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Risk of Skin Cancers in Older Persons Living With HIV: A Systematic Review

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Abstract

Skin cancers—including basal cell carcinoma, squamous cell carcinoma, and melanoma—impose high incidence and morbidity in older persons. As life expectancy continues to increase in persons living with HIV (PLWH), this population may face an increased risk of non–AIDS-defining malignancies, such as skin cancers. We conducted a systematic review on skin cancer risks in PLWH, ages 50 years or older, as compared with age-matched, HIV-uninfected persons. Four studies met criteria and were included. No statistically significant associations were demonstrated between HIV infection and skin cancers in older persons. For those with a history of basal or squamous cell carcinoma, HIV infection was associated with higher risks of subsequent squamous cell carcinoma. Future studies are needed to elucidate and reduce morbidity of primary and multiple skin cancers to promote successful aging in PLWH.

Keywords

aging; HIV; non-AIDS defining malignancies; older persons; skin cancer; skin neoplasms; systematic review

Skin cancers are the most common cancers in the United States. More than 5.4 million keratinocyte carcinomas (basal cell carcinomas [BCC] and squamous cell carcinomas [SCC]) and 87,110 melanomas are diagnosed annually (American Cancer Society, 2017; Rogers, Weinstock, Feldman, & Coldiron, 2015). Many skin cancers are preventable by reducing ultraviolet radiation exposure and are curable at early stages (U.S. Department of Health & Human Services, 2014). Because the number of persons living with HIV (PLWH)

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older than 50 years quadrupled in the past decade due to effective antiretroviral therapy, many PLWH may face higher risk in the future of developing non-AIDS-defining malignancies (NADM) in the setting of long-term immune dysfunction, antiretroviral exposure, comorbid chronic diseases, and behavioral risk factors (Althoff, Smit, Reiss, & Justice, 2016; Deeks, 2011; Justice, 2010; Nguyen, Farrell, & Gunthel, 2010). Multiple cohort studies of PLWH have noted skin cancers as one of the most common NADMs (Barnes, Saxon, & Ahmad, 2014; Burgi et al., 2005; Lanoy et al., 2011; Petoumenos et al., 2013; Sofia Fernandes, 2012).

Meta-analyses of available cohort studies until 2009 suggested that HIV infection may be an independent risk factor for keratinocyte carcinomas and melanomas (Olsen, Knight, & Green, 2014; Zhao, Shu, & Wang, 2016). However, significant research gaps on the interaction between HIV infection and aging in the context of skin cancer development pose critical barriers to skin cancer risk stratification, prevention, and treatment (Alam et al., 2018). Further understanding of skin cancer epidemiology will allow personalized assessments of an individual's NADM risks to optimize benefits, risks, and costs from screening and prevention for older PLWH and to preserve and extend the quantity and quality of life gained from effective HIV treatment (High et al., 2012). To address these knowledge gaps, this systematic review aimed to determine the risks of BCC, SCC, and melanoma among PLWH older than 50 years as compared with age-matched, HIV-uninfected counterparts.

Methods

A systematic review was performed using the PubMed database, including all results as of November 4, 2017, and compiled using EndNote X8 software. The results are reported in accordance with PRISMA guidelines (Moher et al., 2009). Records were first identified in the search strategy, with search terms used shown in Table 1. Each search combination consisted of each term from Category 1 in conjunction with one term each from Category 2 and Category 3, all connected with the "AND" modifier. In total, there were 420 total search combinations performed. After duplicates were removed, titles and abstracts were screened, and full-text articles were reviewed to identify eligible studies (Figure 1).

Studies that were included in the study met the following inclusion criteria: English-language articles on the risk of skin cancers among PLWH older than 50 years with comparison to age-matched, HIV-uninfected individuals. Exclusion criteria were articles published before 1981 when AIDS was first described, publications in languages other than English, case reports or series, non-original research, studies that examined nonhuman subjects, studies that did not include a comparison group of HIV-uninfected individuals, and studies unrelated to HIV and either keratinocyte carcinoma or melanoma. We excluded studies with the mean age of study participants being younger than 50 years and those without specified skin cancer risks for age groups older than 50 years. Two independent abstractors (H.Y. and V.B.) reviewed full-text articles; discrepancies were resolved on further discussion. Quality of included studies was assessed using the Newcastle-Ottawa Scale (Wells et al., 2013). Meta-analysis was not performed due to the heterogeneity of identified studies.

Results

There were 4,008 unique English-language studies identified that were screened using title and/or abstracts. Each was assessed for eligibility, and critically reviewed through the lens of our inclusion criteria (Figure 1). Full-text review of 99 articles meeting inclusion criteria and 4 eligible full-text articles were included into the qualitative synthesis.

We found four studies that met our inclusion criteria (Table 2). All four studies were assessed to have good quality based on the Newcastle-Ottawa Scale. For melanomas, two studies were included and did not show any significantly increased risk of melanoma in older PLWH. In a first study, 23,974 melanoma cases and 119,704 control subjects in a SEER-Medicare-linked study of non-Hispanic White adults of 67 years or older showed no statistical difference in the odds of having a prior HIV diagnosis (Lanoy, Costagliola, & Engels, 2010). However, the study may be underpowered with only 0.13% of the study population (30 melanoma cases and 158 control subjects) with a history of HIV infection (Lanoy et al., 2010). In a second study, the cumulative incidence of melanoma between ages 65 and 75 years in 86,620 PLWH and 196,987 uninfected adults in a North American AIDS Cohort Collaboration on Research and Design cohort was estimated (Silverberg et al., 2015). No significant difference in crude cumulative incidence at age 75 years or at age 65 years by HIV status was noted, although only 2% to 3% of the population had follow-up person-time after age 70 years (Silverberg et al., 2015).

For keratinocyte carcinomas, 9,429 PLWH in the Swiss HIV Cohort study were linked to 9 Swiss cantonal cancer registries and showed that, among adults between 45 and 69 years, the standardized incidence ratio of BCC and SCC was not statistically higher than that for the general population (Franceschi et al., 2010). For non-Hispanic White persons with a history of keratinocyte carcinomas, a private health plan's patient cohort with a mean age older than 50 years showed higher hazard ratio (HR) (HR, 1.15; 95% confidence interval [CI], 1.02–1.31) of subsequent primary keratinocyte carcinoma in PLWH than in HIV-uninfected patients (Asgari, Ray, Quesenberry, Katz, & Silverberg, 2017). The excess skin cancer risk was most notable for the development of subsequent primary SCC in PLWH with CD4+ T-cell count less than 200 cells/mL (HR, 2.22; 95% CI, 1.42–3.48) and viral load greater than 10,000 copies/mL (HR, 2.28; 95% CI, 1.39–3.75) as compared with HIV-uninfected patients. Subsequent primary BCC was not significantly associated with CD4+ T-cell count or viral load.

Discussion

This systematic review included four studies, three of which did not reveal a significant independent association between HIV infection and the risk of keratinocyte carcinoma or melanoma in patients older than 50 years. These results contrasted with recent meta-analyses showing that HIV infection is independently associated with higher incidence of keratinocyte carcinomas (standardized incidence ratio, 1.95; 95% CI, 2.55–2.98) and melanoma (relative risk, 1.50; 95% CI, 1.12–2.01; Olsen et al., 2014; Zhao et al., 2016). Many of these prior studies contained larger and younger cohorts that were not included in our study due to the lack of age-stratified analysis. Future research focused on skin cancer

incidence in PLWH should focus on the complex interaction between aging, HIV, and behavioral risk factors in clarifying the association.

Higher risks of subsequent primary keratinocyte carcinoma was noted in older PLWH in one study, with dose–response relationships demonstrated between risks, low CD4+ T-cell count, and high viral load. This is consistent with prior research showing poorer prognosis of skin cancer in PLWH of all ages. For example, keratinocyte carcinomas were more likely to recur in PLWH than in HIV-uninfected patients 5 years after treatments (20.8% vs. 2.8%; Chren et al., 2013). Melanomas are more likely to present in advanced stages such as regional disease or distant metastasis in PLWH than in HIV-uninfected patients and lead to higher melanoma-specific mortality (Coghill, Shiels, Suneja, & Engels, 2015; Shiels et al., 2015; Zucchetto et al., 2016). Routine clinical skin examination and self-surveillance of skin in older PLWH is warranted in those with a history of keratinocyte carcinomas.

Current guidelines on caring for PLWH have not incorporated specific recommendations on skin cancer risk reduction counseling or screening (Aberg et al., 2014). The U.S. Preventive Services Task Force recommends selectively offering behavioral counseling to adults with fair skin to minimize ultraviolet radiation exposure and reduce skin cancer risks (level C recommendation), particularly those with the presence of risk factors such as HIV. Although no standard guidelines exist on optimal prevention and surveillance strategies after skin cancer diagnosis in PLWH (National Comprehensive Cancer Network, 2018), counseling on primary and secondary prevention of skin cancers in PLWH should be part of long-term survivorship care. Counseling on frequent photoprotective behavior and sunscreen use, regular self-examination of skin and clinical skin examination, and treatment of pre-malignant lesions are key to reduce additional skin cancers (Geller et al., 2018). Strict avoidance of indoor tanning—a known carcinogen commonly used among gay and bisexual men and among women—will be important to avoid further skin cancer risks (Mansh, Katz, Linos, Chren, & Arron, 2015; Yeung & Chen, 2015, 2016, 2018).

Limitations of our study include the lack of duplication in the initial search strategy and inclusion of only one search engine. Reviewing other database search engines (such as EMBASE, Cochrane, Web of Science, etc.) in duplicate may improve methodological rigor of our review.

Conclusions

These results can help optimize the primary and secondary prevention for skin cancers and may ultimately reduce the morbidity of skin cancers and advance the overall health of aging PLWH. Future studies are needed to elucidate and reduce morbidity of primary and multiple skin cancers to promote successful aging in PLWH.

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Key Considerations

- Skin cancers are common NADM that increasingly affect aging PLWH and impose significant quality of life and treatment burden. Previous meta-analyses showed that HIV infection is an independent risk factor for keratinocyte carcinoma and melanoma.
- Limited data from three studies in this systematic review that were focused on PLWH older than 50 years did not reveal significant associations between HIV infection and risks of keratinocyte carcinomas and melanoma. HIV infection, particularly if not virally suppressed, may increase the risk of subsequent keratinocyte carcinomas for those with a skin cancer history.
- Further understanding of skin cancer epidemiology will allow personalized assessments of an individual's skin cancer risks to optimize benefits, risks, and costs from screening and prevention in aging PLWH and preserve and extend the quantity and quality of life gained from effective HIV treatment.

Figure 1.

Flow chart (Moher, Liberati, Tetzlaff, & Altman, 2009) of the literature search for studies on the association between HIV infection in people ages 50 years or older and skin cancer risks.

Table 1.

Search Terms and Medical Subject Headings Used in the Literature Search.

Column 1	Column 2	Column 3
HIV [MeSH]	Skin Neoplasms [MeSH]	Aged [MeSH]
HIV Infections [MeSH]	Carcinoma, Basal Cell [MeSH]	Aging [MeSH]
Acquired Immunodeficiency Syndrome [MeSH]	Carcinoma, Squamous Cell [MeSH]	Middle Aged [MeSH]
HIV	Melanoma [MeSH]	Frail Elderly [MeSH]
HIV Infection	Neoplasms, Basal Cell [MeSH]	Aged, 80 and over [MeSH]
AIDS	Neoplasms, Squamous Cell [MeSH]	Aging
	Skin cancer	Elderly
	Basal cell carcinoma	
	Squamous cell carcinoma	
	Melanoma	

Note. MeSH = Medical subject headings.

Table 2

Summary of the Four Studies Included in the Systematic Review Synthesis

Study	Design	Population and Comparators	Time	Exposure	Outcome	Effect Summary	Quality
Lanoy et al. (2010)	Population-based, case-control study in SEER-Medicare-linked database	23,974 non-Hispanic White U.S. adults ages 67 years or older with melanomas and 119,704 without skin cancers. Median ages were 76 years for both groups.	1987–2002	History of HIV infection	Melanoma	Odds ratio for a history of HIV infection was not significant for melanoma cases as compared with controls (0.89, 95% CI 0.60–1.33), after adjustment for age, sex, year, and prior physician claims.	Selection: three stars; comparability: two stars; exposure: two stars
Silverberg et al. (2015)	Prospective cohort study in NA-Accord	86,620 PLWH and 196,987 uninfected adults. Mean age at study entry was 43–45 years depending on calendar year of entry.	1996–2009	HIV infection	Cumulative incidence of melanoma by age 75 years	Cumulative incidence of melanoma by age 75 years does not significantly differ between PLWH (0.5%; 95% CI, 0.4–0.6%) and uninfected persons (0.6%; 95% CI, 0.5–0.7%).	Selection: four stars; comparability: one star; outcome: three stars
Franceschi et al. (2010)	Prospective cohort study of Swiss PLWH linked with nine cancer registries	9,429 PLWH age > 16 years, compared with general population data. Age distribution was not described.	1985–2006	HIV infection	Incident BCC or SCC	Age-specific sex-standardized incidence ratio of BCC and SCC in PLWH was not significant as compared with the general population. Incidence rates of BCC or SCC are 1.66–2.93 per 1,000 person-year in PLWH ages 45–54 years, and 3.34 to 4.45 per 1,000 person-year in PLWH ages 55–69 years but not specified for general population.	Selection: three stars; comparability: two stars; outcome: three stars
Asgarietal. (2017)	Retrospective cohort study of patients with at least one BCC or SCC in Kaiser Permanente Northern California	6,567 HIV-infected non-Hispanic White persons with history of BCC or SCC and 36,887 age-, sex- and race-matched HIV-uninfected persons. Mean ages at study entry were 52.5 and 55.5 years, respectively	1996–2008	HIV infection	HR for the subsequent BCC or SCC	PLWH had a HR of 1.15 (95% CI, 1.02–1.31) for a subsequent BCC or SCC, as compared with HIV-uninfected patients.	Selection: four stars; comparability: two stars; outcome: three stars

Note. BCC = basal cell carcinoma; CI = confidence interval; HR = hazard ratio; SCC = squamous cell carcinoma; SEER = Surveillance, Epidemiology, and End Results Program; NA-ACCORD = North American AIDS Cohort Collaboration on Research and Design; PLWH = persons living with HIV.