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SCREENING GUIDELINES FOR NON-AIDS DEFINING CANCERS IN HIV-INFECTED INDIVIDUALS

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Abstract

Purpose of the Review—The growing burden of non-AIDS-defining malignancies (non-ADM) among people living with HIV/AIDS (PLWHA) highlights the need for cancer prevention and early detection. In this article we propose screening guidelines for non-ADM in PLWHA.

Recent findings—Screening for lung cancer with low-dose helical chest computerized tomography (LDCT) in the National Lung Screening Trial data demonstrated a decrease in lung cancer and all-cause mortality. Recent studies have demonstrated a favorable experience among PLWHA with liver transplantation. Over-diagnosis is common with breast and prostate cancer screening. Anal cancer rates were substantially higher for HIV-infected men who have sex with men (MSM), other men, and women compared with HIV-uninfected individuals.

Summary—Screening recommendations for the general population can be applied to PLWHA patients for breast, colon and prostate cancer. Screening for lung cancer with LDCT could be considered in PLWHA at risk. American Association for the Study of Liver Diseases screening recommendations with biennial ultrasonography may be applied to at-risk PLWHA for hepatocellular carcinoma. All HIV-infected adults should be offered anal cancer screening as part of clinical care at specialized centers.

Keywords

non-AIDS-defining malignancies; cancer screening; HIV/AIDS

Introduction

HIV-associated morbidity and mortality have decreased dramatically in the economically developed world with the advent of highly active anti-retroviral therapy (HAART) [1]. With HIV infection transforming from a fatal disease to a chronic condition, there is renewed public and clinical interest in long-term morbidities, including malignancies that occur

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disproportionately within this population. The decision to screen an HIV-infected patient for cancer should include an assessment of individualized risk for the particular cancer, life expectancy, the harms and benefits associated with the screening test and its potential outcome [2]. We review the potential cancer screening strategies for lung, liver, breast, colorectal, anal, and prostate cancer in people living with HIV/AIDS (PLWHA).

Lung Cancer

In PLWHA, lung cancer is the most common non-ADM and leading source of non-ADM mortality [3]. Initial randomized control trials (RCTs) in lung cancer screening evaluated chest radiography with or without sputum cytology and showed no reduction in lung cancer mortality [4,5]. The National Lung Screening Trial (NLST) compared annual screening by low-dose helical chest computerized tomography (LDCT) scanning with chest x-ray for three years in 53,454 high-risk persons at 33 U.S. medical centers [5]. Participants were between the ages of , 55 - 74 years had a history of at least 30 pack-years of smoking, and included current smokers and those who had discontinued smoking within 15 years of enrollment. At a median follow-up of 6.5 years, there was a 20% relative reduction in mortality from lung cancer with LDCT screening and a 6.7 % (CI 1.2-13.6 %) reduction in all-cause mortality in the LDCT group compared to the conventional chest-x-ray group.

Benefits and Harms of LDCT Screening of LDCT

Screening of high-risk individuals with LDCT, including motivated PLWHA with significant smoking history similar to the NLST participants, may shift the diagnosis of cancer from advanced- to early-stage disease and provide a better opportunity for curative treatment[5] The NLST study population, while ethnically representative of the high-risk U.S.Smoker population, was a highly motivated, primarily urban group screened at major medical centers with multidisciplinary coordinated care and a comprehensive process for screening, image interpretation, management of findings, and evaluation and treatment of potential cancers. The results may not accurately predict the effects of screening for other populations including PLWHA in the community. The potential harms of LDCT screening include the cumulative effects of radiation from multiple CT scans, surgical and medical complications in patients who prove not to have lung cancer but who need additional testing to make that determination, and over-diagnoses and over-treatment of lung cancers [5,6**]

A model simulating cohorts of individuals representative of the U.S. population suggests that the cost-effectiveness of LDCT screening programs will be strongly influenced by smoking cessation rates among screened participants [7]. A substantial amount of data on LDCT screening will be reported in the near future, including planned analyses of the NLST data both by its investigators and by the Cancer Intervention and Surveillance Modeling Network (CISNET) team. Ongoing RCTs in Europe will also soon be reporting estimates of both the magnitude of LDCT's mortality benefit and harms. In addition, results of two clinical trials which specifically address CT screening of HIV-seropositive heavy smokers are eagerly awaited [8,9]. These data may help address some of the important questions that still linger regarding LDCT screening.

Screening Guidelines

In 2004, the U.S. Preventive Services Task Force (USPSTF) guidelines concluded that the evidence was insufficient to recommend for or against screening asymptomatic persons for lung cancer. Based on more recent NLST data, we suggest that clinicians with access to high-volume, high-quality lung cancer screening and treatment centers initiate a discussion about screening with apparently healthy PLWHA aged 55 - 74 years who have at least a 30–pack-year smoking history and who currently smoke or have quit smoking within the past 15 years. A process of informed shared decision-making with a clinician related to the potential benefits, limitations, and harms associated with screening for lung cancer with LDCT must occur before any decision is made to initiate lung cancer screening [6**,10*].

The importance of stopping smoking is a crucial message during clinical encounters. A recent cohort study from Denmark where HIV care is well organized and antiretroviral therapy is free, showed that HIV- infected smokers lose more life-years to smoking than to HIV (12.3 vs 5.1 yrs) [11*]. Lung cancer screening must not be viewed as an alternative to smoking cessation.

Hepatocellular Carcinoma

Hepatocellular carcinoma (HCC) is of distinct concern in PLWHA because they are frequently co-infected with hepatitis B virus (HBV) and hepatitis C virus (HCV), placing them at heightened risk of accelerated progression of viral hepatitis to chronic liver disease and cirrhosis. Recent data indicates that individuals with AIDS have a 4-fold higher HCC risk than the general population, and the magnitude of this excess has remained relatively unchanged over time, including in the HAART era [12*].

Benefits and Harms of HCC Screening

HCC screening interventions may improve survival when the disease is detected at an early stage, and although non-cirrhotic patients may be eligible for limited surgical resections, most patients would require liver transplantation for cure [13]. Surgical resection is the treatment of choice for HCC in non-cirrhotic patients. The 2010 screening guidelines of the American Association for the Study of Liver Diseases (AASLD) advocate liver ultrasonography every 6 months for individuals at high risk for HCC [13]. Harms associated with ultrasonography as a screening test include potential liver biopsy complications if an abnormality is detected, as well as excess radiation and contrast dye exposure due to follow-up imaging in false-positive tests.

A large Chinese RCT of HCC screening of patient with HBV infection demonstrated a 37% mortality reduction with the use of biennial liver ultrasonography and serum alpha-fetoprotein (AFP) testing [14]. Application of these trial results to PLWHA and co-infected with viral hepatitis in developed countries is problematic. Patients in the Chinese trial were less likely to have advanced liver disease, and were HBV co-infected, whereas HCV infection predominates in the U.S. Moreover, in a Cochrane review of RCTs evaluating HCC screening in patients with persistent HBV surface antigenemia, the authors concluded that there was insufficient evidence to support or refute the value of AFP or ultrasound screening, or both, of HBV surface antigen positive patients for HCC [15*]. The authors’

ambivalence was forged by the high risk of bias in the studies they reviewed and methodological flaws and incomplete outcome data amongst the studies they reviwed. Furthermore, liver transplantation was not an option for HCC patients in these RCT studies. Recent studies have demonstrated a favorable experience amongst PLWHA with liver transplantation, including a Spanish study demonstrating liver transplantation as an effective short-term (1 year) treatment in HCV/HIV-coinfected liver recipients, with a survival rate similar to that observed in HCV mono-infected patients [16]. Post-transplant survival in HCV/HIV-coinfected patients after 5 year follow-up was lower than for mono-infected patients, although acceptable.

Screening Guidelines

Data from RCTs does not support recommendations for or against screening for HCC with both serum AFP and liver ultrasonography in PLWHA. For early stage HCC HIV seropositive patients, a survival benefit is achieved with liver transplantation [16,17,18]. Assuming early and aggressive HCC treatment is available, AASLD screening recommendations may be applied to at-risk PLWHA [13,19]. In addition to HBV and HCV status, FIB-4 may also have a role in identifying high-risk individuals who could opt for HCC screening. FIB-4 is an index score calculated from platelet count, alanine transaminase, aspartate transaminase, and patient age and is predictive tool of advanced hepatic fibrosis and cirrhosis. In one study, elevated FIB-4 was a strong, independent HCC risk factor in PLWHA [20].

As we wait for more, and better designed RCTs and cost-effectiveness data in HCC screening, clinical and public health prevention efforts should continue to focus on reducing the risk of chronic liver disease among HIV-infected individuals, through counseling on risk factor modification and HBV vaccination and by offering both HAART and antiviral treatments for HCV and HBV infection before advanced cirrhosis can occur [21*].

Breast cancer

Breast cancer is the most common cancer worldwide in women [22]. When compared to the general population, PLWHA have a similar or slightly lower risk of breast cancer [23,24]. Women with HIV infection, especially in the pre-HAART era, may have had other causes of morbidity and mortality that prevented them from being diagnosed with breast cancer or living long enough to develop breast cancer. Also, low breast cancer risk with HIV has been reported to be specifically linked to CXCR4-using variants of HIV. Binding of the HIV envelope protein to CXCR4 expressed by the neoplastic breast cells may induce apoptosis resulting in a lesser risk of breast cancer [25].

Screening modalities for breast cancer include mammography, screening ultrasonography, clinical and self-breast examination, magnetic resonance imaging (MRI), and breast tomosynthesis. Mammography, however, is the best studied and proven method to reduce mortality from breast cancer in the average-risk population [26].

Benefits and Harms of Breast Cancer Screening Mammography

Over the past 30 years, breast cancer mortality in the United States has been decreasing, mostly attributable to advances in treatment and increasing use of screening mammography [26,27**]. The harms related to screening include over-diagnoses and subsequent overtreatment of inconsequential disease, and risk of false-positive results leading to recall, with or without biopsy, which may cause psychological distress. Radiation-induced cancers, false-negative results leading to false reassurance, and discomfort from the breast compression necessary for a technically optimal mammogram are additional reasons for concern [26].

The rationale behind mammography screening is that early detection of breast cancer prevents late-stage cancer. If screening is effective, advanced stage cancer incidence decreases. Surveillance, epidemiology, and end results data examining trends from 1976 -2008 in early- and late-stage breast cancer incidence among US women ≥40 years showed that despite substantial increases in the number of early-stage breast cancer cases detected, screening mammography only marginally reduced the rate at which women present with advanced cancer[27**]. Although it is not certain which women have been affected, the imbalance suggests that there is substantial over-diagnosis, accounting for nearly a third of all newly diagnosed breast cancers. A recent Norwegian study analyzing the incidence of invasive breast cancer between 1996- 2005, estimated 15- 25% of detected breast cancers represented over-diagnosis [28*]. The true contribution of mammography to decreasing breast cancer mortality must be lower than previously estimated, given the extent of over diagnosis and limited reduction in advanced disease.

Screening Guidelines

Application of USPSTF or other national breast cancer screening guidelines to HIV-infected women seems appropriate, provided prognosis conferred by HIV or other comorbidities is considered in the decision-making process (Table 1). Although all industrialized nations' guidelines recommend screening mammography for women between 50-69 years of age, there is a considerable difference regarding screening in other age groups, screening frequency, and clinical or self-breast examination utility owing to varying judgments of the available data [29,30]. A meta-analysis of survival data from population-based RCTs from the U.S., Denmark, United Kingdom, and Sweden suggests that screening for breast cancer is most appropriate for patients with a life expectancy greater than 10 years [31*].

Colorectal Cancer

Globally, colorectal cancer is the third most commonly diagnosed cancer in males and the second most commonly diagnosed cancer in females [22]. The relative risk of colorectal cancer in PLWHA remains uncertain. Although a prospective cohort study in PLWHA from 1992 to 2003 showed a higher incidence of colorectal cancer (standardized rate ratio 2.3) compared to the general population [32], other meta-analyses and cohort studies have failed to demonstrate an elevated risk [33,34]. At least one case series suggested that colorectal cancer may occur at a younger age and be more aggressive in patients infected with HIV [35]. In contrast, a recent registry linkage study demonstrated, after accounting for the ages

of at-risk populations, that the age of colorectal cancer diagnosis is similar in the AIDS and general populations. [36].

Benefits/Harms of Colorectal Cancer Screening

Evidence-based screening modalities which have shown to decrease colorectal cancer mortality include fecal occult blood testing (FOBT), sigmoidoscopy and colonoscopy[37*, 38]. The primary established harms of colorectal cancer screening are due to the use of invasive procedures initially or in the evaluation sequence and include colon perforation, major bleeding, diverticulitis, severe abdominal pain, and cardiovascular events[38].

Screening Guidelines

The USPSTF recommends colorectal cancer screening using high sensitivity FOBT annually, sigmoidoscopy every five years with FOBT every three years , or colonoscopy every 10 years in adults at average risk for colorectal cancer, beginning at age 50 and continuing until age 75[38]. The joint guidelines from the American Cancer Society, the US Multi Society Task Force on Colorectal Cancer, and the American College of Radiology also endorse CT colonography, double-contrast barium enema and stool DNA for screening, although the evidence and outcome data on these modalities are less robust [39]. Application of USPSTF or other national colorectal cancer screening guidelines to PLWHA seems appropriate, provided prognosis conferred by HIV or other comorbidities is considered in the decision-making process, as there is approximately a 10-year time lag to observe the mortality benefit from screening [31*]. Interventions to increase general population screening recommendations adherence may be applied to PLWHA. A recent RCT found that, compared with usual care, a centralized, electronic health record–linked, mailed colorectal cancer screening program led to twice as many persons being current for screening over two years[40*].

Anal Cancer

Anal cancer is rare in the general U.S. population, but it is the fourth most common cancer in PLWHA, following NHL, KS, and lung cancer [3]. Most anal carcinomas are caused by human papillomavirus (HPV), with the vast majority linked to oncogenic HPV types 16 and 18. An analysis of 13 cohort studies from the US and Canada showed that anal cancer rates were substantially higher for HIV-infected men who have sex with men (MSM), other men, and women compared with HIV-uninfected individuals, suggesting a need for universal prevention efforts [41*]. Anal cancer rates increased early in the antiretroviral therapy era and then plateaued. HIV-infected MSM experienced the greatest risk for anal cancer with incidence rates >80 times as high as HIV-uninfected individuals [41*].

Benefits and Harms of Anal Cancer Screening

Anal cancer screening is currently based on cytological detection of HPV-induced abnormalities, or possibly by direct detection of HPV-related biomarkers, followed by histological confirmation of the presumed cancer-precursor lesion, high-grade anal intraepithelial neoplasia (AIN), and treatment.

Commonly proposed screening methods for detecting high-grade AIN include anal cytology testing, high-resolution anoscopy (HRA) and digital rectal examination (DRE), which detect benign genital condylomata and palpable cancers [42]. Anal cytology is a reasonable predictor of AIN, with sensitivity ranging from 61–98% in various studies [43]. HRA and subsequent biopsy are used as an adjunct and are the gold standard for AIN diagnosis. However, there is poor correlation between the cytological and histological grade of AIN. Cytology underestimates dysplasia grade compared to the corresponding biopsy. Biomarkers evaluated for cervical cancer screening, including HPV16/18 genotyping, HPVE6/E7 mRNA expression, and p16/Ki-67 cytology, also have a promising role in anal cancer screening [44*]. Harms related to screening include disease-specific anxiety and procedural discomfort from HRA and biopsy [45*].

Currently, no RCTs document the value of screening for AIN in an at-risk population. Instead, the rationale for screening relies upon the histologic similarities between the anus and cervix, and the established success of cervical cytology screening in reducing the incidence of cervical cancer. However, significant differences between the natural history of anal HPV infection and that of cervical HPV infection may exist as reflected by a meta-analysis that showed progression rates of AIN to cancer may be substantially lower than for cervical pre-cancerous lesions [46**]. Clearly, large, high quality, prospective natural history studies, coupled with RCTs involving treatment interventions are needed to inform evidence- based guidelines for anal cancer screening.

Screening Guidelines

The New York State AIDS Institute guidelines for anal cancer screening of PLWHA recommends annual DRE for all patients, and targeted anal cytology for MSM, for individuals with a history of anogenital warts, and for women with a history of abnormal cervical or vulvar histology [42]. Given the high burden of anal cancer in PLWHA, we suggest that all HIV-infected adults be offered screening as part of clinical care at specialized centers with screening protocols in place and expertise in specimen collection, interpretation of results, and treatment modalities. This approach may maximize the potential benefit to the highest risk population, and contribute to answering some important questions about anal dysplasia screening. Vaccination against HPV holds great promise for anal cancer prevention for those not HPV-infected, though it remains to be seen how efficacious the vaccine will be for HIV-infected patients [47,48].

Prostate Cancer

Prostate cancer is the most common malignancy in US men. There are no significant differences in the clinical characteristics of prostate cancer in HIV-infected men and the general population. The deficit in prostate cancer observed among HIV-infected men is largely an artifact due to differential prostate specific antigen (PSA) screening practices, and is likely not due to a protective effect of HIV against the development of prostate cancer [49].

Benefits and Harms of Prostate Cancer Screening

The PSA test and DRE are primary screening tools in the early detection of prostate cancer. Trans rectal ultrasound (TRUS) and TRUS-guided needle biopsies are performed to confirm diagnosis following primary screening [50*,51*].

Since the advent of PSA screening, there has been uncertainty about screening benefit and concern about screening harms. Thirteen-year follow-up data from the US Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial showed no mortality benefit for organized annual screening with PSA and DRE [52*]. However, the rate of contamination with non-study screening in the control group was high, and the rate of biopsy compliance was low. The European Randomized Study of Screening for Prostate Cancer trial (ERSPC) reported a 20% reduction of prostate cancer-specific mortality in a pre-specified subgroup of men aged 55 to 69 but was associated with a high risk of over-diagnosis. [53,54*]. In a combined meta-analysis of five RCTs, including the PLCO and ERSPC trials, data showed that prostate cancer screening did not significantly decrease prostate cancer-specific mortality and overall mortality [51*]. Screening harms include pain, fever, bleeding, infection, and transient urinary difficulties associated with prostate biopsy, psychological harm of false-positive test results, and over diagnosis [55*]. The latter leads to overtreatment and treatment-related harms including urinary incontinence, erectile dysfunction, bowel dysfunction, gynecomastia, and hot flashes.

There are many potential avenues to more efficient prostate cancer screening algorithms because many variables define the screening strategy: ages to start and stop screening, the screening interval, and the threshold for biopsy referral. A recent modeling study demonstrated that compared with standard screening, PSA screening strategies that use higher thresholds for biopsy referral for older men and that screen men with low PSA levels less frequently can reduce harms while preserving lives [56*].

Screening Guidelines

The USPSTF recommends against PSA-based screening for prostate cancer in the general U.S. population [55*]. The ACS emphasizes informed decision-making and recommends men at average risk receive information regarding screening beginning at age 50 [57]. The American Urological Association recommends PSA screening and DRE be offered to asymptomatic men aged 40 who wish to be screened, if estimated life expectancy is >10 years [58]. Available data do not support unique screening processes in HIV-positive men. Although there are limited data on outcomes, HIV-positive men do appear to tolerate surgical or radio therapeutic interventions with little increased morbidity.

Conclusion

The decision to screen PLWHA for cancer should include considering the risk of the particular cancer, patient life expectancy , and the specific benefits and harms that may stem from the screening intervention. Screening for lung cancer with LDCT based on the NLST data may be considered after informed shared decision-making in apparently healthy PLWHA at risk who have access to high-volume, high-quality lung cancer screening and

treatment centers and who have insurance plans that will include this cancer screening effort. Lung cancer screening must not be viewed as an alternative to smoking cessation and the importance of stopping smoking needs to be an ever-present message during clinical encounters.

Screening recommendations for the general population can be applied to PLWHA patients for breast and colon cancers. Assuming early and aggressive HCC treatment is available; AASLD screening recommendations with ultrasonography may be applied to at-risk PLWHA for HCC. Given the high burden of anal cancer in PLWHA, all HIV-infected adults could be offered screening as part of clinical care at specialized centers, although data on mortality benefits associated with these tests are still evolving. Harms may outweigh the benefits of routine prostate cancer screening in the general population, and this is also likely true in HIV-infected men.

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Key points

- Screening for lung cancer with low-dose helical chest computerized tomography based on the National Lung Screening Trial data could be considered after a process of informed shared decision-making in apparently healthy people living with HIV/AIDS (PLWHA) at risk who have access to high-volume, high-quality lung cancer screening and treatment centers.
- Assuming early and aggressive hepatocellular carcinoma (HCC) treatment is available, the American Association for the Study of Liver Diseases screening recommendations with ultrasonography may be applied to at-risk PLWHA for HCC.
- Screening recommendations for the general population can be applied to PLWHA patients for breast, colon and prostate cancers.
- Given the high burden of anal cancer in PLWHA, all HIV-infected adults may be offered screening as part of clinical care at specialized centers with screening protocols in place and expertise in collection of specimens, interpretation of results, and treatment modalities.

Table

Breast Cancer Screening Guidelines

Organization (Year guideline issued)	Mammography	Clinical Breast Examination	Breast Self-Examination
United States Preventive Services Task Force	Age 40-49, individualize the decision (every 2 yrs, if performed) Age 50-74 yr, every 2 yrs ≥75, insufficient evidence	Insufficient evidence for recommendation	Not recommended
American Cancer Society	Age ≥40 yr, annually	Age 20-39 yr, every 3 yrs Age ≥40 yr, annually	Optional, ≥20 yr of age
National Health Service, United Kingdom	Age 47-73 yr, every 3 yrs	Not stated	Not stated
Canadian Task Force on Preventive Health Care	Age 40-49 yr, routine screening not recommended Age 50-74 yr, every 2-3yrs ≥75 no recommendation	Not recommended	Not recommended