Chapter 3
The Epidemiology of Non-AIDS-Defining Malignancies

Andrew E. Grulich

Abstract AIDS-defining malignancies are those which are included in the case definition of AIDS, namely Kaposi Sarcoma, non-Hodgkin Lymphoma, and cervical cancer. *Non-AIDS-defining malignancies* are those other malignancies whose incidence is increased in individuals with HIV infection. In some instances, the term can also refer to any malignancy occurring in an individual with HIV infection. More recently, as the incidence of AIDS has declined in people with access to antiretroviral therapy, the term "HIV-associated malignancy" has become more widely used to describe the same group of malignancies.

3.1 Introduction

In the early 1980s, a rare form of skin cancer, Kaposi sarcoma (KS), occurring at greatly increased rates among homosexual men, was a harbinger of the AIDS epidemic. Over the subsequent decade, when it became apparent that non-Hodgkin lymphoma (NHL) and cervical cancer occurred at increased rates in people with HIV, these two cancers were added to the case definition of AIDS when they occurred in an HIV infected person. Collectively, KS, NHL, and cervical cancer are called AIDS-defining cancers and are separately considered in the section *AIDS-defining malignancies*.

Even early in the AIDS epidemic, it was recognized that other cancers also occurred with increased rates. In the mid-1990s, the introduction of highly active anti-retroviral therapy (HAART) changed the clinical face of HIV disease. In particular, it led to immune recovery and the much longer survival of people with HIV.

A.E. Grulich (✉)
HIV Epidemiology and Prevention Program, The Kirby Institute,
University of New South Wales, Sydney, NSW 2052, Australia
e-mail: agrulich@kirby.unsw.edu.au

R. Yarchoan (ed.), *Cancers in People with HIV and AIDS: Progress and Challenges*,
DOI 10.1007/978-1-4939-0859-2_3,

In general, immune recovery was only partial, and subtle effects of long-term mild immune deficiency, including the occurrence of certain cancers, began to emerge.

In this chapter, the spectrum of non-AIDS-malignancies is defined, and then individual cancer types are examined in detail. These cancers are grouped as (1) cancers with a known infectious cause that occur at increased incidence in people with HIV; (2) other cancers occurring at increased incidence in people with HIV and (3) cancer types that do not occur at increased incidence in people with HIV.

3.2 The Spectrum of Non-AIDS-Defining Malignancies

In the late 1990s, as the survival of people with HIV began to increase, it became more apparent that people with HIV were experiencing higher rates of a number of types of cancer than in the general population. This was identified within large-scale studies which linked population-based AIDS and/or HIV registers with cancer registries in several countries including the USA, Italy, and Australia. Increased rates of a wide range of cancers were identified. Initially, there was considerable debate about whether these cancers occurred at increased rates because of HIV-associated immune deficiency. The alternate explanation was confounding, because people with HIV also experience increased exposure to a number of other common carcinogens including tobacco smoke, and sexually transmitted and blood-borne oncogenic viral infections. The answer to whether cancer was truly caused by HIV came in part from studying cancer patterns in solid organ transplant recipients. Solid organ transplant recipients are required to take lifelong immune suppressive medications, and so share long-term immune deficiency with people with HIV. In other respects, they do not share similar carcinogenic exposures. A study published in 2007 conclusively demonstrated that these two populations have a broadly similar pattern of cancer occurrence, with increased rates of about 20 mostly infection-related cancer types (Grulich et al. 2007). The pattern of increased risk of cancer types is summarized in Fig. 3.1. More recently, cohort studies of people with HIV, which have included data on CD4-positive lymphocyte count and HIV viral load have demonstrated that many of these cancers are associated with impaired immune function.

In the remainder of this chapter, I will review the epidemiology of specific types of cancer in people with HIV, focussing in particular on the association with level of immune function.

3.3 Infection-Related Cancers

Cancers Related to Epstein–Barr Virus

The World Health Organization's International Agency for Research on Cancer (IARC) classifies Epstein–Barr virus (EBV) as carcinogenic in humans with respect to certain types of NHL (including Burkitt lymphoma, immunosuppression-related

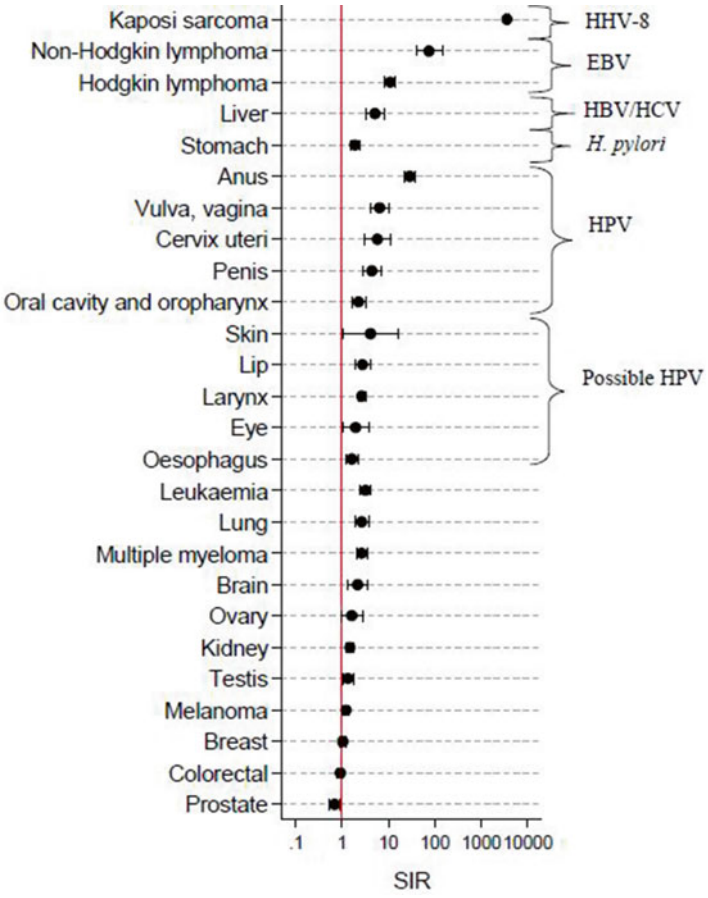

Fig. 3.1 Standardized incidence ratios of cancer types in people with HIV, grouped by infectious cause (figure based on data presented in Grulich et al. 2007)

NHL, extranodal NK/T cell lymphoma of nasal type), Hodgkin lymphoma, and cancer of the nasopharynx (IARC 2009). Data on NHL are summarized in *AIDS-defining malignancies* and are not further considered here.

EBV can be detected in 40–50 % of cases of Hodgkin lymphoma in developed countries, and is even more commonly detected in people with HIV (IARC 2009). Hodgkin lymphoma occurs about 11-fold more commonly in people with HIV than in the general population, and is raised about fourfold in organ transplant recipients (Grulich et al. 2007). The increase in risk in people with HIV is not consistent across Hodgkin lymphoma subtypes, and is confined to the mixed cellularity and lymphocyte-depleted subtypes. In recent years, rates of Hodgkin lymphoma in people with HIV have been relatively constant, and despite improvements in antiretroviral therapy and immune function they have not declined. Three cohort studies with longitudinal measurements of CD4 lymphocyte count have described an asso-

ciation between increasing rates of Hodgkin lymphoma and declining CD4 count (Guiguet et al. 2009; Reekie et al. 2010; Silverberg et al. 2011). At least part of the reason why rates of Hodgkin lymphoma have not declined in people with HIV in recent years is that the association with immune deficiency is much weaker than with NHL and Kaposi sarcoma.

Prospective studies have identified a strong relationship between serological markers of EBV infection and future risk of nasopharyngeal carcinoma (IARC 2009). As nasopharyngeal carcinoma is a rare cancer except in people originating from certain areas of South-East Asia, there are relatively few data on the association with HIV infection. A US-based linkage study of AIDS and cancer registers described a twofold increase in risk, based on only 39 cases, and a sixfold increase in risk was reported in a Chinese cohort of people with HIV.

Cancers Related to Human Papillomavirus

The IARC classifies certain types of human papillomavirus (HPV) infection as carcinogenic in humans with respect to cancers of the cervix, vulva, vagina, penis, anus, oral cavity, oropharynx, and tonsils (IARC 2009). There is weaker evidence that HPV may be associated with cancer at some other sites, including cancer of the larynx (IARC 2009).

Globally, the most common HPV-associated tumor is cervical cancer. Cervical cancer is an AIDS-defining cancer and is reviewed in AIDS-defining malignancies.

HPV can be detected in over 80 % of cases of anal cancer (IARC 2009). Anal cancer occurs at approximately 30-fold increased rates in people with HIV, and is also raised about fivefold in organ transplant recipients (Grulich et al. 2007). Risk is greatest in homosexual men with HIV, but substantial elevations in risk (greater than tenfold) are also seen in men with other risk factors for HIV, and in women with HIV (Chaturvedi et al. 2009). Some cohort studies have described an increase in anal cancer incidence in the HAART era, although a plateau in rates appears to have emerged in recent years. In some settings where homosexual men comprise a majority of people with HIV, anal cancer has become the most commonly occurring non-AIDS-defining malignancy (van Leeuwen et al. 2009). Anal cancer is not strongly related to current immune function, although a more moderate association with declining CD4 count has been described in two recent cohort studies (Reekie et al. 2010; Silverberg et al. 2012). Associations with prolonged duration below a CD4 cell count of 200 cells per microliter (Guiguet et al. 2009) and lower CD4 cell count nadir have also been described. The high incidence of this cancer in people with HIV, and the lack of a decline in incidence in recent years has led to anal cancer becoming a substantial health issue in people with HIV. Preventive interventions, including the possibility of a screening test for early detection of anal cancer and its precursors, have received considerable research attention in recent years. However, introduction of screening at a population level has been impeded by the lack of evidence of the efficacy of treatment of the pre-invasive lesion, and concerns about the accuracy and the complexity of the screening test.

Fewer data have been published on other HPV-related cancers and only small numbers have been described in cohort studies of people with HIV (IARC 2009), making a description of the relationship with immune function impossible. For cancer of the vulva and vagina, HPV can be detected in about 40 and 70 % of cases, respectively (IARC 2009). The cancers are increased about 6- and 23-fold in people with HIV and in organ transplant recipients, respectively (Grulich et al. 2007). HPV can be detected in about 50 % of cases of penile cancer (IARC 2009), and incidence rates are increased 4- and 16-fold in people with HIV and in organ transplant recipients, respectively (Grulich et al. 2007). Within the oral cavity, there is substantial variation in the association of cancer types with HPV. The strongest association is with cancer of the oropharynx and tonsils. In recent series 60 % or more of cases have detectable HPV (IARC 2009). For oral cavity cancer overall, incidence rates are increased two and threefold in people with HIV and in organ transplant recipients, respectively (Grulich et al. 2007). A US-based AIDS-cancer linkage study reported a modest 1.6-fold increase in oropharyngeal cancer in people with AIDS (Chaturvedi et al. 2009).

Cancers Related to Hepatitis B Virus and Hepatitis C Virus

The IARC classifies Hepatitis B virus (HBV) and Hepatitis C virus (HCV) as carcinogenic in humans with respect to hepatocellular carcinoma (liver cancer), and, for HCV only, for certain subtypes of NHL. There is weaker evidence that HBV may be related to NHL, and that both viruses may be related to cholangiocarcinoma (IARC 2009).

Liver cancer is increased about five and twofold in people with HIV and organ transplant recipients, respectively (Grulich et al. 2007). Risk of liver cancer is greatly increased in people with HIV who are co-infected with HBV and/or HCV (Guiguet et al. 2009), and thus incidence is particularly high in injection drug users and hemophiliacs with HIV. Two cohort studies have reported a moderate association of increased liver cancer risk with impaired immune function (Clifford et al. 2008; Guiguet et al. 2009).

A US-based AIDS-cancer linkage study has recently reported that risk of cholangiocarcinoma was increased by about 40 % in people with AIDS, but this did not reach statistical significance (Sahasrabuddhe et al. 2012).

Cancers Related to Helicobacter pylori

The IARC classifies *H. pylori* as carcinogenic in humans with respect to gastric carcinoma and low grade B cell mucosa-associated lymphoid tissue (MALT) gastric lymphoma (IARC 2009).

The incidence of stomach cancer is increased about twofold in people with HIV and in organ transplant recipients (Grulich et al. 2007). When examined by sub-site

within the stomach, increased risk does occur at non-cardia sites, where *H. pylori* has been casually associated with cancer (Persson et al. 2012). There is some evidence that EBV may cause a proportion of cases of gastric cancer (IARC 2009), and this is another potential reason why the incidence of gastric cancer is increased in people with HIV.

In the US AIDS-cancer match, gastric MALT lymphoma occurred about sixfold more commonly in people with AIDS than in the general population (Persson et al. 2012). *H. pylori* eradication is frequently associated with complete remission of the MALT lymphoma (IARC 2009).

Merkel Cell Carcinoma

Merkel cell carcinoma (MCC) is a rare but very aggressive skin cancer. In people with HIV, MCC occurs about 13-fold more commonly than in the general population, and it also occurs at greatly increased rates in organ transplant recipients and other immunosuppressed states including chronic lymphocytic leukemia. In 2008, it was discovered that a polyomavirus, now termed Merkel cell polyomavirus, is clonally integrated in Merkel cell carcinoma tissue (Feng et al. 2008). It is now recognized that Merkel cell polyomavirus is the cause of about 80 % of cases of Merkel cell carcinoma.

3.4 Cancers Occurring at Increased Rates in People with HIV with No Accepted Infectious Cause

In this section, cancers that have been documented to occur at increased rates in people with HIV, but do not have a well-accepted infectious cause, are discussed.

Lung Cancer

The incidence of lung cancer is increased about 2.7- and 2.2-fold in people with HIV and in transplant recipients, respectively (Grulich et al. 2007). Lung cancer is a common cancer in the general population of developed countries, and in many developed countries, lung cancer is the most common non-AIDS-defining carcinoma as assessed by the number of cases year. It is thus a very important cause of morbidity. Assessing the cause of this excess risk is made complex by the fact that people with HIV have a substantially raised prevalence of tobacco smoking. While tobacco smoking has been controlled for using multivariate techniques in several studies, it is difficult to confidently exclude the possibility of residual confounding by dose or timing of tobacco exposure (IARC 2009).

Another possible cause of the increased lung cancer incidence in people with HIV is an unknown pulmonary infection. In favor of this hypothesis is the fact that several cohort studies have found an association between lower CD4 count and increased lung cancer risk (Guiguet et al. 2009; Reekie et al. 2010; Silverberg et al. 2011), although one well-conducted cohort reported no association with immune function (Clifford et al. 2012). One study reported an association of lung cancer risk in people with HIV with recurrent pneumonia (Shebl et al. 2010), but another found no association of lung cancer with AIDS-related pulmonary disease. Irrespective of the cause, lung cancer is a major public health issue in people with HIV.

Conjunctival Cancer

Squamous cell cancer of the conjunctiva is a rare cancer that has been described as occurring at approximately 12-fold increase in people with AIDS in the USA, and also occurs at increased risk in kidney transplant recipients. A marked increased in risk of this cancer has been described in African settings (IARC 2009). Both solar ultraviolet radiation and HPV have been hypothesized to contribute to the etiology of this cancer (Chaturvedi et al. 2009).

Non-Melanoma Skin Cancer

In most parts of the world, data on basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) of the skin are not recorded by cancer registries, and hence there are relatively few data on their occurrence in people with HIV. In solid organ transplant recipients, SCCs occur about 50 times more commonly than in the general population. In that population, SCC also behaves much more aggressively than in the general population, and is a substantial clinical management issue. It is clear that people with HIV are less predisposed towards SCC than are solid organ transplant recipients. Nevertheless, a recent cohort study in California reported that rates of SCC were increased about twofold, which was a similar increase to the incidence of BCC (Silverberg et al. 2013). In that study, SCC but not BCC was related to lower recent CD4 count. The association with immune deficiency is suggestive evidence that an infective agent may be related to SCC. There is suggestive but not definitive evidence that HPV may play a role.

Melanoma

The incidence of melanoma is increased marginally, by about 24 %, in people with HIV, and by 2.3-fold in organ transplant recipients (Grulich et al. 2007). In kidney transplant recipients, the current receipt and intensity of immune suppression

increase melanoma risk, suggesting that impaired immunity is related to melanoma risk. The absence of a substantially increased risk in people with HIV suggests that HIV-induced immune deficiency may be less closely linked to melanoma risk than the pharmacological immune suppression in transplant recipients.

Lip Cancer

The incidence of lip cancer is increased by 2.8-fold in people with HIV, and is increased very markedly, by about 30-fold, in organ transplant recipients (Grulich et al. 2007). In organ transplant recipients, the increase in lip cancer probably reflects the very large increase in risk of SCC of the skin. In this population, increased risk is associated with current immune suppression, and risk rapidly returns to normal in kidney transplant recipients who stop receiving immune suppression because of kidney graft failure.

Esophageal Cancer

The incidence of esophageal cancer is increased by 1.6-fold in people with HIV, and is increased about threefold in organ transplant recipients (Grulich et al. 2007). The increase in incidence in people with HIV appears to be similar for adenocarcinoma and SCC of the esophagus (Persson et al. 2012). The increased alcohol and tobacco exposure of people with HIV is a potential explanation for these increased rates.

Laryngeal Cancer

The incidence of laryngeal cancer is increased by 2.7-fold in people with HIV, and is increased about twofold in organ transplant recipients (Grulich et al. 2007). Based on a small case-series, HPV does not appear to be associated with this cancer in people with HIV. Increased tobacco is a likely cause of the increased occurrence in HIV disease.

3.5 Cancers That Do Not Occur at Increased Rates in People with HIV Infection

Given the large range of cancer types that occur at increased rates in people with HIV, it is notable that for several of the cancer types that occur commonly in the general population, incidence is not increased. These cancers include breast cancer, prostate cancer, and colorectal carcinoma.

Breast Cancer

In a meta-analysis of prospective research, breast cancer incidence was neither increased in people with HIV (meta-analysis SIR 1·03, 95 % CI 0·89–1·20) nor in transplant recipients (meta SIR 1·15, 95 % CI 0·98–1·36) (Grulich et al. 2007). Studies from earlier in the HIV epidemic described a decreased incidence of breast cancer compared to the general population. Incidence increased towards that of the general population in more recent years. A potential explanation for that pattern is that prior to effective anti-retroviral therapy, women with AIDS received less breast cancer screening, and that with prolonged survival screening rates are likely to have increased.

Prostate Cancer

In the meta-analysis described above, prostate cancer incidence was decreased about 30 % in men with HIV. In transplant recipients incidence was not significantly different to 1 (meta-SIR 0·97, 95 % CI 0·78–1·19) (Grulich et al. 2007). In the USA, the decreased incidence of prostate cancer in people with AIDS was confined to the era when prostate-specific antigen was being used as a screening test. The deficit in incidence was confined to early stage-cancers and not present for advanced cancer. These findings suggest that decreased prostate cancer incidence is related to decreased cancer screening in men with AIDS.

Colorectal Cancer

In the meta-analysis described above, colorectal cancer incidence was not increased in people with HIV (meta-SIR 0·92, 95 % CI 0·78–1·08). In transplant recipients incidence was increased by about 70 % (Grulich et al. 2007). The reason for the increased incidence in organ transplant recipients is unclear.

3.6 Conclusion

As the HIV epidemic unfolds, the pattern of cancer occurrence in people with HIV has continued to change. A constant theme has been that people with HIV experience increased oncogenic exposure compared to the general population, and this has led to patterns of cancer that are often very distinct. Over the years, these increased exposures have changed, but in most populations have included immune deficiency, tobacco and alcohol, and oncogenic blood-borne and sexually transmitted infectious agents. The occurrence of immune deficiency in millions of people has given

us a unique opportunity to examine the role of infection in carcinogenesis. For many types of cancer, this has helped us delineate the role of infection in causing cancer. For a few others, most particularly for prostate and breast cancer, the absence of any increased risk in either people with HIV or organ transplant recipients has provided strong evidence that infection appears not to be an important cause.

The HIV epidemic is over 30 years old, and most people with HIV have acquired infection in early adulthood. With effective anti-retroviral therapy, these individuals are living substantially longer and a substantial ageing of the HIV-infected population is occurring. As a result, the large-scale interaction of the carcinogenic effects of mild immune deficiency with the much higher cancer incidence that is experienced in old age will occur. If people with HIV carry the relative risks of HIV-related cancer into older age, that will lead to a very large increase in the burden of HIV-related cancer. Such increases are already beginning to happen. However, to the extent that effective anti-retroviral therapies can completely or nearly completely remove the oncogenic effect of immune deficiency, then such increases may be lessened. Further follow-up of large cohorts of people with treated HIV is required to clarify these issues.

References

Chaturvedi AK, Madeleine MM, Biggar RJ, Engels EA. Risk of human papillomavirus-associated cancers among persons with AIDS. J Natl Cancer Inst. 2009;101:1120–30.

Clifford GM, Rickenbach M, Polesel J, Dal Maso L, Steffen I, et al. Influence of HIV-related immunodeficiency on the risk of hepatocellular carcinoma. AIDS (London, England). 2008;22:2135–41.

Clifford GM, Lise M, Franceschi S, Egger M, Bouchardy C, et al. Lung cancer in the Swiss HIV Cohort Study: role of smoking, immunodeficiency and pulmonary infection. Br J cancer. 2012;106:447–52.

Feng H, Shuda M, Chang Y, Moore PS. Clonal integration of a polyomavirus in human Merkel cell carcinoma. Science. 2008;319:1096–100.

Grulich AE, van Leeuwen MT, Falster MO, Vajdic CM. Incidence of cancers in people with HIV/AIDS compared with immunosuppressed transplant recipients: a meta-analysis. Lancet. 2007;370:59–67.

Guiguet M, Boue F, Cadranel J, Lang JM, Rosenthal E, Costagliola D. Effect of immunodeficiency, HIV viral load, and antiretroviral therapy on the risk of individual malignancies (FHDH-ANRS CO4): a prospective cohort study. Lancet Oncol. 2009;10:1152–9.

International Agency for Research on Cancer (IARC). A review of human carcinogens. Part B: Biological agents. Lyon: International Agency for Research on Cancer; 2009.

Persson EC, Shiels MS, Dawsey SM, Bhatia K, Anderson LA, Engels EA. Increased risk of stomach and esophageal malignancies in people with AIDS. Gastroenterology. 2012;143:943–50, e2.

Reekie J, Kosa C, Engsig F, Monforte AD, Wiercinska-Drapalo A, et al. Relationship between current level of immunodeficiency and non-acquired immunodeficiency syndrome-defining malignancies. Cancer. 2010;116:5306–15.

Sahasrabuddhe VV, Shiels MS, McGlynn KA, Engels EA. The risk of hepatocellular carcinoma among individuals with acquired immunodeficiency syndrome in the United States. Cancer. 2012;118:6226–33.

Shebl FM, Engels EA, Goedert JJ, Chaturvedi AK. Pulmonary infections and risk of lung cancer among persons with AIDS. J Acquir Immune Defic Syndr (1999). 2010;55:375–9.

Silverberg MJ, Chao C, Leyden WA, Xu L, Horberg MA, et al. HIV infection, immunodeficiency, viral replication, and the risk of cancer. Cancer Epidemiol Biomarkers Prev. 2011;20:2551–9.
Silverberg MJ, Lau B, Justice AC, Engels E, Gill MJ, et al. Risk of anal cancer in HIV-infected and HIV-uninfected individuals in North America. Clin Infect Dis. 2012;54:1026–34.
Silverberg MJ, Leyden W, Warton EM, Quesenberry Jr CP, Engels EA, Asgari MM. HIV infection status, immunodeficiency, and the incidence of non-melanoma skin cancer. J Natl Cancer Inst. 2013;105:350–60.
van Leeuwen MT, Vajdic CM, Middleton MG, McDonald AM, Law M, et al. Continuing declines in some but not all HIV-associated cancers in Australia after widespread use of antiretroviral therapy. AIDS (London, England). 2009;23:2183–90.