windows, version 25.0. Descriptive statistics were used to analyze data. Frequency and percentages were used to resume categorical variables, while mean  $\pm$  standard deviation (SD) to resume continuous variables. Pearson's  $\chi^2$ -test (Confidence Interval, CI, 95%) was used to determine statistically significant differences between a case HIV-positive population and a control HIV-negative population.

## RESULTS

One hundred and nine individuals (53 HIV-positive cases, 48.6%, and 56 HIV-negative controls, 51.4%) were included in the study. Ninety-four (86.2%) were males, 46/53 (86.8%) cases and 48/56 (85.7%) controls, 13 females (11.9%), 5/53 (9.4%) cases and 8/56 (14.3%) controls; 2/53 (3.8%) were female transsexuals. Mean age of the cohort included in the study was 46.0 years (SD  $\pm$  12.4 years). Cases were slightly younger (45.3  $\pm$  11.5 years) than controls (46.7  $\pm$  13.2 years). There were no statistically significant differences between cases and controls regarding gender ( $p = 0.265$ ) or age ( $p = 0.569$ ). Regarding sexual orientation, a statistically significant difference ( $p < 0.001$ ) existed between cases and controls, with cases including more homosexual and bisexual people than controls.

Characteristics of the population are resumed in Table 1.

With regards to risk factors, smoking was the most frequent one, with a statistically significant difference existing between cases, with 66.0% smokers, and controls, with 19.6% smokers ( $p < 0.001$ ). Moreover, controls were more prone to quit smoke, with a mean duration of the smoke habit before dismissal in HIV-positive people of 26.4 years (SD  $\pm$  8.0 years) against 12.6 years (SD  $\pm$  11.7) in controls ( $p = 0.001$ ). No statistical difference was found regarding the number of cigarettes smoked per day, the number of quitters and the number of cigarettes smoked per day before quitting. We also investigated hormonal contraception, radiological testing before the age of 30 years, and the use of corticosteroid drugs. No statistical difference was found between cases and controls. Fourteen cases and 14 controls received a proposal to undergo a screening test during their lifetime. Of these, only ten cases and 10 controls underwent them, with an overall adherence of 18.9% both in cases and controls. The proposal was made more often by the infectious diseases specialist with regards to cases, while the Provincial Health Authority was the most

**TABLE 1.** Characteristics of the population.

	Cases (%)	Controls (%)	p-value
<b>Comorbidities</b>			
None	15/53 (28.3%)	27/56 (48.2%)	0.070
1-3	37/53 (69.8%)	29/56 (51.8%)	
> 3	1/53 (1.9%)	0	
<b>Previous cancer</b>			
None	48/53 (90.6%)	53/56 (94.6%)	Not performed
Yes	5/53 (9.4%)	3/56 (5.4%)	
<b>Familiar pathologies</b>			
None	24/53 (45.3%)	26/56 (46.4%)	0.993
1-3	28/53 (52.8%)	21/56 (51.8%)	
> 3	1/53 (1.8%)	1/56 (1.8%)	
<b>Drugs (other than cART)</b>			
None	33/53 (62.3%)	35/56 (62.5%)	0.480
1-3	14/53 (26.4%)	18/56 (32.1%)	
> 3	6/53 (11.3%)	3/56 (5.4%)	

influential among the controls. With regards to prostate cancer screening, 17/53 cases (32.1%) and 20/56 controls (35.7%) met the criteria for inclusion. Only 8/17 cases (47.1%) and 7/20 controls (35.0%) underwent a Specific Prostatic Antigen (SPA) dosing and a Digital Rectal Exploration (DRE). No statistically significant differences were found ( $p = 0.46$ ). Among the 13 women included in the population, 7 met the criteria to be screened for breast cancer, 2 cases and 5 controls, and 6 of them (2 cases and 4 controls) underwent the recommended test. Of note, also 3 women not meeting the criteria, 2 cases and 1 control, underwent mammography. No statistical analysis was performed.

Forty-two of 109 (38.5%) individuals included in the study, 32/53 (60.4%) cases and 10/56 (17.9%) controls, were eligible for colon-rectum cancer screening with fecal occult blood (FOB). However, only 5/32 cases (15.6%) and 5/10 controls (50.0%) underwent it. Of note, 14 people, 10/53 cases (18.9%), 4/56 controls (7.1%) not meeting the criteria underwent the screening. Curiously, a chest CT-scan was performed in 38 people included in the study, 32/53 cases (60.4%) and 6/56 (10.7%) controls. Of interest,

among the 15 people (11/53 cases, 20.8%, 4/56 controls, 7.1%) that met the criteria for inclusion in the screening, only 7/11 cases (63.6%) and no control underwent the test. This difference was statistically significant ( $p = 0.003$ ). However, patients and controls did not undergo the CT-scan for lung cancer screening: 14/32 cases (43.8%) had a chest CT-scan done for a suspect of infectious disease (bronchitis, pneumonia, tuberculosis), while 18/32 cases (56.2%) underwent a CT-scan for other reasons (trauma, rheumatological disorders, gastro-intestinal disorders); 100% of the controls underwent the examination for a suspect of infectious disease. Papanicolau test (PAP-test) for cervical cancer screening was performed only in 9 of the 13 women (3/53 cases, 5.7%, 6/56 controls, 10.7%) included in the study, who were all eligible for the proposal of the screening test. Only one of the people that met the criteria for inclusion in the anal cancer screening (anal PAP-test), 27/53 cases, 50.9%, and 4/56 controls, 7.1%, underwent it.

Details about the percentages of the screening tests carried out in patients and controls are resumed in Table 2.

**TABLE 2.** Patients and controls who were eligible for screening and underwent it.

Cancer	Patients eligible for screening (%)	Patients who underwent screening (%)	Controls eligible for screening (%)	Controls who underwent screening (%)
Prostate	17/53 (32.1%)	8/17 (47.1%)	20/56 (35.7%)	7/20 (35.0%)
Breast	2/53 (3.8%)	2/2 (100%)	5/56 (8.9%)	4/5 (80.0%)
Colorectal	32/53 (60.4%)	5/32 (15.6%)	10/56 (17.9%)	5/10 (50.0%)
Lung	11/53 (20.8%)	7/11 (63.6%) *	4/56 (7.1%)	0/4 (0.0%)
Cervical Cancer	5/53 (9.4%)	3/5 (60.0%)	8/56 (14.3%)	6/8 (75.0%)
Anal Cancer	27/53 (50.9%)	1/27 (3.7%)	4/56 (7.1%)	0/4 (0.0%)

\*No one underwent the test for screening reasons



## DISCUSSION

The introduction of ART has had a significant impact on PLWH survival. As a consequence, we assisted to an increase in the incidence of non-AIDS defining cancers, and a relative decrease in AIDS defining ones, thus highlighting the need for screening tests for an early detection, when prevention is not possible<sup>47-49</sup>. Screening tests, when available, represent an effective weapon in cancer prevention, together with an early onset of therapy, lifestyle changes, coinfection treatment and vaccinations. To understand the needs of the patients we follow on a daily basis in our outpatient clinic, we decided to investigate risk factors for cancer, evaluate the promotion and adherence to screening programs, comparing HIV+ patients with the general population.

Statistically significant differences highlighted by our study among PLWH and the general population do not differ from the epidemiology of the HIV infection<sup>50, 51</sup>. HIV affects more non-heterosexual people than heterosexual ones, PLWH are more often smokers than the general population, and less prone to quit the habit. However, surprisingly, we did not find many statistically significant differences in the number of proposals to undergo screening tests. As the HIV infection is an anonymous condition, no difference should be made regarding selection, but PLWH were thought to access cures more frequently than the general population, and thus, to undergo screening tests more often than them. Moreover, not every patient who was counselled to undergo a screening test actually put through with it. Thus, we have to put a new attention on the problem: maybe our communication is not so effective, and we have to spend more time with our patients to persuade them of the importance of screening and early diagnosis. Hopefully, raising our awareness to this disappointing rate of screening tests performed in PLWH in the future we will assist to a decline in NADCs as we assisted to a decrease in the rate of ADCs.

## CONCLUSIONS

The promotion of screening tests is essential: despite their existence, however, only a low percentage of patients underwent any screening test for cancers, as well as a very low percentage of controls, not only in the HIV positive population, but also in the control group.

General practitioners and the infectious specialists hold the opportunity to propose and promote cancer screening tests as an integral part of the clinical management of patients, especially if at high risk, such as PLWH. The introduction of HIV-specific screening strategies for certain cancers should be considered.

## AUTHORS' CONTRIBUTIONS:

FDAn, MC and EVR wrote the article; GA, CI, FDAn, FDAI and AF recruited the patients; AC performed the statistical analysis; GN, BC and GFP revised the manuscript.

## FUNDINGS:

This research was funded with the 2016 Gilead Fellowship Program grants, project identifier b5318762615.

## INFORMED CONSENT:

Cases and controls signed a standard form of consent, expressing their informed consent for the scientific use of their clinical data.

## CONFLICT OF INTEREST:

The authors declare that they have no conflict of interests.

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