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Epidemiology of Malignant Tumors among HIV-infected Population in China

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Epidemiology of Malignant Tumors among HIV-infected Population in China

A dissertation submitted in partial satisfaction of the requirements for the degree Doctor of Philosophy in Epidemiology

by

Weiming Zhu

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ABSTRACT OF THE DISSERTATION

Epidemiology of Malignant Tumors among HIV-infected Population in China

by

Weiming Zhu

Doctor of Philosophy in Epidemiology

University of California, Los Angeles, 2013

Professor Zuo-feng Zhang, Chair

HIV/AIDS population is known has higher risk of many malignant tumors, but cancer spectrum among HIV/AIDS population in China has not been reported, and risk factors of Kaposi Sarcoma (KS) among HIV-infected Chinese population remains unknown. This dissertation study

describes the spectrum of malignancies among HIV/AIDS population in China, 2008-2011, and explores associated factors of KS both in the national HIV/AIDS cohort and in a hospital-based case-control study among HIV-infected Uyghur people in Xinjiang, China.

In part I, we used cohort data of national HIV/AIDS surveillance and information system during 2008-2011 to calculate standardized incidence rates (to China census 2010) and standardized incidence ratios (with China tumor registry 2008) of all reported cancers. Totally 3819 cancer reports were found from 399,451 subjects with followed-ups between 2008 and 2011. Higher risk was found in both AIDS-defining cancers (KS, lymphomas and cervical cancer) and non-AIDS-defining cancers (lung, liver, stomach, etc.) Comparing with western countries, HIV/AIDS population in China had lower risk of Kaposi Sarcoma, lymphomas, similar risk of female cervical cancer but higher risk of non-AIDS-defining cancers including lung, liver, and stomach cancers.

In part II, we analyzed risk factor of KS in the national HIV/AIDS cohort using Cox proportional hazard model. Being male (Hazard Ratio, HR 1.68, 95%CI 1.13-2.40), Uyghur ethnic (HR 5.30, 95%CI 3.68-7.64), HIV transmission route (heterosexual vs. intravenous drug use, HR 1.75 95%CI 1.12-2.74), lower CD4 cell count at HIV diagnose (comparing with subjects with CD4 $\geq$ 350/μL at HIV diagnosis, HR for CD4<200/μL was 4.07, and 3.27 for CD4 200~349/μL). Antiretroviral treatment was found a protective factor of KS, with HR 0.39 95%CI 0.27-0.56. Sub-set cohort of Uyghur results were similar.

In part III, we established a hospital-based matched case-control study among HIV-infected Uyghur people and got 39 KS cases and 93 controls. Using conditional logistic regression models, we found HIV transmission route (heterosexual vs. intravenous drug use, Odds Ratio, OR 0.37, 95%CI 0.14-1.00) was risk factor of KS while antiretroviral treatment was protective (OR 0.13, 95%CI 0.03-0.72). Bayesian analysis with priors from Part II and sensitivity analysis found posterior ORs of HIV transmission routes and ART were consistent with national HIV-infected Uyghur cohort.

The dissertation of Weiming Zhu is approved.

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Chapter 1. Introduction

HIV/AIDS associated malignancies

Kaposi Sarcoma (KS), non-Hodgkin Lymphoma (NHL) and cervical cancer have been found associated with Acquired Immunodeficiency Syndrome (AIDS) at the very beginning of the identification of AIDS. In 1981, Kaposi Sarcoma (KS), as well as Pneumocystis carinii Pneumonia, were first reported in men who have sex with men (MSM) in New York and California and thus KS has been known as the first HIV/AIDS-associated malignant tumor (1-7). Later in 1987, the KS, NHL, and cervical cancer were defined as "AIDS defining cancers" according to the criteria of AIDS diagnosis by the US Centers for Disease Control and Prevention (CDC) (8). Among HIV-positive population in the US and Europe, KS is the most prevalent malignant tumor, followed by NHL and cervical cancer. Anal cancer in MSM, cancers of oral cavity, liver, lung, penis as well as Hodgkin Lymphoma have also been reported in HIV-positive population, although with much lower incidence than the three AIDS defining cancers (4, 9-16).

HIV/AIDS patients have been expected and observed to live longer during the era of antiretroviral therapy (ART) (17-20). The incidence of chronic diseases especially malignancies has been increasing in countries where ART has been widely available for the last two decades (21-29). These studies, however, were reported mostly from Caucasian (White) and African (Black) populations (10, 21, 24, 30-44).

Kaposi Sarcoma

Kaposi Sarcoma was first described by Dr. Moriz Kaposi in 1872, defined as “idiopathic multiple pigmented sarcoma of the skin” based on observation of five cases with skin nodules without known causes, which could appear on mucous of larynx, stomach and intestines, implying potential “carcinoma pigments” (45). Generally, there are four major types of KS without distinguishable histology difference: Classic KS, African-endemic KS, post-transplantation/ iatrogenic KS, and HIV/AIDS-associated KS. KS can invade skin, oral mucosa, gastric-intestine ducts, lymph nodes and many other organs, and it is significantly associated with immunocompromised status (46)

Classic KS is usually seen in elder males in Mediterranean area or population of Mediterranean/eastern European heritage, e.g. Israel, Southern Italy and Northern African (47). Risk factors of classic KS identified from western population were male, having diabetes, use of oral corticosteroid medications, infrequent bathing, and history of asthma. Cigarette smoking may be inversely associated with classic KS (48, 49)

African-endemic KS cases were first recognized in sub-Saharan Africa since 1950s and the highest incidence of KS were found in a strip-region near the equator, including Uganda, Zaire, etc, overlapping with the epidemic area of Hodgkin lymphoma (50). Most African-endemic KS were found in young adult males and seem to be localized lesion. However, lymphadenopathic

KS, a subtype of African-endemic KS, occurs in children with rapidly metastasis through lymph circulation system. The male-to-female ratio of this subtype is about 3 to 1. Without proper treatment, children with lymphadenopathic KS may die from 1 to 3 years after diagnosis (51).

Post-transplantation/iatrogenic KS was identified from organ-transplant recipients that under immunosuppressive therapies. This type of KS may invade skin, mucosa, gastrointestinal tract, lungs and lymph nodes. Some patients with post-transplantation KS might have other malignancies such as NHL simultaneously (52).

Kaposi Sarcoma in the era of AIDS

Since 1981, "irregular" KS cases were found in young homosexual men, or men who have sex with men (MSM) (5-7, 53-56). After the identification of AIDS, the new type HIV/AIDS-associated KS was also defined. The AIDS-associated KS is aggressive and often combine with other opportunistic infections that before the era of highly active antiretroviral treatment (ART), the average survival period of KS in AIDS patients was about 5~18 months (57, 58). After ART started in 1996, the average survival for AIDS-KS was improved to about 20 months to over 5 years (58-60).

Not only the survival time of AIDS-KS get improved, the incidence of KS also declined after HAART (61). The increased incidence of HIV-related KS has been paralleling to the early period of HIV/AIDS epidemic before ART era, and the decrease of KS incidence of KS is correlated

with the start period of ART. Such a decrease in incidence may be due to not only the initiation of ART but also the behavior changes leading to decline of HIV infection in MSM population in the US during early 1990s (62). Similar decline in KS incidence has also been observed in Europe (63-65).

Kaposi Sarcoma-associated Herpes Virus (KSHV/HHV-8)

In 1994, a new kind of human herpesvirus, human herpesvirus type-8, also known as Kaposi Sarcoma-associated herpesvirus (HHV-8/KSHV) was identified from the KS tissue (66). KSHV belongs to γ-herpesvirus family (Gammaherpesvirinae) with a close relative - Epstein-Barr Virus (EBV). Both viruses were found capable of latent infection in cells with potential of carcinogenesis. Besides KS, KSHV is also identified in tissues of primary effusion lymphoma (PEL) and multicentric Castelman disease (MCD) (67). KSHV may express several proteins that can disrupt normal cell cycle process. For instance, v-Cyclin, coded by K14 gene of KSHV, is a homologue of human Cyclin-D and can inhibit retinoblastoma (RB) protein (68); latent nuclear antigen (LANA), coded by open reading frame (ORF) 73, can inhibit p53 and then impact apoptosis (69). As the virus can be detected in most of KS tissues, it is now considered as necessary cause of KS (70, 71).

In the study of KS among MSM, having more sex partners were found to be a strong risk factor of KS among HIV positive population, indicating that there might potentially be another sexually transmitted agent, in addition to HIV, that may be associated with KS (72-74). Orogenital sex has

been found as a main transmission route of KSHV among MSM (75). Other transmission routes such as vertical/mother-to-child transmission, horizontal transmission among children via saliva, transmission via blood transfusion or organ transplant were also identified (76-81). Prevalence of KSHV varies among different population. It was about 6% in MSM in the US(82), about 10% in injection drug users (IDU) in New York (83), 10% in general population of Sicily, Italy (84), about 70% in Swiss HIV+ MSM cohort (85), about 25% in HIV- MSM and 40~50% in HIV+ MSM in San Francisco City Clinic Cohort (86).

Prevalent HHV-8/KSHV infection varies across different areas and populations in China. In eastern and central provinces with majority population of Han, prevalence of KSHV infection less than 5% in general population in the eastern area (87-96), however, the prevalence in Xinjiang Autonomous Region is much higher — about 20~30% in the general population (94, 95, 97, 98) and in drug users (about 21% to 32%) (99, 100).

Caner in China

Cancer has been the leading cause of death in the Chinese population since 2006. The estimated incidence cancer cases and deaths in 2008 were approximately 2.82 million and 1.96 million, respectively. The current and projected cancer burden indicates that cancer is and will continue to be a serious public health problem for China. Compared to other regions in the world, China is a high-risk area for lung, liver, stomach, and esophageal cancers (101, 102). Both Liver and stomach cancers are infection-related, and lung cancer in Chinese male is highly related to

tobacco smoking.

HIV/AIDS in China

The first HIV infection in Chinese population was detected in 1983 and the first HIV death in 1985. It was estimated that the virus entered China in 1982. The HIV epidemic in China began among injecting drug users in southern Yunnan Province in the late 1980s and among plasma donors in the early 1990s. By 2000, however, the epidemic has spread to every province of China. In the areas with the highest prevalence of HIV among IDUs in Yunnan, Guangxi, Xinjiang and Guangdong, infection through sex workers has also been considered one of the transmission routes(103-106). It has been estimated that 740,000 individuals are living with HIV (PLHIV) in China; 105,000 are diagnosed with AIDS; 26,000 die each year due to AIDS and related conditions; and 48,000 are diagnosed as new HIV infection each year. The prevalence of HIV in total population is about 0.057% (107).

HIV/AIDS-associated cancers in China

The spectrum of malignant tumors among HIV infected has not been fully described in Chinese population, and there has been no national-wide study on HIV/AIDS related malignancies in China. The only one hospital-based report showed that the incidence of non-Hodgkin lymphoma, cervical, liver and nasopharyngeal cancers in the hospital were higher than these in the local cancer registry as measured by the standardized incidence ratio (SIR) (108).

Given the ART treatment in China has been implemented nationally since 2003, leading to a significant improvement in survival among HIV/AIDS individuals (109, 110), it is likely that China will experience a high incidence of HIV/AIDS-related malignancies, including both AIDS defining and non-AIDS defining cancers. However, the spectrum of malignant tumors among PLHIV has not yet been fully described in China.

Summary

The spectrum of malignant tumors among HIV infected is not fully described in Chinese population. Because of ART therapy for HIV/AIDS, we would expect prolonged survival that might increase of cancers among people living with HIV/AIDS in China in the future. Since the cancer spectrum is different in Chinese population from Western population, we would expect that cancer spectrum in Chinese population might be different from the western population(102). A national level study on spectrum of malignancies on both AIDS-defining and non-AIDS defining cancers in PLHIV would be essential to find out whether the disparity exits in HIV-infected population between China and western countries, and how HIV infection changes spectrum of tumors in Chinese PLHIV.

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Chapter 2. Spectrum of Malignancies among HIV/AIDS Population in China, 2008-2011

Introduction

In the US, Europe and Africa, Kaposi Sarcoma (KS) is the most prevalent malignant tumor among HIV/AIDS population, followed by non-Hodgkin lymphoma (NHL) (1-19). KS, NHL, and cervical cancer have been established as "AIDS defining cancers" by the US Centers for Disease Control and Prevention (US CDC) (20). Increased risk of other non-AIDS defining cancers (NAC) such as cancers of oral cavity, liver, lung, penis, anus prostate, Hodgkin Lymphoma, and other cancers in HIV/AIDS population have also been reported, although with a lower incidence than these three AIDS defining cancers (1-19).

The spectrum of malignant tumors among HIV infected population in China has not yet been systematically described, and the only report based on data of one hospital, showed that non-Hodgkin lymphoma, cervical, liver and nasopharynx cancer were top cancers in HIV positive patients in the hospital using standardized incidence rate (SIR) with reference cancer incidence from local cancer registry (21).

It is also not clear that whether there is potential difference in spectrum of cancers between Chinese population and European heritage population. Cancer related infection patterns in China are different from that of western countries. For instance, human hepatitis virus B, Epstein-Barr

Virus (EBV) and Helicobacter pylori are highly prevalent in Chinese population (22-27), which might lead to different profile of HIV-associated cancers in China. To compare spectrum of HIV-related malignancies with that of western countries, we describe patterns of malignancies among HIV-infected population in China during the study period of 2008-2011 of the national level.

Hypothesis 1

We hypothesize that due to different profile of prevalent infections, the HIV-related cancer sites in China might be different from what we observed in the western countries. Specifically, because of higher prevalence of HBV (around 10%), HCV (3~5%) and HP (over 50%) in Chinese general population, we hypotheses that incidence of cancers of liver and stomach will also be higher in HIV/AIDS population in China. In addition, because tobacco smoking is highly prevalent among Chinese males (28, 29), incidence of lung cancer in Chinese HIV/AIDS population may also be higher. On the other hand, because of relatively lower prevalence of Kaposi Sarcoma-associated Herpes Virus infection in Chinese population (30-33), incidence of Kaposi Sarcoma may be lower in Chinese HIV/AIDS population.

Specific Aim 1

To describe patterns of HIV-related malignancies among Individuals with HIV infection and to compare the incidences with that of general population.

By using a historical cohort from the Chinese National HIV/AIDS Surveillance and Information System, totally 444712 participants in the system covering all identified HIV-infected person who was followed-up during 2008-2011. We will calculate age and sex- specific incidence rates of reported cancers in HIV/AIDS population and compare them with that of general population in China (China Tumor Registry Data 2008) using standardized incidence ratio (SIR) and standardized incidence rate (sIRate, standardized to Chinese population, the 6^{th} national census, 2010). Epidemiological pattern of malignant tumors in HIV-infected population in China with those in the western countries with sex specific SIRs and sIRates.

Material and Methods

Data Source

In 2005, China established a web-based HIV/AIDS case report system that required all diagnosed HIV/AIDS cases in China be reported (34). All identified HIV infected individuals have been surveyed at baseline and followed-up every 6 months. If individuals meet the national free antiretroviral treatment (ART) criteria, they will get free treatments and be followed-up 4 times in

the first 3 months after ART initiation, and once every 3 months thereafter (35). After a major data upgrade check and work quality promotion in 2008, the system now comprehensively collects all these records.

A cancer diagnosis in the system is based on reports of AIDS related complications or causes of death at each follow-up (35). However, current system has not been collecting detailed pathological information on cancer diagnosis. Thus, about half of lymphoma records are not specified into Hodgkin Lymphoma (HL) or NHL, so we have to combine HL, NHL and all other unspecified lymphomas together and calculated the risks for all lymphomas. All subjects with HIV infection diagnosed before 01/01/2012 and with at least one follow-up record between 1/1/2008 and 6/30/2012 were extracted from the database.

The study was approved by IRB in the UCLA, IRB#11-002905 and in the China CDC, Project No.X130205248.

Statistical Analysis

Demographic characteristics, HIV/AIDS disease stage and first CD4 cell counts were described by frequency.

Person-time calculation

The date of HIV infection diagnosis (for participants diagnosed HIV+ in and after 2008) or

1/1/2008 (for those participants with HIV diagnosed before 2008) was set as the initial date of observation. For cases with cancer records, the inferred date of cancer incidence is defined as the median between the date of follow-up with cancer record and the previous follow-up. Participants with inferred cancer diagnose date after 12/31/2011 were counted as cancer-free during the study period 2008-2011. For cancer-free participants, the end of follow-up (date of censor) is defined as the last follow-up date for who lost-to-follow-up, or the date of death if one died during study period, or 12/31/2011 if one survived after the end of study period. (Figure 1-1).

Age and Sex-specific Incidence Rates

Sex and age-specific incidence rates for overall cancers and site-specific cancers were calculated using observed case number divided by Sex and 5-year-age specific observed person-time, For each observed rate, 95% confidence interval was calculated assuming Poisson distribution (36). Selected overall and site-specific rates were compared with China national tumor registry 2008 data with line plots.

Standardized Incidence Rate (sIRate)

Direct standardization was employed to calculate standardized incidence rates and their 95% confidence intervals (36). Age and sex distribution in Chinese population census 2010 data (37) was used as weights for age standardized sex-specific incidence rates (per 10^5 person-years).

Standardized Incidence Ratio (SIR)

Sex and 5-year-age specific person-years were calculated for indirect standardization to compare observed cancer incidence (overall and cancer site specific) with that of the general Chinese population, stratified by gender. Observed sex and 5-year-age specific person-time was multiplied with sex and 5-year-age specific cancer incidence rates from the 2008 Chinese tumor registry data (38) to estimate the expected numbers of cases. SIR was calculated using the ratio of observed cases divided by expected cases. Poisson distribution was assumed for cancer cases in order to estimate 95% exact confidence intervals of the SIR (39).

Ecological Comparison

Calculated site and sex-specific sIRates and SIRs from Chinese HIV/AIDS population were compared with published statistics from western populations with forest plots. Characteristics of each population, including sex, antiretroviral treatment, country and study period were used to group different studies.

SAS 9.3 (SAS Institute Inc., Cary, NC) software was used for data management and analysis.

Results

Overall Description

In the raw database, there were 444,712 subjects aged over 15 diagnosed as HIV infected before 1/1/2012. Among them, 45,261 died, or were lost to follow-up before 1/1/2008, or registered with

invalid information that cannot be identified. Finally, 399451 subjects were included in the analyses, contributing 813,238.9 person-years (pys) between 1/1/2008 and 12/31/2011. The average follow-up time is 2.0 years. Most of the individuals were younger than 45 years old. The sex ratio (male vs. female) is about 2.3. Other demographic and disease related characteristics distributions are presented in Table 1-1.

Totally 3,819 cancer reports were identified, and SIR for overall cancers was 3.4 (95%CI 3.3-3.5) in males, and 2.6 (95%CI 2.4-2.7) in females. The 5 most prevalent cancers in males were cancers of lung (n=713), liver (n=539), lymphomas (n=299), brain/central nervous system (n=216) and stomach (n=137), and in females were cancers of lung (n=140), cervix (n=128), lymphoma (n=117), brain/central nervous system (n=105) and liver (n=84). There were 284 cancer reports in males and 113 reports in females with unspecified cancer sites (Table 1-2b, Figure 1-2a, 1-2b). Excluding cancer cases with unspecified primary sites, the SIR for over all cancer was 3.1 (95% CI 3.0-3.2) in males, and 2.3 (95%CI 2.2-2.5) in females (Table 1-2b).

AIDS-defining Cancers

Incidence Rates

The total numbers of AIDS-defining cancers (including KS, NHL and Cervical cancer, ADC) plus Hodgkin Lymphoma (HL) were 715 during the study period. Comparing with general Chinese population, higher sex and age-specific incidence rates of KS (Figure 1-3a), lymphomas (Figure 1-4a, 1-4b) and cervical cancer (Figure 1-5a) were found in nearly all age groups of HIV/AIDS

population.

Standardized incidence rates of Kaposi Sarcoma (KS, n=171) were 25.1 per 10^5 person-years (pys) in males (Figure 1-2a) and 14.5 per 10^5 pys in females (Figure 1-2b). For age-specific rates, KS in males were found a little bit higher than in females (Figure 1-3a). The standardized incidence rate of lymphomas (NHL+HL, n=416) was 69.1 per 10^5 pys and 51.8 10^5 pys for males and females (Figure 1-2a,1-2b). For female cervical cancer (n=128), sIRate was 51.5 per 10^5 pys (Figure 1-2b)

Incidence Ratios

Comparing with Chinese general population, overall SIRs of ADC+HL were 19.9 (95%CI: 18.1-21.9) for males and 7.0 (95%CI: 6.2-7.8) for females. Although the total number of Kaposi sarcoma was not on the top prevalent list in China, the SIR for KS was found extremely high for both males and females, with SIRs 2639.8 (95%CI 2208.7-3130.5) and 1593.5 (95%CI 1133.0-2178.4), respectively, considering the extremely low incidence of KS among general Chinese population (Table 1-2). The SIRs for lymphomas were 13.9 (95%CI 12.3-15.5) and 16.0 (95% CI 13.2-19.1) for males and females, respectively (Table 1-2). The SIR of cervical cancer among females was 3.8 (95%CI 3.2-4.6) (Table 1-2).

Non-AIDS defining Cancers

Incidence Rates

The total number of Non-AIDS-defining cancers (without Hodgkin Lymphoma) was 3,104, five times higher than total numbers of AIDS-defining malignancies. Higher age-specific incidence rates of all non-AIDS-defining cancers were found in both males (Figure 1-6a) and females (Figure 1-6b). After excluding cancer cases without specified primary site, sex and age-specific incidence rates of non-AIDS-defining cancers changed very limited in estimated incidence rates of all non-AIDS defining cancers in all age-groups (Figure 1-6a, 1-6b).

In males, cancers with top standardized incidence rates were cancers of lung (n=713, 268.6 per 10^5 pys), liver (n=539, 165.9 per 10^5 pys), stomach (n=137, 52.0 per 10^5 pys), brain and CNS (n=216, 50.2 per 10^5 pys) and colon-rectum (n=121, 40.7 per 10^5 pys). sIRates for other cancers among males were presented in the Figure 1-2a.

In females, cancers with top standardized incidence rates were cancers of lung (n=140, 74.5 per 10^5 pys), stomach (n=60, 54.9 per 10^5 pys), brain and CNS (105, 44.5 per 10^5 pys), liver (n=84, 44.2 per 10^5 pys) and corpis uteri (n=32, 23.5 per 10^5 pys). sIRates for other cancers among females were presented in the Figure 1-2b.

Incidence Ratios

Overall, the SIR of non-AIDS defining cancers was 2.9, (95%CI 2.8-3.1) in males and 2.1, (95%CI 1.9-2.2) in females (Table 1-2). Elevated SIRs were observed for infection-related cancers such as cancers of liver (related to hepatitis virus B and C, HBV/HCV), nasopharynx

(related to Epstein-Barr virus, EBV), head and neck cancer, penis, skin (related to Human Papilloma Virus, HPV), and stomach (related to Helicobacter pylori, HP), as well as for non-infection related cancers such as cancer of lung and brain and central nervous system (Table 1-2).

The SIRs of lung cancer were 4.8 (95%CI 4.4-5.1) and 4.2 (95% CI 3.5-5.0) in males and females, respectively (Table 1-2). The SIR of liver cancer in females (5.2, 95% CI 4.2-6.5) was higher than in males (3.9, 95% CI 3.6-4.2). Risk of stomach cancer, brain/central nerve system tumors, leukemia, head and neck cancers (expect nasopharynx) and tumors in eye were found higher in both genders, and risk of thyroid gland cancer was lower. In males, colon/rectum, pancreas and nasopharynx cancer were slightly higher while risk of renal, and bladder were lower. In females, risk of connective/soft tissue sarcomas and uteri cancer increased but risk of breast cancer and ovary/other female genital cancers were lower (Table 1-2).

Discussion

To the best knowledge based on literature review, this is the first report of the spectrum of malignant tumors among HIV-infected persons in China at the national level, and our results showed higher risk of cancers among the HIV-infected persons than the general population. Different from western pattern, AIDS-defining cancers are not the most frequent cancers,

compared with non-AIDS defining cancers among HIV-infected persons in China.

AIDS-defining cancers

Kaposi Sarcoma

The overall incidence rates of KS in Chinese HIV/AIDS population were much lower than that those reported in western populations in the ART era (Figure 1-3b), (1, 3, 5, 7, 9-12, 15, 17, 19, 40-46). In the Mediterranean area, the incidence rates of classic KS among Italians and Jewish population were about 1 to 2 per 10^5 in males and 0.2 to 0.7 per 10^5 in females (47-49) and AIDS-KS were around 200 to 1500 per 10^5 pys(41, 46). KS is now the most prevalent cancer in some parts of Africa (50-53), and incidence rate in general population ranged from 5 to 50 per 10^5 in the countries with highest prevalence of HIV in the eastern African, 10 to 33 per 10^5 in the southern African area, and lower in the middle Africa (54), which is parallel with the pandemic of HIV/AIDS in African and the high prevalence of KSHV infection. In the United States, incidence of KS was found increased rapidly during the early time of AIDS epidemic in 1980s and 1990s, and it decreased fast after the application of antiretroviral treatment (ART) (55) and incidence rate of KS in HIV/AIDS population dropped from over 2000 to about 200 per 10^5 pys in the US (1-6, 19).

One major reason of difference in KS may be due to different genetic background and prevalence of KSHV (56). Prevalence of KSHV among Chinese general population was much lower than in western population (22, 57-59), and the incidence rates of KS in general Chinese population are

far lower than those in the US (38, 55). However, in our crude comparison with studies in the US and Europe, the SIRs in Chinese HIV/AIDS population were higher than in ART era but lower than those in pre-ART era (Figure 1-3c). Although China has established national-wide free ART program, around one third subject were already at the AIDS stage when they were diagnosed as HIV infected (Table 1-1.). So late diagnose and therefore late initiation of ART may explain why the SIR of KS in our study between previous Pre-ART and ART data. In summary, the HIV infection clearly elevate the risk of KS among Chinese HIV/AIDS population, and further risk factors analysis will be presented in the Part II of this dissertation.

Lymphomas

In current analysis we could only calculate statistics for over all lymphomas because half of lymphoma reports were not differentiated into Hodgkin or non-Hodgkin Lymphoma. According to previous studies in HIV/AIDS population (1, 3-5, 19, 41, 42, 46) and general population of China (38) and the US (55), incidence rate of Hodgkin lymphoma were about 3-15% as non-Hodgkin lymphomas (Table 1-3, Figure 1-4a, 1-4b). Thus, estimated incidence rate of all lymphomas might be 10% higher than rate of NHL. Even with the incidence rate of all lymphomas, we still find that incidence rate were much lower than most previous studies (Figure 1-4c). One possible reason is that Incidence rate of NHL is much lower in general population in China than in the western population (Table 1-3). Additionally, some kind of HIV/AIDS related NHL were found associated with KSHV infection (60, 61), and lower prevalence of KSHV in Chinese population which may also explain part of this disparity. The SIRs of lymphomas in

China were found around 13.9 times higher in males and 16.0 times higher in females among HIV/AIDS individuals than in the general population, and such increase was found in all age groups and in both sex groups (Figure 1-4a, 1-4b). Because we used the combined numbers of NHL and HL and SIR of HL in HIV/AIDS is much lower than HL, so current number is lower than SIR for NHL. On the other hand, if we use expected number of NHL in Chinese generation only, the over-estimated SIR for NHL in HIV/AIDS population in China was 15.2 in males and 17.2 in females. Nevertheless, these SIRs are indicating HIV may escalate risk of lymphomas among HIV/AIDS population in China, and relative risk might be lower than in previous reports in the western populations (Figure 1-4d).

Cervical cancer

The incidence rates of cervical cancer in Chinese HVI/AIDS population were found higher than in general population in all age group (Figure 1-5a), and were lower than most western studies (Figure 1-5b). However, incidence rate of cervical cancer in general Chinese women is higher than in the US ($8.32/10^5$Pys, China TR 2008 vs. $6.71//10^5$Pys, US SEER 2010). Thus, SIR of cervical cancer was found lower in Chinese HIV/AIDS population than in most of the reports of western population.

Non-AIDS defining Cancers

Infection-related Cancers

Considering behavior of unsafe sex, drug abuse have been already known as risk of HBV, HCV

and other sexually transmitted infections as well as HIV, these infections are similarly higher among HIV-infected persons in China (23, 24, 62). These infections, as well as other high prevalent behavior of drug abuse, tobacco smoking and alcohol drinking may seriously elevate risk of carcinogenesis and this hypothesis is supported by findings in this study.

Liver cancer

Liver cancer was found extremely higher in our study than in other western studies (Figure 1-7b) (1, 3, 19, 41, 42), except the US veterans study (4). With high prevalence of HBV infection in the Chinese population(25), the liver cancer is the third most frequent malignant tumor in China with much higher incidence rate than in the US (38, 54, 55), Additional to HBV, over 28% of HIV infected subjects in China were intravenous drug users (Table 1-1) in our data base, and HCV infection among Chinese IDUs were over 60% (23). Thus, similar excess risk introduced by HIV infection (Figure 1-7a, 1-7c) increased the liver cancer risk into a much higher level. Furthermore, other carcinogens such as tobacco smoking and alcohol abuse may also interact with hepatitis viruses, while antiretroviral treatment may accelerate the hepatotoxicity (63-65).

Other Infection-related Cancers

It is also worthwhile to notice that the incidence of infection-related cancers, such as cancers of nasopharynx (EBV related), head and neck cancer, penis, and skin (HPV related), and stomach (HP related) (Figure 1-8a, 1-8b, 1-8c) were higher in Chinese HIV-infected people than in the

general population. To our knowledge, co-infection of EBV and HP are very high in Chinese general population (26, 27), thus, incidences of these cancers among Chinese are much higher (54). Besides, although anal cancer was found very rare in our report, however, considering men who have sex with men have already become a significant part of HIV-infected people, and prevalence of HIV in young MSM in some area is over 10% (66), potential increase of anal cancer among MSM in China might be probable in the future.

Non-infection Related Cancers

Other cancers that considered not infection-related were also found higher risk among HIV-infected persons in China including cancers of lung, brain and central nerve system, and leukemia.

Lung Cancer

Lung cancer was found to be the top cancers among HIV/AIDS population in China. Compare with western patterns, the incidence rate of lung cancer in Chinese male HIV/AIDS population was higher than nearly all previous study, except one in US veterans, SIR of lung cancer among HIV/AIDS population was also high (3, 5, 11, 12, 15, 17, 19, 40, 41, 43, 45, 46, 67-71). However, standardized incidence rate and SIR of female were similar as other studies (Figure 1-9b, 1-9c). High prevalence of tobacco smoking among Chinese males (29) may be the major reason of high incidence rate, while immunocompromised status caused by HIV should also be considered to explain the high SIR (69). Prevalence of tobacco smoking among females in China is much lower

than males (29) and in the western countries. Currently, prevalence of tobacco smoking among female HIV/AIDS population in China has not been reported. Empirically, tobacco smoking is highly prevalent among drug users, sex workers, and HIV/AIDS population may have higher prevalence of smoking, and we found higher prevalence of smoking among HIV-infected controls, both males and females in our hospital-based case control study in HIV-infected Uyghur population in Xinjiang.

Other Cancers

SIR of leukemia was found high and similar with findings in the US (3, 5), and tumor of brain & CNS will be discussed later. Other than higher risk, risk of female breast cancer was found lower than in the general population (Figure 1-12), which is similar to previous study in the US and Belgium (72, 73).

Limitations

A major limitation of this study is that currently national-wide cancer registry is not available for linkage study in China. In addition, considering the variety of economic status and health care services all over China, some HIV/AIDS population might not access a comprehensive health care, which will lead to possible misdiagnose of cancers, especially for those cancers need highly delicate technology. For instance, we cannot differentiate NHL and HL from all lymphomas, so in our results, incidence rates of all lymphomas were higher than NHL, while SIRs of all lymphomas were lower than NHL. Another example is that although we found brain and central

nervous system tumors were very high incidence and SIR and this pattern is much higher than those in the western countries (Figure 1-10b, 1-10c) (2, 3, 10-12, 15, 17, 40, 44, 70, 71, 74). However, diagnoses of CNS tumor require highly complicated neurological surgery, which are much harder than general surgery service. We cannot differentiate CNS NHL form other CNS tumors or other non-tumor diseases with similar clinical and image manifestation. Nevertheless, our findings indicate quite high incidences of CNS manifestations among HIV-infected persons in China, which calls for attention of more neurology service in HIV/AIDS patient care. It is also concerned that current tumor registry 2008 figures does include cancer cases from HIV/AIDS population, and which may bias the estimation of SIR. However, in 2008 TR in China only covered 6.21% of all population (38) and only cancer cases in the covered area will be reported. Furthermore, HIV prevalence in China was less than 0.06% (66), and the impact of countered cancer cases with HIV in TR data should be minimal.

Mortality of HIV/AIDS population in China is decreasing in recent years, however, it is still very high and late diagnose of HIV infection is still a big issue in China (75, 76). Malignant tumors are related to higher mortality and lost-of-follow-up, so potential survival bias may happen in our analysis, and it might cause underestimation of incidence cancer cases. Mathematically SIRs in previous studies and our data represent different HIV-infected populations, so the comparison of SIRs here is only a rough estimate on relative risks. Similarly, most standardized rates found in this study are weighted using different country-specific population weights. Detailed age- and sex-specific incidence rates from all studies are essential for further comparison between different

populations.

In summary, both HIV/AIDS and malignant tumors are now causing a serious public health burden in China (38, 66). From this national level study we observed similar pattern of AIDS-defining cancers among HIV/AIDS individuals, however, the profile of non-AIDS defining cancers were different from western countries among HIV-infected persons in China. Specifically, higher risk of infection related and smoking related cancers indicates different spectrum of HIV/AIDS-related malignancies in Chinese population. Our finding also indicates potential burden that warrants serious consideration for further investigations in order to develop strategy for prevention and control of malignancies among HIV/AIDS population in China.

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Tables

Table 1-1. Characteristics of Cohort of HIV/AIDS Population in China, 2008-2011

Characteristics	Categories	N	%	Person-Years	%
Age	15-29	116082	29.1	213789.8	26.0
	30-44	196848	49.3	440565.2	53.5
	45-59	60917	15.3	124932.1	15.2
	60+	25604	6.4	33951.8	4.1
Sex	Male	278908	69.8	550228.6	66.8
	Female	120543	30.2	263010.3	31.9
Ethnic Group	Han Chinese	271375	67.9	557772.6	67.8
	Uyghur	27782	7.0	57804	7.0
	Other	100294	25.1	197662.4	24.0
Education	Illiteracy	37577	9.4	75273.2	9.1
	Primary School	112932	28.3	232735.9	28.3
	Junior School	146270	36.6	303861.8	36.9
	High School	41180	10.3	74439.9	9.0
	College and Higher	22881	5.7	36115.5	4.4
	Missing	38611	9.7	90812.7	11.0
Marriage	Married	199434	49.9	409950.4	49.8
	Unmarried	110405	27.6	218079.2	26.5
	Divorced or Widowed	59628	14.9	122128.2	14.8
	Missing	24953	6.2	53648.2	6.5
Transmission	Heterosexual	173853	43.5	290022.6	35.2
Routes	IDU	108911	27.3	259168	31.5
	Blood	40860	10.2	128043.6	15.6
	MSM	29169	7.3	40022.4	4.9
	Sexual + IDU	4900	1.2	10179.8	1.2
	Other/Unknown	41758	10.5	85802.6	10.4
Disease Stage	HIV	247625	62.0	445270.7	54.1
at diagnosis	AIDS	151826	38.0	367968.3	44.7
First CD4 cell count test	<200/μl	108585	27.2	210185.4	25.5
after HIV diagnosis	200~349/μl	88439	22.1	196043.6	23.8
	>=350/μl	102305	25.6	250856.9	30.5
	Missing	100122	25.1	156153.1	19.0

Table 1-2a. Spectrum and standardized incidence ratio of malignant tumors in HIV/AIDS population in China, 2008-2011

		Male				Female			
Site	**ICD-O-3**	**Observed**	**Expected**	**SIR**	**SIR 95% CI**	**Observed**	**Expected**	**SIR**	**SIR 95% CI**
AIDS Defining Cancers									
Kaposi Sarcoma	9140	**132**	**0.05**	**2639.8**	**(2208.7-3130.5)**	**39**	**0.02**	**1593.5**	**(1133.0-2178.4)**
Lymphoma*	959 & 965	**299**	**21.6**	**13.9**	**(12.3-15.5)**	**117**	**7.3**	**16.0**	**(13.2-19.1)**
Cervical	C53	-	-	-	-	**128**	**33.4**	**3.8**	**(3.2-4.6)**
Non-AIDS defining Cancers									
Oral	C00-C09	13	9.9	1.3	(0.7-2.2)	4	3.3	1.2	(0.3-3.1)
Nasopharynx	C11	**38**	**22.9**	**1.7**	**(1.2-2.3)**	9	5.2	1.7	(0.8-3.3)
Other head & neck	C12-C14, C30-C32	**47**	**13.6**	**3.4**	**(2.5-4.6)**	**17**	**1.1**	**16**	**(9.3-25.6)**
Esophagus	C15	**78**	**62.5**	**1.2**	**(1.0-1.6)**	**19**	**10.9**	**1.7**	**(1.0-2.7)**
Stomach	C16	**137**	**116.1**	**1.2**	**(1.0-1.4)**	**60**	**26.7**	**2.2**	**(1.7-2.9)**
Colon & Rectum	C18-C20	**121**	**81.5**	**1.5**	**(1.2-1.8)**	32	29.5	1.1	(0.7-1.5)
Anus	C21	**2**	**0.7**	**2.9**	**(0.3-10.5)**	0	0.2	0.0	(0.0-19.7)
Liver	C22	**539**	**138.3**	**3.9**	**(3.6-4.2)**	**84**	**16.1**	**5.2**	**(4.2-6.5)**
Other Digestive	C23,24, C26	6	12.1	0.5	(0.2-1.1)	1	5.3	0.2	(0.0-1.0)
Pancreas	C25	**41**	**19.7**	**2.1**	**(1.5-2.8)**	2	6.1	0.3	(0.0-1.2)
Lung	C34	**713**	**150.1**	**4.8**	**(4.4-5.1)**	**140**	**33.2**	**4.2**	**(3.5-5.0)**
Mediastinum & pleura	C38	4	4.9	0.8	(0.2-2.1)	2	1.3	1.5	(0.2-5.5)
Bone	C40	11	7.0	1.6	(0.8-2.8)	2	2.5	0.8	(0.1-2.8)
Skin	C44	**17**	**7.5**	**2.3**	**(1.3-3.6)**	**9**	**2.2**	**4.0**	**(1.8-7.7)**
Soft tissue	C47-C49	5	4.5	1.1	(0.4-2.6)	**7**	**1.8**	**3.9**	**(1.5-8.0)**

SIR: Standardized Incidence Ratio, national cancer registry data 2008 of China is used to calculate expected numbers. **95% CI**: 95% exact confidence interval of SIR, assuming cancer counts are in Poisson distribution. *: About half of lymphoma records did not specify Hodgkin or Non-Hodgkin lymphoma, so combined observed and expected lymphoma figures were calculated.

Table 1-2b. Spectrum and standardized incidence ratio of malignant tumors in HIV/AIDS population in China, 2008-2011, Continued

Site	ICD-O-3	Male				Female			
		Observed	Expected	SIR	SIR 95% CI	Observed	Expected	SIR	SIR 95% CI
Breast	C50	2	1.2	1.6	(0.2-5.8)	31	98.8	0.3	(0.2-0.4)
Vagina & Vulva	C51-C52	-	-	-	-	2	0.9	2.2	(0.2-8.0)
Corpus Uteri	C54	-	-	-	-	**48**	**17.4**	**2.8**	**(2.0-3.7)**
Ovary, other female genital	C55-C58	-	-	-	-	5	18.0	0.3	(0.1-0.6)
Penile	C60	**6**	**2.2**	**2.8**	**(1.0-6.1)**	-	-	-	-
Prostate	C61	9	14.8	0.6	(0.3-1.2)	-	-	-	-
Other male genital	C62-C63	5	5.0	1.0	(0.3-2.4)	-	-	-	-
Renal	C64	10	20.6	0.5	(0.2-0.9)	2	5.2	0.4	(0.0-1.4)
Other urinary system	C65-C68	3	2.7	1.1	(0.2-3.3)	0	1.0	0.0	(0.0-3.5)
Bladder	C67	9	24.0	0.4	(0.2-0.7)	1	2.9	0.4	(0.0-1.9)
Eye	C69	**4**	**0.4**	**10.3**	**(2.8-26.4)**	**3**	**0.3**	**9.6**	**(1.9-28.1)**
Brian & CNS	C70,C71	**216**	**26.4**	**8.2**	**(7.1-9.3)**	**105**	**11.9**	**8.8**	**(7.2-10.7)**
Thyroid Gland	C73	2	17.3	0.1	(0.0-0.4)	0	28.8	0.0	(0.0-0.1)
Multiple Myeloma	C90	4	3.8	1.1	(0.3-2.7)	1	1.3	0.8	(0.0-4.3)
Melanoma	872	1	1.6	0.6	(0.0-3.6)	0	0.7	0.0	(0.0-5.2)
Leukemia	981	**50**	**17.2**	**2.9**	**(2.2-3.8)**	**28**	**8.8**	**3.2**	**(2.1-4.6)**
Ill-defined/Unspecified		284	22.3	12.8	(11.3-14.3)	113	10.4	10.9	(9.0-13.1)
All		**2808**	**832.2**	**3.4**	**(3.3-3.5)**	**1011**	**392.6**	**2.6**	**(2.4-2.7)**
All AIDS-defining Cancers + Hodgkin Lymphoma		**431**	**21.6**	**19.9**	**(18.1-21.9)**	**284**	**40.7**	**7.0**	**(6.2-7.8)**
All Non-AIDS-defining Cancers (Without HL)		**2377**	**810.6**	**2.9**	**(2.8-3.1)**	**727**	**351.9**	**2.1**	**(1.9-2.2)**
All (Excluding Unspecified)		**2524**	**809.9**	**3.1**	**(3.0-3.2)**	**898**	**382.2**	**2.3**	**(2.2-2.5)**

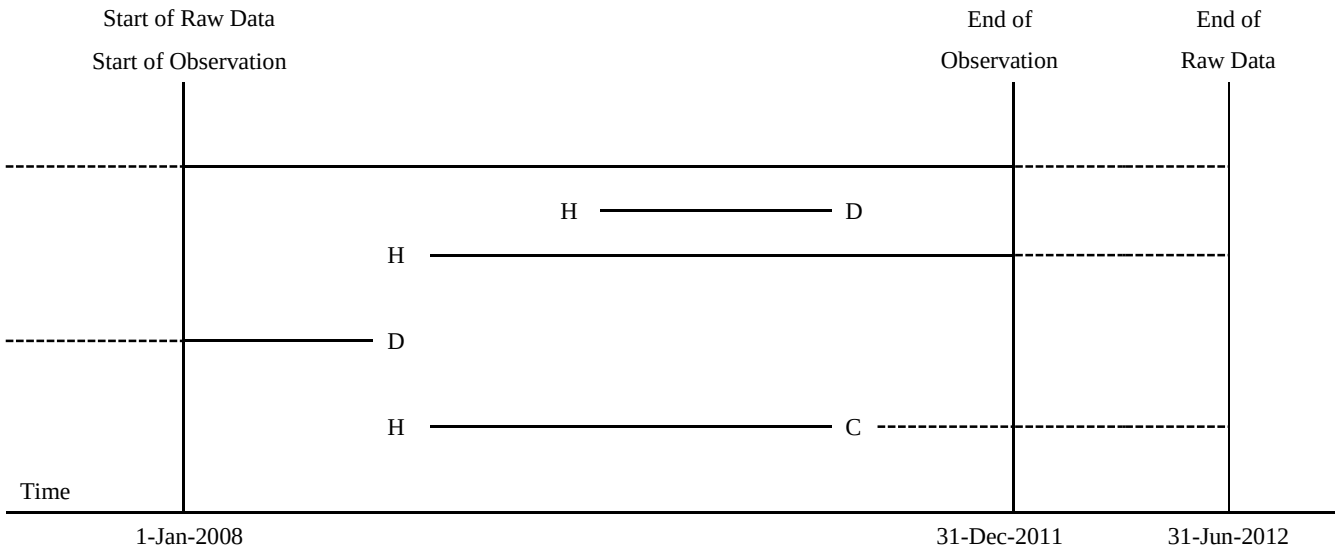
SIR: Standardized Incidence Ratio, national cancer registry data 2008 of China is used to calculate expected numbers. **95% CI**: 95% exact confidence interval of SIR, assuming cancer counts are in Poisson distribution.

Table 1-3. Comparison of Hodgkin Lymphoma, non-Hodgkin Lymphoma Incidence Rates, per 10^5 person years

Study	Population	HAART	Year	Sex	HL	HL Rate / 10^5 Pys	NHL	NHL Rate / 10^5 Pys	HL/NHL Ratio
Patel 2008	US	All	1992-2003	All	81	51.4	875	558.5	0.09
Serraino 2007	Italy France	All	1985-2005	All	18	40.5	201	452.7	0.09
Shiels 2011	US	Pre-HAART	1991-1995	All	426	55.2	12778	1656.2	0.03
Simard 2010	US	Pre-HAART	1990-1995	All	33	20.0	2040	1226.0	0.02
Dal Maso 2009	Italy	Pre-HAART	1986-1996	All	47	83.0	420	741.5	0.11
Franscshi 2010	Switzerland	Pre-HAART	1985-1996	All	7	30.7	191	952.0	0.03
Engels 2008	US	Pre-HAART	1991-1995	All	5	11.0	69	145.0	0.08
Shiels 2011	US	Early HAART	1996-2000	All	682	51.4	7292	549.9	0.09
Franscshi 2010	Switzerland	Early HAART	1997-2001	All	12	42.9	52	252.0	0.17
Shiels 2011	US	HAART	2001-2005	All	897	48.3	5968	321.2	0.15
Simard 2010	US	HAART	1996-2006	All	295	41.0	2198	306.0	0.13
Bedimo 2009	US VA	HAART	1997-2004	All	135	76.9	691	398.1	0.19
Dal Maso 2009	Italy	HAART	1997-2004	All	37	82.2	352	781.8	0.11
Engels 2008	US	HAART	1996-2002	All	30	22.0	134	97.0	0.23
Franscshi 2010	Switzerland	HAART	2002-2006	All	13	52.8	32	98.4	0.54
Dal Maso 2009	Italy	HAART	1997-2004	Female	2	40.9	77	1574.3	0.03
Seaberg 2010	US MACS	All	1984-2007	Male	3	24.8	33	274.9	0.09
Dal Maso 2009	Italy	HAART	1997-2004	Male	35	203.8	275	1601.4	0.13
China Tumor Registry, General Population, China			2008	Female	72	0.17	1542	3.21	0.05
China Tumor Registry, General Population, China			2008	Male	140	0.35	2022	4.42	0.08
SEER, General Population, US			2010	Female		2.4		17.4	0.14
SEER, General Population, US			2010	Male		3.3		26.8	0.12

HL: Hodgkin Lymphoma; NHL: non-Hodgkin Lymphoma; HAART: highly active antiretroviral treatment;

Figures



Solid line: person-time counted; Dash line: person-time not included.

H: New case of HIV infection; D: Death or lost-of-follow-up; C: Diagnose of malignant tumor

Figure 1-1. Calculation of Observed Person-Years in the Cohort of HIV/AIDS Population in China

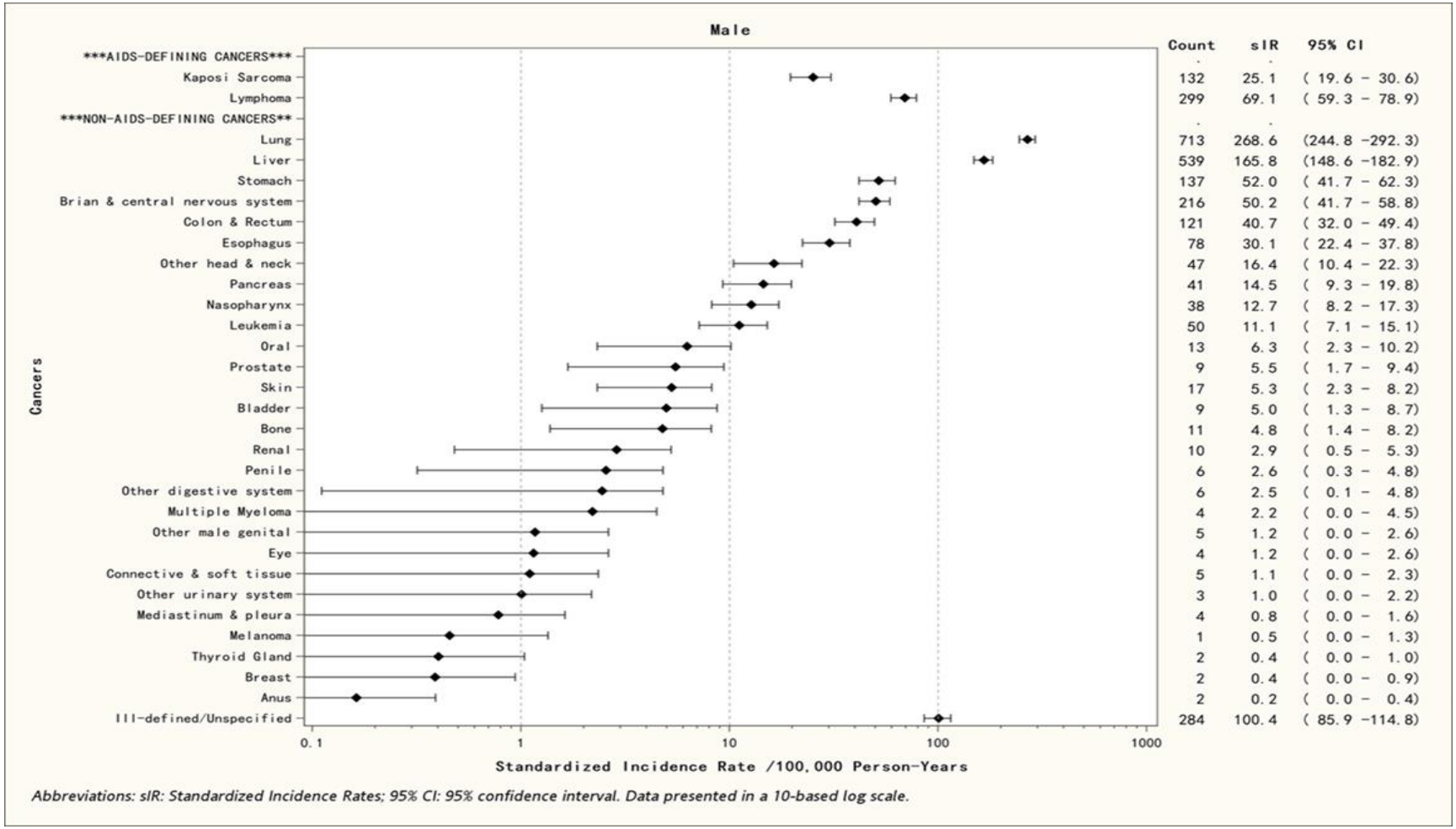


Figure 1-2a. Standardized Incidence Rates of Cancers among HIV/AIDS Population in China, 2008-2011: Male.

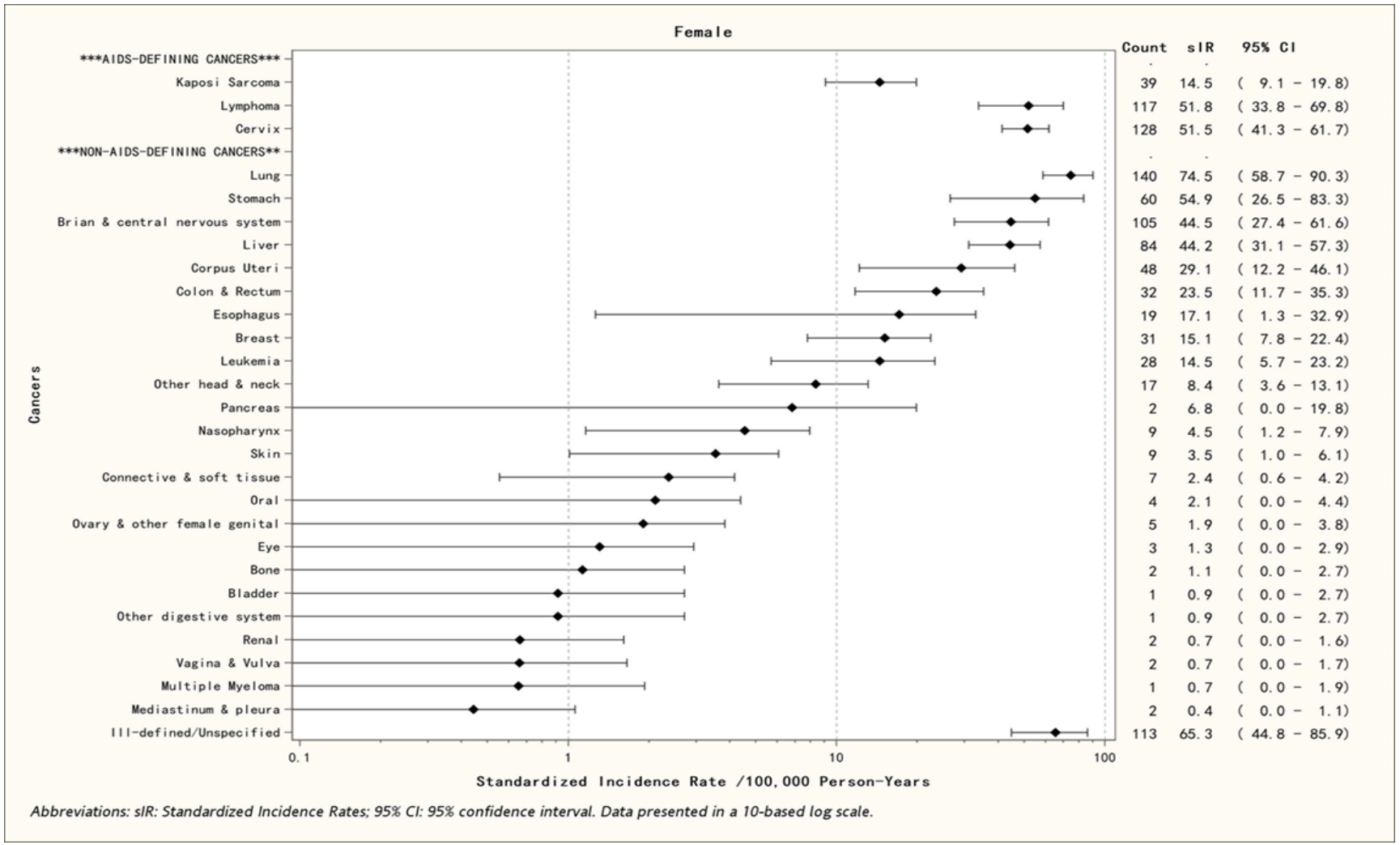
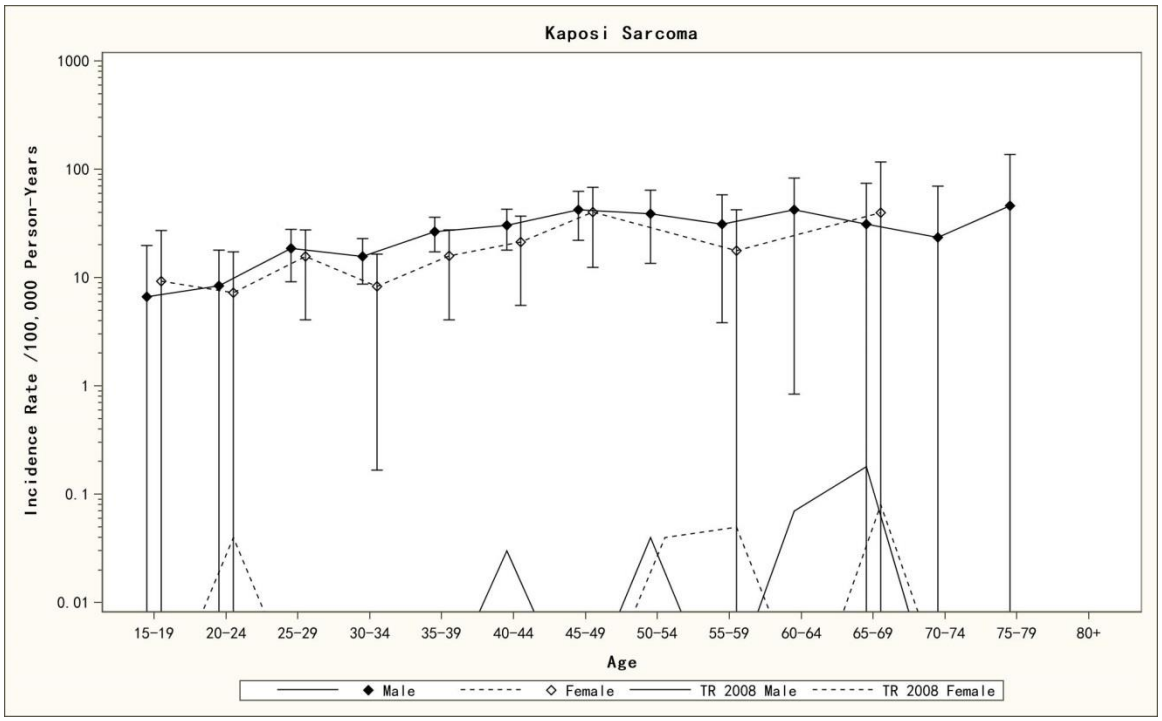


Figure 1-2b. Standardized Incidence Rates of cancers among HIV/AIDS Population in China, 2008-2011: Female.



TR 2008: China National Tumor Registry 2008

Figure 1-3a. Comparison of Sex and Age-specific Incidence Rate of Kaposi Sarcoma between HIV/AIDS Population and General Population in China.

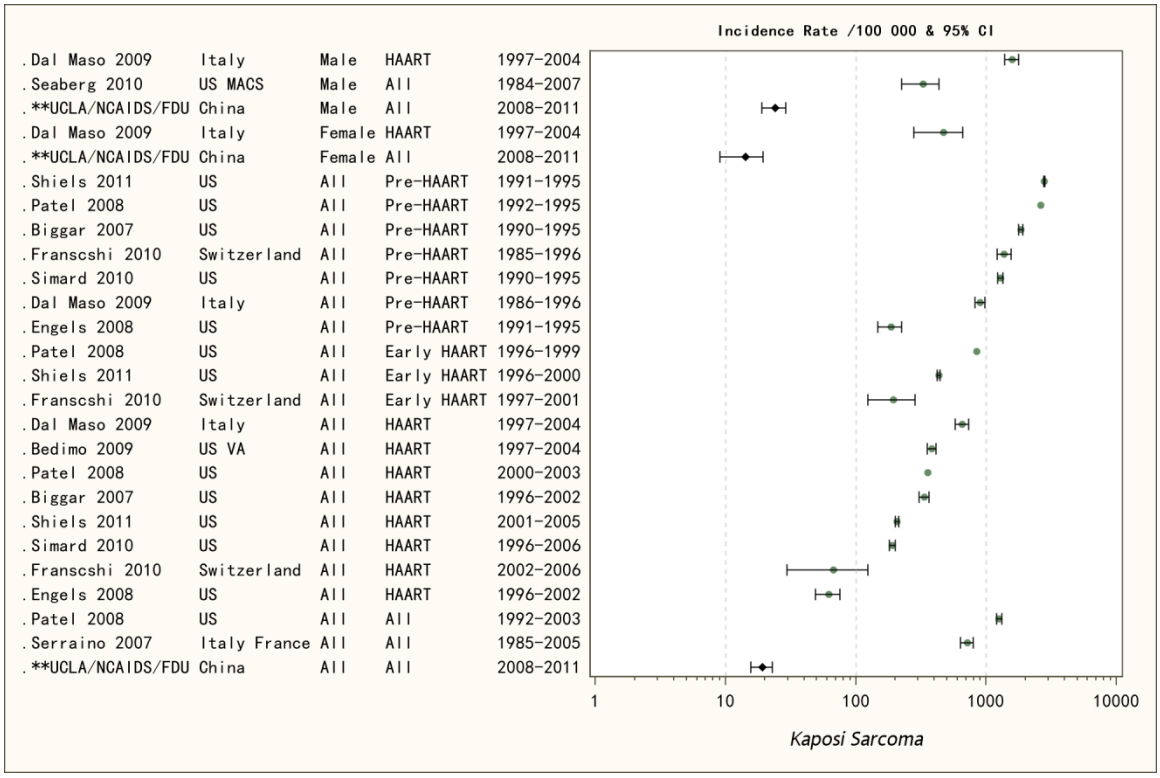


Figure 1-3b. Comparison of Incidence Rate of Kaposi Sarcoma between HIV/AIDS Population in in China and Previous Studies.

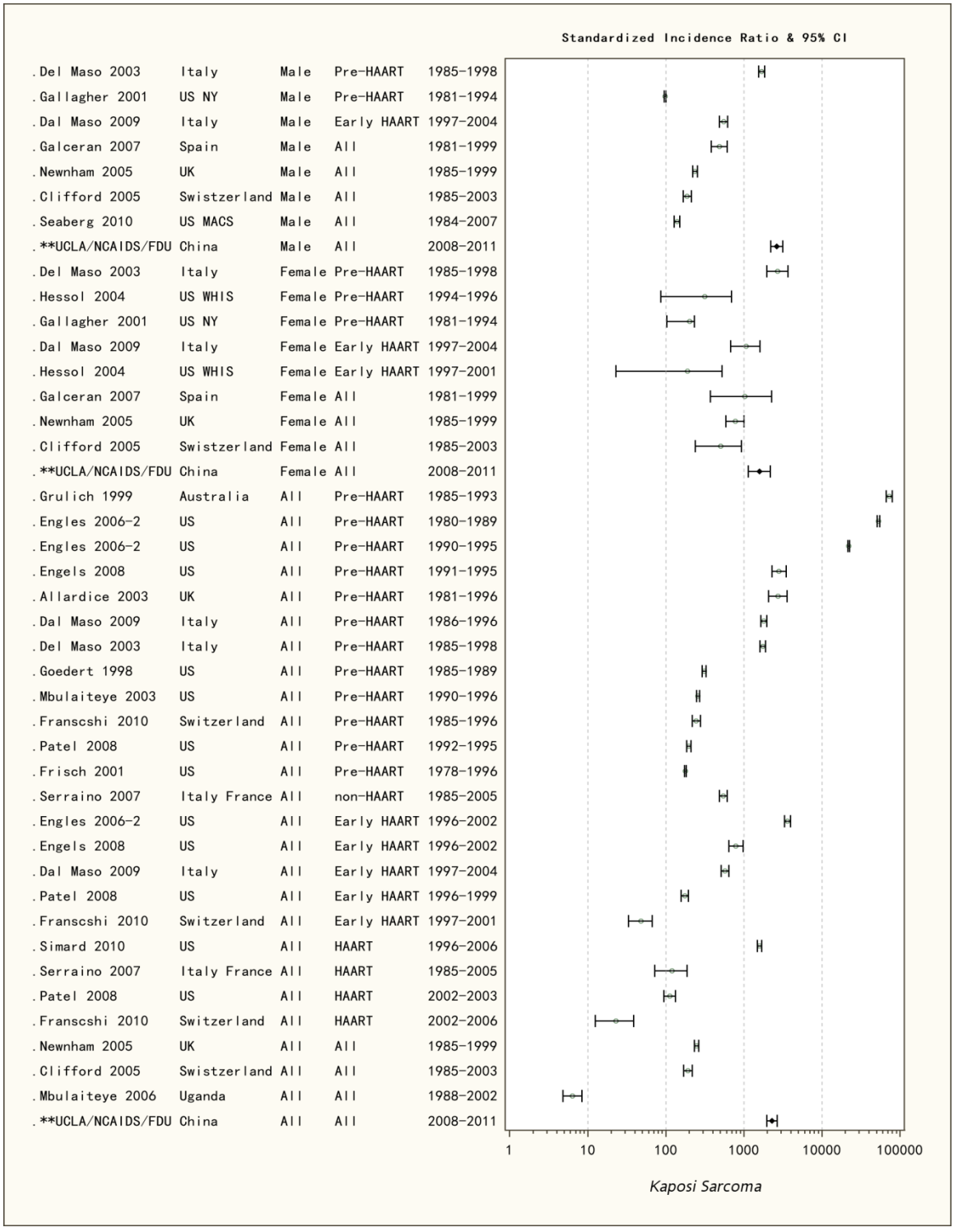
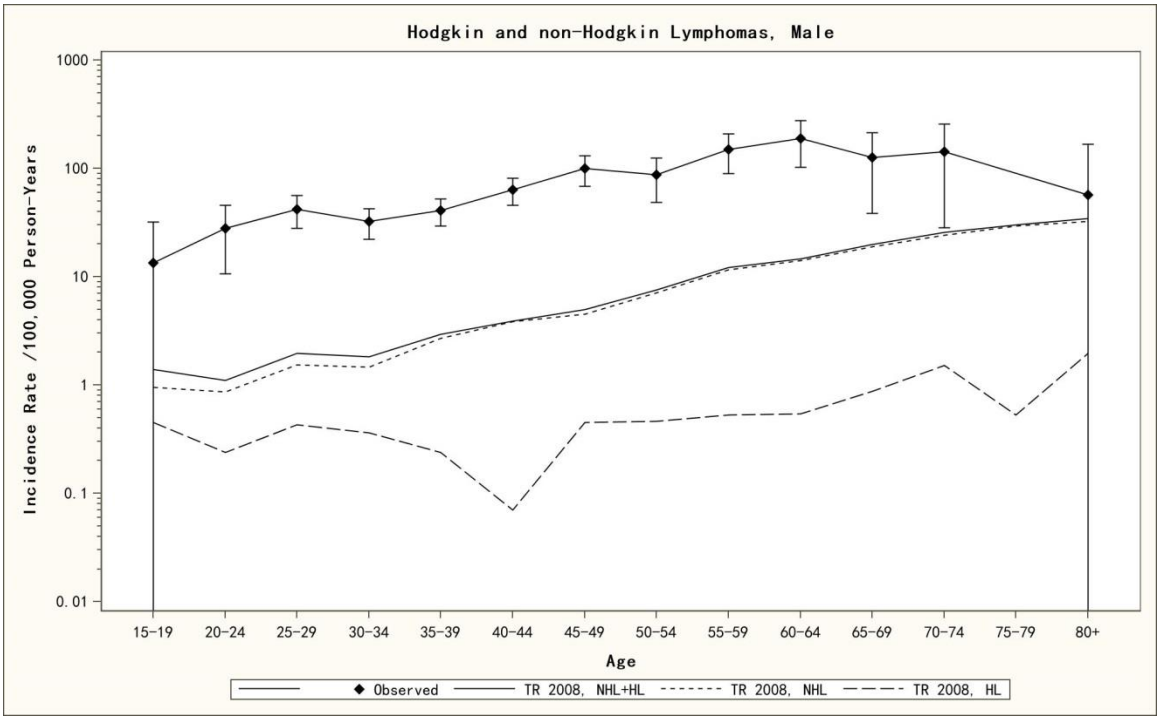
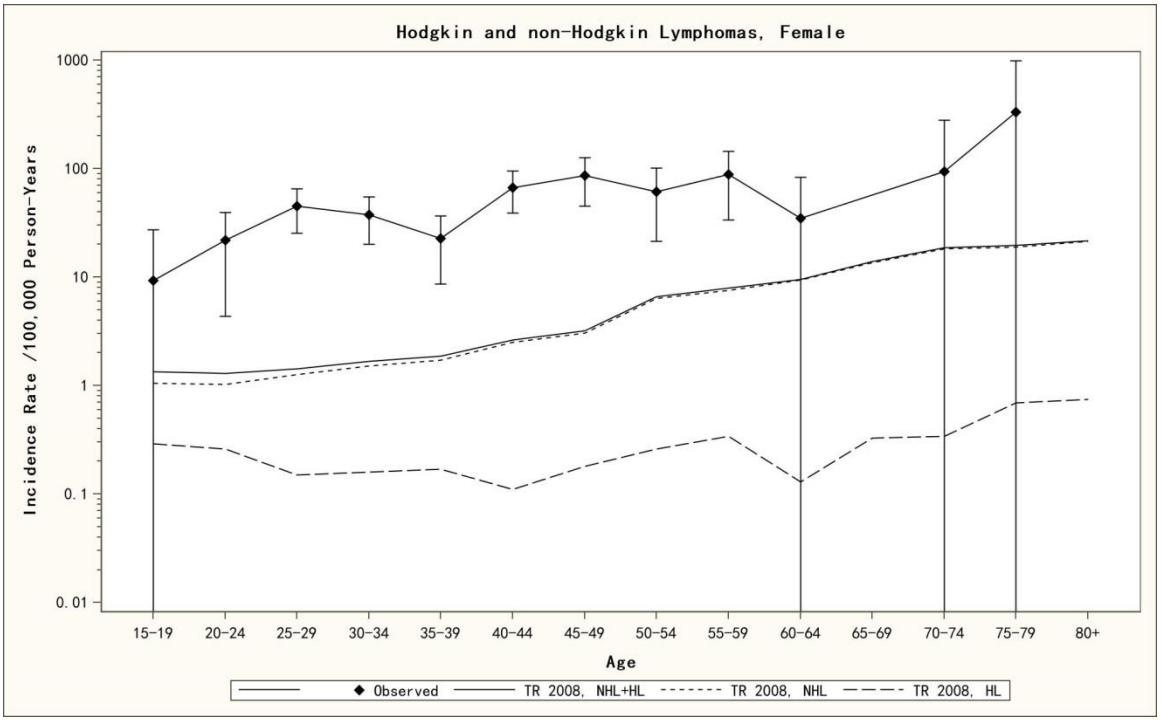


Figure 1-3c. Comparison of Standardized Incidence Ratio (SIR) of Kaposi Sarcoma between HIV/AIDS Population in China and Previous Studies.



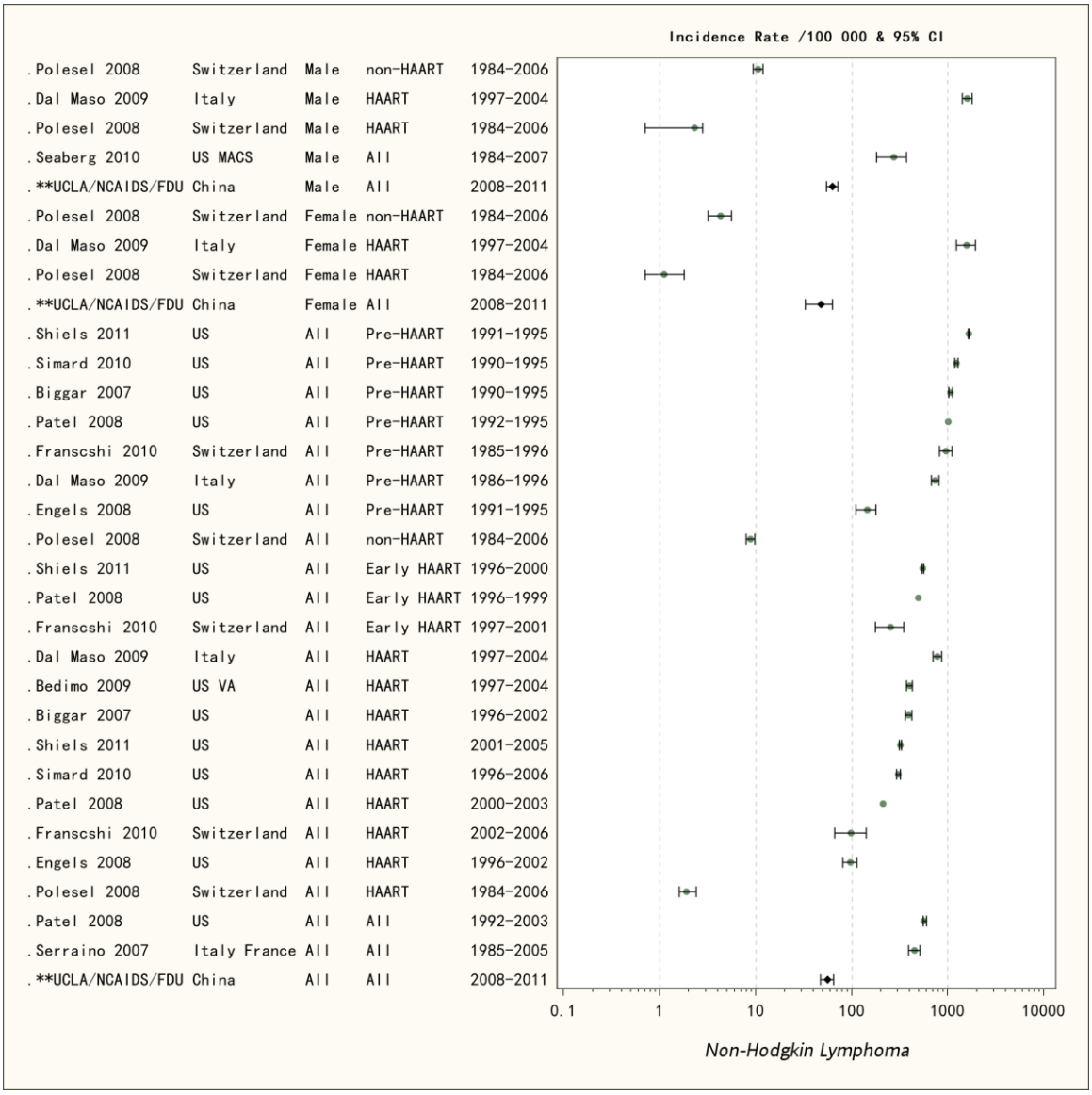
TR 2008: China National Tumor Registry 2008; HL: Hodgkin Lymphoma; NHL: Non-Hodgkin Lymphoma.

Figure 1-4a. Comparison of Sex and Age-specific Incidence Rate of All Lymphomas between HIV/AIDS Population and General Population in China: Male.



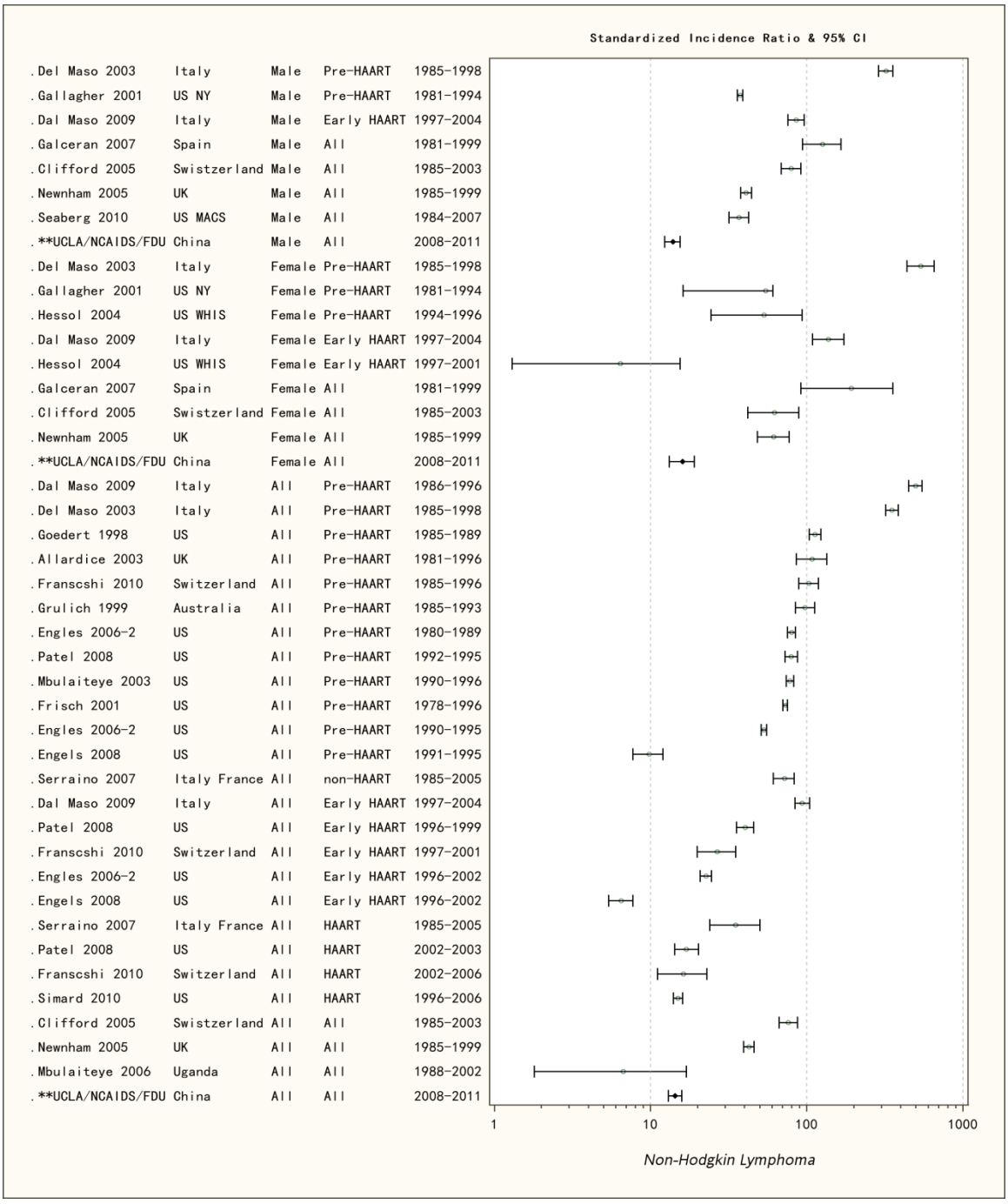
TR 2008: China National Tumor Registry 2008; HL: Hodgkin Lymphoma; NHL: Non-Hodgkin Lymphoma.

Figure 1-4b. Comparison of Sex and Age-specific Incidence Rate of All Lymphomas between HIV/AIDS Population and General Population in China: Female.



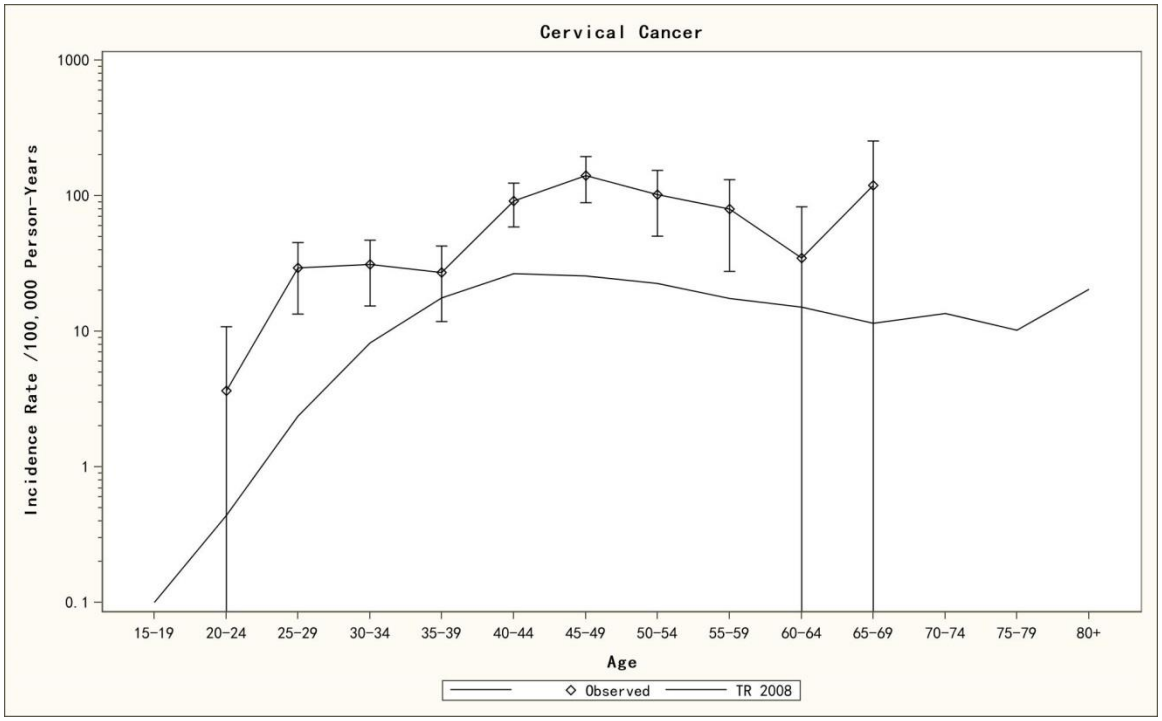
***** *About half of lymphoma records did not specify Hodgkin or Non-Hodgkin lymphoma, so combined observed and expected lymphoma figures were calculated in our UCLA/NCAIDS/FDU study.*

Figure 1-4c. Comparison of Incidence Rate between Lymphomas* in Chinese HIV/AIDS Population and non-Hodgkin Lymphomas in Previous Studies



***** *About half of lymphoma records did not specify Hodgkin or Non-Hodgkin lymphoma, so combined observed and expected lymphoma figures were calculated in our UCLA/NCAIDS/FDU study.*

Figure 1-4d. Comparison of Standardized Incidence Ratio (SIR) of Lymphomas* between HIV/AIDS Population in China and non-Hodgkin Lymphoma in Previous Studies.



TR 2008: China National Tumor Registry 2008.

Figure 1-5a. Comparison of Sex and Age-specific Incidence Rate of Female Cervical Cancer between HIV/AIDS Population and General Population in China.

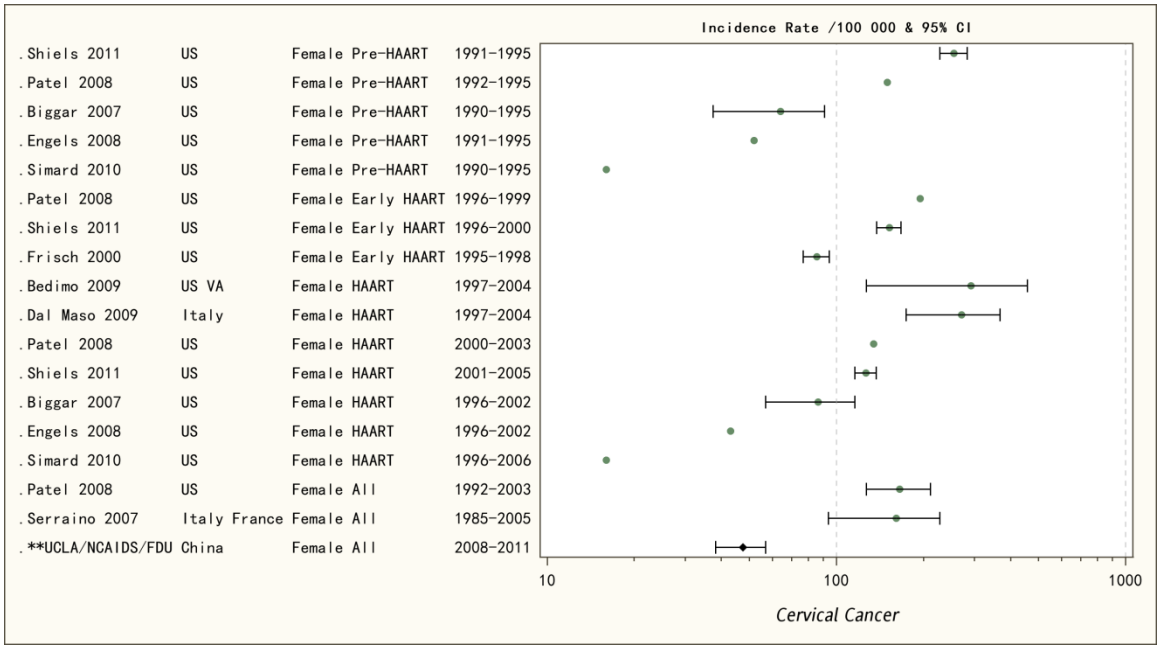


Figure 1-5b. Comparison of Incidence Rate of Female Cervical Cancer between HIV/AIDS Population in China and Previous Studies.

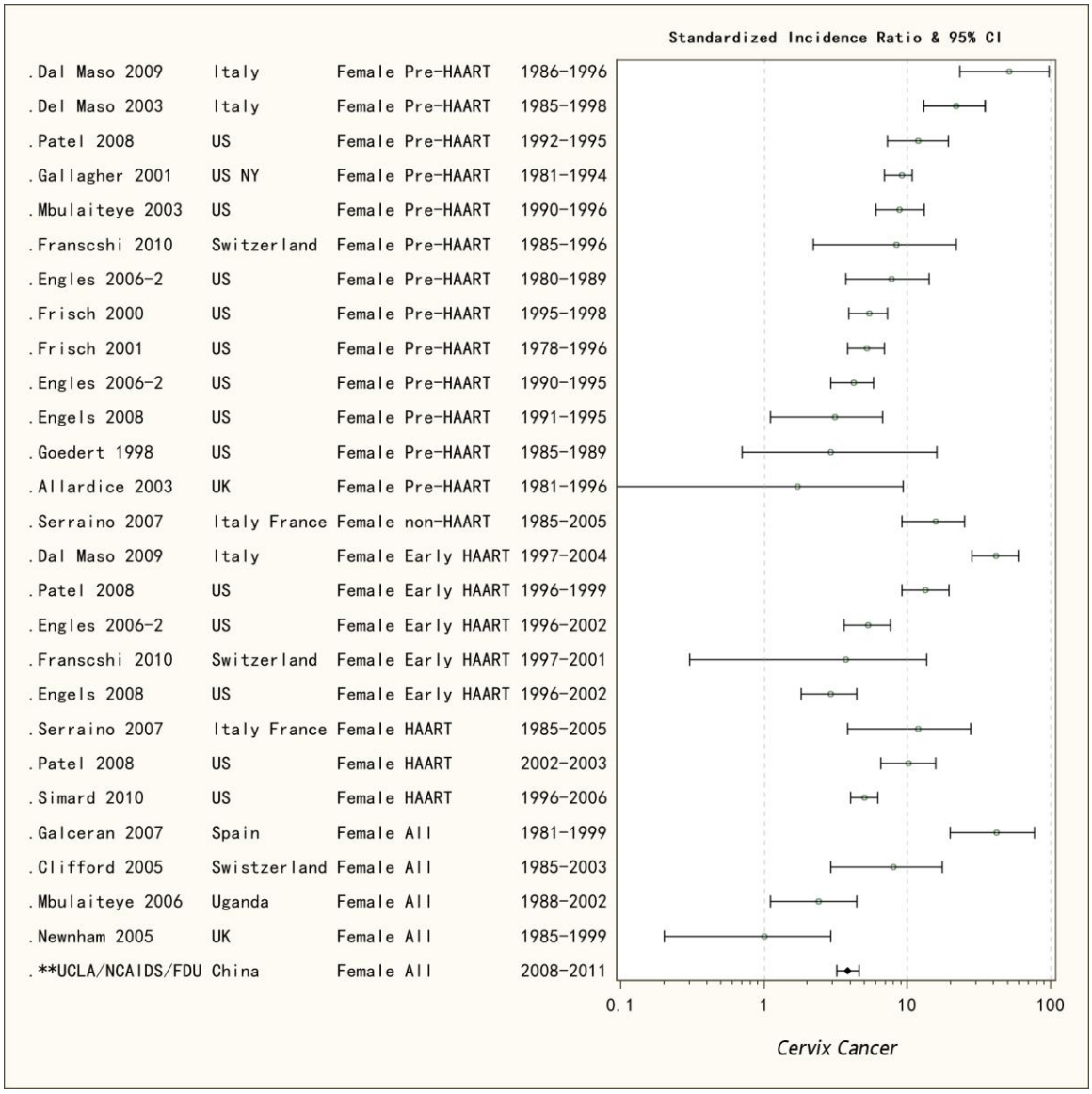
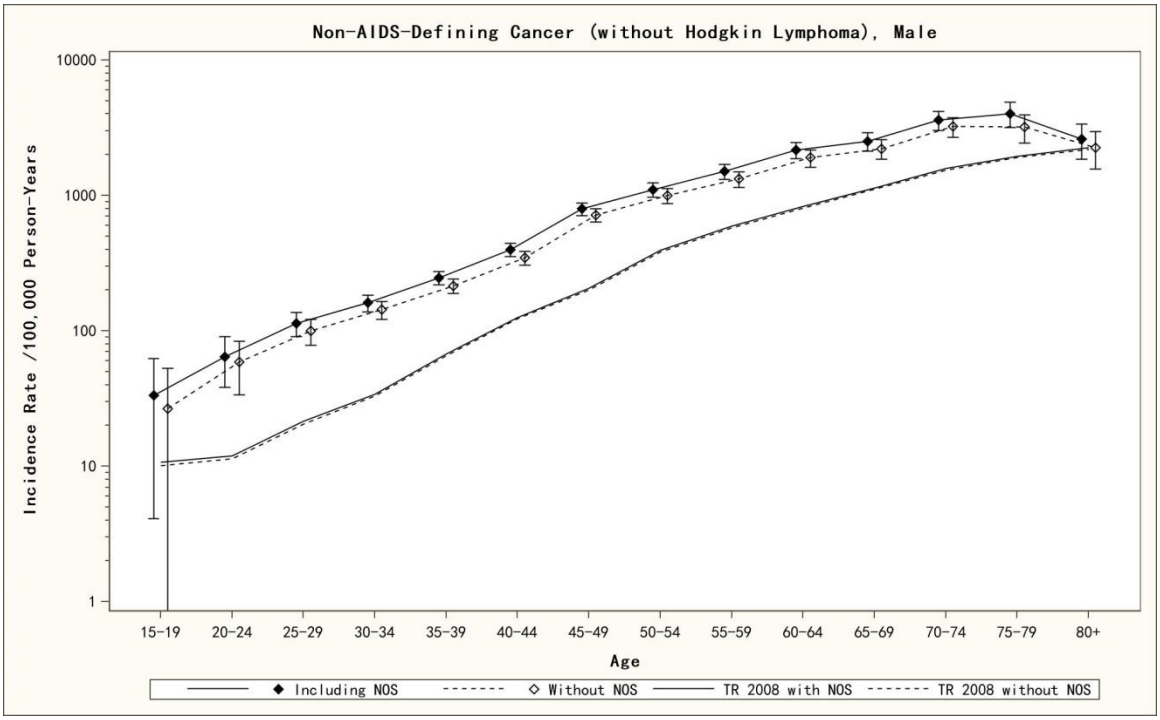
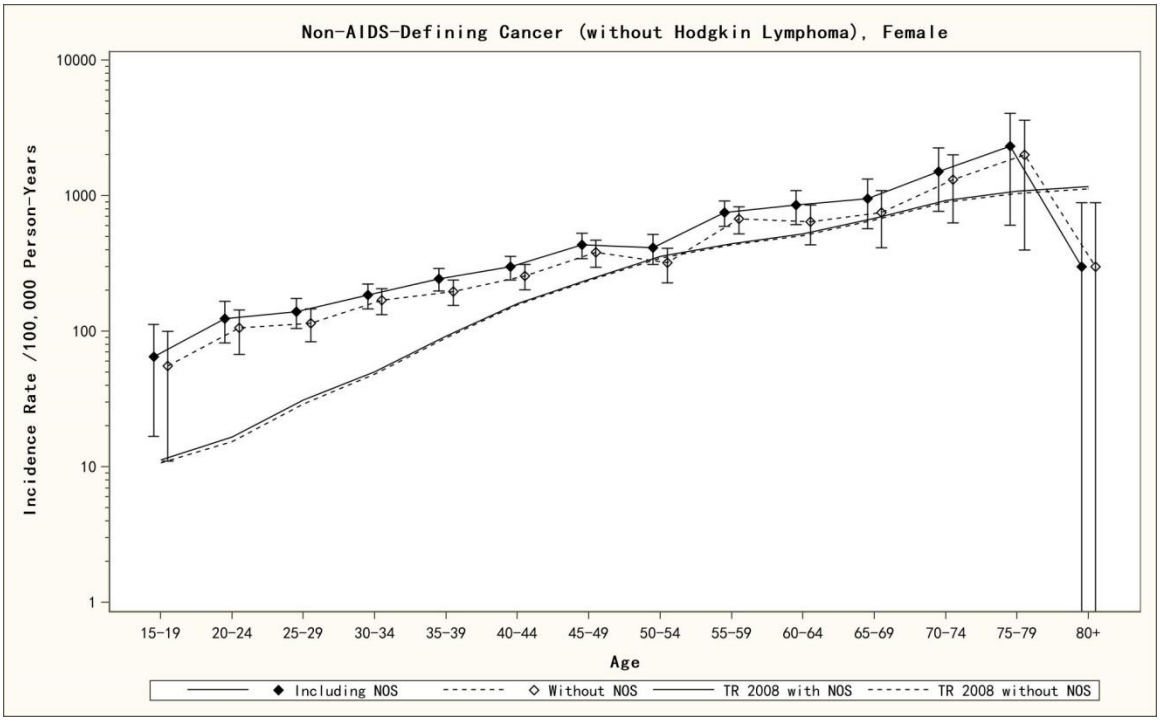


Figure 1-5c. Comparison of Standardized Incidence Ratio (SIR) of female Cervical Cancer between HIV/AIDS Population in China and Previous Studies.



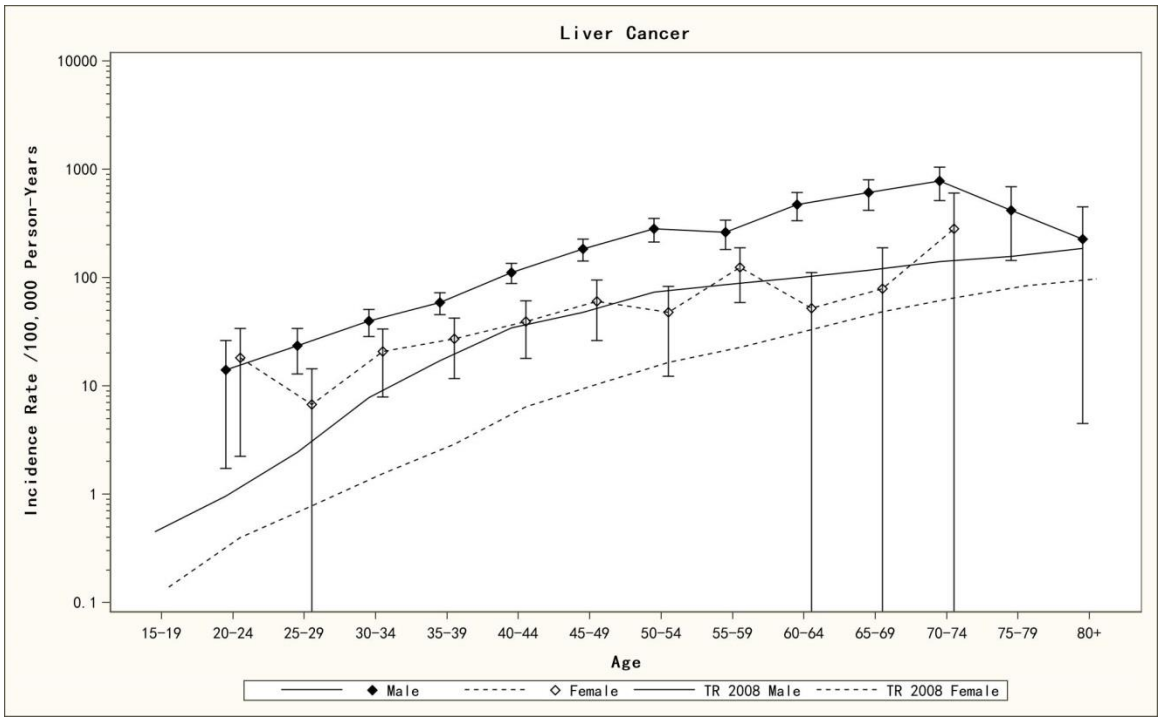
NOS: no specified primary site. TR 2008: China Tumor Registry Data 2008.

Figure 1-6a. Sex and Age-specified Incidence Rates of non-AIDS-defining Cancers (without Hodgkin Lymphoma) in HIV/AIDS Population and General Population in China, Males.



NOS: no specified primary site. TR 2008: China Tumor Registry Data 2008.

Figure 1-6b. Sex and Age-specified Incidence Rates of non-AIDS-defining Cancers (without Hodgkin Lymphoma) among HIV/AIDS Population and General Population in China, Females.



TR 2008: China Tumor Registry Data 2008.

Figure 1-7a. Comparison of Sex and Age-specified Incidence Rates of Liver Cancer in HIV/AIDS Population and General Population in China.

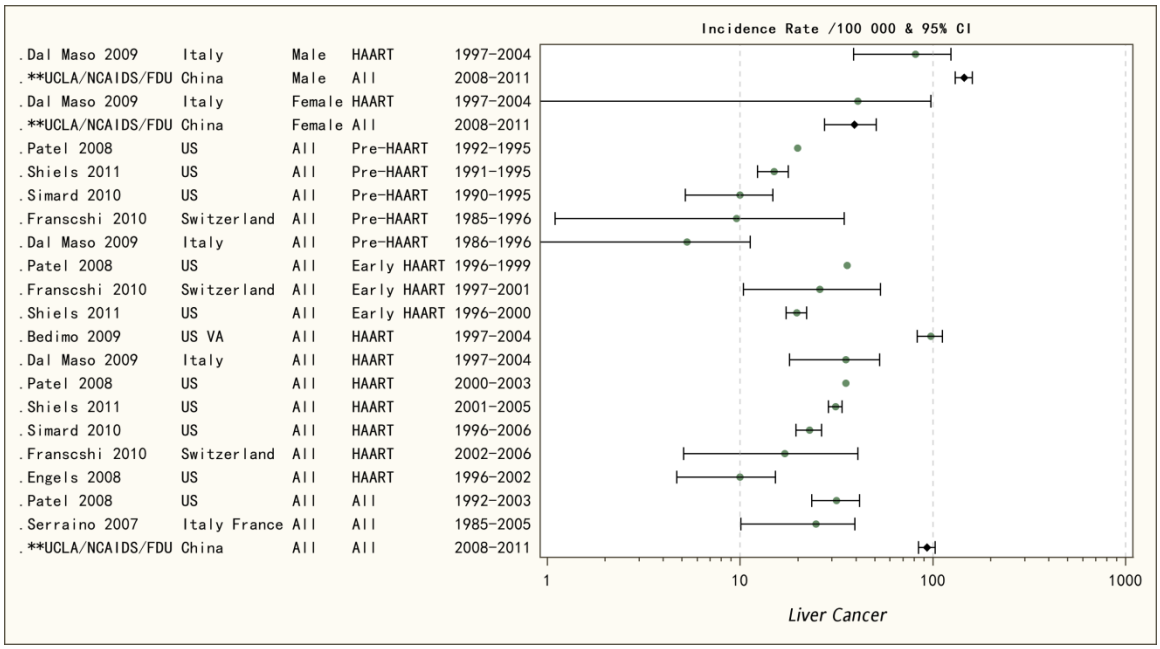


Figure 1-7b. Comparison of Incidence Rate of Liver Cancer between HIV/AIDS Population in China and Previous Studies.

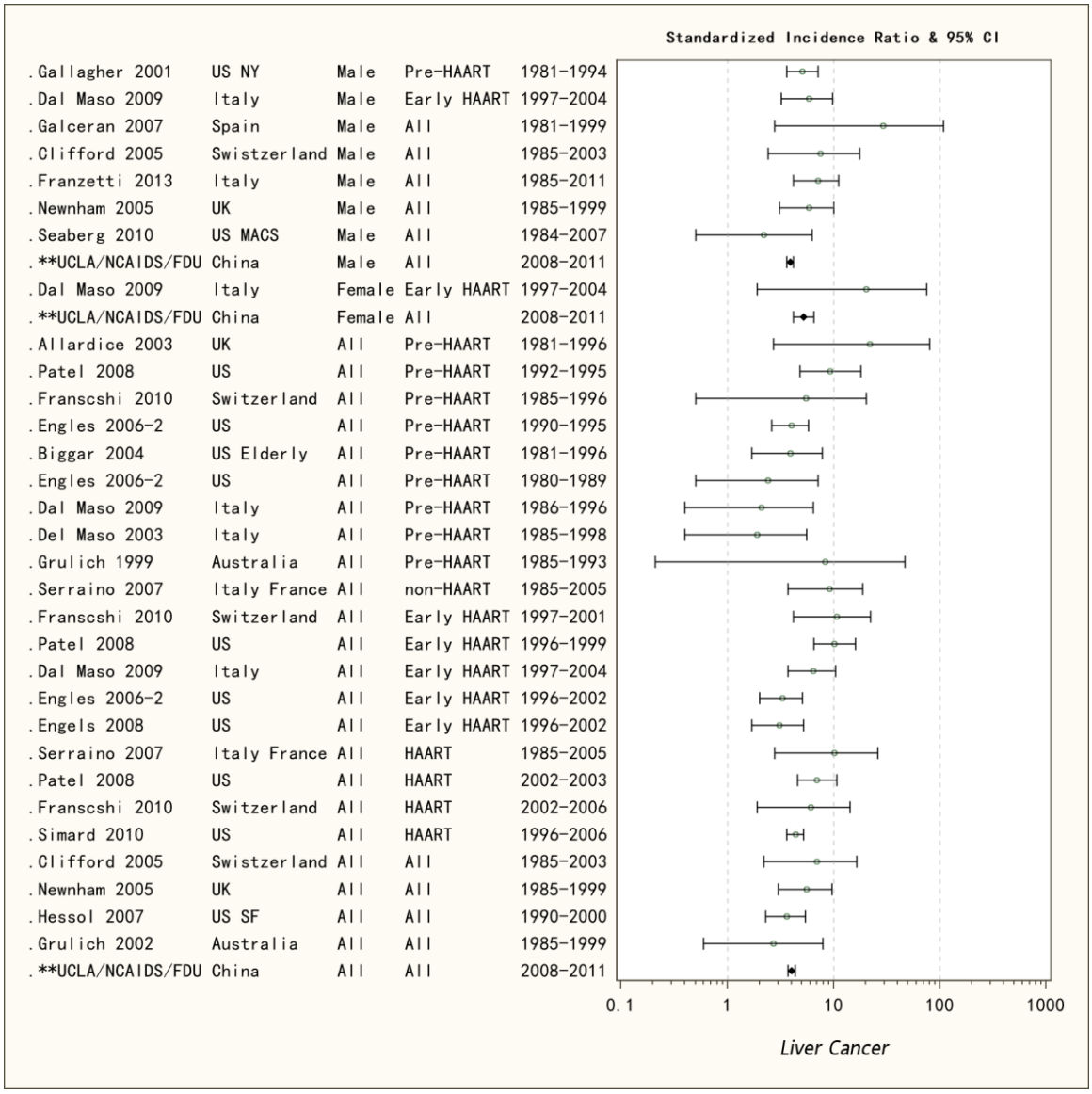
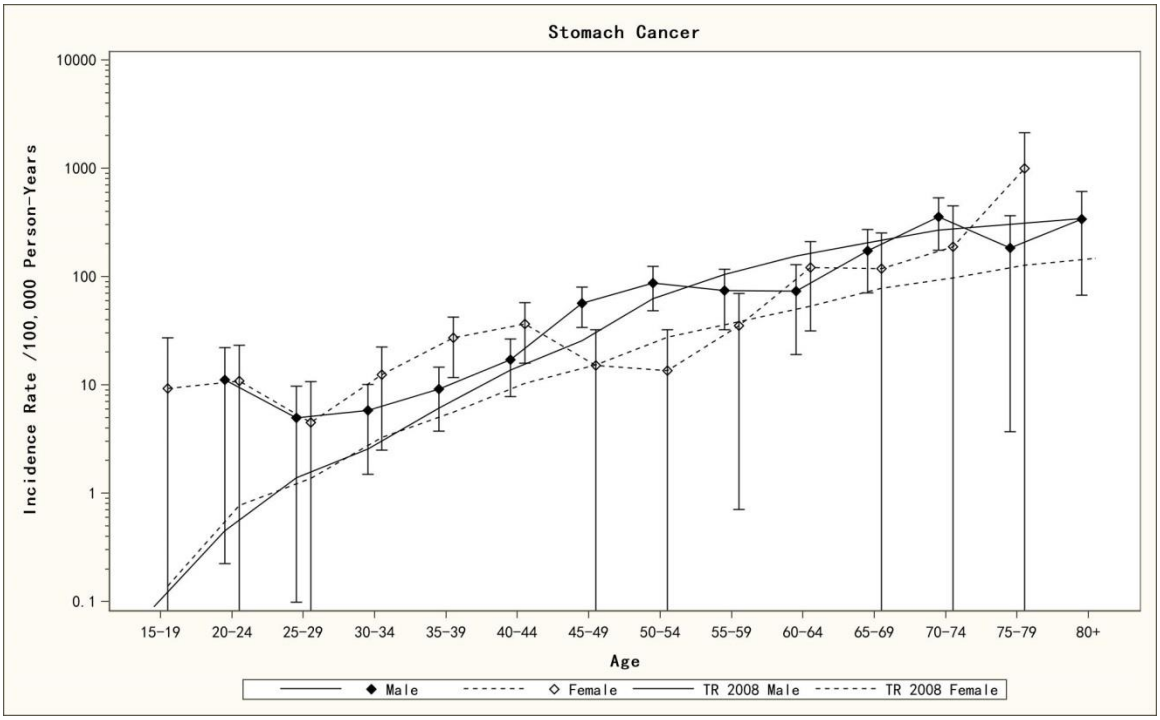


Figure 1-7c. Comparison of Standardized Incidence Ratio (SIR) of female Liver Cancer between HIV/AIDS Population in China and Previous Studies.



TR 2008: China Tumor Registry Data 2008.

Figure 1-8a. Comparison of Sex and Age-specified Incidence Rates of Stomach Cancer in HIV/AIDS Population and General Population in China.

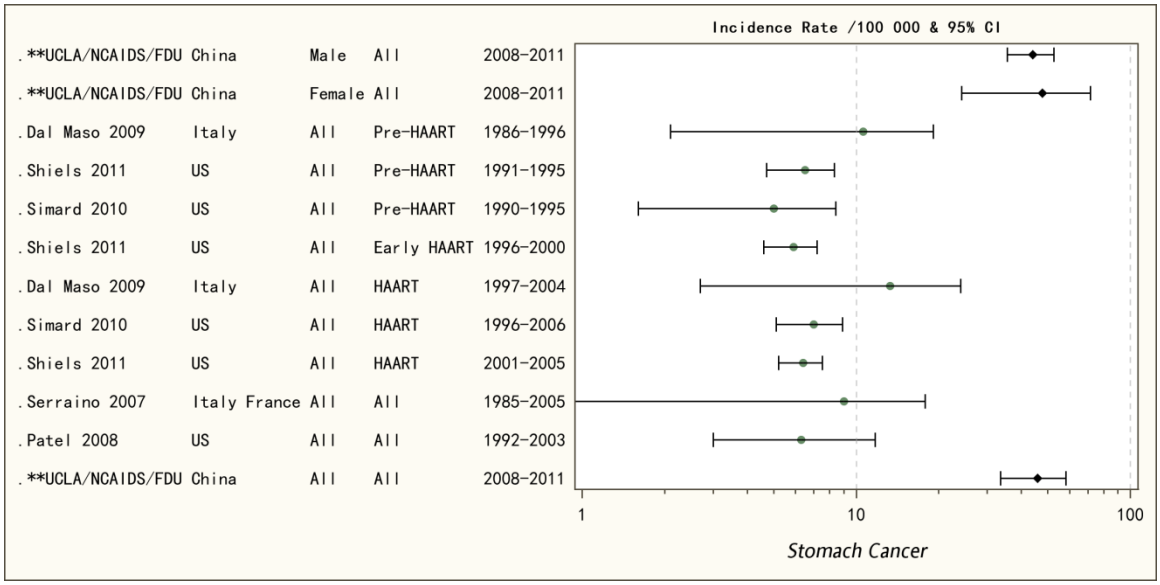


Figure 1-8b. Comparison of Incidence Rate of Stomach Cancer between HIV/AIDS Population in China and Previous Studies.

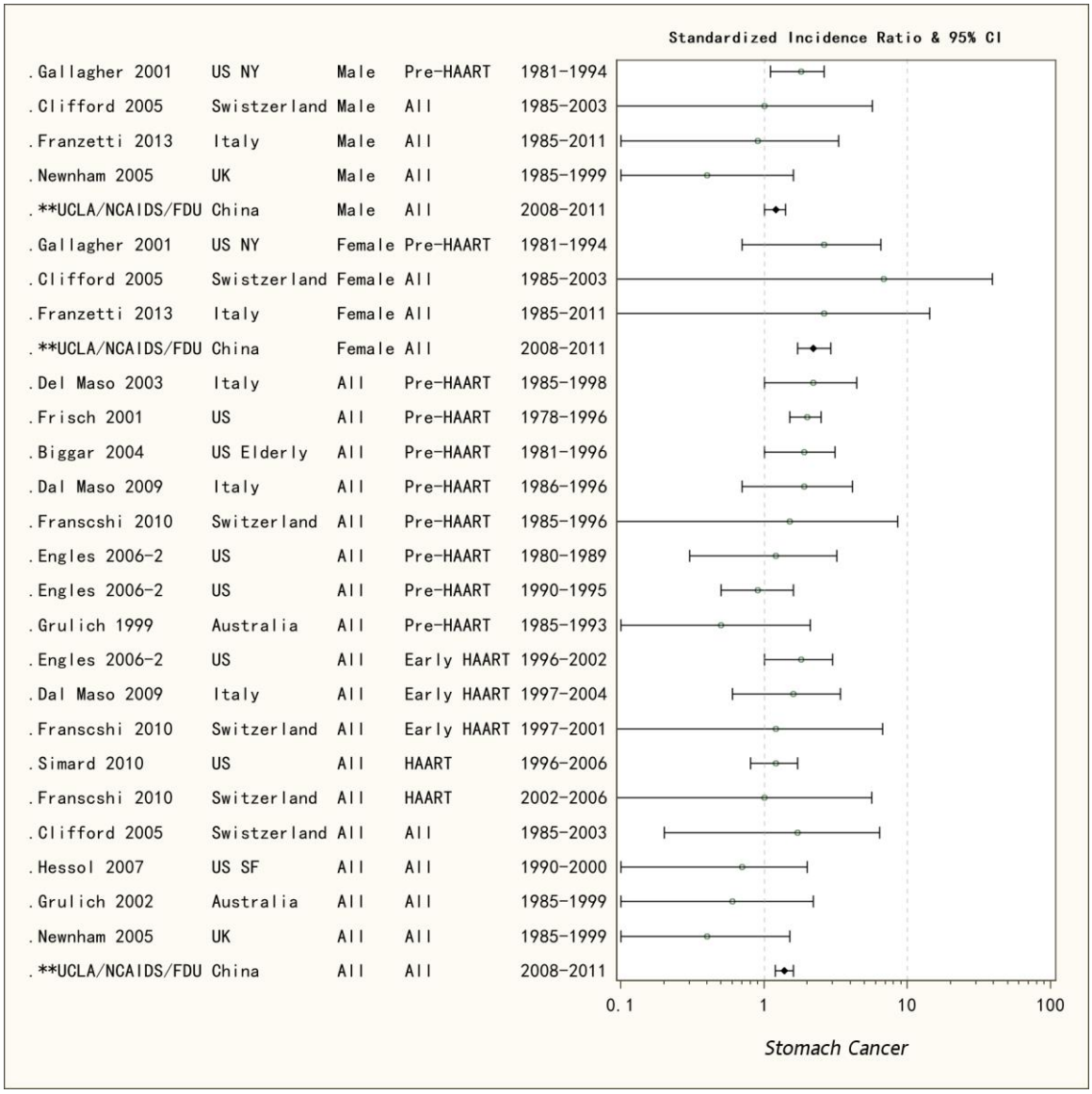
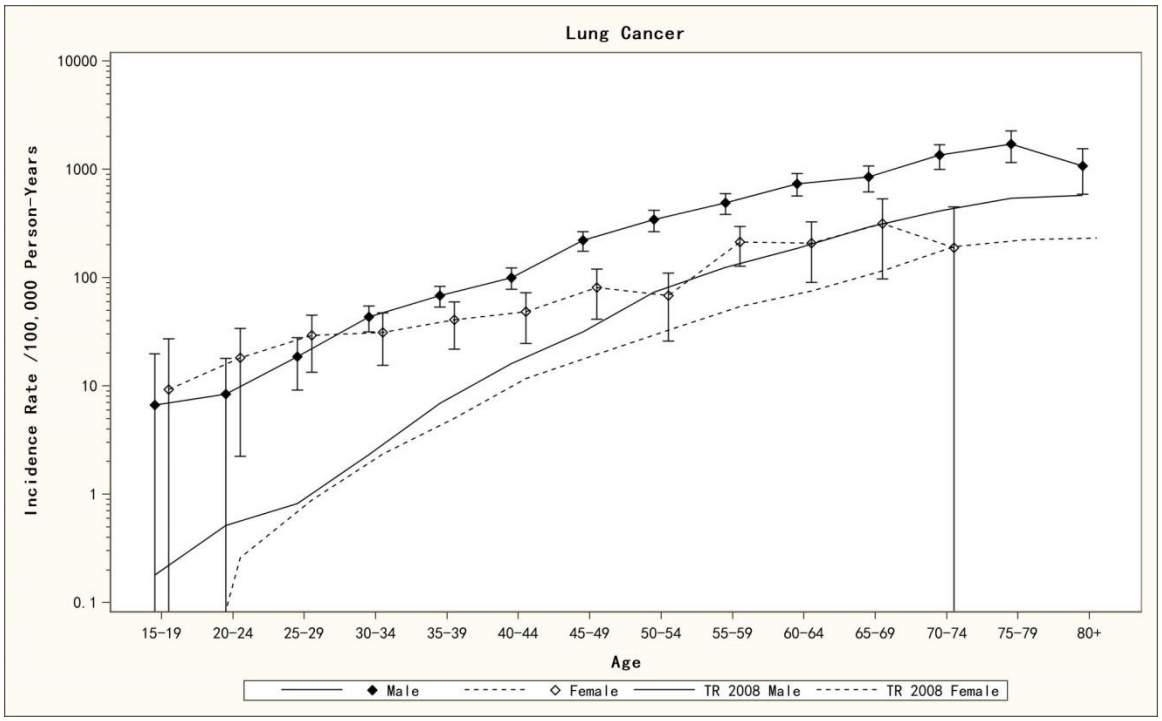


Figure 1-8c. Comparison of Standardized Incidence Ratio (SIR) of Stomach Cancer between HIV/AIDS Population in China and Previous Studies.



TR 2008: China Tumor Registry Data 2008.

Figure 1-9a. Comparison of Sex and Age-specified Incidence Rates of Lung Cancer in HIV/AIDS Population and General Population in China.

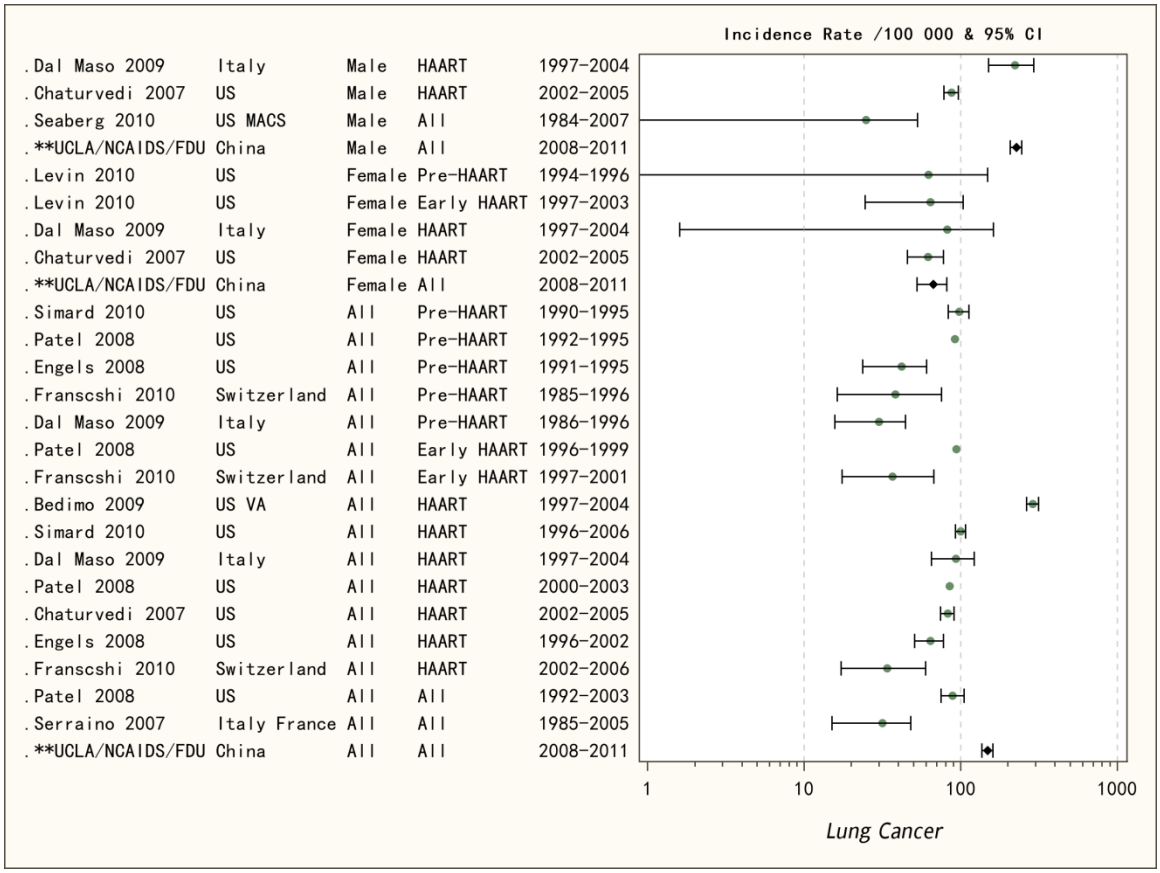


Figure 1-9b. Comparison of Incidence Rate of Lung Cancer between HIV/AIDS Population in China and Previous Studies.

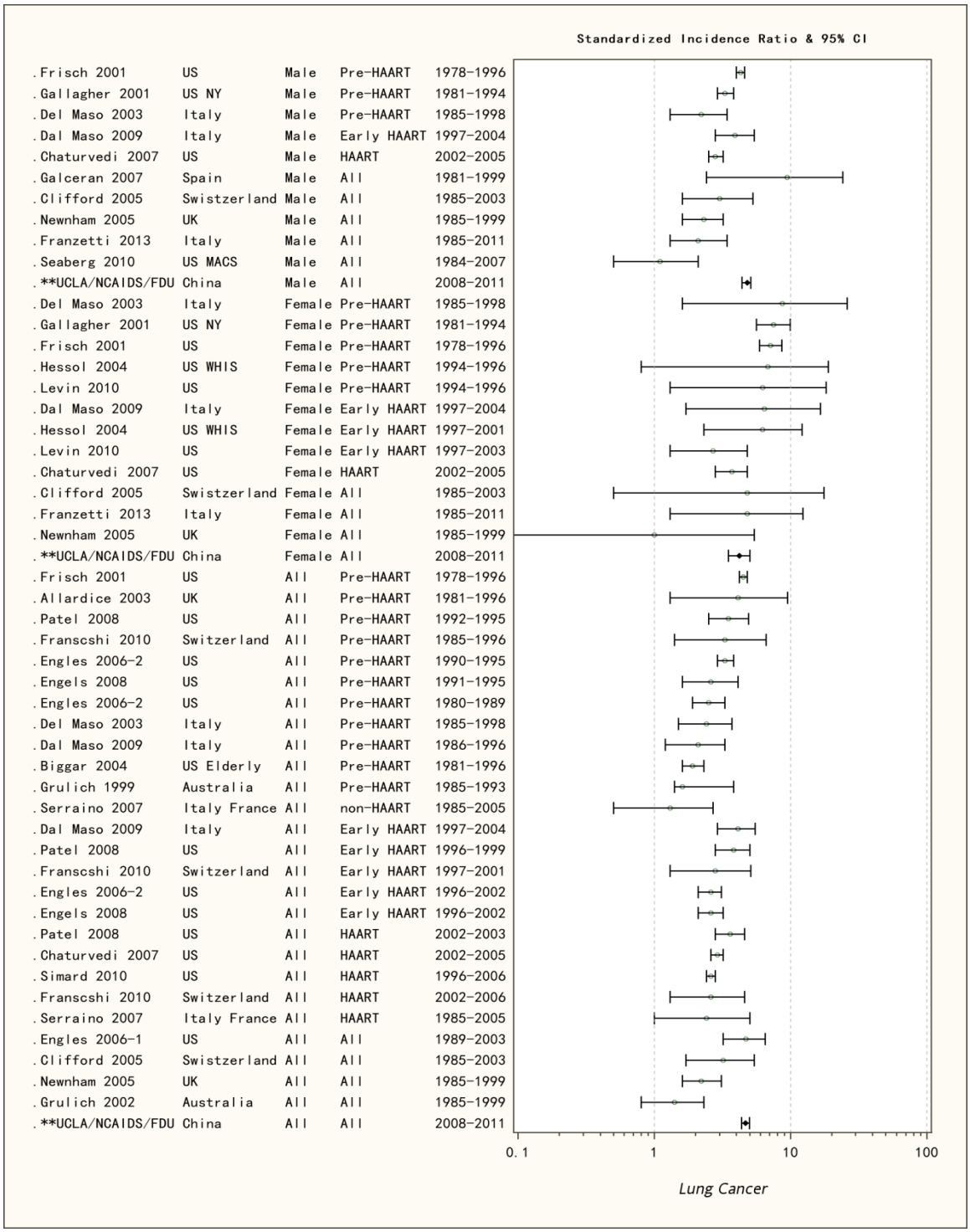
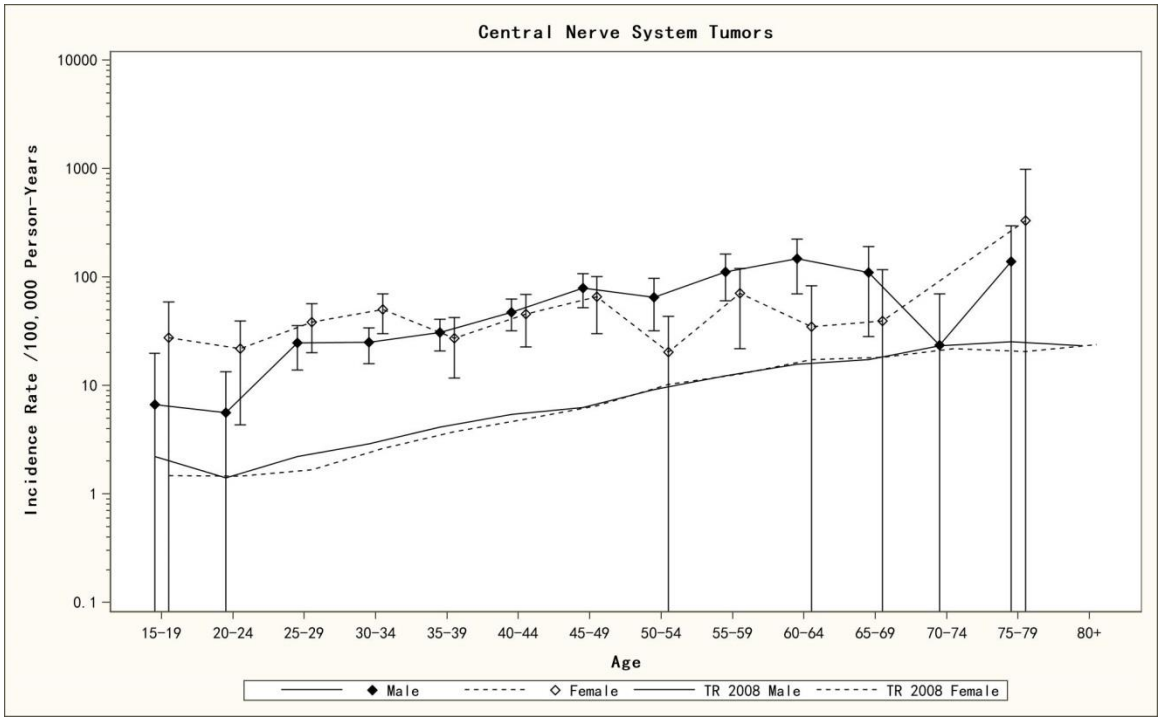


Figure 1-9c. Comparison of Standardized Incidence Ratio (SIR) of Lung Cancer between HIV/AIDS Population in China and Previous Studies.



TR 2008: China Tumor Registry Data 2008.

Figure 1-10a. Comparison of Sex and Age-specified Incidence Rates of Tumors of Central Nerve System in HIV/AIDS Population and General Population in China.

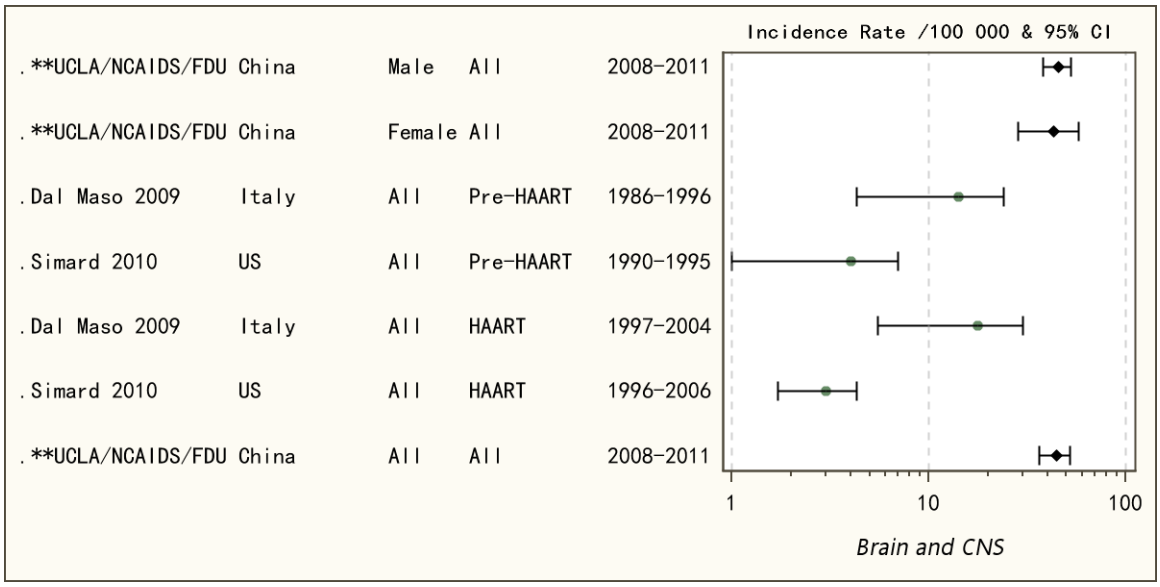


Figure 1-10b. Comparison of Incidence Rate of Tumor of Brain/ Central Nerve System between HIV/AIDS Population in China and Previous Studies.

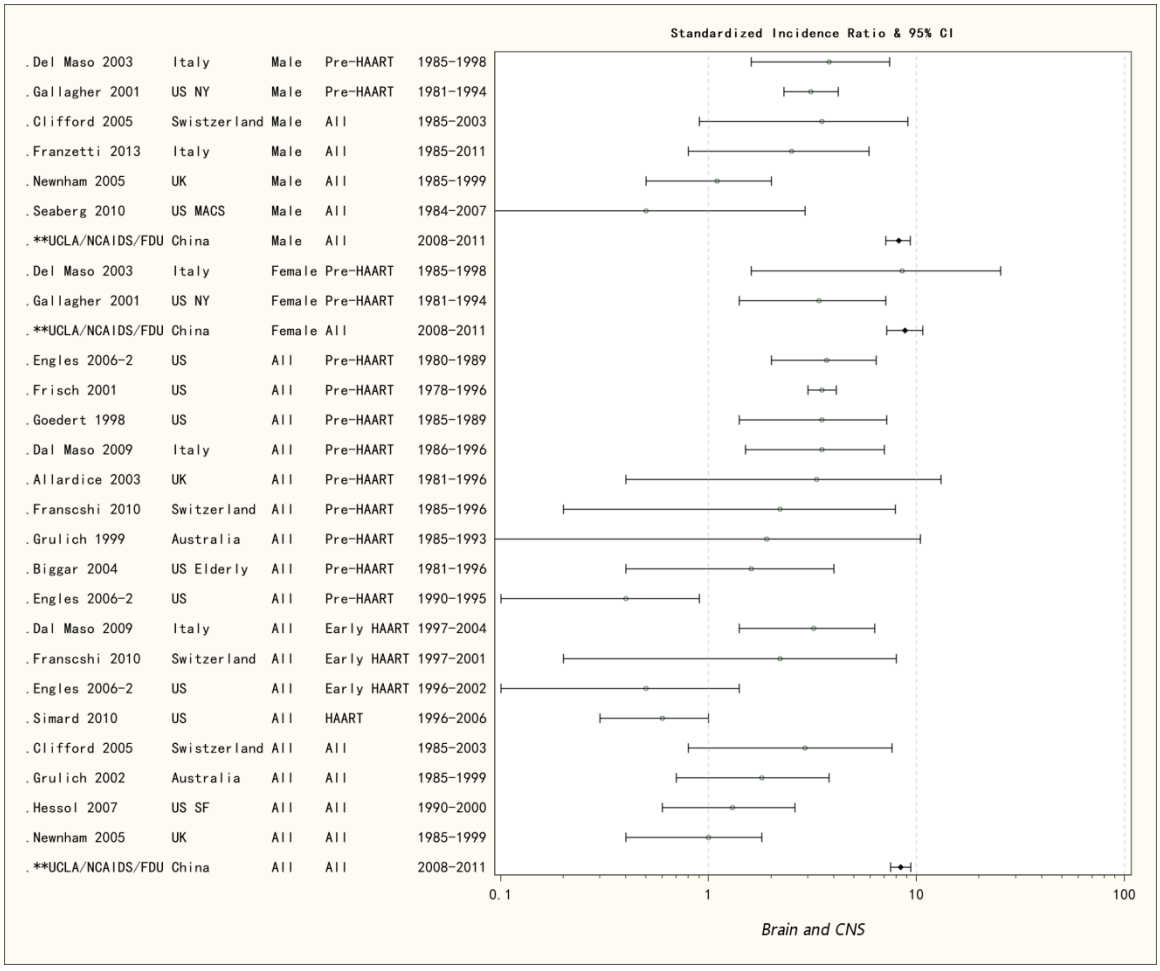
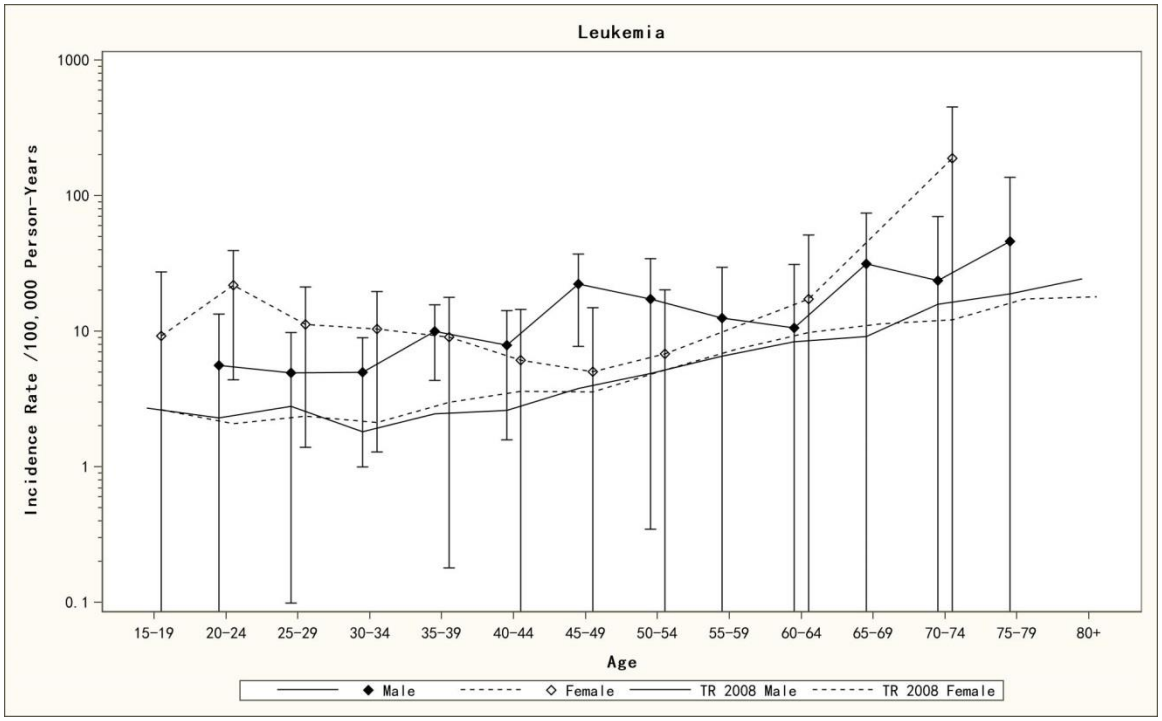
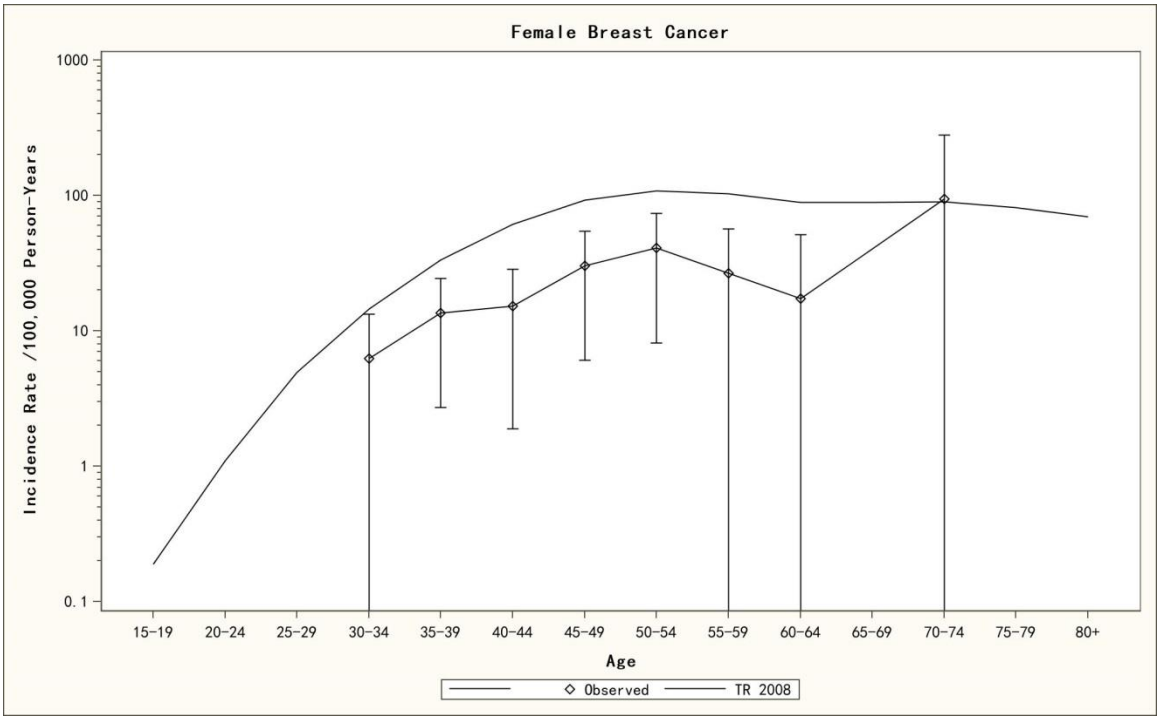


Figure 1-10c. Comparison of Standardized Incidence Ratio (SIR) of Tumor of Brain/ Central Nerve System between HIV/AIDS Population in China and Previous Studies.



TR 2008: China Tumor Registry Data 2008.

Figure 1-11. Comparison of Sex and Age-specified Incidence Rates of Leukemia in HIV/AIDS Population and General Population in China.



TR 2008: China Tumor Registry Data 2008.

Figure 1-12. Comparison of Sex and Age-specified Incidence Rates of Female Breast Cancer in HIV/AIDS Population and General Population in China.

Chapter 3. Epidemiological Factors for Incidence of Kaposi Sarcoma among HIV/AIDS population in China

Introduction

As the first identified HIV/AIDS related cancer with highest incidence rate in western HIV-infected population, Kaposi Sarcoma is the one of the first malignancies need to be studied in Chinese HIV/AIDS population.

Kaposi Sarcoma in China

Report on AIDS-associated KS is rare in China, and there have been only limited case reports of HIV-related KS. Most of studies report one or two cases in areas with major Han population (1-11), for instance, in the only hospital-based study of HIV-related cancer, of 3,554 HIV/AIDS patients with 11,072 person-years observation, only 2 KS cases were identified (12). Most studies of Kaposi Sarcoma among HIV-negative population (13-16), and HIV/AIDS-associated KS in China have been reported from Uyghur and Kazakh population in Xinjiang region (17). In part I of this study, we found higher incidence of Kaposi Sarcoma among People Living with HIV (HIV/AIDS population) in China, although it was not the most prevalent malignant tumor.

KSHV infection in China

The prevalence of KSHV infection varies across different areas and populations in China. In eastern and central provinces with majority population of Han, prevalence of KSHV infection is about 1~9.5% (18-25), however, the prevalence in Xinjiang Autonomous Region is much higher — about 20~30% in the general population (25-28) and in drug users (about 21% to 32%) (29, 30). Furthermore, although studies showed that seroprevalence of KSHV in Uyghur and Kazakh population were higher than that in Han population in Xinjiang, prevalence of KSHV in local Han population in Xinjiang (16% to 26%) is higher (25, 26, 31) than in Han population in other regions (1-9.5%) (20-22, 24, 32) in China . Seroprevalence of HHV-8/KSHV infection in HIV positive population was not independently reported in the region. In one study of IDU with 90% Uyghur participants, the prevalence of KSHV infection was 31.9% among HIV-infected IDUs (29).

Risk factor of Kaposi Sarcoma

For classic Kaposi Sarcoma, being male, elder and population of Mediterranean/ eastern European heritage were thought to be risk factors (33), although some studies found cigarette smoking may be inversely associated with classic KS (34, 35). For AIDS-KS, antiretroviral treatment (ART) is not only used as treatment of AIDS and AIDS-KS, the incidence of KS were also found declined after the introduction of ART (36). However, factors related to AIDS-KS in China remain unclear, and it would be essential to describe patterns of the disease among HIV-positive population and to explore its risk/protective factors.

Hypothesis 2

We hypothesize that due to genetic background and compromised immunological status by HIV infection, the risk or protective factors of HIV-related Kaposi Sarcoma in Chinese population might be similar to that of Western countries. Risk factors include being male, older, lower CD4 cells count level and protective factors include antiretroviral treatment.

Additionally, Since Uyghur population in Xinjiang is one high risk population of classic Kaposi Sarcoma in China, we hypothesize that HIV-infected Uyghur people are also at a high risk of AIDS-related Kaposi Sarcoma.

Specific Aim 2

Epidemiological factors of the HIV-related Kaposi Sarcoma in Chinese will be analyzed in a retrospective cohort study.

We analyzed the cohort of all HIV-infected population in China national HIV/AIDS surveillance information system as a dynamic prospective cohort study to explore epidemiological risk/protective factors for HIV-related Kaposi Sarcoma. Additionally, we ran a sub-set analysis to

explore KS associated factors in Uyghur population in China. Explored factors include age group (15 years category, start since 15 years old), sex (category), ethnic group (categorized into Han, Uyghur and other), Education (category), reported HIV transmission routes, First CD4 cells counts (<200/μl, 200~349/μl, ≥350/μl as reference), antiretroviral treatment (>90 days before KS diagnose), and Year of HIV diagnosis (before 2003, 2003 to 2007 and since 2008).

Material and Methods

Study Design

The original data source is the same as in the Chapter 2, and the data was treated as a dynamic cohort study. A sub-cohort of all Uyghur ethnic participants was extracted from the whole database and a parallel sub-set analysis was done in the Uyghur cohort.

Person-time calculation

For the analysis of incidence risk of KS, person time was calculated in the same way as in Chapter 2, and it is briefly stated in Figure 1-1. Basically, all subjects with follow-up records between January 1st, 2008 to December 31st, 2011 were included. Inferred KS incidence date was set as the median of the first time of KS report and the most recent follow-up time before the KS report.

Cases

Kaposi Sarcoma cases were defined as all participants with at least one follow-up between 2008-2011, had first reports of KS diagnose, and inferred KS diagnosis date between Jan 1, 2008 and Dec 31, 2011.

Statistical Analysis

Description

Continuous variables such as age and CD4 cells count were described with mean±standard deviation. Demographic characteristics, HIV/AIDS disease stage and first CD4 cells counts categories (<200/μL, 200~349/μL, ≥350μL, Not Available) were described by frequency.

Association Analysis

Univariate Proportional Hazards (Cox) models were used to estimate crude hazard ratio estimation and 95% confidence intervals, and multivariate Cox regression models were used to adjust potential confounding factors (37, 38). To adjust potential survival bias, all multivariate models were adjusted with Year of HIV diagnosis. KS diagnosis was the outcome variable, person-time during 2008-2011 were set as survival time, and censor status was set if KS-free participants died, was lost-to-follow-up during the study period, or was alive without KS after December 31, 2011. Modeled factors include age group (15 years category, start since 15 years old), sex (category), ethnic group (categorized into Han, Uyghur and other), Education (category),

inferred HIV transmission routes, First CD4 cells counts (<200/μl, 200~349/μl, with ≥350/μl as reference), antiretroviral treatment (>90 days before KS diagnose), and Year of HIV diagnosis (before 2003, 2003 to 2007 and since 2008). The models of Uyghur sub-cohort is the same as in the whole data analysis except the variable ethnic group was not included. All missing data were categorized into as missing or not available in each category variable.

All data management and analysis was performed using SAS 9.3 (SAS Institute Inc., Cary, NC) software.

Results

Overall Description

A total of 444,712 subjects aged over 15 years were diagnosed as HIV infected before 1/1/2012. Among them, 45,261 were found dead or lost to follow-up before 1/1/2008, or registered with invalid information that cannot be identified. Finally, a total of 399,451 subjects were included in the analyses, contributing 813238.9 person-years (pys) between 1/1/2008 and 12/31/2011. The average follow-up time was 2.0 years. Other demographic and disease related characteristics distributions are listed in Table 2-1. A total of 171 cases of Kaposi Sarcoma were identified. The average age of cases was 39.4±10.8 years old, and among these cases, 132 were males and 39

were females, 103 were Han ethnicity and 43 were Uyghur ethnicity, 143 KS cases were found at AIDS stage when they were firstly diagnosed as HIV- infected (Table 2-1).

Association Analysis

Being older was found to be associated with higher risk of KS, KS risk of participants aged between 15-29 was 0.52 (95%CI 0.34-0.78) as participants aged between 30-44, and hazards ratio age group 45-59 vs. 30-44 was 1.53 (95%CI 1.04-2.26). Males had higher hazards than females with an adjusted HR of 1.68 (95%CI 1.17-2.40). Uyghur ethnic group has much higher risk than Han Chinese, with an adjusted HR of 5.30 (95%CI 3.68-7.64) (Table 2-2a).

HIV transmission routes were found to be associated with KS risk, and compare with intravenous drug users (IDUs), adjusted HR of potentially heterosexually transmitted participants was 1.75 (95%CI 1.12-2.74), adjusted HR of blood transmitted participants was 3.15 (95%CI 1.77-5.58), men who have sex with men (MSM) was 2.68 (95%CI 1.30-5.49), and heterosexual plus IDU was 3.49 (95%CI 1.36-8.99) (Table 2-2b).

Lower CD4 cells count level was found to be risk factors of KS. Compare with participants with first CD4 cells count over 350/μL, adjusted HR for participants <200/μl was 4.07 (95%CI 2.57-6.46), and adjusted HR for participants CD4 cells counts level between 200 to 350/μL was 3.27 (95%CI 2.06-5.18). Test for trend with p-value<0.01 (Table 2-2b). Antiretroviral treatment

(>90 days before KS diagnose) was found as a protective factor with adjusted HR 0.39 (95%CI 0.27-0.56).

Participants diagnosed with HIV in earlier period were found with lower risk of KS. Comparing with those diagnosed in 2008 and later, adjusted HR for participants with HIV diagnose before 2003 was 0.10 (95% CI, 0.41-0.93), and 0.47, 95%CI (0.34-0.65) for those diagnosed between 2003 and 2007 (Table 2-2b).

Uyghur Cohort

There were 27,782 Uyghur participants identified from the whole cohort contributing 57804.1 person-years to the analysis, and 43 of them developed KS during 2008-2011. Average age of them was 33.1±8.1 years, and 18,232 (65.6%) of them were male while 9,550 (34.4%) were female. Intravenous drug use was the top transmission route of HIV followed by heterosexual transmission. About 23% (6,461/27,782) were found first CD4 cells count lower than 200/μL and 20% (5511/27782) were found CD4 cells level between 200-350/μL. Furthermore, 32% (8771/27782) subjects didn't have data on CD4 cells level in the database. The average first CD4 cells count among KS cases was 233±161/μL, ranged from 7/μL to 655/μL. The average first CD4 cells count among non-KS subjects was 333±274/μL, ranged from 0 to 9983/μL. Detailed demographic characteristics, transmission routes, CD4 cells counts and antiretroviral treatment (ART) history were presented in Table 2-3.

Association Analysis of Uyghur Cohort

Consistent with analysis of overall population, being older was also found associated with higher risk of KS in Uyghur cohort, KS risk of participants aged between 15-29 was 0.38 (95%CI 0.17-0.87) as participants aged between 30-44, and hazards ratio age group 45-59 vs. 30-44 was 2.65 (95%CI 1.20-5.83). Males had higher hazards than females with an adjusted HR of 1.67 (95%CI 0.85-3.28). (Table 2-4a).

HIV transmission routes were also found to be associated with KS risk in the Uyghur sub-cohort, and compare with intravenous drug users (IDUs), adjusted HR of potentially heterosexually transmitted participants was 1.47 (95%CI 0.69-3.10), and heterosexual plus IDU was 5.08 (95%CI 1.16-22.26). HRs of blood transmitted and MSM were not available because there were no KS cases in the two categories (Table 2-4b).

Lower CD4 cells counts were found to be associated with KS in the Uygur cohort. Compare with participants with first CD4 cells count over 350/μL, adjusted HR for participants <200/μl was 6.40 (95%CI 2.59-15.80), and aHR for participants CD4 cells count level between 200 to 350/μL was 4.73 (95%CI 1.93-11.57). Test for trend with p-value<0.01 (Table 2-2). Antiretroviral treatment (>90 days before KS diagnose) was found as a protect factor with aHR 0.12 (95%CI 0.05-0.32) (Table 2-4b).

Participants diagnosed with HIV in earlier period were also found with lower risk of KS. Comparing with those diagnosed in 2008 and later, aHR for participants with HIV diagnose before 2003 was 0.10 (95% CI, 0.41-0.93), for those diagnosed between 2003 and 2007 (Table 2-4b).

Discussion

In general Chinese population, incidence of classic KS is extremely low (39) and most previous case reports were classic KS in Uyghur population (14-16), and sporadic case reports of other types of KS (1, 3-5, 17). Our result supports the hypothesis that HIV-infected Uyghur subjects had relatively high risk of AIDS-KS. Major findings in the whole cohort and the sub-analysis of Uyghur cohort were similar.

The reason of ethnical difference has not been systematically revealed yet. The only case-control study with 17 cases in Xinjiang found that Kaposi Sarcoma-associated Herpes Virus, or Human Herpes Virus type 8 (KSHV/HHV-8) were the strongest risk factor of classic KS (40), and all subjects in that study were all Uyghur. Although in general Uyghur population in Xinjiang had higher prevalence of KSHV infection than Han population in other provinces of China(18, 20-22, 24, 26, 27, 30, 32), however, the prevalence of KSHV infection was also found higher in general Han population in Xinjiang, one HIV-infected population in central China, and intravenous drug users in eastern China (41-45). Thus, KSHV prevalence difference between Uyghur and other population in HIV-infected population in China may not fully address all the differences in

AIDS-KS risk, and genetic factors may be an important risk factor to be studied, considering Uyghur population had mixed genotype between Caucasians and Mongolians (46, 47).

We found antiretroviral treatment (ART) reduced the incidence of KS among HIV-infected population in China, which is also reported by previous studies in western populations (48-54). Lower CD4 cells count level was found to be a strong risk factor of KS incidence (Table 2-2, 2-4).

Transmission routes of HIV are associated with KS incidence, and sexually transmission of HIV may be associated with higher KS incidence than intravenous drug use, which is very similar as in previous studies (55-57). Two hypotheses could be possible: 1) there may be risk factors of KS related to sexually transmission and 2) there may be factors related to IDU that negatively associated with KS incidence. For the first hypothesis, sexual transmission of KSHV was considered at the beginning of AIDS epidemic (58). However, transmission routes of KSHV has been found through saliva, mother-to-child/vertical, blood, intravenous drug use or transplant in more recent studies (59-67), although sexual transmission is still considered important. Considering the high prevalence of KSHV infection among IDUs in China (41, 43, 68), more directed information on KSHV infection among HIV/AIDS population of different HIV transmission routes in China is essential for testing this hypothesis. For the alternative hypothesis 2, one possible reason is that IDUs may have higher all-cause mortality that such association may

be caused by survival bias. This hypothesis is partially supported by former analysis of China CDC, which reported the IDUs had higher mortality and lower ART coverage than those of sexually transmitted subjects (69). However, the magnitude of the difference showed in that study is not large enough to fully address this question. Another alternative hypothesis is that opiate drug may act on angiogenesis related pathways, considering most intravenous drug users in China are injecting heroin (70), an opiate drug and a derivative of morphine. Former studies showed morphine may inhibit angiogenesis (71-76) through different pathways (77, 78). Nevertheless, to verify or falsify these hypotheses, detailed information on KSHV infection and further explore in molecular epidemiology study.

In our sub-set analysis of all Uyghur participants of HIV/AIDS population in China, similar associations were found in age, CD4 cells count, ART and year of diagnose on the risk of, however, we didn't found strong association between sex and KS incidence in the Uyghur cohort.

The major limitation of the current analysis was that the detailed clinical KS records were not captured by current system, and we only modeled whether there was an incidence KS, and potential KS of immune reconstitution inflammatory syndrome (IRIS-KS) (79) were not differentiable in the original data. When evaluating the effect of ART, we chose ART started 90 days before KS diagnose as a working criterion to reduce the bias caused by IRIS-KS. As mentioned in part I, because of high mortality of HIV/AIDS population in China, potential survival bias is inevitable in our current analysis, and we adjusted Year of HIV diagnosis in

multivariate models to reduce this bias. However, because of limited KS cases size, we cannot run models with enough covariates and residual confounding by social economic status is possible. Another limitation in current analysis is that lost-of-follow-up in the cohort was not fully analyzed and potential selection bias due to differential lost-of-follow-up may bias the estimation of year of HIV diagnose, ART, HIV transmission route and CD4 cell count. Marginal structure model (80) could be a solution to address this issue in next step.

In summary, our result strongly indicated that early diagnoses with initiation of highly active antiretroviral treatment reduce the incidence of Kaposi Sarcoma among HIV/AIDS population in China. We found Uyghur population has higher risk of AIDS-KS, and factors such as age, HIV transmission routes, first CD4 cells count level and ART were similar as in the national-wide cohort. To explore more KS risk among HIV-infected Uyghur people, a hospital-based case-control study in Xinjiang among this particular population will be presented in the next part.

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Tables

Table 2-1. Characteristics of Cohort of HIV/AIDS Population in China, 2008-2011

Characteristics	Categories	N	%	Person-Years	%	KS (N)
Age	15-29	116082	29.1	213789.8	26	30
	30-44	196848	49.3	440565.2	53.5	96
	45-59	60917	15.3	124932.1	15.2	37
	60+	25604	6.4	33951.8	4.1	8
Sex	Male	278908	69.8	550228.6	66.8	132
	Female	120543	30.2	263010.3	31.9	39
Ethnic Group	Han Chinese	271375	67.9	557772.6	67.8	103
	Uyghur	27782	7	57804	7	43
	Other	100294	25.1	197662.4	24	25
Education	Illiteracy	37577	9.4	75273.2	9.1	13
	Primary School	112932	28.3	232735.9	28.3	48
	Junior School	146270	36.6	303861.8	36.9	82
	High School	41180	10.3	74439.9	9	16
	College and Higher	22881	5.7	36115.5	4.4	9
	N/A	38611	9.7	90812.7	11	3
Marriage	Married	199434	49.9	409950.4	49.8	92
	Unmarried	110405	27.6	218079.2	26.5	38
	Divorced/ Widowed	59628	14.9	122128.2	14.8	37
	N/A	24953	6.2	53648.2	6.5	4
Transmission	Heterosexual	173853	43.5	290022.6	35.2	77
Routes	IDU	108911	27.3	259168	31.5	37
	Blood	40860	10.2	128043.6	15.6	28
	MSM	29169	7.3	40022.4	4.9	14
	Sexual + IDU	4900	1.2	10179.8	1.2	5
	Other/Unknown	41758	10.5	85802.6	10.4	10
Disease Stage	HIV	247625	62	445270.7	54.1	37
at diagnosis	AIDS	151826	38	367968.3	44.7	134
First CD4 cells count	<200/μl	108585	27.2	210185.4	25.5	72
test after HIV	200~349/μl	88439	22.1	196043.6	23.8	59
diagnosis	>=350/μl	102305	25.6	250856.9	30.5	27
	Unknown	100122	25.1	156153.1	19	13
ART started >90 days	Yes	123520	30.9	257047.1	31.2	130
Before KS diagnose	No	274931	68.8	556191.9	67.6	41
Year of HIV	Before 2002	24830	6.2	69670.0	8.5	3
Diagnosis	2003-2007	139947	35	429660.6	52.2	62
	2008 and after	234674	58.7	313908.4	38.1	106

Table 2-2a. Risk factor of Incident Kaposi Sarcoma among HIV/AIDS Cohort in China.

	Person-		Crude Hazard Ratio		Adjusted Hazard Ratio		
Characteristics	**Years**	**KS**	**HR**	**95%CI**	**HR**	**95%CI**	**Adjusted Factors**
Age							
15-29	213789.8	30	**0.62**	**(0.41-0.93)**	**0.52**	**(0.34-0.78)**	Sex, Ethnicity,
30-44	440565.2	96	Ref	-	Ref	-	YHD
45-59	124932.1	37	1.33	(0.91-1.94)	**1.53**	**(1.04-2.26)**	
60+	33951.8	8	0.96	(0.47-1.97)	0.91	(0.44-1.89)	
			p- trend	**<0.01**	**p- trend**	**<0.01**	
Sex							
Male	550228.6	132	**1.60**	**(1.12-2.28)**	**1.68**	**(1.17-2.40)**	Age, Ethnicity,
Female	263010.3	39	Ref	-	Ref	-	YHD
Ethnic Group							
Han Chinese	557772.6	103	Ref	-	Ref	-	Age, Sex, YHD
Uyghur	57804.0	43	**4.14**	**(2.90-5.91)**	**5.30**	**(3.68-7.64)**	
Other	197662.4	25	0.68	(0.44-1.06)	0.75	(0.49-1.17)	
Education							
Illiteracy	75273.2	13	0.63	(0.35-1.14)	0.67	(0.38-1.26)	Age, Sex, Ethnicity,
Primary School	232735.9	48	0.76	(0.53-1.09)	0.72	(0.50-1.03)	YHD
Junior School	303861.8	82	Ref	-	Ref	-	
High School	74439.9	16	0.77	(0.46-1.33)	0.63	(0.37-1.08)	
College and Higher	36115.5	9	0.88	(0.44-1.74	0.73	(0.37-1.47)	
N/A	90812.7	3	0.13	(0.04-0.42)	0.25	(0.08-0.85)	

Table 2-2b. Risk factor of Incident Kaposi Sarcoma among HIV/AIDS Cohort in China. (Continued)

	Person-		Crude Hazard Ratio		Adjusted Hazard Ratio		
Categories	**Years**	**KS**	**HR**	**95%CI**	**HR**	**95%CI**	**Adjusted Factors**
HIV Transmission Routes							
Heterosexual	290022.6	77	**1.72**	**(1.16-2.54)**	**1.75**	**(1.12-2.74)**	Age, Sex, Ethnicity,
IDU	259168.0	37	Ref	-	Ref	-	Education, YHD
Blood	128043.6	28	**1.55**	**(0.95-2.55)**	**3.15**	**(1.77-5.58)**	
MSM	40022.4	14	**2.19**	**(1.18-4.05)**	**2.68**	**(1.30-5.49)**	
Sexual + IDU	10179.8	5	**3.28**	**(1.29-8.34)**	**3.49**	**(1.36-8.99)**	
Other/Unknown	85802.6	10	0.80	(0.40-1.61)	1.53	(0.74-3.19)	
First CD4 cells count test after HIV diagnosis							
<200/μl	210185.4	72	**3.05**	**(1.96-4.75)**	**4.07**	**(2.57-6.46)**	Age, Sex, Ethnicity,
200~349/μl	196043.6	59	**2.76**	**(1.75-4.35)**	**3.27**	**(2.06-5.18)**	Education, YHD
>=350/μl	250856.9	27	Ref	-	Ref	-	
Unknown	156153.1	13	0.75	(0.39-1.46)	0.84	(0.43-1.65)	
			p-trend	**<0.01**	**p-trend**	**<0.01**	
ART started >90 days Before KS diagnose							
Yes	257047.1	130	**0.68**	**(0.48-0.96)**	**0.39**	**(0.27-0.56)**	Age, Sex, Ethnicity,
No	556191.9	41	Ref	-	Ref	-	Education, YHD, CD4
Year of HIV infection Diagnose							
Before 2003	69670.0	3	**0.15**	**(0.05-0.48)**	**0.10**	**(0.03-0.32)**	Age, Sex, Ethnicity
2003-2007	429660.6	62	**0.47**	**(0.34-0.65)**	**0.47**	**(0.34-0.65)**	
2008 and after	313908.4	106	Ref	-	Ref	-	
			p-trend	**<0.01**	**p-trend**	**<0.01**	

YHD: Year of HIV infection Diagnose

Table 2-3. Characteristics of Uyghur Sub-cohort among HIV/AIDS Population in China

Characteristics	Categories	N	%	Person-Years	%	KS (N)
Age	15-29	9488	34.2	18072.0	31.3	7
	30-44	16522	59.5	36499.4	63.1	28
	45-59	1491	5.4	2803.1	4.8	8
	60+	281	1.0	429.6	0.7	0
Sex	Male	18232	65.6	38821.1	67.2	31
	Female	9550	34.4	18982.9	32.8	12
Education	Illiteracy	2300	8.3	4222.7	7.3	7
	Primary School	8918	32.1	18190.1	31.5	13
	Junior School	8291	29.8	17018.3	29.4	18
	High School	3004	10.8	6225.2	10.8	5
	College and Higher	1203	4.3	2189.5	3.8	0
	N/A	4066	14.6	9958.2	17.2	0
Marriage	Married	13525	48.7	28387.8	49.1	26
	Unmarried	6654	24.0	13689.3	23.7	4
	Divorced or Widowed	5109	18.4	10064.3	17.4	12
	N/A	1776	6.4	3885.2	6.7	1
Transmission	Heterosexual	9713	35.0	17397.8	30.1	21
Routes	IDU	15331	55.2	34993.2	60.5	17
	Blood	34	0.1	76.1	0.1	0
	MSM	55	0.2	78.3	0.1	0
	Sexual + IDU	227	0.8	379.4	0.7	2
	Other/Unknown	2422	8.7	4879.1	8.4	3
Disease Stage	HIV	21966	79.1	42656.2	73.8	15
at diagnosis	AIDS	5816	20.9	15147.8	26.2	28
First CD4 cells count test	<200/μl	6461	23.3	13775.5	23.8	17
after HIV diagnosis	200~349/μl	5511	19.8	12384.0	21.4	16
	>=350/μl	7039	25.3	16642.2	28.8	7
	Unknown	8771	31.6	15002.3	26.0	3
ART started >90 days	Yes	20457	73.6	43554.4	75.3	38
Before KS diagnose	No	7325	26.4	14249.5	24.7	5
Year of HIV Diagnosis	Before 2002	4641	16.7	12261.4	21.2	0
	2003-2007	8540	30.7	24648.1	42.6	10
	2008 and after	14601	52.6	20894.5	36.1	33

Table 2-4a. Risk Factors of Incident Kaposi Sarcoma among HIV-infected Uyghur Cohort in China.

	Person-		Crude Hazard Ratio		Adjusted Hazard Ratio		
Characteristics	**Years**	**KS**	**HR**	**95%CI**	**HR**	**95%CI**	**Adjusted Factors**
Age							
15-29	18072.0	7	0.49	(0.21-1.12)	**0.38**	**(0.17-0.87)**	Sex, YHD
30-44	36499.4	28	Ref	-	**Ref**	-	
45-59	2803.1	8	3.56	(1.62-7.82)	**2.65**	**(1.20-5.83)**	
60+	429.6	0	N/A	-	N/A	-	
Sex							
Male	38821.1	31	1.29	(0.66-2.51)	1.67	(0.85-3.28)	Age, YHD
Female	18982.9	12	Ref	-	Ref	-	
Education							
Illiteracy	4222.7	7	1.53	(0.64-3.67)	1.58	(0.66-3.82)	Age, Sex, YHD
Primary School	18190.1	13	0.67	(0.33-1.38)	0.68	(0.33-1.39)	
Junior School	17018.3	18	Ref	-	Ref	-	
High School	6225.2	5	0.76	(0.28-2.05)	0.68	(0.25-1.83)	
College and Higher	2189.5	0	N/A	-	N/A	-	
N/A	9958.2	0	N/A	-	N/A	-	
Year of HIV infection Diagnose							
Before 2003	12261.4	0	N/A	-	N/A	-	Age, Sex
2003-2007	24648.1	10	**0.26**	**(0.12-0.56)**	**0.24**	**(0.11-0.52)**	
2008 and after	20894.5	33	Ref	-	Ref	-	

Table 2-4b. Risk factor of Incident Kaposi Sarcoma among HIV-infected Uyghur Cohort in China. (Continued)

	Person-		Crude Hazard Ratio		Adjusted Hazard Ratio		
Characteristics	**Years**	**KS**	**HR**	**95%CI**	**HR**	**95%CI**	**Adjusted Factors**
HIV Transmission Routes							
Heterosexual	**17397.8**	**21**	**2.34**	**(1.23-4.45)**	**1.47**	**(0.69-3.10)**	Age, Sex,
IDU	34993.2	17	Ref	-	Ref	-	Education, YHD
Blood	76.1	0	N/A	-	N/A	-	
MSM	78.3	0	N/A	-	N/A	-	
Sexual + IDU	379.4	2	**10.2**	**(2.35-44.21)**	**5.08**	**(1.16-22.26)**	
Other/Unknown	4879.1	3	1.23	(0.36-4.20)	1.06	(0.30-3.76)	
First CD4 cells count test after HIV diagnosis							
<200/μl	13775.5	17	**2.87**	**(1.19-6.91)**	**6.40**	**(2.59-15.80)**	Age, Sex,
200~349/μl	12384.0	16	**3.03**	**(1.25-7.36)**	**4.73**	**(1.93-11.57)**	Education, YHD
>=350/μl	16642.2	7	Ref	-	Ref	-	
Unknown	15002.3	3	0.44	(0.11-1.71)	0.69	(0.18-2.71)	
				p-trend<0.01		**p-trend<0.01**	
ART started >90 days Before KS diagnose							
Yes	14249.5	5	**0.39**	**(0.16-1.00)**	**0.12**	**(0.05-0.32)**	Age, Sex, Education,
No	43554.4	38	Ref	-	Ref	-	YHD, CD4, Route

YHD: Year of HIV infection Diagnose

Chapter 4. Risk Factors of Kaposi Sarcoma among Uyghur Population in Xinjiang, China: a Hospital-based Case-Control Study with Bayesian Analysis

Introduction

Kaposi Sarcoma in Xinjiang

Most Kaposi Sarcoma among HIV-negative population (1-4), and HIV/AIDS-associated KS in China are reported from Uyghur population in Xinjiang (5). In genetic background, Uyghur population was found admixture of Eastern and Western anthropometric traits (6, 7), and classic KS was thought as an endemic disease in the Uyghur population in Xinjiang. Previous studies of KS in Xinjiang were mostly brief case reports (1, 2, 4, 5, 8), only a case-control study with 17 cases (9) explored association between serum IL-6, VEGF and KSHV infection of classic KS in Xinjiang without epidemiologic data.

KSHV infection in Xinjiang

Previous study showed that seroprevalence of KSHV in Uyghur and Kazakh population was higher than in Han population in Xinjiang, and simultaneously, prevalence of KSHV among Han population in Xinjiang (16% to 26%) is much higher (10-12) than that in other regions (13-17) of China. Seroprevalence of KSHV infection in HIV positive population was not independently

reported in the region. In one study of IDU with 90% Uyghur participants, the prevalence of KSHV infection was 31.9% among HIV+ IDUs, (18).

HIV/AIDS in Xinjiang

The first case of the HIV infection in Xinjiang was reported in 1995. Until September 2010, the cumulative numbers of HIV positive individuals or AIDS patients in Xinjiang were 32,532 and the estimated numbers of prevalent HIV infection were about 60,000 (19). The estimated prevalence of HIV in the Xinjiang population was about 0.28%, ranking the second highest province in China. Injection drug use (IDU) and sexual transmission are the two major transmission routes for HIV infection in Xinjiang (20).

We have confirmed in the analysis of national cohort of HIV/AIDS population that HIV-infected Uyghur people also has higher risk of AIDS-KS. However, the national HIV/AIDS surveillance data is a large cohort and does not have detailed behavior and other exposure measure such as tobacco smoking, alcohol drinking, and detailed clinical characteristics for KS are not available in the national database, neither.

Bayesian Analysis

Bayesian analysis calculates posterior distribution with a prior distribution of the parameter and the observed data, and results can be presented with posterior parameters and their n% credible intervals. Subjective conclusion on these statistics will be if one believe the prior is correct, given

current data, one can get a posterior parameter, and one can believe that the probability of the "true parameter" falls in the interval calculated from posterior distribution is n% (21-25). This method has been discussed in the settings of case-control study design (26-28) and cancer epidemiology studies (22, 29). With the prior, Bayesian analysis can incorporate information from various data sources, and it is also a practical tool for bias analysis (21, 23, 30-32). In our study, Bayesian method can is used to check whether the results from two difference sources are consistent with each other.

Hypothesis 3

We hypothesize that due to compromised immunological status by HIV infection, the risk/protective factors of HIV-related Kaposi Sarcoma in Xinjiang Uyghur population might be similar to that of Western countries. Specifically, we hypothesis low CD4 cell count is a risk factor of KS while antiretroviral treatment is a protective factor.

We also hypothesize that most important risk/protective factors associated with Kaposi Sarcoma among HIV-infected Uyghur population will be found with similar results from national surveillance data source and local hospital-based cased control study, and estimations of association are consistent across different data source.

Specific Aim 3

Epidemiology of the HIV-related Kaposi Sarcoma in Xinjiang, a hospital-based case-control study with Bayesian analyses

We studied epidemiological risk/protective factors for HIV-related Kaposi Sarcoma in Xinjiang in a hospital-based case-control study. Related factors including Social-demographic characteristics, HIV-infection related behavior, Substance Abuse, Year of HIV diagnosis, HIV transmission routes, CD4 cell counts and Antiretroviral Treatment, and Co-infections such as HBV, HCV, and Tuberculosis. Furthermore, Bayesian analyses with priors from the Uyghur cohort in national HIV/AIDS surveillance system will be used to test and combine the two study results together.

Methods

Study Design

A hospital-based, individually matched case-control study was designed and conducted in Xinjiang Uyghur Autonomous Region Hospital of Infectious Diseases (XJHID). All subjects enrolled in this study were given an informed consent that translated in Uyghur by local physicians or nurses.

Cases and Controls

Kaposi Sarcoma cases were selected from cases newly diagnosed or referred to the hospital during February 2012 to January 2013. Enrollment criteria were aged≥18, from all ethnic groups and in stable condition for a 30-minitue face-to-face interview. In research protocol, for each case, 4 matched controls were randomly selected from individuals who were enrolled in the HIV/AIDS treatment program in the XJHID, who seek medical services for diseases other than KS or other tumors, and who understood and gave informed consent. The controls were individually matched to cases with ratio of 1:4 by age (±3 years, and≥18), gender and ethnic group.

Interview

A face-to-face interview was conducted for cases and controls using a structured questionnaire, which includes information on lifestyle, medical history with the following parts: diagnosis, demographic characteristics, medical history, family history of cancers, brief history of alcohol

drinking, cigarette smoking, dietary history, drug abuse and sexual behavior, history of physical activity and sun exposure. Average time of interview was about 30 minutes.

Medical Chart Review

We reviewed medical charts of all cases and controls. Medical records of current clinical manifestation, pathological diagnosis, and symptoms related to KS, HIV/AIDS, hepatitis viruses infection and other test findings were collected.

Statistical Analysis

Description

Descriptive analysis was used to describe characteristics using frequency for count data and means ± standard deviation for continuous data. Potential HIV transmission routes were inferred from sexual behavior and drug use history.

Association Analyses

In practice, not every KS cases were matched with 4 controls. Especially for cases aged over 50 years old, less controls were found because less elder HIV/AIDS patients in the hospital. So cases with similar age (±3 years) and same sex were combined in groups and their matched controls were also combined in the matching group. Totally 17 matched group pairs were finalized and the data was analyzed as an M:N matched case-control study design using Conditional Logistic Regression Models to estimate odds ratios of potential risk factors under study.

In all associational analyses, we first used univariate models to detect crude association and then use multivariable models to adjust confounding factors, and all variables were input as categorical variables. Factors analyzed include education (≤Primary School, Junior School, and ≥High School), marriage (Married, Unmarried, Divorce/Widowed), residence area (Urumqi, Other Area), residence type (Urban, Rural), monthly income (0-300RMB, 301-1139RMB, ≥1400RMB), Year of HIV diagnosis (Before 2008, 2008 and later), potential HIV transmission routes (IDU, Heterosexual, Heterosexual + IDU. Participants ever had 1) commercial sex partner or 2) unprotected sex with non-fixed, non-commercial partner or 3) more than 5 sexual partners were set as had potential heterosexual transmission risk. Participants had sexual transmission risk and history of share needles were classified as Hetrosexual+IDU), cumulated sexual partner number (1, 2~5, >5, missing), tobacco smoking (never, ever, missing), cumulated pack-years (0, 1-20, ≥(0, 1-20, p), alcohol drinking (never, ever), drink quantity every day (0, <1/day, ≥1 /day, Missing), ever had antiretroviral treatment (>90 days before KS diagnose, Yes/No), CD4 cell count before antiretroviral treatment (≥ 350/μl, 200~349/μl, <200/μl, Missing), current CD4 cell count (≥ 350/μl, 200~349/μl, <200/μl, Missing), history of HBV (Yes/No), HCV (Yes/No) , Tuberculosis infection (Yes/No), and other AIDS related manifestations (Yes/No, If one have at least on of following manifestations: consistent low fever over 1 month with unspecified reason, edema of lymph node, chronic diarrhea over 3/day, body weight loss >10% in 3 months, oral or organ Candida infection, Pnumocystis Carinii Pneumonia, Infection of human cytomegalovirus, Toxoplasma encephalopathy, Cryptococcus infection, pneumonia or meningitis, Septicemia,

Recurrent bacteria pneumonia, Non-Hodgkin Lymphoma, Recurrent herpes infection, and Dementia at young or middle age). Different confounding factors set were chosen for different estimation, and major confounding factors enrolled include age, sex, Year of HIV diagnose, area, ever had ART, potential HIV transmission routes, CD4 cell count before ART. Because Year of HIV diagnose, area, tuberculosis and other AIDS related manifestations were thought to be associated with selection process of get treatment in study hospital, these variables were also used as indicator of selection bias and are adjusted in some models.

Missing Data

In analysis of original data, all variable with missing values were used as categorical variable and missing values were coded as missing group and were included in all regression models. Multiple imputations method then used to evaluate impact of missing values. With the assumption of missing at random (MAR), we imputed missing data 50 times with fully conditional specification method (33-35), and each variable with missing were assigned with a predictive model using predictive mean matching method(34). Detailed predicted models are following models in Table 3-0. For every variable of interest, we get estimates from each imputation and combined into final estimates(36).

Bayesian Analysis

Estimated adjusted HRs in the Uyghur sub-cohort in the national AIDS surveillance data (Part II) were used as original priors for Bayesian analysis of Xinjiang study data. Adjusted HRs and

confidence intervals were logarithm transformed to coefficients its variance as prior distribution.

For every factors of interest, the informative priors from national Uyghur cohort result were imputed in the form of dummy variables for each categorical variable, and imputed priors include coefficients of HIV diagnosed 2003-2007 vs. 2008 and later, Heterosexual only vs. IDU only, Heterosexual plus IDU vs. IDU only, ever IDU vs. heterosexual only, CD4 cell count <200/μL vs. ≥350/μL, CD4 cell count 200~349/μL vs. ≥350/μL and ever ART (>90 days before KS diagnose) vs. no ART. Non-informative priors (coefficient=0, variance=10^6) were set for all other covariates in the model including age, sex, residence area, Year of HIV diagnosis, IDU and recent CD4 cell count. Markov Chain-Monte Carlo (MCMC) method was used to simulate posterior distribution of odd ratios given prior (25, 37). Totally 5000 times of simulation were performed in each model, and 95% credible intervals were built from the 2.5^{th} and 97.5^{th} percentile of simulated posterior odds ratios. To check the impact of imputed prior, sensitivity analysis for strength of priors we also run using parallel Bayesian models with one non-informative/flat prior, another 3 priors with same coefficient with the original but flattered variance, including 2 times, 4 times and 8 times of original prior variance. Maximum likelihood estimation (MLE) of log odds ratios in conventional analysis and posterior distribution of Bayesian models with different priors were compared in plots of distribution density.

Bayesian analysis was also performed in data with multiple imputations. For each variable of interest, we run same Bayesian models with 5000 time MCMC simulation at each imputation data

to get 50 posterior log odds ratios and standard deviation of the estimates, and we combined these posterior log odds ratio estimates with similar method in conventional multiple imputations models. Maximum likelihood estimation (MLE) of log odds ratios in conventional analysis with and without multiple imputations and posterior distribution of Bayesian models with different priors with multiple imputations were compared in plots of distribution density.

All statistical analyses were finished using the SAS 9.3 software (SAS Inc. NC) (37).

Results

During the study period totally 41 KS cases meet the study criteria. Finally 40 cases and 94 controls were collected. Among them, one case and one control of Kazakh ethnic were not included in the analyses due to lack of participants from the Kazakh population, and all 39 KS cases and 93 controls in the final analysis were Uyghur ethnic.

Demographics

Two thirds (26/39) of these KS cases were males and one third were females. The average age of all cases was 40.8±8.4 years old, and most of them had education of junior middle school or lower. Twelve of these cases were residents of Urumqi, the capital city of Xinjiang region, and 27

came from other areas. 31 of them lived in urban areas, and 8 of them lived in rural areas. Demographic characteristics were presented in Table 3-1.

Associations between age and sex were not estimated because they are matching variables. We did not find obvious association between education, marriage, residence type (urban vs. rural) and KS neither in the original data nor in the multiple imputation models. Not living in the capital city Urumqi were found to be positively associated with KS incidence, with OR 3.73 (95%CI 1.71-8.13) for participants from other area vs. residents of Urumqi. Participants with monthly income higher than 300 RMB Yuan/Month (the social security stipend) and less than 1140 Yuan/Month (local minimum wage per month) were found higher odds of KS (adjusted OR 4.14 95%CI 1.06-16.17) (Table 3-6-1).

Clinical Manifestations of KS

Among the 39 cases, over half cases (23/39) were diagnosed based on clinical manifestation and 16 cases had pathologic confirmation. All KS cases had cutaneous lesions, and the most frequently affected location was skin of lower limbs. There were 2 cases were found lesions in trachea/lung by bronchoscopy, and 9 were found had KS in oral mucosa. Thirteen of these cases, including 10 males and 3 females, were diagnosed with KS before they had HIV test, and 2 cases had antiretroviral treatment less than 90 days before KS diagnose. Details of clinical manifestation of KS cases were shown in Table 3-2.

HIV Diagnose and Antiretroviral Treatment

There were 6 KS case and 27 controls were diagnosed with HIV infection before 2008, and 33 KS cases and 66 controls were diagnosed in 2008 or later. Adjusted OR for participants with HIV diagnosed before 2008 vs. 2008 and later was 0.53 (95%CI 0.19-1.49) (Table 3-6-2).

There were 7 KS cases and 33 controls ever had antiretroviral treatment (for KS cases, >90 days before KS diagnose), and 32 KS cases and 60 controls did not have ART. Had ART was found adjusted OR of 0.28 (95%CI 0.08-0.97) (Table 3-6-4).

HIV infection related behaviors

Sexual Behavior

All cases and controls reported heterosexual intercourse. Over 90% participants had fixed heterosexual partner or spouse, and over 75% of them never use condom when have sex with fixed partner. Having commercial sex was popular among male subjects, with 50.0% (13/26) and 47.1% (24/51) in male cases and controls, respectively. Condom use in study subjects was very low when they have sex with commercial sex workers, and about 84.6% (11/13) of male cases and 50.0% (12/24) of male controls never used condom when they had sex with commercial sex workers. Non-commercial casual partners were also high in male participants, with 53.8% (14/26) in cases and 41.2% (21/51) in controls. Most of subjects (64%, 25/39 of cases and 58% 54/93 of controls) started having sex before 18 years old, and about 10% (4/39) of cases and 20% (19/93) of controls had first sex intercourse before 15 years old. Over 46% (18/39) of cases and about 41%

(38/93) of controls had more than 2 sexual partners. More female participants (61.5% in cases, 57.1 in controls) reported only one partner than males (34.6% in cases and 25.5 in controls). No males subject reported ever had sex with men. Details of sexual behavior were shown in Table 3-4-1.

Drug Abuse

Abuse of drug, in most cases, heroin, was prevalent among all subjects. KS subjects had less drug use history, and more male subjects (42.3% male cases, 84.3% male controls) were drug abuse than females (15.4% female cases, 40.5% female controls). Over 90% of these drug users were intravenous drug users (IDU), and over 90% of IDUs had shared needles with other IDUs. For female participants, 30.8% (4/13) cases and 54.8% (23/42) controls' spouse or fixed partners were drug users (Table 3-4-2).

Potential HIV Transmission Routes

Comparing with IDU only, participants with potential heterosexually transmission of HIV had a crude odds ratio of 4.22 (95%CI 1.54-11.58), however, the aOR was 2.57 (95%CI 0.85-7.74), adjusting Year of HIV diagnosis, education and area. We did not find obvious association between cumulated heterosexual partner and KS. (Table 3-6-2).

Tobacco Smoking and Alcohol Drinking

Tobacco smoking was prevalent in male subjects and 69% male cases and 78% male controls ever smoked at least 1 cigarette per day, at least half a year. In females, 23% cases (3/13) and 29% controls (12/42) ever smoked. Cigarette smoking per day, duration of smoking and calculated pack-years were presented in Table 3-4-3.

Alcohol drinking was highly prevalent among male subjects, and most female subjects reported as never drinker. There were 11.5% of male cases and 7.8% of male controls drank over 5 drinks per day (one drink calculated as 14 grams pure alcohol from combined drinks). Details of alcohol drinking history were presented in Table 3-4-4. No obvious association was found between tobacco smoking, alcohol drinking and KS incidence (Table 3-6-3).

CD4 Cell Count and Plasma HIV Viral Load (VL)

We only got most recent CD4 cell count from the medical chart review. Most of all subjects had CD4 cell count lower than 350/μL and about half of all subjects were lower than 200/μL, and some CD4 count tests were tested after initiation of ART. There were very limited records for viral load test and most of them were tested before ART. In viral load test after ART, one female control had VL higher than 1000 copies/mL. Details of CD4 cell count and viral load test were presented in Table 3-5-2. No obvious association was found in recent CD4 cell count before ART or current CD4 cell count, and no obvious association was found in HIV viral load because of extremely limited VL records (Table 3-6-4).

Other HIV/AIDS related Clinical Manifestations and Co-infections

Over half of all subjects were diagnosed active tuberculosis (38.5% 10/26 in male cases, 62.7% in male controls; 46.2% in female cases and 61.9% in female controls), which was followed by chronic diarrhea. Hepatitis C Virus (HCV) infection history was prevalent among all subjects, with 34.6% in male cases and 78.4% in male controls, 38.5% in female cases and 57.1% in female controls, respectively. Prevalence of HBV infection history was between 15.4% in male case, 15.4% in female cases, 13.7 in male controls and 4.8 in female controls, and prevalence of syphilis infection history was from 5.9% to 15.4%. Details of other HIV/AIDS related clinical manifestations and co-infections were presented in Table 3-5-1.

Association was found in crude OR of HCV infection (OR 0.24, 95%CI 0.10-0.55) and Tuberculosis (OR 0.41 95%CI 0.19-0.89), but not in adjusted models. No obvious association was found between other AIDS related manifestations and KS (adjusted OR 0.72 95%CI 0.28-1.85) (Table 3-6-5).

Other Clinical Laboratory Tests

Among participants with recent serum test for hepatitis infection, 7.1% (1/14) male case, 12.5% (4/32) male controls, 0 female cases and 3.1% (1/32) female controls were found positive in HBV surface antigen (HBsAg). 44.4% (8/18) of male cases, 82.2% (37/45) male controls, 33.3% (4/12) female cases and 54.1% (20/37) female controls who got HCV test were found HCV antibody

positive. Detailed clinical laboratory tests in current inpatient treatment were presented in Table 3-5-3, 3-5-4.

Multiple Imputation of Missing Data

Odds ratios and their 95% confidence intervals estimated using multiple imputation models did not change much from conventional conditional logistic regression models (Tables 3-6-1 to 3-6-5).

Bayesian Analysis

With original priors from the Uyghur cohort in National database, posterior odds ratios (pstOR) of HIV diagnosed before 2008 vs. HIV diagnosed 2008 and later was 0.31, with 95% credible interval (95% CredI 0.16-0.58). PstOR for participants with heterosexual transmission of HIV vs. IDUs only was 1.56, (95% CredI 0.59-4.27). Ever had antiretroviral treatment (>90 days before KS diagnose) was found with pstOR 0.13 (95% CredI 0.05-0.29) (Table 3-7-1, 3-7-2). Sensitivity analysis showed for previous models on Year of HIV diagnosis, heterosexual vs. IDU, antiretroviral treatment, center of posterior distributions did not change much between the models with non-informative prior and informative prior, however, the credible interval got improved with different informative priors (Table 3-7-1, 3-7-2, Figures 3-1, 3-2-1, 3-3-1). In Bayesian analysis in multiple imputation data of antiretroviral treatment and its sensitivity analysis, we also found estimates were stable across different priors. (Table 3-7-1, 3-2-2). However, estimates of heterosexual+IDU vs. IDU were found changed a lot because of the difference between MLE and

original prior (Table 3-7-2, Figure 3-3-2).

Imputed informative prior changed estimations on the posterior distributions of OR on CD4 cell count before ART (Table 3-7-3, Figure 3-4-1, 3-4-2), and comparing with participants with CD4 cell count ≥350/μL, estimated posterior OR for those with recent CD4 cell count <200/μL was 4.40 (95%CredI 2.12-9.23), and OR for those with CD4 between 200 and 349//μL was 3.59 (95%CredI 1.68-7.74) (Table 3-7-3). Bayesian models with multiple imputation were also gave similar estimates. Sensitivity analysis showed difference between original priors and MLE estimates in conventional models, and posterior estimates changes with the strength of priors (Table 3-7-3, Figures 3-4-1, 3-4-2). Bayesian models and sensitivity analysis with multiple imputations showed similar pattern in posterior odds ratios of CD4 cell count before ART (Table 3-7-3, Figures 3-4-3, 3-4-4).

Discussion

As we had confirmed that HIV-infected Uyghur population is of high risk of Kaposi Sarcoma in Chapter 3 of this study, in this part, we further described demographic and behavior characteristics of AIDS-KS patients in HIV-infected Uyghur population in Xinjiang.

Similar as other studies, antiretroviral treatment was found negatively associated with Kaposi Sarcoma incidence (38-44). Late diagnosis and consequent late initiation of ART is still a big issue in the current health care of HIV/AIDS in China, especially in source-limited areas such as Xinjiang. In our study, about 33% (13/39) KS cases got HIV diagnosis after the KS, which indicates potentially late diagnosis, considering KS usually occurs in relatively late stage of HIV/AIDS. Simultaneously, epidemic of Tuberculosis is much higher in Xinjiang than in other areas in China (45, 46), and high proportion of Pulmonary TB, followed by Tuberculosis pleurisy and meningitis, are also common among people living with HIV in Xinjiang. In our study, 10 out of 26 males and 6 out of 13 females were diagnosed with KS and active TB simultaneously, and prevalence of TB in controls was even higher (Table 5.1). In current practice in China, ART is suggested after the stabilization of proper TB chemotherapy (47), and delayed ART will inevitably bring big challenge to both incidence and survival of AIDS-KS. Our finding, as well as results in Part II, indicates the importance of systematic ART in Xinjiang will help reduce KS among HIV-infected Uyghur population.

Multiple sex partners, unprotected sex, as well as drug use were highly prevalent among both KS cases and controls in our study. We found IDUs had lower odds ratio of KS than sexually transmitted subjects, which is similar with previous studies (48-50) as well as our findings in the national cohort analysis in Part II. Due to limited sample size, the estimated confidence interval of the odds ratio was not tested significant in the conventional models, and in Bayesian analysis we found it is consistent using priors from the national data analysis.

Although former studies implied potential negative association between smoking and classic KS and AIDS-KS (51), lower but non-significant odds ratios were found in cigarette smokers (Table 3-6-3). If such negative association exists in AIDS-KS, high prevalence of tobacco smoking among males in our study may cover up the association.

This hospital-based case control study in Xinjiang further explored epidemiologic factors in his population. However, results from our hospital-based case-control study are constrained by its power. HIV-infected Uyghur cohort in the national AIDS surveillance system is now the best available data for all HIV-infected Uyghur population. With tools of Bayesian analysis, multiple imputations, and sensitivity analysis, we compared findings from two different data sources in different study designs and get higher confidence in our results from small-sized local study that was consistent with national cohort. Difference in the estimation of potential HIV transmission routes (Heterosexual+IDU vs. IDU) between our local study and national cohort may be attributed to different classification method in evaluating potential transmission routes based on subject's risk behavior. Difference in estimation was also found in the CD4 cell counts before ART and KS. The sensitivity analysis showed disparity both in study power and estimates, which indicate further improvement in our study, and potential bias in our hospital-based case-control and will be discussed in the limitations of this study.

Limitation of the Study

The Xinjiang Hospital of Infectious Diseases is a newly built hospital specialized in infectious diseases, and it is the clinical quality-control center for ART in Xinjiang. However, it does not have its own department of pathology, and diagnosis of Kaposi Sarcoma is based on clinical manifestation or pathology reports from other comprehensive medical centers.

Major bias is possible due to the small sample size and power of association we found could be not sufficient. Also disparity between actual source population of cases and represented population of the controls, and selection bias is very possible in this hospital-based case-control study. For instance, we did not find significant association between most recent CD4 cell count level and KS incidence, and magnitude of association between ART and KS was smaller than previous studies (48, 51-57). The source of controls, inpatient subjects in our study, may represent patients in more sever status, for instance, patients with active tuberculosis and more AIDS related manifestations were tend to be selected into this hospital, and CD4 cell level among controls may be lower than all HIV-infected Uyghur people. Similarly, because the hospital locates in the capital city Urumqi, most of inpatients are local residents. Most of these Urumqi AIDS patients have been enrolled in the social security stipend for catastrophic diseases including HIV/AIDS (300 RMB Yuan/Month, plus free antiretroviral and anti-Tuberculosis treatment, and up to 18,000 RMB Yuan per year for inpatient treatment). However, medical insurance in other city could not cover all the treatment in XJHID except for free ART and anti-TB regime, and

patients from other city may be richer than local patients. Thus, differences in social and economic status may highly be correlated with area difference.

However, due to small sample size, we may not control all these factors in our current study, and we controlled year of HIV diagnose, residence area, Tuberculosis and other AIDS related manifestations as strong associated factor of selection in hospital. Considering lower CD4 cell count and ART are known to be one of the strongest associated factors of KS among HIV-infected people, estimations in CD4 and ART in our study should be biased towards the null.

In summary, among HIV-infected Uyghur population, the strongest protective factor related to Kaposi Sarcoma was early antiretroviral treatment, and we believe continued service of HIV care and antiretroviral treatment could be most important method to reduce incidence of KS among HIV-infected Uyghur people. Intravenous drug users were found had lower odds of KS than sexually transmitted subjects, and further study examine opiate drug use and angiogenesis related disease will be helpful to explain current epidemiological findings.

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Tables

Table 3-1. Imputation Models of Missing Data in Uyghur Subjects in Xinjiang Study

Variable with Missing	Imputation Model
Education	age, sex, area, residence type
Monthly income	age, sex, area, residence type, education
CD4 cell count before ART	age, sex, area, residence type education, year of HIV diagnose, HIV transmission route, Kaposi Sarcoma, Tuberculosis, Other AIDS related manifestations
Current CD4 cell count	age, sex, area, residence type education, year of HIV diagnose, HIV transmission route, Kaposi Sarcoma, Tuberculosis, Other AIDS related manifestations, antiretroviral treatment
Commercial sex partner	age, sex, area, residence type, education, HIV transmission route
Cumulated sex partner number	age, sex, area, residence type, education, HIV transmission route
Tobacco Smoking	age, sex, area, residence type, education, HIV transmission route, Alcohol Drinking
Pack-years	age, sex, area, residence type, education, HIV transmission route, Tobacco Smoking, Alcohol Drinking
Alcohol Drinking	age, sex, area, residence type, education, HIV transmission route, Tobacco Smoking
Daily Alcohol Consumption	age, sex, area, residence type, education, HIV transmission route, Tobacco Smoking, Alcohol Drinking

Table 3-2. Demographic Characteristics among Kaposi Sarcoma Cases and Controls in HIV-infected Uyghur Subjects in Xinjiang Study

Characteristics	Categories	KS (n=39)	%	Control (N=93)	%
Age	<=30	2	5.1	9	9.7
	31-40	23	59.0	55	59.1
	41-50	8	20.5	23	24.7
	51-60	5	12.8	6	6.5
	60+	1	2.6	0	0.0
Sex	Male	26	66.7	51	54.8
	Female	13	33.3	42	45.2
Education	≤Primary School	14	35.9	29	31.8
	Junior School	13	33.3	36	38.7
	≥High School	9	23.1	9	9.7
	N/A	3	7.7	19	31.8
Marriage	Married	24	61.5	51	54.8
	Unmarried	2	5.1	28	30.1
	Divorced/ Widowed	13	33.3	14	15.1
Residency	Urumqi	12	30.8	62	66.7
	Other	27	69.2	31	33.3
Residency Type	Urban	31	79.5	83	89.2
	Rural	8	20.5	10	10.8
Occupation	Worker	2	5.1	3	3.2
	Farmer	8	20.5	7	7.5
	Office Staff	3	7.7	2	2.2
	Business	6	15.4	17	18.3
	Civil Service	6	15.4	8	8.6
	Service	4	10.3	6	6.5
	Housewife	1	2.6	13	14.0
	Unemployed	8	20.5	35	37.6
Monthly Income (RMB Yuan)	0-300	22	56.4	81	87.1
	301-1140	8	20.5	4	4.3
	1141+	7	17.9	5	5.4
	N/A	2	5.1	3	3.2

N/A: Not Available

Table 3-3. Clinical Manifestations of Kaposi Sarcoma Cases in in Xinjiang Study

	Male (N=26)		Female (N=13)	
	N	%	N	%
Sites **Skin:** Any	26	100.0	13	100.0
Lower Limbs	25	96.2	12	92.3
Upper Limbs	15	57.7	10	76.9
Body	13	50.0	8	61.5
Head & Neck	14	53.8	4	30.8
Organs: Lung	1	3.8	1	7.7
Oral Mucosa	6	23.1	3	23.1
Lymph nodes: Any	1	3.8	1	7.7
Lower Limbs	0	0.0	1	7.7
Upper Limbs	1	3.8	0	0.0
Head & Neck	1	3.8	0	0.0
Time of HIV Diagnose				
Before 2008	3	11.5	3	23.1
2008 and after	23	88.5	10	76.9
Time between HIV and KS diagnose				
KS Dx before HIV Dx	10	38.5	3	23.1
KS Dx 1-6 Months after HIV Dx	6	23.1	0	0.0
KS Dx 7 Month-1 Year after HIV Dx	3	11.5	2	15.4
KS Dx 1Year-5 Years after HIV Dx	6	23.1	6	46.2
KS Dx >5 Years after HIV Dx	1	3.8	2	15.4
Ever had ART	4	15.4	6	46.2
Time between ART and KS diagnose				
ART started >90 days before KS Dx	3	75.0	4	66.6
ART started ≤90 days before KS Dx	**1**	**25.0**	**0**	**0.0**
ART started after KS Dx	0	0.0	1	16.7
Missing	0	0.0	1	16.7
Ever had ART, >90 Days before KS Diagnose				
Yes	3	11.5	4	44.4
No	23	88.5	9	55.6
KS Diagnose Department				
Infectious Disease	20	76.9	11	84.6
Surgery	6	23.1	2	15.4
Diagnose Criteria				
Pathology	8	30.8	8	61.5
Clinical	18	69.2	5	38.5

Table 3-4-1. Sexual Behavior among Kaposi Sarcoma Cases and Controls in HIV-infected Uyghur Subjects in Xinjiang Study

		Overall		Male				Female			
		KS (n=39)	Control (n=93)	KS (n=26)	%	Control (n=51)	%	KS (n=13)	%	Control (n=42)	%
Ever had heterosexual behavior		39	93	26	100	51	100	13	100	42	100
Ever have spouse/fixed partner		39	88	26	100	46	90.2	13	100	42	100
Condom use when have sex with spouse/fixed partner	Never	31	72	21	80.8	38	74.5	10	76.9	34	81
	Sometimes	6	14	3	11.5	6	11.8	3	23.1	8	19
	Always	1	2	1	3.8	2	3.9	0	0	0	0
Had commercial partner		13	27	13	50	24	47.1	0	0	3	7.1
Condom use when have sex with commercial heterosexual partner	Never	11	12	11	84.6	12	50	-	-	0	0
	Sometimes	1	6	1	7.7	4	16.7	-	-	2	66.7
	Always	1	7	1	7.7	6	25	-	-	1	33.3
Had non-commercial casual partner		17	31	14	53.8	21	41.2	3	23.1	10	23.8
Condom use when have sex with non-commercial casual partner	Never	9	20	8	57.1	15	71.4	1	33.3	5	50
	Sometimes	5	5	4	28.6	4	19	1	33.3	1	10
	Always	2	2	2	14.3	2	9.5	0	0	0	0
Age, First Heterosexual Behavior	<15	4	19	4	15.4	10	19.6	0	0	9	21.4
	15-18	21	35	13	50	20	39.2	8	61.5	15	35.7
	>18	14	39	9	34.6	21	41.2	5	38.5	18	42.9
Cumulated heterosexual Partners	1	17	37	9	34.6	13	25.5	8	61.5	24	57.1
	2~5	13	15	10	38.5	9	17.6	3	23.1	6	14.3
	>5	5	23	5	19.2	18	35.3	0	0	5	11.9
	N/A	4	18	2	7.7	11	21.6	2	15.4	7	16.7
Ever had homosexual behavior		0	0	0	0	0	0	0	0	0	0

Table 3-4-2 Drug abuse and Blood Transfusion among Kaposi Sarcoma Cases and Controls in HIV-infected Uyghur Subjects in Xinjiang Study

		Overall		Male				Female			
		KS cases (n=39)	Controls (n=93)	KS (n=26)	%	Control (n=51)	%	KS (n=13)	%	Control (n=42)	%
Ever used drug	Yes	13	60	11	42.3	43	84.3	2	15.4	17	40.5
	No	25	32	14	53.8	8	15.7	11	84.6	24	57.1
	Missing	1	1	1	3.8	0	0	0	0	1	2.4
Duration of drug use	1-10y	4	16	4	36.4	10	23.3	0	0	6	35.3
	11-20y	8	33	6	54.5	25	58.1	2	100	8	47.1
	20y+	1	8	1	9.1	5	11.6	0	0	3	17.6
	Missing	0	4	0	0	3	7	0	0	1	5.9
Ever injected drug	Yes	12	55	10	90.9	39	90.7	2	100	16	94.1
	No	1	5	1	9.1	4	9.3	0	0	1	5.9
Duration of drug injecting	1-10y	6	30	6	60	23	59	0	0	7	43.8
	11-20y	5	22	4	40	13	33.3	1	50	9	56.3
	Missing	1	3	0	0	3	8.7	1	50	0	0
Ever shared needle	Yes	10	53	9	90	37	94.9	1	50	16	100
	No	2	2	1	10	2	5.1	1	50	0	0
Is Spouse/fixed partner a drug user?	Yes	6	25	2	7.7	2	5.1	4	30.8	23	54.8
	No	21	50	16	61.5	37	72.5	5	38.5	13	31
	Missing	12	18	8	30.8	12	23.5	4	30.8	6	14.3
Blood Transfusion Before HIV diagnose	Yes	2	5	0	0	1	2	2	15.4	4	9.5
	No	37	88	26	100	50	98	11	84.6	38	90.5

Table 3-4-3 Tobacco Smoking among Kaposi Sarcoma Cases and Controls in HIV-infected Uyghur Subjects in Xinjiang Study

		Overall		Male				Female			
		KS (n=39)	Control (n=93)	KS (n=26)	%	Control (n=51)	%	KS (n=13)	%	Control (n=42)	%
Tobacco Smoking	Ever Smoked	21	52	18	69.2	40	78.4	3	23.1	12	28.6
	Never	16	29	6	23.1	6	11.8	10	76.9	23	54.8
	Missing	2	12	2	7.7	5	9.8	0	0	7	16.7
Cigarettes/day	Non-smoker	16	29	6	23.1	6	11.8	10	76.9	23	54.8
	1-10/day	7	15	5	19.2	12	23.5	2	15.4	3	7.1
	11-20/day	7	20	6	23.1	13	25.5	1	7.7	7	16.7
	20+/day	7	15	7	26.9	14	27.5	0	0	1	2.4
	Missing	2	14	2	7.7	6	11.8	0	0	8	19
Duration of	Non-smoker	16	29	6	23.1	6	11.8	10	76.9	23	54.8
Smoking	1-10 Years	2	5	1	3.8	2	3.9	1	7.7	3	7.1
	11-20 Years	8	23	8	30.8	17	33.3	0	0	6	14.3
	20+ Years	9	10	7	26.9	10	19.6	2	15.4	0	0
	Missing	4	26	4	15.4	16	31.4	0	0	10	23.8
Pack-years	Non-smoker	16	29	6	23.1	6	11.8	10	76.9	23	54.8
	1-10 pky	5	14	4	15.4	9	17.6	1	7.7	5	11.9
	11-20 pky	8	12	6	23.1	8	15.7	2	15.4	4	9.5
	21-30 pky	3	7	3	11.5	7	13.7	0	0	0	0
	30+ pky	3	4	3	11.5	4	7.8	0	0	0	0
	Missing	4	27	4	15.4	17	33.3	0	0	10	23.8
Passive	Yes	12	41	8	30.8	20	39.2	4	30.8	21	50
Smoking in	No	12	18	9	34.6	17	33.3	3	23.1	1	2.4
Family	Missing	15	34	9	34.6	14	27.5	6	46.2	20	47.6

Table 3-4-4 Alcohol Drinking among Kaposi Sarcoma Cases and Controls in HIV-infected Uyghur Subjects in Xinjiang Study

		Overall		Male				Female			
		KS (n=39)	Control (n=93)	KS (n=26)	%	Control (n=51)	%	KS (n=13)	%	Control (n=42)	%
Alcohol Drinking	Never	16	42	5	19.2	14	27.5	11	84.6	28	66.7
	Ever	21	34	19	73.1	27	52.9	2	15.4	7	16.7
	Missing	2	17	2	7.7	10	19.6	0	0	7	16.7
Drink per day	Never	16	42	5	19.2	14	27.5	11	84.6	28	66.7
	<1 drinks/day	5	18	5	19.2	13	25.5	0	0	5	11.9
	1-5 drinks/day	13	12	11	53.8	10	19.6	2	15.4	2	4.8
	>5 drinks/day	3	4	3	11.5	4	7.8	0	0	0	0
	Missing	2	17	2	7.7	10	19.6	0	0	7	16.7
Duration of Alcohol Drinking	Never	16	42	5	19.2	14	27.5	11	84.6	28	66.7
	1-10 Years	4	8	4	15.4	6	11.8	0	0	2	4.8
	11-20 Years	11	18	9	34.6	14	27.5	2	15.4	4	9.5
	20+ Years	3	4	3	11.5	3	5.9	0	0	1	2.4
	Missing	5	21	5	19.2	14	27.5	0	0	7	16.7

Table 3-5-1. Clinical manifestations and co-infections in Xinjiang Study

Complexities and Co-infections	Overall		Male				Female			
	KS (n=39)	Control (n=93)	KS (n=26)	%	Control (n=51)	%	KS (n=13)	%	Control (n=42)	%
Clinical manifestations										
Low-fever, >1 month	2	5	1	3.8	4	7.8	1	7.7	1	2.4
Lymph node	3	3	2	7.7	1	2	1	7.7	2	4.8
Chronic Diarrhea, Bodyweight Drop >10% in 3 Months	6	4	5	19.2	4	7.8	1	7.7	0	0
Mucocutaneous Candidiasis	2	6	2	7.7	4	7.8	0	0	2	4.8
Pneumocystis Pneumonia.	1	3	1	3.8	1	2	0	0	2	4.8
Cytomegalovirus Disease	2	3	1	3.8	3	5.9	1	7.7	0	0
Toxoplasma gondii Encephalitis.	0	3	0	0	2	3.9	0	0	1	2.4
Repeated Bacterial Pneumonia	2	6	1	3.8	2	3.9	1	7.7	4	9.5
Lymphomas	1	1	1	3.8	1	2	0	0	0	0
Tuberculosis	**16**	**58**	**10**	**38.5**	**32**	**62.7**	**6**	**46.2**	**26**	**61.9**
Herpes Zoster	1	1	1	3.8	1	2	0	0	0	0
Progressive Multifocal Leukoencephalopathy	0	2	0	0	2	3.9	0	0	0	0
Other Co-infections History										
Syphilis	**5**	**6**	**4**	**15.4**	**3**	**5.9**	**1**	**7.7**	**3**	**7.1**
HBV	**6**	**9**	**4**	**15.4**	**7**	**13.7**	**2**	**15.4**	**2**	**4.8**
HCV	**14**	**64**	**9**	**34.6**	**40**	**78.4**	**5**	**38.5**	**24**	**57.1**

Table 3-5-2. CD4 cell Counts and HIV Serum Viral Load among Kaposi Sarcoma Cases and Controls in HIV-infected Uyghur Subjects in Xinjiang Study

Laboratory Tests		Overall		Male				Female			
		KS (n=39)	Control (n=93)	KS (n=26)	%	Control (n=51)	%	KS (n=13)	%	Control (n=42)	%
Recent CD4 cell count	**<200/µl**	**21**	**42**	**14**	**53.8**	**23**	**45.1**	**7**	**53.8**	**19**	**45.2**
	200~349/µl	8	21	6	23.1	10	19.6	2	15.4	11	26.2
	>=350/µl	8	21	6	23.1	12	23.5	2	15.4	9	21.4
	Missing	2	9	0	0	6	11.8	2	15.4	3	7.1
Recent CD4 cell count	**<200/µl**	**16**	**34**	**12**	**46.2**	**18**	**35.3**	**4**	**30.8**	**16**	**38.1**
before ART or no	200~349/µl	5	17	4	**15.4**	10	**19.6**	1	**7.7**	7	**16.7**
ART	>=350/µl	7	13	6	**23.1**	9	**17.6**	1	**7.7**	4	**9.5**
	Missing	**11**	**29**	**4**	**15.4**	**14**	**27.5**	**7**	**53.8**	**15**	**35.7**
Recent CD4 cell count	<200/µl	5	9	2	**7.7**	5	**9.8**	3	**23.1**	4	**9.5**
after ART	200~349/µl	3	5	2	**7.7**	0	**0**	1	**7.7**	5	**11.9**
	>=350/µl	1	9	0	**0**	4	**7.8**	1	**7.7**	5	**11.9**
	Missing	30	70	22	**84.6**	42	**82.4**	8	**61.5**	28	**66.7**
Recent HIV viral load	<1000 cps/ml	5	5	2	7.7	4	7.8	3	23.1	1	2.4
	>= 1000 cps/ml	4	9	3	11.5	4	7.8	1	7.7	5	11.9
	Missing	30	79	21	80.8	43	84.3	9	69.2	36	85.7
Recent HIV viral load	<1000 cps/ml	2	2	2	7.7	2	3.9	0	0	0	0
before ART	>= 1000 cps/ml	4	8	3	11.5	4	7.8	1	7.7	4	9.5
	Missing	33	83	21	80.8	45	88.2	12	92.3	38	90.5
Recent HIV viral load	<1000 cps/ml	3	3	0	0	2	3.9	3	23.1	1	2.4
after ART	>= 1000 cps/ml	0	1	0	0	0	0	0	0	1	2.4
	Missing	36	89	26	100	49	96.1	10	76.9	40	95.2

Table 3-5-3. Clinical Laboratory Tests of Kaposi Sarcoma Cases and Controls in HIV-infected Uyghur Subjects in Xinjiang Study

	Overall		Male				Female			
	KS	Control	KS	%	Control	%	KS	%	Control	%
	(n=39)	(n=93)	(n=26)		(n=51)		(n=13)		(n=42)	
Hepatitis Virus Test										
HBV-Untested	14	29	12	46.2	19	37.3	2	15.4	10	23.8
HBV-Tested	25	64	14	53.8	32	62.7	11	84.6	32	76.2
HBsAg+	1	5	1	7.1	4	12.5	0	0	1	3.1
HBsAb+	7	10	3	21.4	4	12.5	4	36.4	6	18.8
HBeAg+	0	1	0	0	1	3.1	0	0	0	0
HBeAb+	2	4	2	14.3	3	9.4	0	0	1	3.1
HBcAb+	3	4	2	14.3	3	9.4	1	9.1	1	3.1
HCV-Untested	9	11	8	30.8	6	11.8	1	7.7	5	11.9
HCV-Tested	30	82	18	69.2	45	88.2	12	92.3	37	88.1
Anti-HCV+	12	57	8	44.4	37	82.2	4	33.3	20	54.1
Blood Type										
A	10	26	7	26.9	15	29.4	3	23.1	11	26.2
B	10	18	5	19.2	9	17.6	5	38.5	9	21.4
AB	4	11	4	15.4	3	5.9	0	0	8	19
O	9	32	7	26.9	21	41.2	2	15.4	11	26.2
Untested	6	6	3	11.5	3	5.9	3	23.1	3	7.1

Table 3-5-4. Recent Blood Cell Counts among Kaposi Sarcoma Cases and Controls in HIV-infected Uyghur Subjects in Xinjiang Study

Blood Cell Type	Male						Female					
	Case (N=26)			Control (N=51)			Case (N=13)			Control (N=42)		
	N	Mean	S.D.	N	Mean	S.D.	N	Mean	S.D.	N	Mean	S.D.
Hemoglobin g/L	25	111.6	22.2	51	116.3	26.7	13	113.2	28.5	42	102.5	26.9
Red Blood Cell 10^{12}/L	25	3.62	0.78	51	3.85	0.91	13	3.74	0.97	42	3.46	0.75
White Cell 10^{9}/L	25	5.21	1.52	51	5.92	2.8	13	5.51	3.69	42	4.87	2.08
Neutrophil 10^{9}/L	25	2.85	1.19	51	3.64	1.98	13	3.5	3.22	42	3.01	1.62
Lymphocyte 10^{9}/L	25	1.7	0.74	51	1.54	0.98	13	1.47	1.11	42	1.37	0.84

Table 3-6-1 Association analysis of Kaposi Sarcoma in Xinjiang Study: Socio-demographic Factors

				Conditional Logistic Regression Model*				Multiple Imputation Model**			
		KS	Control	OR	OR 95%CI	aOR	aOR 95%CI	OR	OR 95%CI	aOR	aOR 95%CI
Education	≤Primary School	14	29	Ref	-	Ref	-	Ref	-	Ref	-
	Junior School	13	36	0.78	0.30-2.02	0.75 [a]	0.26-2.13	0.79	0.31-2.01	0.72 [a]	0.25-2.05
	≥High School	9	9	1.68	0.49-5.76	1.88 [a]	0.50-7.05	1.6	0.49-5.22	1.72 [a]	0.48-6.15
	Missing	3	19	0.27	0.06-1.16	0.32 [a]	0.07-1.42	-	-	-	-
				P-trend=0.58		*P-trend=0.39*		*P-trend*=0.59		*P-trend*=0.55	
Marriage	Married	24	51	Ref	-	Ref	-	Ref	-		
	Unmarried	2	14	0.31	0.06-1.59	0.24 [b]	0.04-1.47	0.31	0.06-1.59	0.30 [b]	0.05-1.78
	Divorce /Widow	13	28	1.19	0.49-2.87	1.09 [b]	0.40-2.84	1.19	0.49-2.87	1.12[b]	0.43-2.96
Area	Urumqi	12	62	Ref	-	N	-	N	-	N	-
	Other Area	27	31	**3.73**	**1.71-8.13**						
Residence	Urban	31	83	Ref	-	N	-	N	-	N	-
Type	Rural	8	10	1.73	0.63-4.79						
Monthly	0-300	22	81	Ref	-	Ref	-	Ref	-	Ref	-
Income	301-1139	8	4	**6.58**	**1.83-23.64**	**4.14[a]**	**1.06-16.17**	**5.93**	**1.68-20.99**	3.86[a]	0.99-15.03
(RMB)	1140+	7	5	**4.45**	**1.27-15.60**	2.77 [a]	0.72-10.67	**4.31**	**1.23-15.12**	2.39[a]	0.59-9.71
	Missing	2	3	1.15	0.12-11.25	1.06[a]	0.11-10.54	-	-	-	-
				P-trend<0.01		*P-trend=0.04*		*P-trend=0.01*		*P-trend=0.11*	

*Conditional on age and sex; **: Missing in data were imputed 50 times using fully conditional specification method; aOR: adjusted Odds Ratios; Ref: reference level. a: additionally adjusted area and residence type; b: additionally adjusted monthly income and education level; N: no missing in original model.

Table 3-6-2 Association analysis of Kaposi Sarcoma in Xinjiang Study: HIV infection and Related Behaviors

				Conditional Logistic Regression*				Multiple Imputation Model**			
		KS	**Control**	**OR**	**OR 95%CI**	**aOR**	**aOR 95%CI**	**OR**	**OR 95%CI**	**aOR**	**aOR 95%CI**
Year of HIV	≥2008	33	66	Ref	-	Ref	-	N	-	N	-
Diagnose	Before 2008	6	27	0.42	0.15-1.16	0.53[a]	0.19-1.49				
Transmission	IDU	6	31	Ref	-	Ref	-	N	-	N	-
Route	Heterosexual	29	40	**4.22**	**1.54-11.58**	2.57[b]	0.85-7.74				
	Sexual + IDU	4	22	0.75	0.19-3.02	0.89[b]	0.20-4.09				
	Heterosexual	29	40	Ref	-	Ref	-	N	-	N	-
	Ever IDU	10	53	**0.21**	**0.09-0.52**	**0.37**[b]	**0.14-1.00**				
	IDU only	6	31	Ref	-	Ref	-	N	-	N	-
	Ever sexual	33	62	**2.71**	**1.04-7.04**	1.97[b]	0.69-5.66				
Cumulated	1	17	37	Ref	-	Ref	-	Ref	-	Ref	-
Heterosexual	2~5	13	15	1.55	0.59-4.10	1.82[b]	0.59-5.64	1.01	0.43-2.37	1.21[b]	0.45-3.21
Partners	>5	5	23	0.4	0.12-1.30	0.35[b]	0.09-1.38	0.36	0.11-1.16	0.32[b]	0.08-1.25
	Missing	4	18	0.41	0.12-1.42	0.52[b]	0.13-2.01	-	-	-	-
				P-trend=0.23		*P-trend=0.35*		*P-trend=0.14*		*P-trend=0.20*	

*Conditional on age and sex; aOR: adjusted Odds Ratios; Ref: reference level. **: Variables with missing were imputed 50 times using fully conditional specification method.
a: additionally adjusted Year of HIV diagnosis, area and residence type; b: additionally adjusted Year of HIV diagnosis, area, tuberculosis and whether have other AIDS related diagnosis. N: no missing in original model.

Table 3-6-3 Association analysis of Kaposi Sarcoma in Xinjiang Study: Tobacco Smoking and Alcohol Drinking

				Conditional Logistic Regression*				Multiple Imputation Model**			
		KS	Control	OR	OR 95%CI	aOR	aOR 95%CI	OR	OR 95%CI	aOR[a]	aOR 95%CI
Tobacco	Never	16	29	Ref	-	Ref	-	Ref	-	Ref	-
Smoking	Ever	21	52	0.52	0.19-1.45	0.73[a]	0.23-2.24	0.55	0.20-1.52	0.87[a]	0.29-2.64
	Missing	2	12	0.24	0.04-1.32	1.08[a]	0.07-16.18				
Pack-years	0	16	29	Ref	-	Ref	-	Ref	-	Ref	-
	1-20	13	26	0.66	0.23-1.91	0.86[a]	0.27-2.67	0.57	0.20-1.62	0.85[a]	0.27-2.62
	≥20	6	11	0.57	0.15-2.24	1.06[a]	0.23-4.96	0.49	0.13-1.89	0.85[a]	0.27-2.62
	Missing	4	27	0.19	0.05-0.76	0.44[a]	0.09-2.08	-	-	-	-
				P-trend=0.61		*P-trend=0.50*		*P-trend=0.29*		*P-trend=0.97*	
Alcohol	Never	16	42	Ref	-	Ref	-	Ref	-	Ref	-
Drinking	Ever	21	34	1.27	0.51-3.17	0.93[a]	0.32-2.70				
	Missing	2	17	0.25	0.05-1.29	0.12[a]	0.01-2.26	1.43	0.57-3.59	1.10[a]	0.38-3.21
Alcohol Drinks per	0	16	42	Ref	-	Ref	-	Ref	-	Ref	-
day	<1 /day	5	18	0.62	0.18-2.13	0.34[a]	0.08-1.53	0.76	0.23-2.58	0.47[a]	0.11-2.02
	≥1 /day	16	16	1.98	0.71-5.49	1.45[a]	0.45-4.66	2.16	0.78-6.04	1.77[a]	0.55-5.72
	Missing	2	17	0.24	0.05-1.24	0.14[a]	0.01-2.80	-	-	-	-
				P-trend=0.11		*P-trend=0.23*		*P-trend=0.13*		*P-trend=0.26*	

*Conditional on age and sex; **: Variables with missing were imputed 50 times using fully conditional specification method; aOR: adjusted Odds Ratios; Ref: reference level.

a: additionally adjusted Year of HIV diagnosis, area , and education;

Table 3-6-4 Association analysis of Kaposi Sarcoma in Xinjiang Study:CD4 cell count, serum HIV viral load and co-infections

				Conditional Logistic Regression*				Multiple Imputation Model**			
		KS	Control	OR	OR 95%CI	aOR	aOR 95%CI	OR	OR 95%CI	aOR	aOR 95%CI
Ever had ART	No	32	60	Ref	-	Ref	-	Ref	-	Ref	-
(>90d before KS)	Yes	7	33	0.56	0.18-1.16	**0.13[a]**	**0.03-0.72**	0.56	0.18-1.16	0.34[a]	0.11-1.05
CD4 cell count	≥ 350/μl	7	13	Ref	-	Ref	-	Ref	-	Ref	-
Before ART	200~349/μl	5	17	0.66	0.17-2.54	0.63[b]	0.13-3.15	0.71	0.19-2.70	0.68[b]	0.13-3.49
	<200/μl	16	34	0.91	0.31-2.68	0.82 [b]	0.21-3.18	0.87	0.29-2.59	0.79 [b]	0.20-3.03
	Missing	11	29	0.88	0.28-2.76	0.70[b]	0.17-2.87	-	-	-	-
				P-trend=0.98		*P-trend=0.76*		*P-trend=0.88*		*P-trend=0.78*	
Current CD4 cell	≥ 350/μl	8	21	Ref	-	Ref	-	Ref	-	Ref	-
count	200~349/μl	8	21	1.16	0.37-3.63	1.33[c]	0.35-5.08	1.13	0.36-3.54	1.33[c]	0.35-5.09
	<200/μl	21	42	1.31	0.50-3.42	1.44[c]	0.45-4.65	1.26	0.48-3.30	1.55[c]	0.48-4.96
	Missing	2	9	0.74	0.13-4.12	0.94[c]	0.14-6.40	-	-	-	-
				P-trend=0.55		*P-trend=0.55*		*P-trend=0.63*		*P-trend=0.36*	

*Conditional on age and sex; **: Variables with missing were imputed 50 times using fully conditional specification method; aOR: adjusted Odds Ratios; Ref: reference level.

a: additionally adjusted Year of HIV diagnosis, area, CD4 cell count before ART, HIV transmission routes, TB and other AIDS related symptoms;

b: additionally adjusted Year of HIV diagnosis, area, HIV transmission route, TB and other AIDS related symptoms;

c: additionally adjusted Year of HIV diagnosis, area,. HIV transmission route, ever had ART, TB and other AIDS related symptoms.

Table 3-6-5 Association analysis of Kaposi Sarcoma in Xinjiang Study: co-infections and other AIDS related manifestations

				Conditional Logistic Regression*				Multiple Imputation Model**			
		KS	**Control**	**OR**	**OR 95%CI**	**aOR**	**aOR 95%CI**	**OR**	**OR 95%CI**	**aOR**	**aOR 95%CI**
HBV infection	No	33	84	Ref	-	Ref	-	Ref	-	Ref	-
	Yes	6	9	1.50	0.50-4.55	1.06[a]	0.29-3.91	1.50	0.50-4.55	1.18 [a]	0.33-4.23
HCV infection	No	25	29	Ref	-	Ref	-	Ref	-	Ref	-
	Yes	14	64	**0.24**	**0.10-0.55**	0.67[a]	0.22-2.06	**0.24**	**0.10-0.55**	0.61 [a]	0.2-1.84
Tuberculosis	No	23	35	Ref	-	Ref	-	Ref	-	Ref	-
	Yes	16	58	**0.41**	**0.19-0.89**	0.62[a]	0.25-1.54	**0.41**	**0.19-0.89**	0.62 [a]	0.26-1.51
Other AIDS related	No	27	62	Ref	-	Ref	-	Ref	-	Ref	-
manifestations[†]	Yes	12	31	0.87	0.38-2.00	0.72[b]	0.28-1.85	N	-	N	-

*Conditional on age and sex; **: Variables with missing were imputed 50 times using fully conditional specification method; aOR: adjusted Odds Ratios; Ref: reference level.

†: If one have at least on of following manifestations: fever (consistent low fever over 1 month with unspecified reason), edema of lymph node, chronic diarrhea (over 3/day, body weight loss >10% in 3 months), Candida infection (oral or organs), Pnumocystis Carinii Pneumonia, Infection of human cytomegalovirus, Toxoplasma encephalopathy, Cryptococcus infection, pneumonia or meningitis, Septicemia, Recurrent bacteria pneumonia, Non-Hodgkin Lymphoma, Recurrent herpes infection, and Dementia at young or middle age.

a: additionally adjusted Year of HIV diagnosis, area, HIV transmission route, and education;

b:additionally adjusted Year of HIV diagnosis, area,. HIV transmission route, ART, and TB.

N: no missing in original model.

Table 3-7-1 Bayesian Analysis of Kaposi Sarcoma in Xinjiang Study with Priors from Uyghur Cohort in the National HIV/AIDS Population Cohort, 1.

Characteristics	Prior				Models with Original Data*		Models with Multiple Imputation**		Adjusted Factors
	Type	HR	β	σ^2	OR	95%CI	OR	95%CI	
Year of HIV Diagnosis									
≥2008		-	-	-	Ref	-	Ref	-	
Before 2008	MLE Estimation†	-	-	-	0.53†	0.19-1.49†	N	-	
	Non-informative Prior	1.00	0	10^6	0.50	0.16-1.40	N	-	
	Original Prior	0.24	-1.41	0.15	**0.31**	**0.16-0.58**	N	-	Area, Residence Type
	Prior 2	0.24	-1.41	0.30	**0.35**	**0.16-0.75**	N	-	
	Prior 3	0.24	-1.41	0.60	**0.40**	**0.16-0.96**	N	-	
	Prior 4	0.24	-1.41	1.20	0.44	0.16-1.14	N	-	
ART (started >90 days before KS diagnose)									
No		-	-	-	Ref		Ref	-	Year of HIV
Yes	MLE Estimation†	-	-	-	**0.13**†	**0.03-0.72**†	0.34†	0.11-1.05†	diagnose, area, CD4
	Non-informative Prior	1.00	0	10^6	**0.13**	**0.02-0.63**	**0.24**	**0.07-0.75**	cell count before
	Original Prior	0.12	-2.12	0.25	**0.13**	**0.05-0.29**	**0.16**	**0.07-0.34**	ART, HIV
	Prior 2	0.12	-2.12	0.49	**0.13**	**0.05-0.36**	**0.18**	**0.07-0.44**	transmission routes,
	Prior3	0.12	-2.12	1.00	**0.13**	**0.04-0.44**	**0.20**	**0.07-0.55**	TB and other AIDS
	Prior4	0.12	-2.12	2.00	**0.13**	**0.03-0.52**	**0.21**	**0.07-0.63**	related symptoms

*:Conditional logistic regression models condition on age and sex. †: Conditional logistic regression without prior . Odds ratios and 95% confidence intervals using MLE estimation. pstOR: posterior odds ratio; pstOR 95% CI: 95% Credible Interval of posterior odds ratios;

Table 3-7-2 Bayesian Analysis of Kaposi Sarcoma in Xinjiang Study with Priors from Uyghur Cohort in the National HIV/AIDS Population Cohort, 2.

Characteristics	Prior				Models with Original Data*		Models with Multiple Imputation**		Adjusted Factors
	Type	HR	β	σ^2	OR	95%CI	OR	95%CI	
HIV Transmission Routes									
IDU only		-	-	-	Ref	-	Ref	-	
Heterosexual	MLE Estimation†	-	-	-	2.57	0.85-7.74	N	-	
Sexual + IDU		-	-	-	0.89	0.20-4.09	N	-	
Heterosexual	Non-informative Prior	1.00	0	10^6	2.79	0.93-9.25	N	-	Year of HIV diagnose, area, TB and other AIDS related symptoms
Sexual + IDU		1.00	0	10^6	0.75	0.14-3.48	N	-	
Heterosexual	Original Prior	1.47	0.38	0.15	**2.02**	**1.09-3.79**	N	-	
Sexual + IDU		5.08	1.63	0.59	1.56	0.59-4.27	N	-	
Heterosexual	Prior 2	1.47	0.38	0.30	**2.20**	**1.03-4.78**	N	-	
Sexual + IDU		5.08	1.63	1.20	1.18	0.37-3.8	N	-	
Heterosexual	Prior3	1.47	0.38	0.60	**2.39**	**1.01-5.78**	N	-	
Sexual + IDU		5.08	1.63	2.40	0.97	0.26-3.48	N	-	
Heterosexual	Prior4	1.47	0.38	1.20	2.56	0.96-6.95	N	-	
Sexual + IDU		5.08	1.63	4.80	0.86	0.20-3.42	N	-	

*:Conditional logistic regression models condition on age and sex. †: Conditional logistic regression without prior.

pstOR: posterior odds ratio; pstOR 95% CI: 95% Credible Interval of posterior odds ratios;

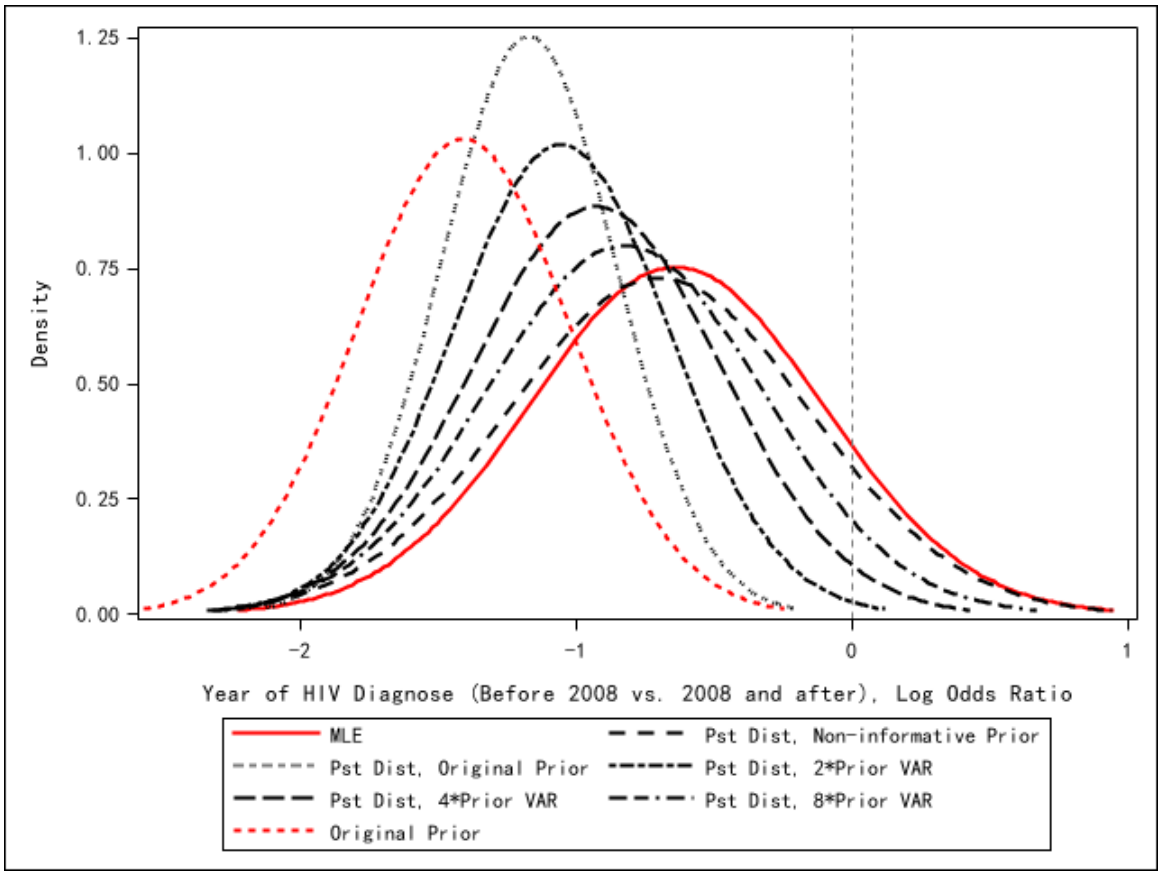
Table 3-7-3 Bayesian Analysis of Kaposi Sarcoma in Xinjiang Study with Priors from Uyghur Cohort in the National HIV/AIDS Population Cohort, 3.

Characteristics	Prior				Models with Original Data*		Models with Multiple Imputation**		Adjusted Factors
	Type	HR	β	σ^2	OR	95%CI	OR	95%CI	
CD4 cell count before ART									
≥and/μl		-	-	-	Ref	-	Ref	-	
200~349/μl	MLE Estimation†	-	-	-	0.63	0.13-3.15	0.68	0.13-3.49	
<200/μl		-	-	-	0.82	0.21-3.18	0.79	0.20-3.03	Year of HIV
200~349/μl	Non-informative Prior	1.00	0	10^6	0.55	0.10-2.95	0.51	0.11-2.38	diagnose,
<200/μl		1.00	0	10^6	0.78	0.19-3.40	0.63	0.16-2.41	area, HIV
200~349/μl	Original Prior	4.72	1.55	0.21	**3.59**	**1.68-7.64**	**3.12**	**1.47-6.63**	transmission
<200/μl		6.39	1.86	0.21	**4.40**	**2.12-9.23**	**3.49**	**1.67-7.27**	route,
200~349/μl	Prior 2	4.72	1.55	0.42	**2.85**	**1.08-7.58**	2.26	0.87-5.83	Tuberculosis and
<200/μl		6.39	1.86	0.42	**3.37**	**1.37-8.70**	2.46	0.99-6.10	other AIDS
200~349/μl	Prior3	4.72	1.55	0.84	2.00	0.61-6.66	1.51	0.49-4.67	related symptoms
<200/μl		6.39	1.86	0.84	2.43	0.80-7.65	1.66	0.58-4.74	
200~349/μl	Prior4	4.72	1.55	1.68	1.35	0.33-5.19	1.04	0.29-3.71	
<200/μl		6.39	1.86	1.68	1.71	0.48-5.99	1.17	0.37-3.72	

*:Conditional logistic regression models condition on age and sex. †: Conditional logistic regression without prior.

pstOR: posterior odds ratio; pstOR 95% CI: 95% Credible Interval of posterior odds ratios;

Figures



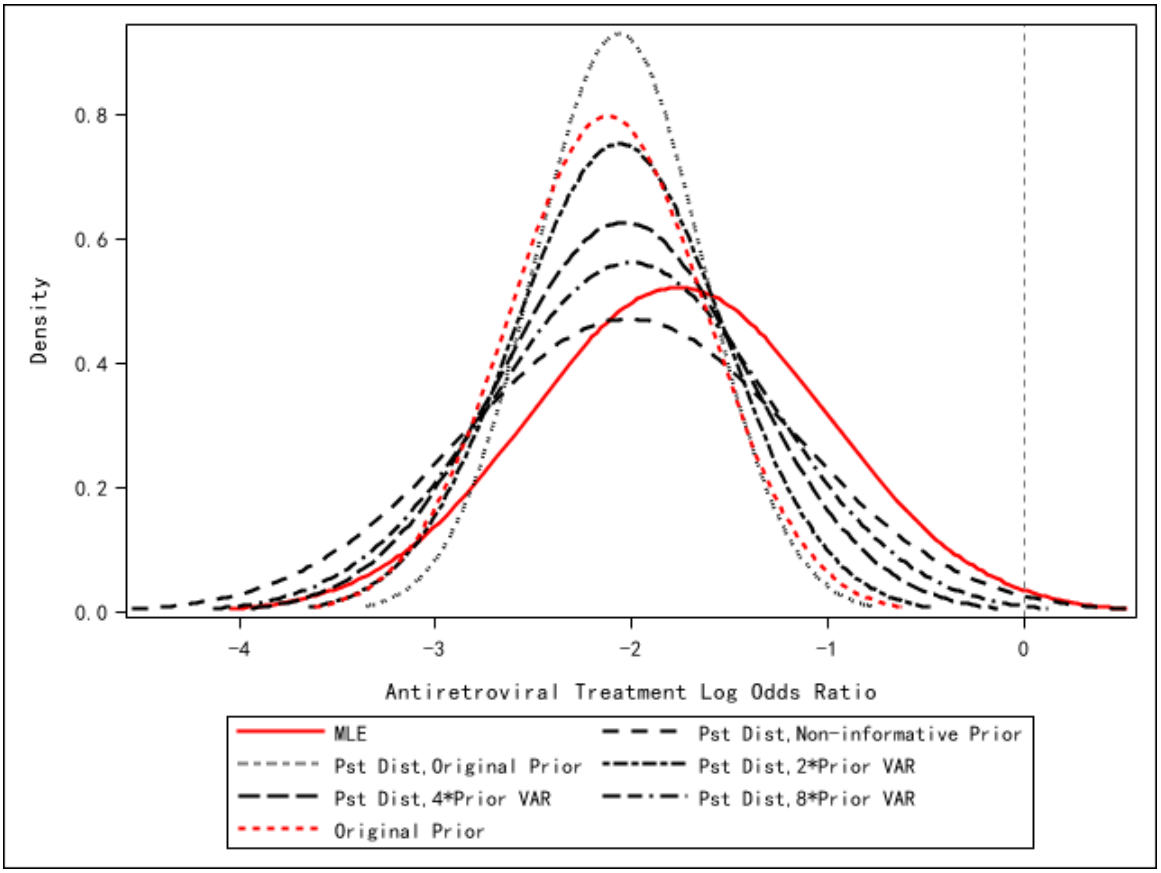
MLE: Maximum likelihood estimation of conditional logistic regression model.

Non-informative: 0 was used as the mean and 10^6 was used as the variance of the Prior distribution .

Pst Dist: Estimated Posterior Distribution of Log Odds Ratios.

VAR: variance of prior; sensitivity analysis was performed using the same mean and flattered variances (2, 4 and 8 times as the original prior variance).

Figure 3-1 Sensitivity analysis of Bayesian estimation on Log odds ratio of Year of HIV Diagnose Diagnose (HIV diagnosed before 2008 vs. 2008 and after) on Kaposi Sarcoma in Xinjiang Study



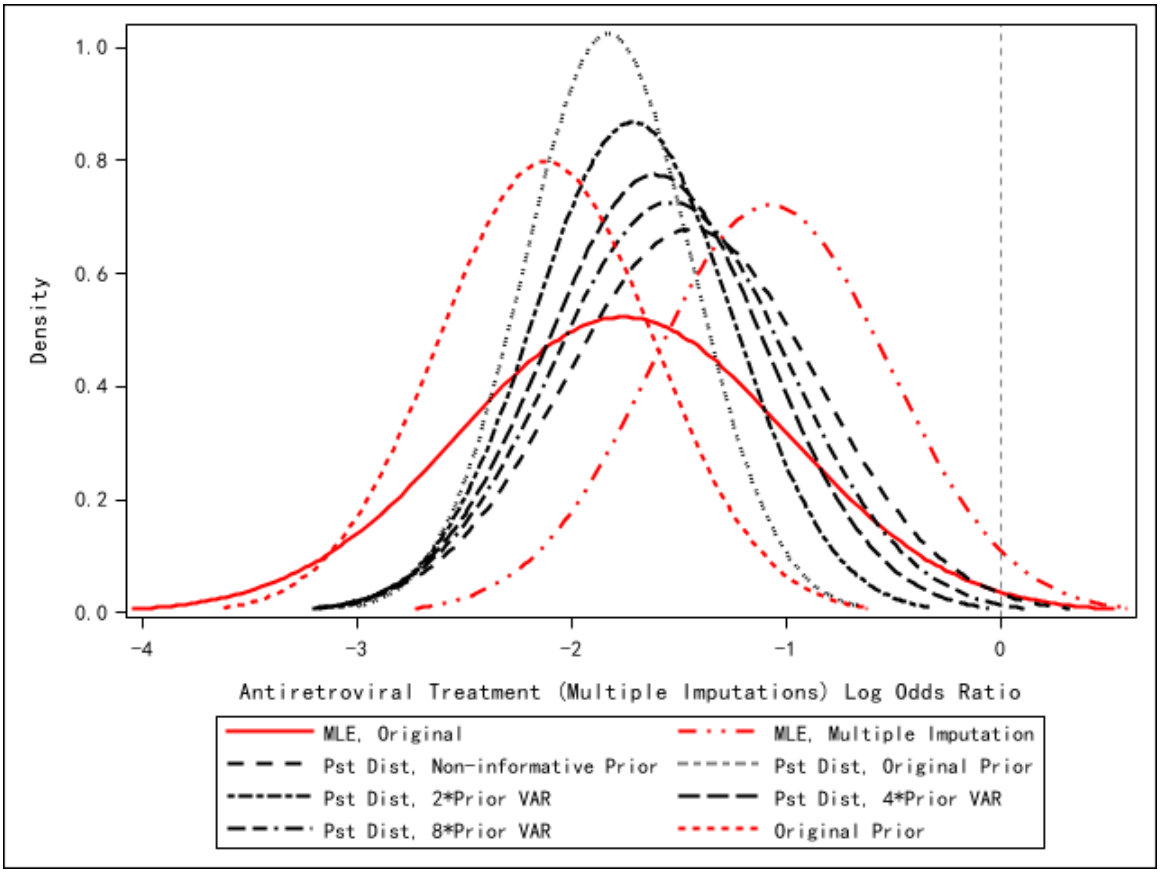
MLE: Maximum likelihood estimation of conditional logistic regression model.

Non-informative: 0 was used as the mean and 10^6 was used as the variance of the Prior distribution .

Pst Dist: Estimated Posterior Distribution of Log Odds Ratios.

VAR: variance of prior; sensitivity analysis was performed using the same mean and flattered variances (2, 4 and 8 times as the original prior variance).

Figure 3-2-1 Bayesian Sensitivity analysis on Log odds ratio of Antiretroviral Treatment (Yes vs. vs. No) and Kaposi Sarcoma in Xinjiang Study



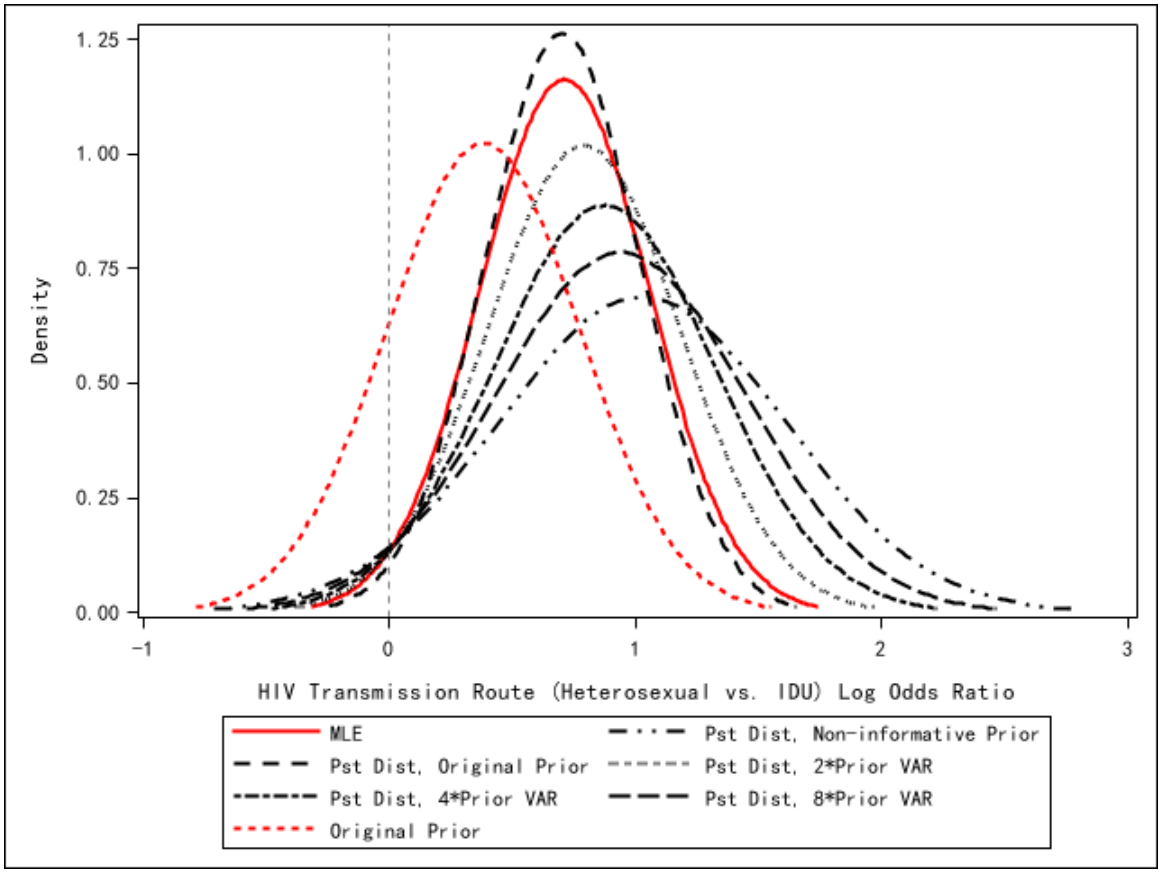
MLE: Maximum likelihood estimation of conditional logistic regression model.

Non-informative: 0 was used as the mean and 10^6 was used as the variance of the Prior distribution .

Pst Dist: Estimated Posterior Distribution of Log Odds Ratios.

VAR: variance of prior; sensitivity analysis was performed using the same mean and flattered variances (2, 4 and 8 times as the original prior variance).

Figure 3-2-2 Bayesian Sensitivity analysis with Multiple Imputations on Log odds ratio of Antiretroviral Treatment (Yes vs. No) and Kaposi Sarcoma in Xinjiang Study



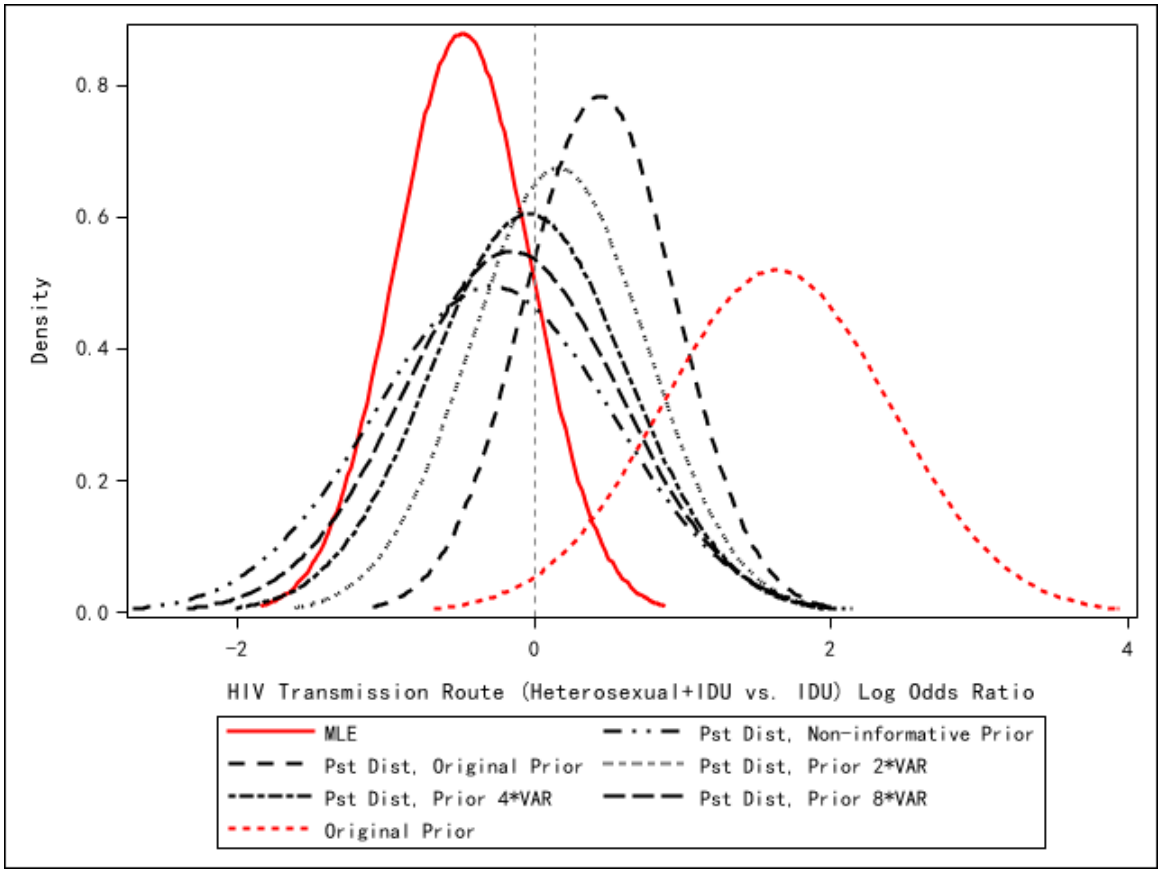
MLE: Maximum likelihood estimation of conditional logistic regression model.

Non-informative: 0 was used as the mean and 10^6 was used as the variance of the Prior distribution .

Pst Dist: Estimated Posterior Distribution of Log Odds Ratios.

VAR: variance of prior; sensitivity analysis was performed using the same mean and flattered variances (2, 4 and 8 times as the original prior variance).

Figure 3-3-1 Bayesian Sensitivity analysis of Log odds ratio of Potential HIV Transmission Routes Routes (Heterosexual vs. IDU) and Kaposi Sarcoma in Xinjiang Study



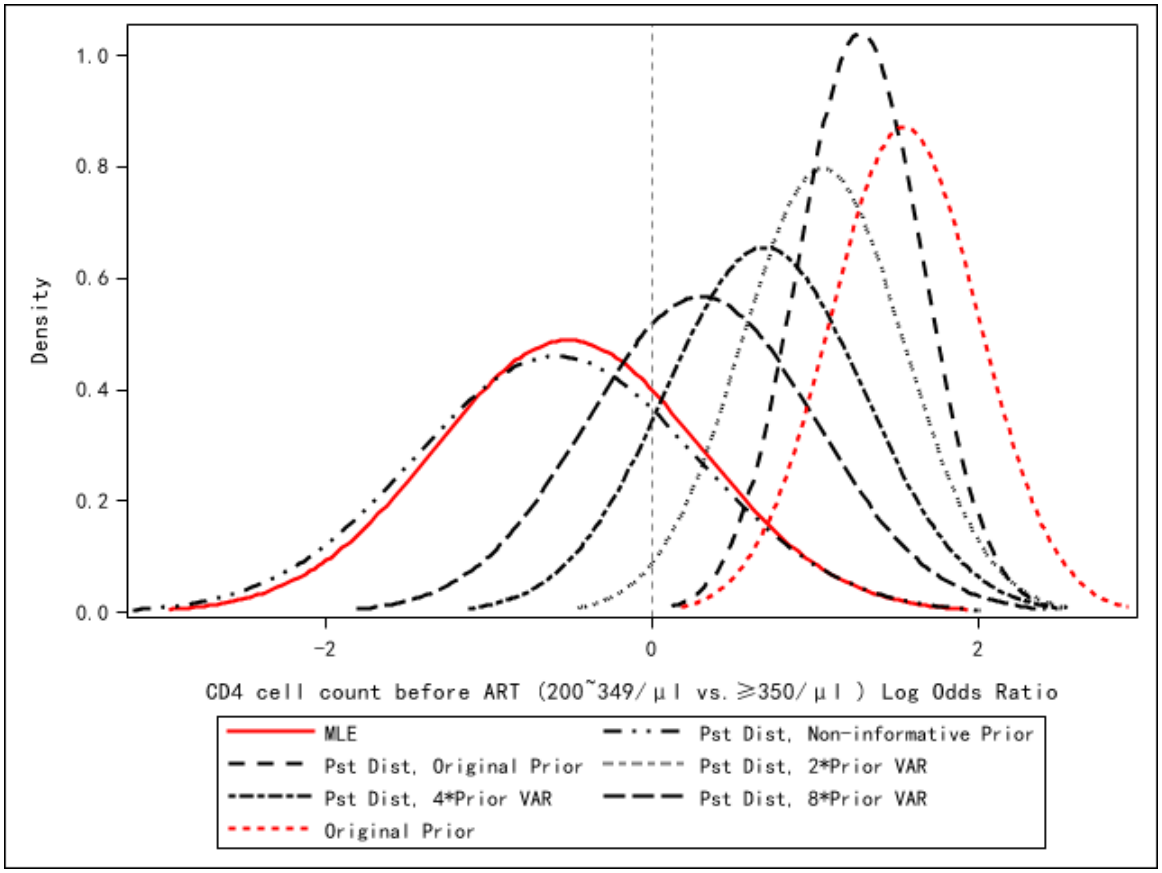
MLE: Maximum likelihood estimation of conditional logistic regression model.

Non-informative: 0 was used as the mean and 10^6 was used as the variance of the Prior distribution .

Pst Dist: Estimated Posterior Distribution of Log Odds Ratios.

VAR: variance of prior; sensitivity analysis was performed using the same mean and flattered variances (2, 4 and 8 times as the original prior variance).

Figure 3-3-2 Bayesian Sensitivity analysis of Log odds ratio of Potential HIV Transmission Routes Routes (Heterosexual+IDU vs. IDU) and Kaposi Sarcoma in Xinjiang Study



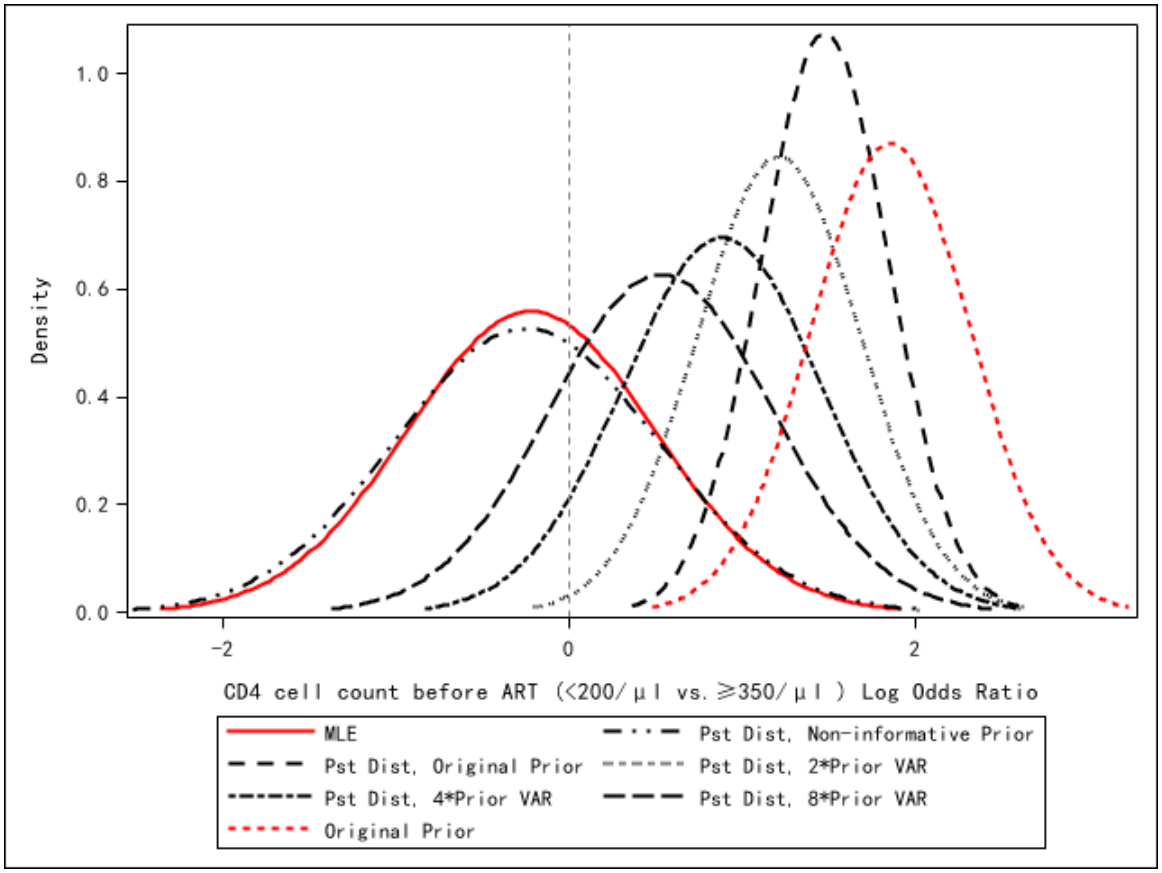
MLE: Maximum likelihood estimation of conditional logistic regression model.

Non-informative: 0 was used as the mean and 10^6 was used as the variance of the Prior distribution .

Pst Dist: Estimated Posterior Distribution of Log Odds Ratios.

VAR: variance of prior; sensitivity analysis was performed using the same mean and flattered variances (2, 4 and 8 times as the original prior variance).

Figure 3-4-1 Bayesian Sensitivity analysis of Log odds ratio of CD4 cell count before Antiretroviral Treatment (200~349/ul vs. ≥350/ul) and Kaposi Sarcoma in Xinjiang Study



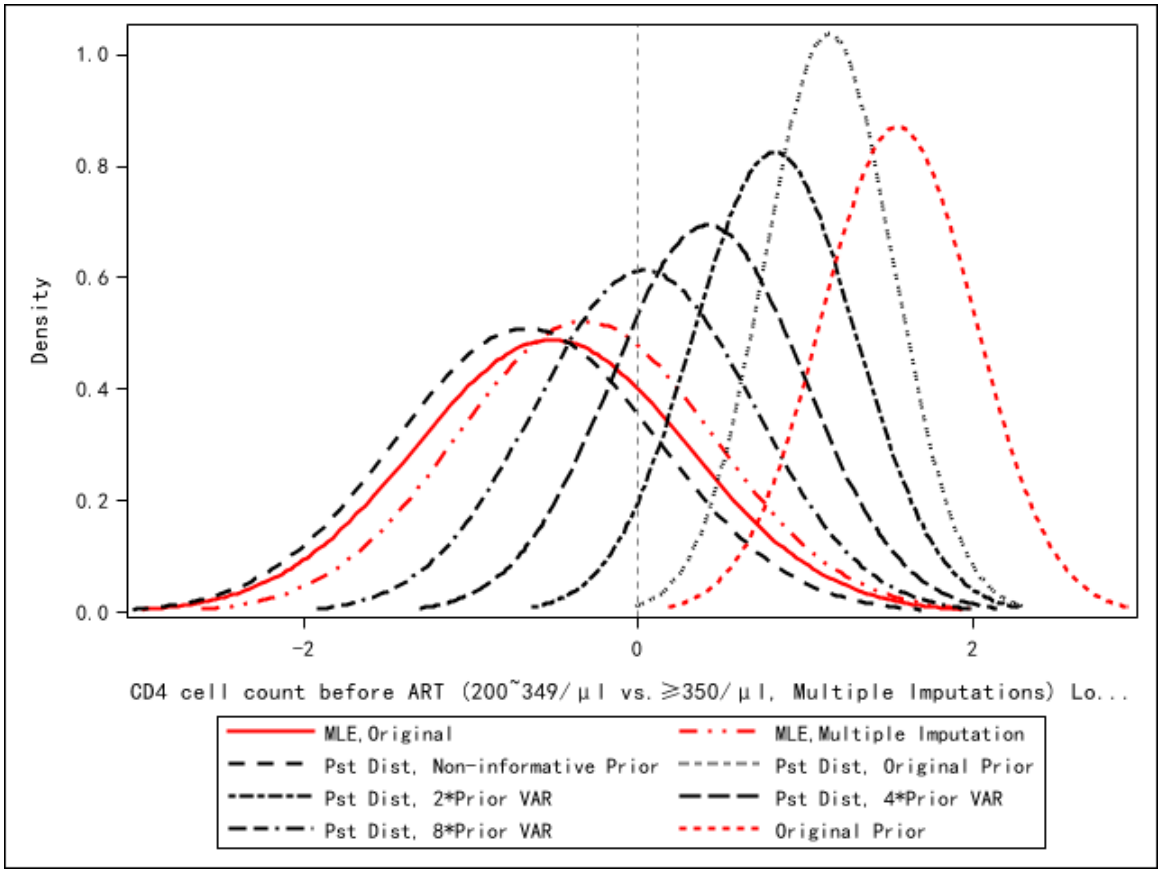
MLE: Maximum likelihood estimation of conditional logistic regression model.

Non-informative: 0 was used as the mean and 10^6 was used as the variance of the Prior distribution .

Pst Dist: Estimated Posterior Distribution of Log Odds Ratios.

VAR: variance of prior; sensitivity analysis was performed using the same mean and flattered variances (2, 4 and 8 times as the original prior variance).

Figure 3-4-2 Bayesian Sensitivity analysis of Log odds ratio of CD4 cell count before Antiretroviral Treatment (<200/ul vs. ≥350/ul) on Kaposi Sarcoma in Xinjiang Study



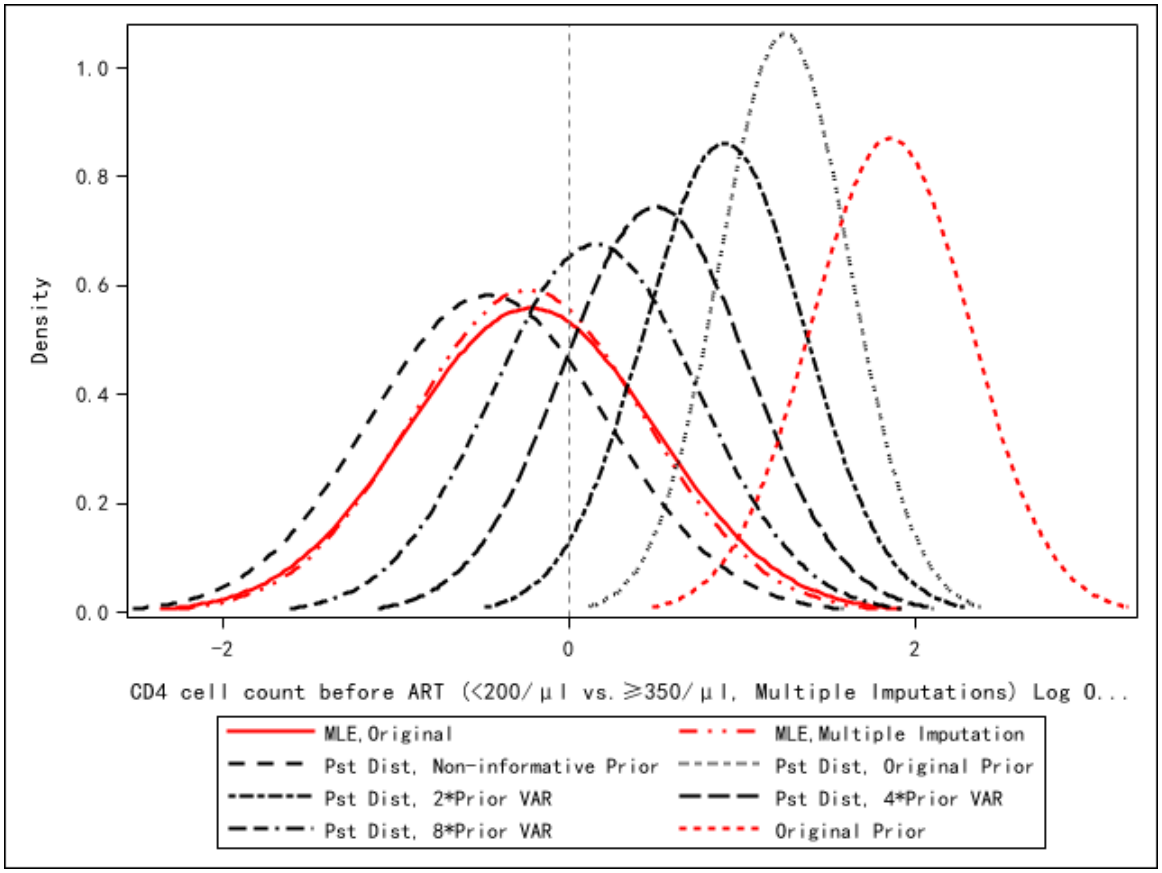
MLE: Maximum likelihood estimation of conditional logistic regression model.

Non-informative: 0 was used as the mean and 10^6 was used as the variance of the Prior distribution .

Pst Dist: Estimated Posterior Distribution of Log Odds Ratios.

VAR: variance of prior; sensitivity analysis was performed using the same mean and flattered variances (2, 4 and 8 times as the original prior variance).

Figure 3-4-3 Bayesian Sensitivity analysis with Multiple Imputations on Log odds ratio of CD4 cell count before Antiretroviral Treatment (200~349/ul vs. ≥350/ul) and Kaposi Sarcoma in Xinjiang Study



MLE: Maximum likelihood estimation of conditional logistic regression model.

Non-informative: 0 was used as the mean and 10^6 was used as the variance of the Prior distribution .

Pst Dist: Estimated Posterior Distribution of Log Odds Ratios.

VAR: variance of prior; sensitivity analysis was performed using the same mean and flattered variances (2, 4 and 8 times as the original prior variance).

Figure 3-4-4 Bayesian Sensitivity analysis with Multiple Imputations on Log odds ratio of CD4 cell count before Antiretroviral Treatment (<200/ul vs. ≥350/ul) and Kaposi Sarcoma in Xinjiang Study

Chapter 5 Conclusions

Summary of Findings

This dissertation study is the report of the spectrum of malignant tumors among HIV-infected persons in China at the national level, and first comprehensive case-control study on Kaposi Sarcoma among HIV-infected Uyghur population in China.

In Chapter 2, we described the spectrum of malignant tumors among people living with HIV/AIDS in the National AIDS Surveillance Information System of National Center for STD/AIDS Control and Prevention (NCAIDS), China CDC during 2008-2011. Our results showed higher risk of cancers among the HIV-infected persons than the general population. Different from western pattern, AIDS-defining cancers are not the most frequent cancers, compared with non-AIDS defining cancers among HIV-infected persons in China.

Kaposi Sarcoma, lymphomas and female cervical cancer were found with escalated standardized incidence ratio (SIR), comparing with general population in China. However, incidence rates of the three AIDS-defining cancers were not as high as in western countries, and lower than some non-AIDS defining cancers. Lung cancer and liver cancer were found the top two malignant tumors among HIV-infected population in China. Other infection related cancers, such as cancers of nasopharynx, head and neck, penis, skin and stomach were also found higher than the general population in China.

In Chapter 3, we analyzed the cohort of NCAIDS and explored factors associated with Kaposi Sarcoma incidence and survival. Uyghur ethnic, a risk ethnic group of classic KS, was confirmed to be higher risk for AIDS-KS. Lower CD4 cell count level and had antiretroviral treatment were the two strongest associated factors, conditioning the age, sex, and ethnic group. Subjects with intravenous drug use were found had lower odds of KS than those infected HIV by heterosexual routes and Year of HIV diagnosis.

In Chapter 4, we conducted a hospital-based case-control study in Xinjiang Uyghur Region Hospital of Infectious Diseases (XJHID) for HIV-infected KS cases and HIV-infected controls. With 39 KS cases and 93 controls, we described and analyzed factors potentially associated with KS risk. Risk behaviors such as multiple and unprotected sex, abuse of drug and sharing needles among IDUs were common among enrolled subjects, and prevalence of tuberculosis, HBV and HCV co-infections were high. About 33% (13/39) KS cases got HIV diagnosis after the KS diagnose, which indicates potential late diagnose of HIV in Xinjiang, similar as that in the national cohort.

Antiretroviral treatment was found negatively associated with Kaposi Sarcoma incidence, and we also found IDUs had lower odds ratio of KS than sexually transmitted subjects in XJHID study. No association was found between smoking and KS. Bayesian analysis using national HIV-infected Uyghur cohort study estimation as prior showed most results from the two different

data sources were consistent with each other in the estimations of Year of HIV diagnosis, HIV transmission routes. Differences were found in the estimated posterior odds ratios of CD4 cell count and ART. Considering the national cohort study has less chance of selection bias between different probability to be inpatient, posterior odds ratio of the XJHID analysis should be less biased than conventional estimation in the association analysis of KS on CD4 cell count and ART.

Public Health Implications

Spectrum of Malignant tumors

With spectrum of malignant tumors among HIV-infected population, our findings is indicating high burden of cancers among people living with HIV/AIDS in China. High prevalence of substance use among subjects, and higher risk of smoking or alcohol related cancers (lung, liver, cervical, etc.) indicate the need of behavior intervention of chronic disease among PLHIV in China as well as sexual/drug use intervention for HIV transmission. High prevalence of co-infections and higher risk of infection related cancers (liver, stomach, cervical, etc.) indicate the need for enhancing treatment and prevention of co-infections beyond current free ART program in China. Also, our findings of poor differentiation in lymphomas and CNS tumor call for better pathology service for diagnose and treatment for HIV/AIDS patients in China.

Kaposi Sarcoma

Our result showed antiretroviral treatment was found to be one of the strongest factors that could

be intervened. Large number of low CD4 cell count level at diagnose or before ART, KS cases without CD4 cell count record had highest fatality rate, which indicates that late diagnose is still an issue and early initiation and efficient service of ART will be the most feasible method to control, prevent and treat Kaposi Sarcoma among HIV-infected population in China. Specifically, HIV-infected Uyghur people have higher risk of KS than other ethnic groups and more attention should be paid on them in Xinjiang.

Future Development

National HIV/AIDS Cohort

My current work is only the very first step of malignant tumor research among HIV-infected population in China. With the overall spectrum, we now have some knowledge about the higher risk of different malignancies among Chinese HIV-infected population, and detailed work on specific cancers will be the next step. Also, to improve the precision of current data, we will try to link current national HIV/AIDS data with available tumor registry data.

For current analysis on tumor spectrum and risk factors of KS, because of the regulation of national data, some bias analysis has not been fully accomplished because all work has to be done in China CDC. In next step, we will make further update in analysis including 1) update observation of person-time of all subjects by setting several different end-points of the observation as sensitivity analysis for estimated incidence rates; 2) we will include more details in

lost-of-follow-up/survival and strength analysis on associated factors of censoring to reduce potential selection bias due to lost-follow-up/survival is possible in current analysis; 3) in national cohort ART and CD4 cell counts are collected in a dynamic and longitudinal pattern, and we will update current analysis with more strict longitudinal analysis. For both 2) and 3), marginal structural model will be useful tool.

NCAIDS surveillance cohort is a large scale longitudinal data set and the best data representing all HIV infected population in China. Although it has fewer variables than detailed case-control study, nested-case-control study design could be considered to collect detailed epidemiological data and biological samples. For risk factors of other cancers, detailed molecular epidemiology study, with environmental exposure such as tobacco smoking and alcohol drinking, on cancers of lung, liver cancer and cervix will be on the top of candidate list. Also, detailed clinical study on differentiating lymphomas will help specify the risk of AIDS-defining lymphoma estimation, and more accurate diagnose of central nerve system tumor-like manifestations is essential to validate current observation on CNS tumor.

Case-control study of Kaposi Sarcoma in Xinjiang

For the case-control study of Kaposi Sarcoma in Xinjiang Hospital of Infectious Diseases, collecting more subjects and extend the molecular epidemiology part of the study will be our continued.

In current data analysis, our result showed potential selection bias due to the selection process of

controls in the hospital. It is possible to get probability of selection from external data because all identified HIV-infected were registered in the national data base. We will try to estimate probability of selection in the hospital based on joint distribution of demographic characteristics and disease stage of all Uyghur patients in Xinjiang and all patients of XJHID. This information could be obtained from the same national individual level data base as in the former part.

We already designed and collected blood samples, and serum test for infection status of KSHV is the priority test for this study. With KSHV infection status, we will make several new comparisons between KSHV+ cases vs. KSHV+ controls, and KSHV+ controls vs. KSHV- controls. The former comparison will help us identify potential factors that interact with KSHV infection and associated with incident KS, and the later one will help identify potential risk factors related to KSHV infection among Uyghur HIV/AIDS population in China.

DNA samples have been extracted from peripheral white cells. Current target SNPs were chosen from NF-kappa B, human cellular targets of KSHV-coded microRNA, and IL-6 receptors that related to virus infection. Unfortunately, genotyping using Fluidgim platform was failed. I will first repeat the genotyping test and analyze potential association between genotype and KS incidence. Also at this stage, have not finished the test of KSHV seroprevalence among all subjects, and our result will also be improved by KSHV infection information to explore potential pathogen-host interaction.

In the future, SNPs related to opioid receptor genes could be new target pathways that related to Kaposi Sarcoma. Furthermore, considering the importance of angiogenesis in the growth and metastasis of various tumors, opioid receptor gene variation identified from KS study may also play roles in other cancers. If the negative association between opiate receptor agonist and Kaposi Sarcoma risk were confirmed by future study, it will be extra public health benefit of methadone maintenance therapy among HIV-infected former intravenous drug users.

Although it is very hard to get KS cases in Han ethnic group, it is essential to extend our study into Han ethnic population, and collaboration on detailed genotype comparison between Caucasian, Mongolian and the admixtured Uyghur population will help illustrate the difference in genetic susceptibility of KS between different ethnic groups, and get new knowledge for KS and angiogenesis in other cancers.