Prevalence and mortality of cancer among people living with HIV and AIDS patients: a large cohort study in Turkey

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Abstract

Background: Cancer is responsible for elevated human immunodeficiency virus (HIV)-related mortality but there are insufficient data about cancer in HIV-positive patients in Turkey.

Aims: We aimed to investigate the prevalence and mortality of cancer among people living with HIVand AIDS patients in Istanbul, Turkey.

Methods: Between January 1998 and December 2016, people living with HIVand AIDS patients were enrolled in this study by the ACTHIV-IST Study Group, which consists of 5 centres to follow-up HIV-positive patients in Istanbul. The cancer diagnoses included AIDS-defining cancers (ADCs) and non AIDS-defining cancers (NADCs).

Results: Among 1872 patients, 37 (1.9%) were diagnosed with concurrent cancer. Eleven patients were diagnosed during follow-up; the prevalence of cancer among people living with HIVand AIDS patients was 2.6%. Among 48 cancer patients, 35 patients had ADCs, and 32 of them were diagnosed at their first hospital admission. There were 1007 late presenters and 39 of them had cancer (29 were ADCs). The most prevalent NADCs were gastrointestinal, genitourinary, and pulmonary cancers. NADCs were mostly diagnosed during follow-up of patients. The mortality of this group was significantly higher than that of patients with ADCs (53.9% vs 22.9%).

Conclusions: These results indicate the importance of cancer screening at diagnosis and during follow-up of HIV infection. A detailed physical examination contributes to diagnosis of the most prevalent ADCs (Kaposi's sarcoma and non-Hodgkin's lymphoma), especially in late presenters. For NADCs, individual risk factors should be considered.

Keywords: human immunodeficiency virus, AIDS, cancer, prevalence, mortality

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Introduction

Patients with human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) are at increased risk of developing cancer (*1*). This link was observed first when Kaposi's sarcoma (KS) was reported in young, homosexual men with severe immunosuppression, which was thereafter referred to as AIDS. The higher risk is mainly attributed to the impaired immune system. HIV-induced immunosuppression is responsible for the higher rates of KS and non-Hodgkin's lymphoma (NHL) and the risk increases steadily as CD4+ cell count decreases. Antiretroviral therapy reduces the increased risk of these cancers (*2,3*). However, non-AIDS-defining cancers (NADCs) do increase and cancer remains a significant cause of mortality in HIV/AIDS patients. Although long lifespan provides time for cancer to develop, the increased cancer risk compared to that in the matched general population demonstrates the role of other factors (*4*). Coinfection with other viruses, alcohol consumption, tobacco smoking and advanced age in HIV/AIDS patients also increase the risk of cancer (*5*). People with HIV/AIDS have higher rates of tobacco smoking, hepatitis B and C coinfection, and human papillomavirus infection (*6,7*).

The increase in the number of NADCs is a challenge to the management of HIV/AIDS patients. The tumours are generally more aggressive and diagnosed at a younger age. HIV-infected patients with Hodgkin's lymphoma are more likely to present with unfavourable histological type and with higher rate of bone marrow involvement (*8*). The antineoplastic agents have a high likelihood of interaction with antivirals since protease inhibitors, non-nucleoside reverse transcriptase inhibitors and many antineoplastic drugs are metabolized by the cytochrome P450 system. Coadministration of these antivirals and antineoplastic agents could result in greater adverse effects and decreased efficacy (*9,10*). Additionally, the risk of death in cancer patients with AIDS is significantly higher than in cancer patients without AIDS for almost all cancer types (*10*).

After nearly 2 decades of the availability of highly active antiretroviral therapy (HAART), the size of the HIV/AIDS population is growing. As well as late presenting cases, patients receiving HAART regimens have a prolonged, mild immunosuppressive state. Especially in the setting of known risk factors for cancer, the increased incidence of cancer in HIV/AIDS patients represents a significant cause of mortality. There are insufficient data in the current literature about cancer in Turkish HIV-infected patients. In the present study, we aimed to investigate the prevalence and mortality of cancer among HIV/AIDS patients in Istanbul, Turkey.

Methods

Between January 1998 and December 2016, 1872 HIV-infected patients were enrolled by the ACTHIV-IST (Action Against HIV in Istanbul) Study Group, which consists of 5 centres, to follow-up HIV-positive patients in Istanbul. All newly diagnosed HIV/AIDS patients had a confirmatory diagnosis using a western blotting verification test (HIV BLOT 2.2; MP Biomedicals Asia Pacific, Singapore). The CD4+ cell counts were obtained by standard flow cytometry (FACScalibur; Becton Dickinson, Franklin Lakes, NJ, USA), and HIV viral load was measured by polymerase chain reaction (COBAS Ampliprep/COBAS TaqMan HIV-1 Test; Roche Molecular Systems, Pleasanton, CA, USA). Demographic data including age, sex, transmission routes, education level, marital status, history of imprisonment, CD4+ cell counts, and HIV RNA were collected from medical records and transferred to an HIV database system.

All the patients at all 5 sites received standardized care and diagnosis services. Diagnosis of cancer was established by clinical (detailed history taking and thorough physical examination), radiological and pathological/histological characteristics. Each cancer was reviewed using a standardized protocol to confirm the diagnosis and collect detailed information regarding cancer type, histology, grade, stage, and treatment from the medical records. Each site in the study used the same protocol for cancer evaluation and data collection. Cancer types were classified according to location (i.e., mucocutaneous, oral, breast, cervix, anus and lung) and/or histopathological reports (i.e., lymphoma and leukaemia). Details of histology, grade, and tumour node metastasis (TNM) staging were obtained from pathology reports and imaging studies. The cancer diagnoses included ADCs (KS, NHL, and cervical cancer) and NADCs.

Survival probability was calculated as the proportion of patients that survived beyond a specified time, and mean survival was the average length of time passed from the date of HIV/AIDS diagnosis. Categorical variables were compared by χ^2 (or Fisher's exact) test and continuous variables (age) were compared by Mann–Whitney U test. $P < 0.05$ was accepted as significant. This study was accepted by the Ethical Committee of Cerrahpasa Medical Faculty (83045809-604.01.02), Istanbul, Turkey.

Results

Among 1907 patients with HIV infection, 35 (1.8%) were lost to follow-up (The remaining 1872 (98.2%) patients were followed up for a total of 146 922 patient-months. Thirty-seven (2.0%) patients were diagnosed with cancer. Additionally, 11 (0.6%) patients were diagnosed during follow-up. The prevalence of cancer among our HIV/AIDS patients was 2.6%. Among the 48 cancer patients, 4 were female and mean age was 41.3 years. Thirty-five (72.9%) patients had ADCs, and 32 (91.4%) were diagnosed at their first hospital admission. Eight (22.8%) of 35 ADC patients and 7 (53.8%) of 13 NADC patients died during the study period. The mortality was 1.75% (32 of 1824) in non-cancer patients.

The 35 ADCs comprised 23 Kaposi's sarcomas and 12 NHLs. Among the 13 patients with NADCs, 5 had gastrointestinal cancer (3 colon, 1 esophageal and 1 liver), 3 urogenital cancer (1 kidney, 1 prostate and 1 testicular), 3 lung cancer, and 1 each laryngeal and spinal cord cancer.

The patients with NADCs were older than those with ADCs (mean age 53 vs 45 years) (Table 1). The patients with NADCs had a higher rate of HBV infection (15.4% vs 5.7%). Most importantly, the mortality rate was higher among patients with NADCs than ADCs, 53.8% vs 22.8% respectively. Moreover, while 91.4% of ADCs were diagnosed with HIV concurrently, this ratio among NADCs was 38.4%.

The survival probability of HIV-infected cancer patients was significantly lower than that of HIV-infected cancer-free patients (31.3% vs 1.7%) (Table 2). Low CD4 count was more frequent in cancer patients; cancer patients (both those diagnosed on admission and those who developed cancer during follow-up) were more likely late presenters, whose CD4 count was below 350 cells/mm3 at the moment of presentation at a healthcare facility or presenting with an AIDS-defining condition. Considering all cancer patients (diagnosed at any time), CD4 count < 350/mm3 was 38/48 (79%) compared with 968/1824 (53%) among patients without cancer ($P < 0.001$) (Table 2).

The survival rate between patients diagnosed with cancer on admission and those diagnosed during follow-up were comparable: 18.9 and 12.2 months, respectively ($P > 0.48$) (Table 3). Similarly, mortality did not differ significantly between the 2 groups. The cancers were more frequently ADCs in patients diagnosed on admission compared to those diagnosed during follow-up (87% vs 27%, $P = 0.0004$).

Thirty-five patients did not come to follow-up visits. Admission from one HIV/AIDS centre to another is frequent among patients in Turkey. However, this was not confirmed since the patients were not reached.

Causes of death other than cancer were: infection (tuberculosis, toxoplasmosis, cryptococcosis, *Pneumocystis jirovecii* pneumonia and sepsis; n = 12), wasting (n = 7), myocardial infarction (n = 2), suicide, cerebrovascular accident, progressive multifocal leukoencephalopathy, gastrointestinal bleeding, illicit drug use/intoxication,

Table 1 Characteristics of HIV-infected patients with cancer

Characteristic	Patients with cancer	
	ADCs n = 35 (%)	NADCs n = 13 (%)
Sex		
Female	3 (8.6)	1 (7.7)
Male	32 (91.4)	12 (92.3)
Mean age (years)	45 ± 11	53 ± 13
Age groups, n (%)		
20–30 years	7 (20)	0 (0)
31–40 years	16 (45.7)	3 (23.1)
41–50 years	5 (14.3)	3 (23.1)
51–60 years	5 (14.3)	4 (30.7)
> 61 years	2 (5.7)	3 (23.1)
CD4 count on diagnosis, n (%)		
0–200/mm3	27 (77.1)	4 (30.7)
201–350/mm3	2 (5.7)	5 (38.5)
351–500/mm3	4 (11.4)	1 (7.7)
> 500/mm3	2 (5.7)	3 (23.1)
Transmission route n (%)		
Heterosexual	15 (42.9)	11 (84.6)
MSM	20 (57.1)	2 (15.4)
IVDU	0	0
Blood transfusion	0	0
HBV coinfection, n (%)	2 (5.7)	2 (15.4)
HCV coinfection, n (%)	0	0
Patients died, n (%)	8 (22.9)	7 (53.8)
Cancer on HIV diagnosis, n (%)	32 (91.4)	5 (38.4)
Cancer during follow-up, n (%)	3 (8.6)	8 (61.5)

ADC = AIDS-defining cancer; IVDU = intravenous drug use; MSM = men who have sex with men; NADC = non-AIDS-defining cancer.

Table 2 Characteristics of HIV-infected patients with or without cancer

Characteristic	No cancer n = 1824	All cancers n = 48	P
Sex			
Female	248	4	> 0.05
Male	1576	44	
Mean age (years)	37 ± 9	42 ± 13	0.02
Age groups, n (%)			
20–30 years	639 (35)	7 (14.5)	0.03
31–40 years	581 (31.9)	19 (39.6)	> 0.05
41–50 years	371 (20.3)	8 (16.7)	> 0.05
51–60 years	167 (9.2)	9 (18.8)	0.049
> 61 years	66 (3.6)	5 (10.4)	0.03
CD4 count on diagnosis, n (%)			
0–200/mm3	445 (24.4)	31 (64.6)	< 0.001
201–350/mm3	523 (28.7)	8 (16.7)	> 0.05
351–500/mm3	386 (21.1)	4 (8.3)	0.03
> 500/mm3	470 (25.8)	5 (10.4)	0.017
Transmission route, n (%)			
Heterosexual	987 (54.1)	26 (54.2)	> 0.05
MSM	821 (45)	22 (45.8)	> 0.05
IVDU	3 (0.2)	0	> 0.05
Blood transfusion	13 (0.7)	0	> 0.05
HBV coinfection, n (%)	104 (5.7)	4 (8.3)	> 0.05
HCV coinfection, n (%)	16 (0.9)	0 (0)	> 0.05
Patients died, n(%)	32 (1.7)	15 (31.3)	<0.001
Cancer on HIV diagnosis, n(%)		37 (77)	–
Cancer during follow-up, n(%)		11 (22.9)	–

ADC = AIDS-defining cancer; IVDU = intravenous drug use; MSM = men who have sex with men; NADC = non-AIDS-defining cancer.

renal failure, HIV encephalopathy, alcohol intoxication, traffic accident, liver failure and undetermined (all n = 1).

Discussion

In this study, there were 32 ADCs and 5 NADCs on admission; however, on follow-up, 3 ADCs and 8 NADCs developed additionally. In other words, most of the HIV-infected patients with concurrent cancer had ADCs. NADCs were mostly diagnosed during follow-up of patients. The mortality of patients with NADCs was significantly higher than that in patients with ADCs. These findings highlight the importance of promoting cancer screening during initial diagnosis of HIV infection as well as during follow-up.

Before HAART, cancer was responsible for a minority (around 10%) of deaths in HIV-infected individuals (*11*). Despite the substantial decrease in ADCs in patients with HAART, cancer is responsible for approximately one third of deaths in this population (*10,12*). This increased role of cancer may be explained by the longer survival expectancy afforded by HAART (*13*), probable oncogenic role of HIV (*12*), effect of other viruses (mainly hepatitis B, hepatitis C, human herpesvirus and human papillomavirus), advancing age, and higher prevalence of risky behaviours (e.g., alcohol consumption and tobacco smoking) (*5*). In the United States of America, from 1991 to 2005, the estimated number of ADCs decreased by >3-fold whereas NADCs increased by ~3-fold (anal, liver, prostate and lung cancers, and Hodgkin's lymphoma). The increase in NADC was mainly attributed to growth and ageing of the AIDS population (*14*). The risk of cancer mortality is higher in patients with than without AIDS for many cancer types (*10*).

Late presentation with AIDS-defining disorders, including cancer, severely affects HIV management and is associated with high morbidity and mortality (*15,16*). Late presentation means missed opportunities for prevention and early diagnosis in most cases (*17*). A multicentre European study in 2013 including 30 454 patients from 34 countries reported that 48.7% were late presenters (*18*). This figure is even higher in Asian (*19*) and African (*20*) cohorts, reaching up to 72% and 85.6%,

Table 3 Time of cancer diagnosis and survival among HIV-infected cancer patients

Characteristic	Patients with cancer on HIV diagnosis (n = 37)	Patients with cancer on follow-up (n = 11)	*P*
Time from HIV diagnosis to cancer diagnosis (months)	–	35.8	
Time from cancer diagnosis to death (months)	18.9	12.2	0.48
ADC/NADC	32/5	3/8	0.0004
Mortality	9/37 (24.3%)	6/11 (54.5%)	0.07

ADC = AIDS-defining cancer; NADC = non-AIDS-defining cancer.

respectively. In Turkey, 50–70% of patients are admitted to clinical care with a CD4 count < 350 cell/mm3 (*21–26*). In the present study, late presenters were 53% and 81.2% of all cancers and 82.8% of ADCs were detected in this group. The fact that the majority of patients with cancers were detected on admission with a low CD4 count emphasizes the importance of early detection of the disease, thus preventing further decrease in CD4 count and allowing screening for other comorbidities including ADCs and NADCs.

In our study, ADCs comprised KS and NHL. The most common NADCs were gastrointestinal, urogenital and lung cancers followed by laryngeal and spinal cord cancers. In 2014, the registry of the Turkish Health Ministry reported that the most prevalent cancers in men were, in decreasing order, lung, prostate, colon, urinary bladder and stomach cancer, NHL, and kidney, laryngeal, thyroid and central nervous system cancer (*27*). In women, breast, thyroid, colon, uterine, lung, stomach and ovarian cancer, NHL, and central nervous system and cervical cancer were the most prevalent. When compared to the general population, urogenital cancer appears to have a higher prevalence among HIV-infected patients in Turkey.

Compared to the general population, HIV-infected patients have a 3640-fold increased risk of KS. This figure is 77-fold for NHL and 6-fold for cervical cancer (*28*). These cancers are associated with human herpesvirus 8, Epstein-Barr virus and oncogenic subtypes of human papillomavirus, respectively. The increased risk of NADCs can be explained by the coinfection theory: anal and oropharyngeal cancer with human papillomavirus, liver cancer with hepatitis B and C viruses, and Hodgkin's lymphoma with Epstein–Barr virus (*2, 29,30*). In our study, nearly two thirds of ADCs were KS and the remainder were NHL. The availability of HAART has improved the immune function and decreased the risk of AIDS and ADCs (*31,32*). Although the incidence of KS decreased significantly after the use of HAART, it is one of the most frequently diagnosed cancers among HIV-infected individuals (*10*). In existing KS, HAART has been shown to induce regression in the size and number of the lesions (*33*). NHL is the most common ADC worldwide and was the second most common in our study. Although its incidence is decreasing in the post-HAART era, its risk is high in HIV-infected individuals (*2*).

Our study had some limitations. First, the sample size was small, which made clear conclusions difficult to draw. Second, the time of onset of HIV infection was not known in most cases and nearly half of the HIV-infected patients presented for clinical care at a late stage. Therefore, the effect of HIV infection on cancer development could not be easily assessed. Third, 35 patients did not attend follow-up visits and they were not reached. This potentially affected the outcomes since it is not known whether the non-attendance was due to any cancer-related morbidity or mortality.

Conclusion

Almost half of the patients with HIV infection are admitted to clinical care or are diagnosed late with AIDS-defining disorders including cancer. Late presentation is highly associated with ADCs. A detailed physical examination contributes to the diagnosis of the most prevalent ADCs (KS and NHL) especially in late presenters. Those diagnosed early still carry a higher risk of cancer. As the HIV/AIDS population survives and gets older, NADCs represent a new challenge in the care of these patients. For NADCs, individual risk factors should be considered. Additionally, the behaviour and relative frequency of NADCs may change in the setting of AIDS. Preventive strategies, screening and management should be clearly determined.

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Competing interests: None declared.

Prévalence et mortalité du cancer chez les personnes vivant avec le VIH et les patients atteints de sida : étude de cohorte à grande échelle en Turquie

Résumé

Contexte : Le cancer est responsable d'une mortalité élevée liée au virus de l'immunodéficience humaine (VIH), mais les données relatives au cancer chez les personnes séropositives en Turquie sont insuffisantes.

Objectifs : Étudier la prévalence et la mortalité du cancer chez les personnes vivant avec le VIH et les patients atteints de sida à Istanbul (Turquie).

Méthodes : Entre janvier 1998 et décembre 2016, des personnes séropositives ont été recrutées comme sujets pour la présente étude par le groupe d'étude ACTHIV-IST, qui se compose de cinq centres de suivi des personnes séropositives pour le VIH à Istanbul. Les diagnostics de cancer incluaient les cancers classant sida et les cancers non classant sida.

Résultats : Sur 1 872 malades, 37 (1,9 %) ont reçu un diagnostic de cancer concomitant. Onze patients ont été diagnostiqués en phase de suivi post-thérapeutique. La prévalence du cancer chez les personnes vivant avec le VIH et les patients atteints de sida était de 2,6 %. Sur 48 patients cancéreux, 35 avaient un cancer classant sida, parmi lesquels 32 avaient été diagnostiqués lors de leur première hospitalisation ; 1 007 personnes se présentaient à un stade avancé de l'infection, et 39 d'entre elles avaient un cancer (29 avaient un cancer classant sida). Les cancers non classant sida les plus prévalents étaient les cancers gastro-intestinal, uro-génital et pulmonaire. Ces cancers avaient principalement été diagnostiqués chez les patients en phase de suivi post-thérapeutique. Dans ce groupe, la mortalité était considérablement plus élevée que celle des patients de cancers classant sida (53,9 % contre 22,9 %).

Conclusions : Ces résultats soulignent l'importance du dépistage du cancer lors du diagnostic et du suivi post-thérapeutique des infections à VIH. Un examen clinique détaillé contribue au diagnostic des cancers classant sida les plus prévalents (sarcome de Kaposi et lymphome non hodgkinien), en particulier chez les patients se présentant à un stade avancé. Concernant les cancers non classant sida, les facteurs de risque individuels devraient être pris en compte.

انتشار السرطان بين مرضى فيروس العوز المناعي البشري/ الإيدز والوفيات الناجمة عنه: دراسة أترابية في تركيا

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الخلاصة

الخلفية: يُعد السرطان مسؤولاً عن ارتفاع نسبة الوفيات المقترنة بفيروس العوز المناعي البشري، ولكن لا تتوافر معلومات كافية بشأن السرطان في صفوف المرضى المصابين بفيروس العوز المناعي البشري في تركيا.

الأهداف: هدفت الدراسة إلى الاستقصاء بشأن انتشار السرطان بين مرضى فيروس العوز المناعي البشري/ الإيدز والوفيات الناجمة عنه في إسطنبول، تركيا.

طرق البحث: في الفترة بين يناير/ كانون الثاني ١٩٩٨ وديسمبر/ كانون الأول ٢٠١٦، سجلت مجموعة دراسة ACTHIV-IST (العمل من أجل مكافحة فيروس العوز المناعي البشري في إسطنبول) المرضى المصابين بفيروس العوز المناعي البشري في هذه الدراسة، التي تشمل ٥ مراكز لمتابعة المرضى المصابين بفيروس العوز المناعي البشري في إسطنبول. وتضمن التشخيص أنواع السرطان التي تحدد مرض الإيدز، وأنواع السرطان التي لا تحدد مرض الإيدز.

النتائج: من بين ١٨٧٢ مريضاً، شُخِّص ٣٧ مريضاً منهم (٩ , ١٪) بالسرطان المُصاحب لفيروس العوز المناعي البشري. وشُخص أحد عشر مريضاً خلال المتابعة؛ وبلغت نسبة انتشار السرطان بين مرضى فيروس العوز المناعي البشري/ الإيدز ٦ , ٢٪. ومن بين ٤٨ مريضاً بالسرطان، كان لدى ٣٥ مريضاً أنواع السرطان التي تحدد مرض الإيدز، وشُخص ٣٢ مريضاً منهم عند دخولهم المستشفى أول مرة. وتأخر ١٠٠٧ من مُقدمي البيانات، منهم ٣٩ شخصاً مصاباً بالسرطان (وكان لدى ٢٩ منهم أنواع السرطان التي تحدد مرض الإيدز). ومن بين أنواع السرطان التي لا تحدد مرض الإيدز الأكثر انتشاراً: سرطان المَعِدة والأمعاء، وسرطان الجِهَاز البَولِيّ التَّناسُلِيّ، وسرطان الرئة. وكانت أنواع السرطان التي لا تحدد مرض الإيدز تُشخص أثناء متابعة المرضى. ومعدل الوفيات في هذه الفئة أعلى بكثير عنه في المرضى المصابين بأنواع السرطان التي تحدد مرض الإيدز (٩ , ٥٣٪ مقابل ٩ , ٢٢٪).

الاستنتاجات: توضح هذه النتائج أهمية تحري الإصابة بالسرطان عند التشخيص بعدوى فيروس العوز المناعي البشري وأثناء متابعة المرضى المصابين به. ويساعد إجراء فحص بدني مُفصل في تشخيص أكثر الأمراض انتشاراً من أنواع السرطان التي تحدد مرض الإيدز (ساركومة كابوزي ولمْفُومة هودجكين)، خاصة في صفوف مُقدمي البيانات المتأخرين. أما أنواع السرطان التي لا تحدد مرض الإيدز، فينبغي أن تؤخذ بعين الاعتبار عوامل الخطر الفردية.

(العمل من أجل مكافحة فيروس العوز المناعي البشري في إسطنبول). [1]

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