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Nationwide Longitudinal Annual Survey of HIV/AIDS Referral Hospitals in Japan From 1999 to 2021: Trend in Non–AIDS-defining Cancers Among Individuals Infected With HIV-1

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Background: Non–AIDS-defining cancers (NADCs) in patients infected with HIV have recently attracted attention because of the improved survival of this patient population. To obtain accurate data, a longitudinal study is warranted for the nationwide surveillance of the current status and national trend of NADCs in patients infected with HIV in Japan.

Setting: An annual nationwide surveillance of NADCs in patients infected with HIV-1 in Japan from 1999 to 2021.

Methods: An annual questionnaire was sent to 378 HIV/AIDS referral hospitals across Japan to collect data (clusters of differentiation 4-positive lymphocytes, time of onset, outcomes, and antiretroviral therapy status) of patients diagnosed with any of the NADCs between 1999 and 2021.

Results: The response and case-capture rates for the questionnaires in 2021 were 37.8% and 81.2%, respectively. The number of reported NADC cases subsequently increased since the beginning of this study. Evaluation of the case counts of NADCs demonstrated a high incidence of lung, colorectal, gastric, and liver cancers as the top 4 cancers. Pancreatic cancer (0.63), lung cancer (0.49), and leukemia (0.49) had the highest mortality rates among the NADCs. Trends of NADCs regarding transmission routes were maintained over the years in male individuals who have sex with male individuals compared with heterosexual male individuals and female individuals.

Conclusions: We demonstrated an increasing trend in the incidence of NADCs over a period of 23 years in Japan. The current data highlighted the importance of raising awareness regarding cancer management for patients infected with HIV in Japan.

Key Words: HIV, acquired immunodeficiency syndrome, incidence, Japan, non–AIDS-defining cancers

(*J Acquir Immune Defic Syndr* 2024;96:1–10)

Received for publication June 10, 2023; accepted January 3, 2024.

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K.T. received a grant (Grant No. 23fk0410038h0003) from the Japan Agency for Medical Research and Development (AMED) (https://www.amed.go.jp/en/). The funders had no role in the study design, data collection and analysis, decision to publish, or manuscript preparation. The remaining authors have no funding or conflicts of interest to disclose.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (www.jaids.com).

Data on the trends of the incidence of malignancies among patients infected with HIV have not been examined across the globe in a country-wise and longitudinal manner. Consequently, we conducted an annual nationwide survey, funded by the Japan Agency for Medical Research and Development, to elucidate the current status and trends in the prevalence of NADCs among patients infected with HIV-1 in Japan between 1999 and 2021.

Conceptualization: A.Y., K.T., and K.I. Data curation: T.T., K.O., K.K., Ma.T., S.K., A.T., A.F., N.A., Mi.T., A.Y., and K.I. Funding acquisition: K.T. Investigation: T.T., K.O., K.K., Ma.T., S.K., A.T., A.F., N.A., Mi.T., A.Y., and K.I. Project administration: T.T., K.O., K.K., Ma.T., S.K., A.T., A.F., N.A., Mi.T., A.Y., and K.I. Supervision: K.T. and K.I. Visualization: T.T. and K.O. Writing—original draft preparation: T.T. Writing—review and editing: K.I. All authors contributed substantially to this study. All authors have read and approved the final version of the article.

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INTRODUCTION

As of 2020, a total of 37.7 million people were living with HIV, including 10.2 million who were not receiving treatment and 1.5 million who were newly diagnosed with HIV infection. Globally, 680,000 people die annually of HIV-related causes.[1] Significant improvements in the life expectancy of HIV-infected individuals have been achieved with the introduction of universal antiretroviral therapy (ART).[2] At

the same time, as patients age, comorbidities often act as prognostic factors or factors that cause a decline in quality of life, and appropriate management of these comorbidities is desirable.[2] The expansion of ART coverage has decreased the incidence of AIDS and AIDS-related morbidity and mortality, as well as HIV transmission.[3–6]

According to the Millennium Development Goals report,[7] the incidence of new HIV infections declined by 40% from 2000 to 2013 worldwide. One study reported a decrease in the incidence of AIDS-defining malignancies (ADMs), namely Kaposi sarcoma, non-Hodgkin lymphoma, and invasive cervical cancer.[8] Since 1998, we have conducted an annual national surveillance of opportunistic complications among people infected with HIV in Japan. In a previous report,[9] we showed that the number of AIDS-defining illnesses (ADIs) has decreased continuously since 2012. Globally, as of 2020, the number of newly diagnosed patients with cancer was 19,292,789; furthermore, 9,958,133 people died from cancer.[10] In Japan, as of 2018, the number of newly diagnosed patients with cancer was 980,856, and 376,425 people died from cancer.[11]

By contrast to the decreasing trend of ADIs and ADMs, there is a growing body of evidence supporting an increase in the incidence of non–AIDS-defining cancers (NADCs). The reasons for the increase in NADCs have been discussed using a multifactorial approach because organ-specific factors affect the pathogenesis of each cancer, such as age-matched factors, smoking status, transmission routes, contaminated blood product use, coinfection with other viruses, cigarette smoking, alcohol consumption, and advanced age.[12–15]

METHODS

Patient Group

This study was conducted annually, using 2 main content surveys at the same time: (1) the annual national surveillance of opportunistic complications in patients infected with HIV and (2) the annual national surveillance of NADCs. The former survey analysis was reported by us previously,[9] and similarly, in this study, HIV/AIDS referral hospitals in Japan were used for the survey. As of September 2021, these hospitals were located at 378 sites throughout Japan. Since 1999, we have posted an annual questionnaire on NADCs for patients diagnosed with NADCs among individuals infected with HIV-1 from January to December of the previous year.

Questionnaire Development

The questionnaire was divided into 2 parts. The first included questions regarding the presence of patients with NADCs in each hospital. The second part gathered information regarding patients with NADCs. This included questions on the type and onset of NADCs, clusters of differentiation 4-positive ($CD4^+$) lymphocyte levels at the onset, diagnostic procedures used for NADCs, outcomes of cancer treatment, ART initiation at the onset, elapsed time from the initial HIV diagnosis until the onset of NADCs, and ART initiation time after the diagnosis of NADCs. A detailed survey of each disease was omitted because the aim of this study was to determine the trends in patients with NADCs in Japan. Outcomes, including survival status, were recorded at the time when each physician responded to the questionnaire. Questionnaires were posted to HIV/AIDS referral hospitals throughout Japan annually for 23 years. As this surveillance was an annual report, the outcome was a clinical judgment made by each physician a year after diagnosis.

The questionnaire responses were recorded in a database created using Microsoft Access 2010 (Microsoft Corporation, Redmond, WA) for further analysis. The questionnaire was developed in accordance with the ethical guidelines for medical research targeting human subjects[16] and therefore did not include identifiers such as patient initials or record numbers by which patients could be linked or identified.

Mortality Rate

The mortality rate was calculated as "the accumulated number of deaths reported in the survey per accumulated number of diagnosed cancer patients."

Capture Rate

The annual capture rate was calculated on the basis of the number of AIDS cases reported to the AIDS Surveillance Committee of the Ministry of Health, Labour, and Welfare (MHLW) in Japan. The capture rate (average of the last 2 years) was calculated as the number of AIDS cases reported through our questionnaires (total number in the past 2 years) divided by the number of AIDS cases reported through the MHLW surveillance (total number in the past 2 years).

Statistical Analysis

All data were analyzed using IBM SPSS 23 (IBM Corp, Armonk, NY). We performed an aggregate analysis in this study, in which the number of cases by the responders to the questionnaire was calculated, and the percentage of each response was examined for each year.

Ethics

The study was approved annually by the Institutional Review Board of Nagasaki University Hospital (Approval Number: 18111929-2) and by the institutional review boards of each participating hospital. Informed consent was waived in this study because the information did not include any human samples or personal information.

TABLE 1. Baseline Study Data

Research period	23 yrs (1999–2021)
Number of facilities in 2021	378
Response rate in 2021 (%)	37.8
Case capture rate in 2021 (%)	81.2
Sex (%)	Female (6.9)/Male (93.1)

RESULTS

Trends and Number of Cases of NADCs

The baseline data of the study are summarized in Table 1. The response and case-capture rates for the questionnaires in 2021 were 37.8% and 81.2%, respectively (see Table, Supplemental Digital Content 1, http://links.lww.com/QAI/C225). A total of 93% of the patients were male patients. Data of sex-specific tabulations of key data are shared in the Table, Supplemental Digital Content 2, http://links.lww.com/QAI/C226.

Questionnaires were posted to HIV/AIDS referral hospitals throughout Japan annually from 1995 to 2021. In 2021, questionnaires were sent to 378 hospitals, and a response rate of 37.8% (143 hospitals) was observed. In 2021, 60 cases of NADCs were reported from a total of 922 NADCs to date. In the annual occurrence of NADCs (Fig. 1A), the number of cases of NADCs increased

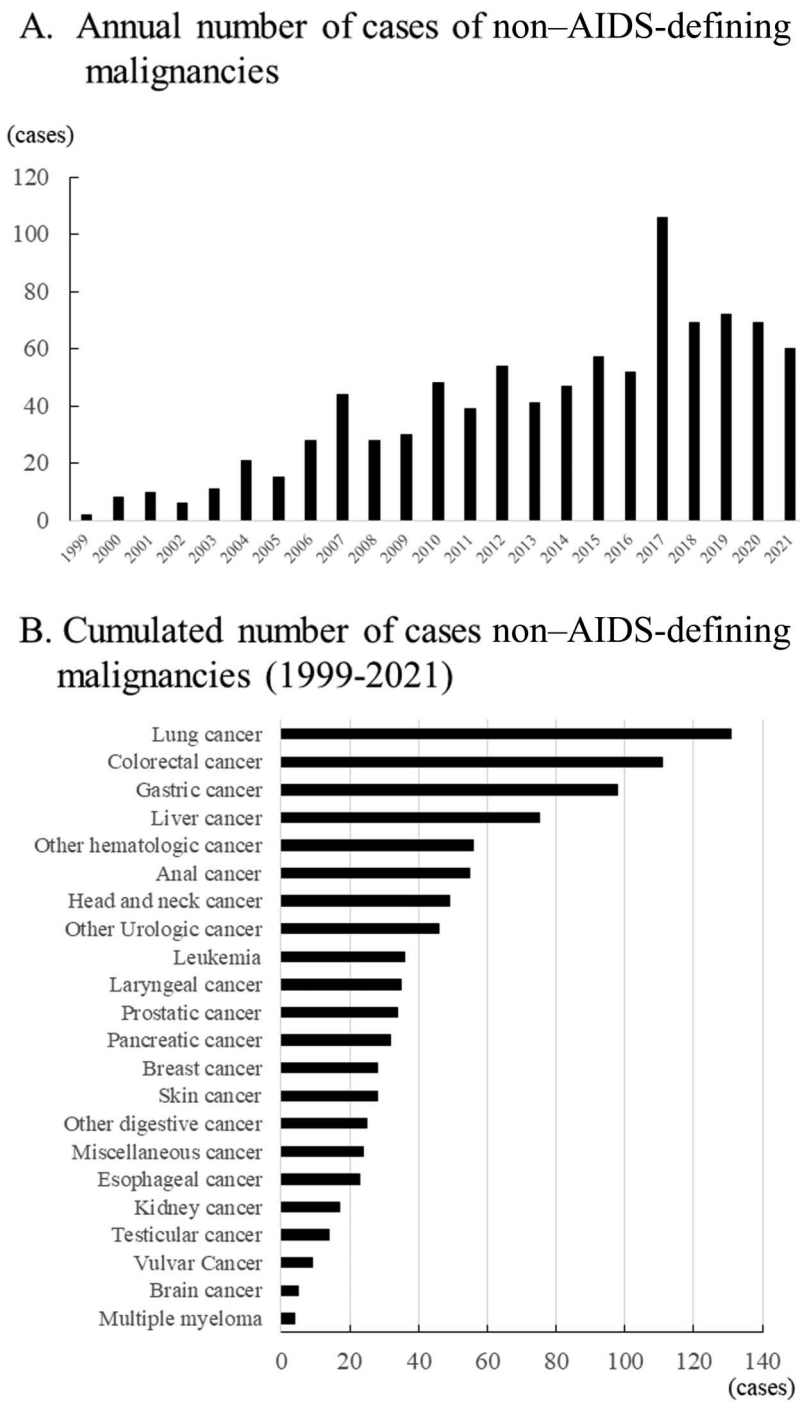

FIGURE 1. Change over time in the number of cases of NADCs (1999–2021). A, Annual number of cases of NADCs. The numbers present a continuously increasing trend since 1999. B, Case counts number of cases of NADCs. NADCs, non–AIDS-defining cancers.

significantly in 2000, with 8 cases compared with the previous year of 1999, which only had a few cases. After that, the number of NADCs increased every year, with approximately 40–50 cases annually after 2010, and then leveled off but reached a peak in 2017 before slightly decreasing again after 2018.

The case count numbers of NADCs is shown in Figure 1B, with lung cancer being the most frequent (131 cases in total). Liver cancer was the most frequent NADC until 2009, after which its incidence declined. By contrast, lung cancer became the most frequent NADC, with an increase in the number of cases to 11 in 2010, and remained the most frequently occurring disease cumulatively, although it showed a decreasing trend after that. The proportions of each NADC in descending order were as follows: lung cancer (14.0%), colon cancer (11.9%), stomach cancer (10.5%), liver cancer (8.0%), other hematologic tumors (6.0%), anal cancer (5.9%), head and neck cancer (5.2%), other urogenital tumors

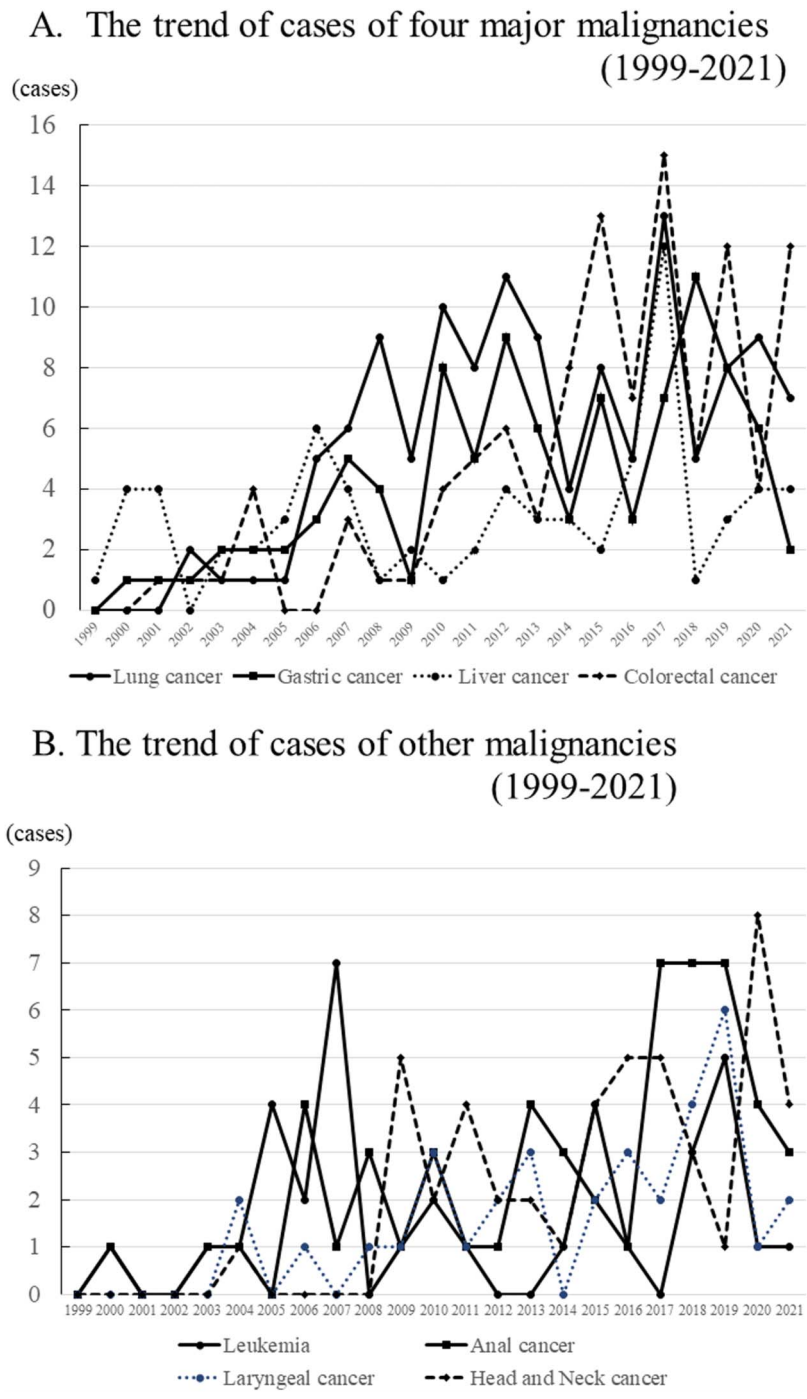

FIGURE 2. Change over time in the incidence of each cancer (1999–2021). A, The trends observed in the incidence of 4 major cancers (1999–2021). B, The trends observed in the incidence of other cancers.

(4.9%), leukemia (3.9%), laryngeal tumors (3.7%), prostate cancer (3.6%), pancreatic cancer (3.4%), skin cancer (3.0%), breast cancer (3.0%), esophageal cancer (2.5%), renal cancer (1.8%), testicular cancer (1.5%), vulvar cancer (0.9%), brain cancer (0.5%), and multiple myeloma (0.4%).

In the single-year data for 2021, there were 12 cases of colorectal cancer, 7 cases of lung cancer, 2 cases of stomach cancer, 3 cases of anal tumors, 2 cases of laryngeal cancer, 4 cases of liver cancer, and 4 cases of head and neck cancer (Figs. 2A, B). In the graphs showing the annual incidence of the 8 major diseases (Figs. 2A, B), the rapid increase in the incidence of colorectal cancer since 2009 was particularly conspicuous. Liver cancer peaked at 6 cases in 2006, then decreased, and then increased again to 11 cases in 2017, after an almost stable rate of 1–4 cases/year for the past several years.

Prognosis of Malignancies

Regarding mortality, categorized according to tumor type (Fig. 3A), pancreatic cancer, which originally had a poor prognosis, had the highest mortality rate, followed by leukemia and lung, liver, laryngeal, and esophageal cancer. In patient outcomes (Fig. 3B), complete/partial remission was observed in 62% of the patients.

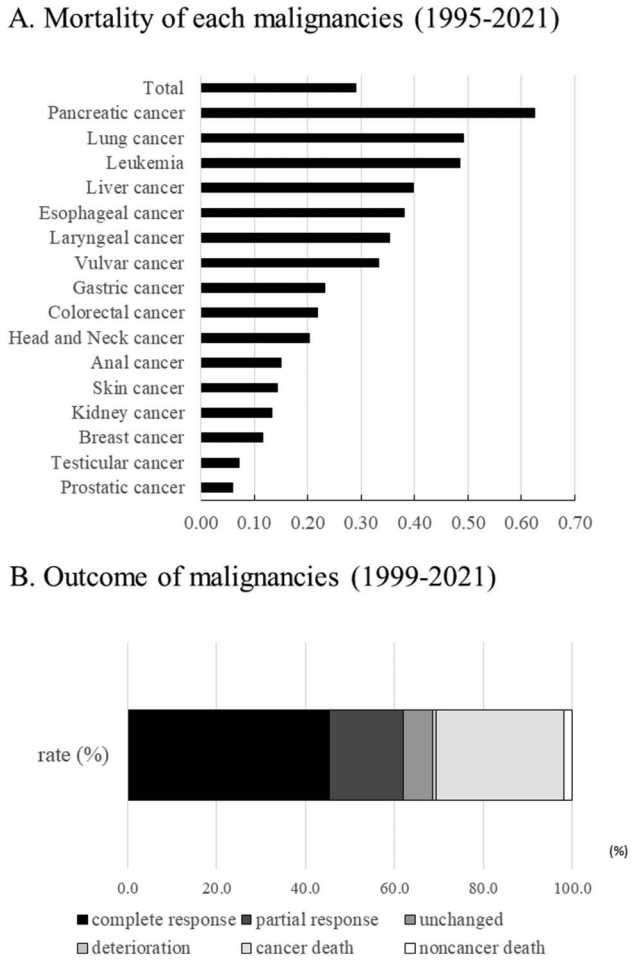

FIGURE 3. Mortality and morbidity of NADCs. A, Mortality in each NADC (1995–2021). B, Outcomes of NADCs.

Transmission Routes

The annual number of NADCs, classified according to the route of infection (Fig. 4A), showed an increasing trend over time, with more cases reported in male patients who have sex with male individuals (MSM) (n = 477 cases) than in others (n = 182 cases) (Fig. 4B). The incidence of lung, colorectal, gastric, anal, and head and neck cancers was particularly high among MSM. Lung cancer was the most common in both MSM and others. Although the number of iatrogenic infections (mainly in patients with hemophilia due to contaminated blood coagulation factor products) was relatively small (n = 65), which is not included in the Figure 4 data, it is noteworthy that liver cancer accounted for approximately 50% of cases, which may be attributed to hepatitis C virus caused by blood product contamination (data not shown).

Age Distribution

The most common age group of tumor onset (Fig. 5A) was in the 60s, and 2.1% of patients infected with HIV were in their 80s, an age group that generally has a small population of patients infected with HIV. Compared with the age of onset of opportunistic infections,[9] which is close to the age of detection in patients infected with HIV, there was a clear shift toward an older age group. There was no significant difference in age distribution by route of infection, that is, among MSM and others (Fig. 5B). Regarding age distribution by tumor, testicular tumors tended to occur at younger ages; head and neck tumors, anal tumors, and leukemia were more common in the middle-aged group; and laryngeal, liver, colon, stomach, and lung cancers were more common in the older group (Fig. 5C).

Distribution of $CD4^+$ Lymphocytes and Time From Diagnosis

The distribution of $CD4^+$ lymphocytes in peripheral blood at the time of cancer diagnosis showed a trend toward a higher number of patients with lower $CD4^+$ lymphocyte counts (see Figure A, Supplemental Digital Content 3, http://links.lww.com/QAI/C227). The distribution of $CD4^+$ lymphocytes in major malignancies is shown in Figure B, Supplemental Digital Content 3, http://links.lww.com/QAI/C227. Regardless of the tumor type, $CD4^+$ lymphocytes were widely distributed, with no CD4 bias in any particular tumor. The onset of tumor development occurred more than 1 year after HIV diagnosis in 80% of all patients infected with HIV (see Figure C, Supplemental Digital Content 3, http://links.lww.com/QAI/C227). By contrast, in more than 80% of patients with opportunistic infections, tumor development occurred within 3 months (including simultaneous detection).[9] Specifically, tumor development occurred after a period of time had elapsed since the diagnosis of HIV.

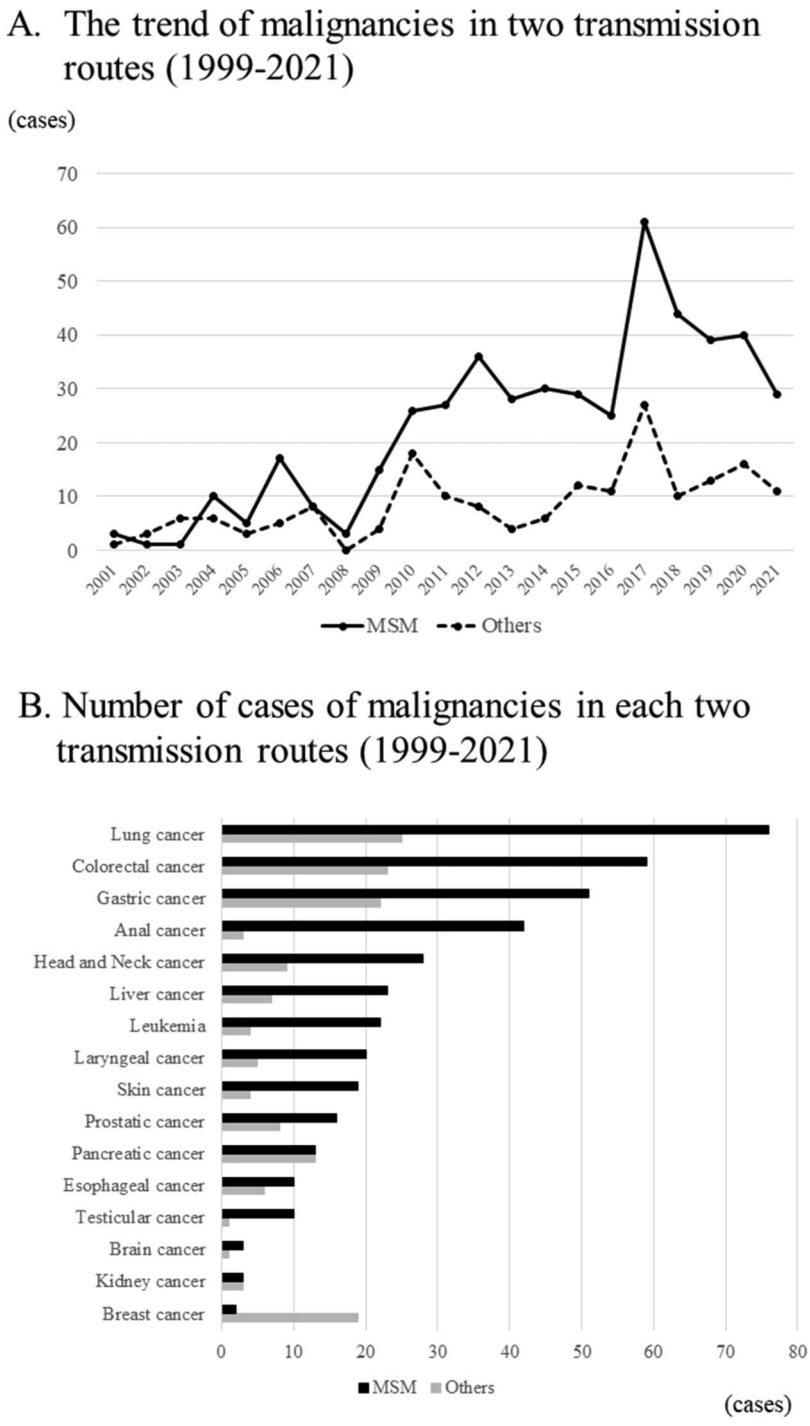

FIGURE 4. Comparison between 2 transmission routes (1999–2021). A, Trends observed in malignancies according to the 2 transmission routes. B, Number of cases of malignancies for each of the 2 transmission routes.

DISCUSSION

In this study, we investigated the prevalence and long-term trends of NADCs among patients with HIV in Japan from 1999 to 2021. For patients infected with HIV in Japan, most treatments for complications, including malignancies, are provided at HIV/AIDS referral hospitals. Thus, the results of this survey provided a comprehensive picture of malignant tumors among such patients in Japan.

With the introduction of ART, the long-term prognosis of patients infected with HIV has improved,[1] and the occurrence of malignant tumors has become a cause for concern.[12,13] Furthermore, as conventional infection-linked cancers, NADCs have higher mortality rates than ADIs and have recently been the focus of attention because the disease burden has increased over time.[17–21] Data on the incidence trends of NADCs have been reported from several

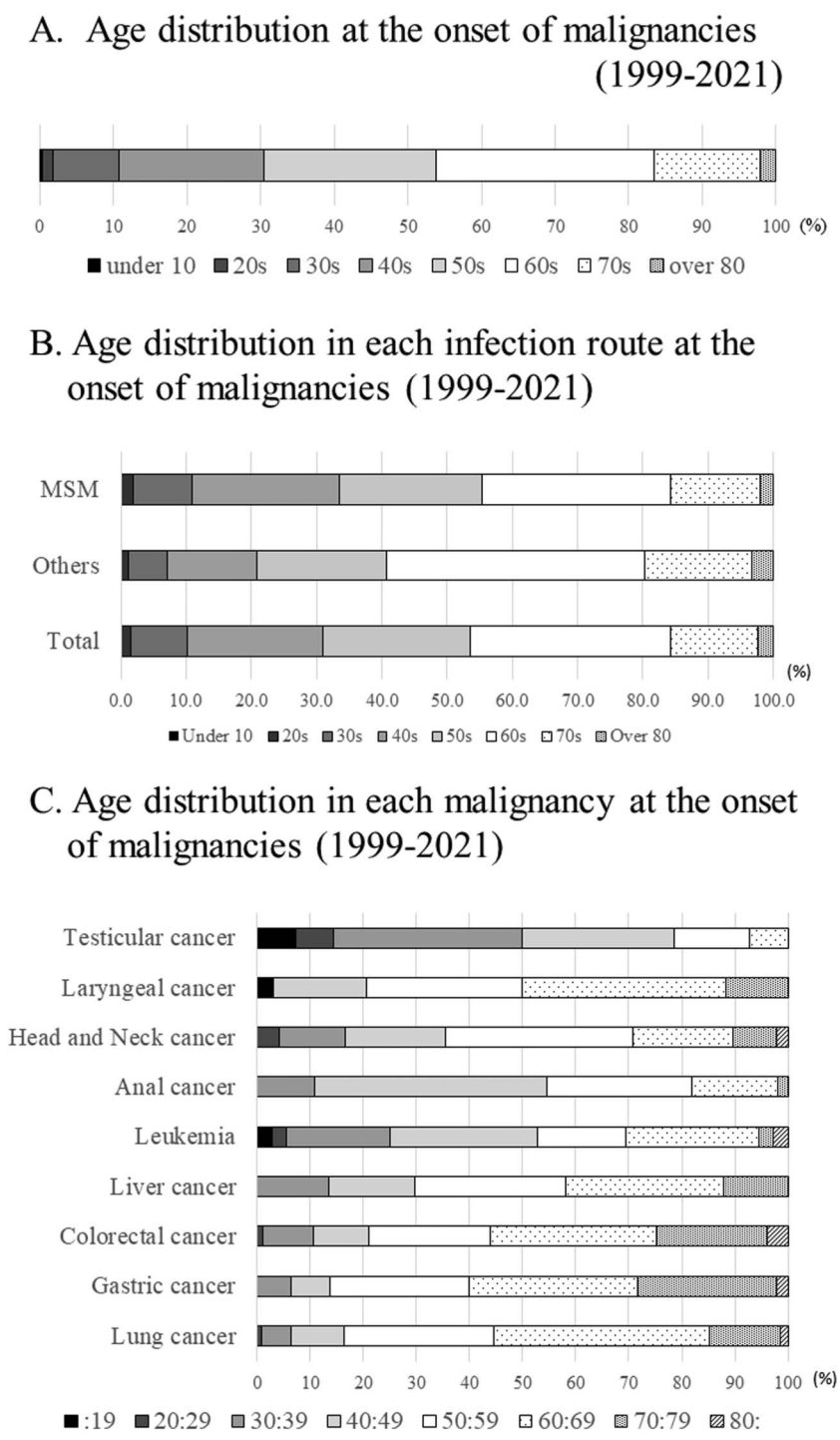

FIGURE 5. Age distribution in NADCs (1999–2021). A, Age distribution at the onset of malignancies. B, Age distribution in each infection route at the onset of malignancies. C, Age distribution in each malignancy at the onset of malignancies.

countries[22–27]; however, there is a paucity of published data originating from Japan.[28,29]

This study highlighted several interesting characteristics of NADCs in Japan, categorized according to trends and number of cases, prognosis, transmission routes, age distribution, and $CD4^+$ lymphocyte distribution. In our study, the number of NADCs among patients infected with HIV in Japan was found to have increased over time. To prevent the duplication of cases, the target year was specified in the questionnaire form to avoid confusion when surveying newly diagnosed cases for each year in the annual questionnaire. The theoretical possibility exists that duplicate enrollment is possible when patients are transferred between HIV/AIDS referral hospitals. However, in Japan, all the HIV/AIDS referral hospitals are high care medical institutions that are able to provide most of the specialized

services; thus, transferring cases between these facilities is rare.

In Japan, the number of newly reported cases of HIV infection or AIDS has peaked, based on the Infectious Disease Surveillance System for HIV/AIDS diagnosis by the MHLW of Japan (see Table, Supplemental Digital Content 4, http://links.lww.com/QAI/C228). The increasing trend in NADC case counts may be related to an aging population of people living with HIV who acquired the infection in the 1990s/early 2000s, which explains why cases accumulated over time and why most individuals were aged in their 60s.

The distribution of cancer among patients infected with HIV clearly differed from the general tumor frequency in the Japanese population. Cancer incidence data among the general population in Japan were collected using the National Cancer Registry system, and data for the year 2018 are available on the website.[30] When the Japanese epidemiological data were compared with the results of our study, anal (<1% vs. 5.9%, respectively), testicular (<1% vs. 1.5%, respectively), and laryngeal cancer (<1% vs. 3.7%, respectively) were found to be more common in our survey on patients infected with HIV. Cancer types that were infrequent in the general population were relatively common in our study, and diversity was observed. Moreover, 22 cancer types were identified in our survey. Excluding the major cancers (lung, colon, stomach, and liver), 18 other cancer types constituted 55.6% of all NADCs, which is similar to the proportion of 55.2% reported in the Japanese epidemiological data. Although it was difficult to determine whether there was a significant difference in the frequency of each cancer type because the overall number was not large, this trend of diversity is noteworthy, and the data may suggest that HIV infection itself is related to cancer immunity.

The fact that the proportion of cancer cases in MSM was higher than that of others may also be a factor. However, different types of cancer in HIV-positive populations may reflect a phenomenon affecting cancer immunity. The well-known human oncoviruses are human papillomavirus (HPV), hepatitis B virus, hepatitis C virus, Epstein–Barr virus, human herpesvirus 8, human T-cell lymphotropic virus, and Merkel cell polyomavirus.[31] Epstein–Barr virus has been implicated in the pathogenesis of Burkitt lymphoma, Hodgkin disease, non-Hodgkin lymphoma, nasopharyngeal carcinoma, lymphomas, and leiomyosarcomas[32,33]; HPV with anal, laryngeal, and recently lung cancer[34–36]; and hepatitis B virus and hepatitis C virus with liver cancer.[37] No association with viral infection has been found in other types of cancer, such as colon cancer.

According to the Department of Health and Human Services guidelines,[38] HPV vaccination is beneficial and is recommended for the age group of 13–26 years because they may have sexual contact; moreover, vaccination for those older than 27 years is deprecated because of low benefits. Although HPV vaccination for male patients has not gained momentum,[39–42] vaccination of patients younger than 26 years is recommended, given the risk of HPV-related malignancies. Therefore, with the introduction of the HPV vaccine, analysis of future trends in the prevalence of anal or laryngeal cancer can help determine the vaccination effect.

An increase in the incidence of lung cancer has been noticeable over the past few years. In 2014, a report from the United States documented a notable increase in anal, liver, and prostate cancers.[22] A 2014 report from France also documented that lung and anal cancer rates have decreased since the beginning of the ART era.[23] A single-center study in Japan reported an increased risk of liver and colorectal cancers, while the risk of gastric cancer, which is common in Japan, also increased.[29] As a projection of future frequencies, a study from the United States predicted a rise in prostate and lung cancers by 2030.[43] Continuous monitoring of the frequency of occurrence of NADCs is important because various factors are related to the occurrence of malignant tumors, including lifestyle variations in various countries.

Smoking is a pivotal factor in the development of malignancies. The average smoking rate among the general Japanese population from the 2019 national survey by the MHLW was 27.1% for male patients and 7.6% for female patients.[44] A Japanese single-center study in 2011 analyzed 149 HIV-positive patients and reported a smoking rate of 42.2%.[45] Because the average smoking rate in Japan in 2011 was 32.4% for male patients and 9.7% for female patients, it can be said that the smoking rate among patients infected with HIV in Japan is higher than that in the general population. Although there are no clear data, it is possible that factors contributing to the incidence of lung and laryngeal cancers, such as smoking, are higher among individuals with infected HIV, especially MSM, and the promotion of smoking cessation among individuals infected with HIV will be an important issue in the future. Smoking is also a high-risk factor of malignant tumors other than lung cancer (genitourinary system and throat cancers), and future trends should be closely monitored.

Considering the factors that contribute to the development of malignancies in patients with HIV, it would be reasonable to compare them with malignancies in other immunosuppressed populations. There is growing evidence of increased cancer incidence in immunosuppressed patients.[46,47] As for the association with $CD4^+$ lymphocyte counts, our present findings did not suggest an association; however, previous reports have shown that lower $CD4^+$ lymphocyte counts are associated with lower survival rates.[48,49] In addition to the association between HIV and the development of cancer based on conventional epidemiological information, recent studies have reported an association between HIV-derived microRNAs and interactions with tumorigenesis.[22,50] This microRNA evidence may prove a link to malignancies that have been identified from previous ADIs. It is also expected that associations with malignancies not previously recognized as infection-linked cancers will be proven. Future advances in microRNA functional analyses may reveal a direct association between the target genes and tumorigenesis, which is impaired by age, smoking history, and other known risk factors.

In future HIV care, in addition to controlling antiviral therapy and paying attention to metabolic complications, it is important to conduct regular screening for the early detection

of malignant tumors.[51–54] The results of this study emphasize the need for screening for malignant tumors by focusing on the risk of acquiring certain cancers according to age. However, our results and previous reports suggest that patients infected with HIV may have a wide variety of malignant tumors and that it is difficult to detect all of them by commonly used cancer screening.[55] To cope with the rapid increase in the number of cancers due to the aging of patients infected with HIV, there is an urgent need to develop screening and preventive methods for malignant tumors.[20]

In the epidemiological context of HIV in Japan, intravenous (IV) drug users account for a very small proportion of all blood-borne infection routes (see Table, Supplemental Digital Content 5, http://links.lww.com/QAI/C229). In these data, not a single case of IV drug use corresponded to this category. However, owing to the overlap of infection routes (MSM + IV drug use), it is possible that the IV drug use infection route in Japan is underestimated.

The retrospective design of this study had some limitations. First, a response rate of 37.8% from all HIV/AIDS referral hospitals may have led to a selection bias. However, most of the high-volume centers in each region of Japan responded to our survey every year, and the case capture rate of HIV/AIDS cases was 81.2%; therefore, we do not believe that there was a large selection bias. Second, the context of the questions was minimized for simplicity and ease of completion; therefore, the background information of patients was inadequate for performing additional analyses. Third, the calculation of the mortality rate in this study was not performed in accordance with the standard evaluation method; however, the percentage of annual deaths in the applicable year of the study period could be collected because of the limited information requested in the questionnaire. Fourth, although information on the time of diagnosis of malignancy was included in the questionnaire items, the time of ART initiation and the duration of ART were not included as information items. Therefore, it was not possible to analyze the relationship between ART and the risk of malignancy. Finally, there was the possibility of missing data for patients who received NADC treatment outside HIV/AIDS referral hospitals. In Japan, under the health care system, most patients with HIV/AIDS are managed at HIV/AIDS referral hospitals. Patients are rarely managed at hospitals other than the HIV/AIDS referral hospital. The HIV/AIDS referral hospitals provide both primary care and HIV management for people living with HIV, as outpatients and inpatients. Based on the above, it is assumed that most of the patients with NADCs in Japan are captured by this surveillance, based on the number of cases at HIV/AIDS referral hospitals in Japan.

In conclusion, our data, based on high-volume information obtained through annual national surveillance, clarified accurate 21-year trends in NADC status and occurrence in Japan. Our survey is a valuable resource because it collected serial data from across Japan. As changing lifestyles and social backgrounds are elements that influence the occurrence of malignancies to some extent, continuous surveillance is warranted to obtain future trends and disease outcomes.

ACKNOWLEDGMENTS

The cooperation of all personnel involved in the participating HIV/AIDS referral hospitals made it possible to continue the study every year. The authors express their deepest gratitude to them for their support in the survey, which they provided while encumbered with the increasing burden of duties. The authors would like to thank Editage (www.editage.com) for English language editing.

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