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Complete List of Authors:	Swart, Alexander; University of New South Wales, Prince of Wales Clinical School Burns, Lucinda; University of New South Wales, National Drug and Alcohol Research Centre Mao, Limin; University of New South Wales, National Centre in HIV Social Research Grulich, Andrew; National Centre in HIV Epidemiology Amin, Janaki; University of New South Wales, Kirby Institute O'Connell, Dianne; The Cancer Council NSW, Cancer Epidemiology Research Unit Meagher, Nicola; University of New South Wales, Prince of Wales Clinical School Randall, Deborah; University of Western Sydney, Degenhardt, Louisa; University of NSW, National Drug and Alcohol Research Centre Vajdic, Claire; University of New South Wales, Prince of Wales Clinical School
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The importance of blood-borne viruses in elevated cancer risk among opioid dependent people: a population-based cohort study

Alexander Swart[1], Lucinda Burns[2], Limin Mao[3], Andrew E. Grulich[4], Janaki Amin[4], Dianne L. O'Connell[5,6,7,8], Nicola S. Meagher[1], Deborah A. Randall[9], Louisa Degenhardt[2,10], Claire M. Vajdic[1]

1 Adult Cancer Program, Lowy Cancer Research Centre, Prince of Wales Clinical School, Faculty of Medicine at the University of New South Wales, NSW 2052, Australia.

2 National Drug and Alcohol Research Centre, Faculty of Medicine at the University of New South Wales, NSW 2052, Australia

3 National Centre in HIV Social Research, Faculty of Arts and Social Sciences at the University of New South Wales, NSW 2052, Australia

4 Kirby Institute, Faculty of Medicine at the University of New South Wales, NSW 2052, Australia

5 Cancer Research Division, Cancer Council NSW, NSW 2011, Australia

6 School of Medicine and Public Health, Faculty of Health, University of Newcastle

7 School of Public Health and Community Medicine, University of New South Wales, NSW 2052, Australia

8 Sydney Medical School – Public Health, University of Sydney, NSW 2006, Australia

9 School of Medicine, University of Western Sydney, NSW 2751, Australia

10 Centre for Health Policy, Programs and Economics, School of Population Health, University of Melbourne, Victoria 3010, Australia

Corresponding author

Claire M. Vajdic, Adult Cancer Program, Lowy Cancer Research Centre, University of New South Wales, NSW 2052, Australia. Phone (61-2) 9385 1424; fax (61-2) 9385 1430; email: claire.vajdic@unsw.edu.au

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ARTICLE SUMMARY

Article focus

- Opioid dependence is associated with exposure to a number of carcinogens, including the blood-borne viruses hepatitis B, hepatitis C and HIV.
- The risk of cancer in opioid dependence has been examined in two studies with insufficient power to address risk for all cancer types.
- There is no prior evidence on the association between blood-borne virus infection and cancer risk in people who are opioid dependent.

Key messages

- People who are opioid dependent have an excess risk of a range of cancers compared with the general population.
- The excess cancer risk is predominantly restricted to those with blood-borne virus infection.
- Cancer incidence rates have increased dramatically over time, supporting use of the opioid substitution therapy setting to implement targeted cancer prevention strategies.

Strengths and limitations

- The study is based on a large population-based cohort with infections and outcomes obtained from registries.
- Misclassification of infection by blood-borne viruses is possible because not all OST recipients will have been routinely tested.
- Data on blood-borne virus treatment and vaccination are not available.

ABSTRACT

Objective To quantify cancer risk in opioid dependence and the association with infection by the oncogenic blood-borne viruses (BBVs) hepatitis C (HCV), hepatitis B (HBV), and HIV infection.

Design Cohort study.

Setting New South Wales, Australia.

Participants 45 412 adults aged 16 years or over registered for opioid substitution therapy (OST) between 1985 and 2007. Notifications of cancer, death, and infection with HCV, HBV, and HIV were ascertained by record linkage with registries.

Main outcome measures The ratios of observed to expected number of cancers, standardised incidence ratios (SIRs), and the average annual percent change (AAPC) in overall age and sex-standardised cancer incidence.

Results Overall cancer risk was modestly increased compared to the general population (SIR 1.15, 95% CI 1.07 to 1.23). Excess risk was observed for 11 cancers, particularly lung (4.02, 95% CI 3.32 to 4.82), non-Hodgkin lymphoma (1.51, 95% CI 1.20 to 1.88), and liver (8.04, 95% CI 6.18 to 10.3). Reduced risk was observed for six cancers, including prostate (0.16, 95% CI 0.06 to 0.32) and breast (0.48, 95% CI 0.35 to 0.62). Individuals notified with HCV or HBV had a markedly increased risk of liver cancer; lung cancer risk was also increased in those with HCV. HIV was associated with an elevated risk of liver, anus, and kidney cancer, non-Hodgkin lymphoma and Kaposi sarcoma. Cancer risk was not increased in individuals without a BBV notification, apart from pancreatic cancer (3.92, 95% CI 1.07 to 10.0). Cancer incidence increased significantly over time (AAPC 9.4%, 4.2 to 15%, p=0.001).

Conclusions BBVs play a major role in the cancer risk profile of opioid-dependent individuals registered for OST. To address the dramatic increasing trend in cancer incidence,

the OST setting should be utilised for targeted strategies including BBV prevention and treatment.

INTRODUCTION

Opioid-dependent individuals are exposed to a multitude of carcinogens. People who inject drugs are more likely to have hepatitis C (HCV), hepatitis B (HBV) or human immunodeficiency virus (HIV).[1] Tobacco-smoking and hazardous alcohol use are extremely common,[2] as are risky sexual practices, resulting in high rates of infection with human papillomavirus (HPV).[3] Although it is an effective treatment for heroin and other opioid dependence,[4] opioid substitution therapy (OST) use is typically cyclic,[5] with relapse to drug injection a common occurrence.

In Australia, the long-standing and widespread availability of OST and public health initiatives such as needle and syringe programmes (NSPs) have extended the life expectancy of opioid-dependent people.[4, 6] In injecting drug users, the prevalence of HIV is low (<1% in heterosexuals), whereas the prevalence of hepatitis C is high (50-60%),[7] and one of the consequences of this success is the attendant risk of age-related health conditions, including cancer.[8] The OST agents themselves are not considered risk factors for cancer as murine studies indicate they are not carcinogenic.[9, 10]

Despite evidence of exposure to multiple cancer risk factors and the public health impact that this may have upon ageing cohorts of opioid-dependent people, there has been no population-based study of the spectrum of cancer risk in this group and no study of this risk in relation to blood-borne virus (BBV) infection. We examined these associations among 45412 people who entered OST in New South Wales (NSW), Australia over a 23-year period, considering 1) overall and site-specific cancer incidence, 2) the cancer risk profiles of those infected with HCV, HBV, and HIV, and 3) trends in cancer incidence over time.

METHODS

Study population

We conducted a cohort study using record linkage between existing population-based health datasets. The study population comprised individuals registered on the Pharmaceutical Drugs of Addiction System, a record of all NSW Health Department authorities that administer methadone or buprenorphine to opioid-dependent people. Included were all adults (≥16 years) registered for OST between 1st January 1985, the date of inception of the system, and 31st December 2007, the latest date for which cancer diagnoses were available (n=45 483). Individuals were excluded from the cohort if information essential for record linkage was incomplete (n=10, 0.02%) or if the OST end date preceded the start date (n=61, 0.13%). Registrants diagnosed with cancer prior to commencing OST (n=183, 0.40%) were not excluded; however they did not contribute time at risk for that cancer.

HBV and HCV notification data were available for NSW residents only from 1993. Therefore our analyses of cancer risk in those with hepatitis notifications and those with no BBVs (no HCV, HBV, or HIV notification) were restricted to a sub-cohort of individuals registered for OST from 1st January 1993 (n=32 075). To limit the potential for under-ascertainment of hepatitis notifications, interstate OST registrants (n=2 462, 7.68%) were excluded and other OST registrants where censored when they moved interstate OST (n=2 297, 7.76%).

Data collection

In Australia, all deaths, newly diagnosed cancers (excluding basal and squamous cell carcinoma of the skin), and HCV, HBV, and HIV infections must be reported to government agencies by statute. Dates of death in OST registrants were ascertained by linkage with the National Death Index (1980–2007). The date of diagnosis, topography and morphology of

incident cancers were identified by linkage with the Australian Cancer Database, a register of incident primary invasive neoplasms (1982–2007). Solid cancers were classified according to the International Classification of Diseases (ICD), 10th revision while haematopoietic neoplasms and Kaposi sarcomas were classified according to the ICD for Oncology, 3rd edition. Dates of HIV and acquired immunodeficiency syndrome (AIDS) notifications were ascertained by linkage with the National HIV Database (1985–2007) and the National AIDS Register (1982–2007), respectively. Linkage with the NSW Health Notifiable Conditions Information Management System (1993–2007) identified dates of HBV and HCV notifications for the sub-cohort, based on detection of HBV surface antigen or HBV DNA and anti-HCV antibody or HCV RNA, respectively.

The name, sex, date of birth, date of death, and state of residence of registrants were used for record linkage. All linkages used probabilistic matching techniques except the HIV/AIDS linkage which used deterministic methods because only the first two letters of the given name and surname, not full name, were recorded on these registers.

Cancer incidence rates for the Australian population were obtained from the Australian Cancer Database by five-year age group, sex, calendar year, and state/territory, for 1985 to 2007.

Data analysis

Cancer incidence

Person-years of follow-up accumulated from the date of first OST registration and terminated at the first occurrence of cancer diagnosis, death, age 80, interstate transfer (for BBV analyses only), or 31st December 2007.

Crude and age/sex-standardised cancer incidence rates, standardised to the 1996 Australian population, and Poisson 95% confidence intervals (CIs) were calculated using annual Australian population estimates from the Australian Bureau of Statistics. To describe overall cancer incidence trends over time the average annual per cent change (AAPC) was estimated using Poisson regression.[11]

Relative risk of cancer

Risk of cancer overall and for each cancer type were examined in the full cohort (1985–2007) and the sub-cohort (1993–2007) using the standardised incidence ratio (SIR), the ratio of the observed and the expected numbers of cancers. The expected numbers of incident cancers were calculated by multiplying cohort person-years at risk by five-year age-, sex-, state-, and calendar year-specific population cancer incidence rates. The exception was Kaposi sarcoma, where 1982 population rates were used to avoid the impact of AIDS on the incidence of this cancer. The SIRs were computed for cancer overall and for the most frequently occurring cancers by sex and age at follow-up (<40, 40–49, ≥50years). In addition, SIRs were calculated by BBV notification status; HIV with or without HBV or HCV; HBV monoinfection; HCV monoinfection; HBV/HCV co-infection; and HBV/HCV/HIV uninfected. BBV infection was examined in a time-dependent manner, accounting for change in notification status over time.

For registrants with an AIDS notification only or an HIV notification occurring less than five years before the AIDS notification (n=59, 0.13%), the date of HIV infection was backdated to five years prior to the AIDS notification or to the date of cohort entry, whichever occurred later, to more accurately estimate the date of HIV infection. The resultant retrospectively

defined person-years were survival-adjusted by applying period-specific, all-age, sex-, and site-specific cancer survival rates to account for those individuals with HIV infection who may have developed cancer and subsequently died before being diagnosed with HIV.[12] A similar adjustment was performed as a sensitivity analysis for liver cancer risk in those notified with HCV, assuming a median age at infection of 25 years for injecting drug user (IDU)-acquired infection[13] and backdating HCV infection up to 15 years.

We compared patterns of cancer risk for the BBV subgroups but could not compare SIRs statistically because of the heterogeneity in subgroup age and sex distributions.[14]

Within-cohort risk factors were examined for the most frequently occurring cancers in the sub-cohort (1993–2007); liver, lung, and non-Hodgkin lymphoma. Sex and the time-dependent factors—current age, calendar year, and HBV, HCV, and HIV notification—were *a priori* included in all multivariable models. Poisson regression was used to determine incidence rate ratios (IRRs) with 95% CIs.

Analyses were performed using SAS® software v9.2 (SAS Institute Inc., Cary, NC, USA) and Joinpoint Regression Program, v3.5 (Statistical Methodology and Applications Branch and Data Modeling Branch, Surveillance Research Program, National Cancer Institute). Person-years were calculated using the *%stratify* macro.[15]

RESULTS

After applying exclusion criteria, 45412 individuals registered for OST between 1985 and 2007 were included in the study cohort (Table 1a). This cohort accumulated 481936 person-

years of follow-up for cancer, a median of 9.9 person-years per registrant (interquartile range [IQR] 5.61 to 15.2; Table 1a). Two-thirds of the cohort was male. The median age at OST registration was 27 years and the median cumulative time on OST was 2.6 years (IQR 0.6 to 6.5). A total of 423 (0.8%) registrants were notified with a HIV/AIDS diagnosis prior to or after OST registration.

We observed 819 (1.8%) incident primary cancers (803 first, 16 second cancers) after OST registration and the median age at diagnosis of first cancer was 43 (IQR 37 to 49) years.

After applying further exclusion criteria, the sub-cohort with assessable hepatitis data comprised 29 613 participants entering OST between 1993 and 2007 (Table 1b). They were of similar age and sex as the full cohort (median age at OST registration, 26 years; 69% male). A total of 14 892 (50%) registrants were notified with HCV alone, 598 (2%) with HBV alone, and 898 (3%) with HBV and HCV. Over the 213 008 person-years of follow-up in the sub-cohort, 240 (0.8%) incident cancers were observed.

Cancer incidence

For the period 1985 to 2007 the crude cancer incidence rate was 170 per 100 000 person-years (95% CI 159 to 182). The age-standardised rate was 349 per 100 000 person-years (95% CI 337 to 361) and the annual age-standardised rate increased significantly between 1985 and 2007 (AAPC=9.4%, 95% CI 4.2 to 15%; p=0.001).

Cancer risk

Risk of cancer overall was slightly higher in OST registrants compared to the Australian population (SIR=1.15, 95% CI 1.07 to 1.23). SIRs were significantly greater than unity for

cancers of the tonsil, anus and anal canal, liver, pancreas, larynx, trachea bronchus and lung, vulva and cervix, Kaposi sarcoma, non-Hodgkin lymphoma and cancer of unknown primary site (Figure 1). Conversely, SIRs were significantly less than unity for melanoma and cancers of the colorectum, breast, prostate, brain and central nervous system and thyroid.

Risk of any cancer was significantly increased in men and in those more than 40 years of age (Table 2). Liver and lung cancer risk was increased in men and women; liver cancer risk was significantly increased only for those more than 40 years of age, while lung cancer risk was increased regardless of attained age. Similarly, women of all ages experienced half the risk of breast cancer.

Blood-borne viruses and cancer risk

Thirty-four cancers were observed in registrants notified with HIV (irrespective of infection with other BBVs), with an SIR of 6.68 (95% CI 4.63 to 9.34; Figure 2). SIRs were significantly greater than unity for several cancers, including Kaposi sarcoma, non-Hodgkin lymphoma, and anal cancer.

In those notified with HCV monoinfection, the overall risk of cancer was not significantly different from that of the general population (SIR=1.06, 95% CI 0.89 to 1.25; Figure 3) but the SIR for liver cancer was 6.61 (95% CI 3.02 to 12.5). After adjusting for an assumed age of HCV infection of 25 years and for survival, the SIR for liver cancer increased to 13.1 (95% CI 6.00 to 24.9). Risk of lung cancer and mouth cancer were also elevated. On the other hand, breast cancer risk was decreased and while six prostate cancers were expected, none were observed. Few cancers were observed in those notified with HBV (one case) or HBV-

HCV co-infection (18 cases). The risk of liver cancer in individuals notified with HBV-HCV co-infection was markedly elevated (SIR=35.9, 95% CI 7.41 to 105).

Registrants without a notification of BBV infection were at decreased risk of cancer overall (SIR=0.68, 95% CI 0.54 to 0.84; Figure 3) and melanoma. In this subgroup, no infection-related cancers occurred at rates significantly different to the general population; however the risk of pancreatic cancer was significantly elevated.

In multivariable analyses adjusting for age, calendar year, sex and HCV, HBV, and HIV notification status, age was an independent risk factor for the most frequently occurring cancers (Table 3). Notification of HBV and HCV infection predicted risk of liver cancer, and notification of HIV infection predicted risk of non-Hodgkin lymphoma. Notification of HCV infection independently predicted risk of lung cancer.

DISCUSSION

We found that cancer risk in opioid-dependent people registered for OST was significantly increased for a number of cancers causally related to infection with oncogenic viruses, smoking, and alcohol consumption. The excess cancer risk was almost entirely restricted to those notified with a BBV infection, except for pancreatic cancer. The most common cancers for which there was an excess risk were independently associated with increasing age and infection by one or more BBVs; liver cancer (HCV, HBV), lung cancer (HCV), and non-Hodgkin lymphoma (HIV). Cancer incidence also increased significantly over time, highlighting cancer as an emerging public health concern for this population.

Strengths and weaknesses

The strengths of this study include the large population size and the lengthy follow-up, which provided the statistical power to improve upon sparse knowledge of the cancer risk faced by the opioid dependent population. Additionally, use of national, population-based registers for ascertainment of cancer diagnoses, HIV/AIDS diagnoses, and deaths enabled unbiased and comprehensive follow-up of the cohort. On the other hand, although routine testing for BBV infection is recommended, it is likely that not all OST recipients were routinely tested, and use of the notification date in analysis underestimates the timing of the infection. We also lacked data on BBV treatment and HBV vaccination. Furthermore, it was not possible to determine serological clearance of HCV. Thus it is possible that we have misclassification with respect to BBV infection, meaning that we have under-estimated the association of chronic HCV infection with cancer in OST registrants.

In addition, this study was retrospective, relying upon linkage with routinely collected administrative data, and some false positive and negative linkages do occur. Nevertheless, quality assurance practices performed by the data linkage units can result in high sensitivity and specificity (e.g. hepatitis linkage sensitivity >99.9%, specificity 99.8%).[16] Given it is likely that around 50% of Australians with opioid dependence enter OST at some point,[17] our findings are likely to be generalisable to the broader opioid dependent population. Our cohort being a representative sample is supported by the similarity of BBV prevalence with NSP survey results.[7] With respect to other OST populations, our data may represent a conservative estimate of the public health burden given the markedly lower incidence of HIV infection in comparison to most other countries.[18]

Context

This is the first population-based study of cancer incidence among people who are opioid dependent, and the first study to examine cancer incidence in relation to BBV infection. Of the two prior studies measuring cancer incidence in opioid dependent populations, one had very limited statistical power and examined a US cohort of mostly Hispanic injecting drug users with a high prevalence of HIV,[19] while the other studied Israeli OST recipients but did not link with a population-based death registry and examined risk for only eight cancer types.[20]

Explanations

Apart from Kaposi sarcoma, the strongest excess cancer risk in those registered for OST was observed for liver cancer. Stratification by BBV notification and within-cohort risk factor analyses showed that this excess risk occurred only in those with BBV infection, especially HCV alone or HCV/HBV co-infection. Surveillance bias did not strongly affect our risk estimates, as only one liver cancer was diagnosed within six months of commencing OST. Lung cancer risk was elevated in the cohort overall and in the subgroup with HCV. Whilst HCV notification independently predicted lung cancer risk, there is no evidence of a biological link and this result may indicate those with HCV smoke more heavily than those without HCV. Tobacco exposure may also explain the excess risk of mouth cancer in this subgroup. The excess risk of liver[20] and lung[19, 20] cancer is consistent with prior evidence.

An excess risk of Kaposi sarcoma, non-Hodgkin lymphoma, and anal cancer was observed in OST registrants overall, particularly those with HIV. These cancers have an established causal association with HIV-related immunosuppression and are likely to result from impaired immune surveillance in people with infection by Kaposi sarcoma-associated herpesvirus, Epstein-Barr virus, and HPV, respectively.[21] An excess risk of five non-AIDS-

defining malignancies was also observed, supporting evidence that these cancers are becoming increasingly important for those with HIV infection.[22]

A number of cancers occurred at rates significantly lower than in the matched general population. For melanoma, two explanations are suggested. Firstly, Aboriginal Australians, who experience one-tenth the risk of melanoma compared to non-Aboriginal Australians, are over-represented in the OST population compared to the general population (11% vs. 1.5–2.0%).[23] Secondly, 69% of a recent sample (n=154) of active IDUs in NSW reported a history of incarceration,[17] which limits sun exposure, an established risk factor for melanoma. Under-participation in population-based and other cancer screening programs may explain the reduced risk of breast, colorectal and prostate cancer in OST recipients. However, only 4% of the total follow-up time was contributed by individuals who were age-eligible for these programs, substantially weakening the case for attenuation in risk due to under-participation in screening. A reduced risk of colorectal and breast cancer was observed in Israeli OST recipients,[20] and there is some evidence that opioid use may impart a decreased risk of certain cancers. For example, a side-effect of chronic opioid use is hypogonadism, resulting in low oestrogen (women) and testosterone (men).[24] Low levels of these hormones may decrease premenopausal breast cancer and prostate cancer risk, however the evidence is inconclusive.[25, 26] Characteristics common to OST registrants, high parity and early age at first pregnancy,[17, 27] both considered protective for breast cancer,[28] as well as reduced prevalence of overweight and obesity,[29] may also contribute to the observed risk reduction.

Implications

The observed cancer risk profile strongly supports the implementation of targeted cancer prevention strategies in the OST setting. Given the concentration of excess risk among those

with BBV notifications, and the high prevalence of HCV among this population, there is a clear need for interventions that reduce HCV incidence[4] and that treat people who have developed chronic infections.[1] NSPs are highly effective at reducing the rate of acquisition of BBVs.[4] Antiviral treatments for HCV and HBV infection induce regression of fibrosis and decrease liver cancer risk.[30] People with a history of injecting drug use respond positively to HCV therapies, with acceptable levels of sustained virological response[31] and antiviral therapy is also not contraindicated in people with HIV receiving OST. The issue, however, is one of coverage. Many physicians remain unwilling to provide such treatments to people who use illicit drugs in the face of evidence that they have similar levels of adherence to treatment as other patient groups.[32] Thus, despite HCV being one of the strongest risk factors for cancer in OST, very few people in OST have received treatment to address this risk.[1]

As the risks for cancers with established causal links to tobacco-smoking and alcohol use were elevated, namely lung, larynx, and pancreatic cancer (smoking), and liver, oral, larynx, and oesophageal cancer (alcohol), a reduction in these behaviours would similarly mitigate cancer risk. OST clients show strong interest in smoking cessation programs,[33] and they do not adversely impact OST,[34] but again few are offered such treatments in routine healthcare settings. The excess risk of cancer of the cervix, vulva and anus, cancers caused by chronic infection with HPV, may be reduced by safer sexual practices. The increased risk of cervical cancer also supports the need for greater participation in cervical screening.

Conclusions

Opioid-dependent people registered for OST face an excess risk of a variety of cancers compared to the general population, in particular cancers associated with infection by BBVs. The implementation of harm reduction strategies in the OST setting represents an evidently

underutilised opportunity to respond to the escalating cancer burden facing this marginalised population.

LIST OF FIGURE LEGENDS

Figure 1 Risk of cancer among NSW opioid substitution therapy registrants, 1985–2007

Key

Obs=observed number of cancers. Exp=expected number of cancers. SIR=standardised incidence ratio. CI=confidence interval. CNS=central nervous system.

*Includes non-Hodgkin lymphoma not otherwise specified (International Classification of Diseases for Oncology, 3rd edition: 9590).

Non-melanoma skin cancer excludes diagnoses of basal cell and squamous cell carcinoma.

Figure 2 Risk of cancer in NSW opioid substitution therapy registrants with notified HIV infection, 1985–2007

Key

Obs=observed number of cancers. Exp=expected number of cancers. SIR=standardised incidence ratio. CI=confidence interval.

*Includes non-Hodgkin lymphoma not otherwise specified (International Classification of Diseases for Oncology, 3rd edition: 9590).

Figure 3 Risk of cancer among NSW opioid substitution therapy registrants with notified hepatitis C infection and registrants without notified hepatitis B, hepatitis C or HIV infection, 1993–2007

Key

*Includes non-Hodgkin lymphoma not otherwise specified (International Classification of Diseases for Oncology, 3rd edition: 9590)

[†]SIRs not estimated for cancers with less than 3 observed cases

Table 1a Characteristics of all NSW opioid substitution therapy registrants and those with notified HIV infection, 1985–2007

	Entire cohort			HIV infection		
		Person-years			Person-years	
	No. (%) of registrants	Total	Median (IQR)	No. (%) of registrants	Total	Median (IQR)
Total	45 412 (100)	481 936	9.94 (5.61–15.2)	426 (100)	3511	7.60 (3.66–12.4)
Sex						
Men	30 147 (66.4)	310 632	9.67 (5.31–14.8)	346 (81.2)	2796	7.58 (3.63–11.8)
Women	15 265 (33.6)	171 304	10.6 (6.30–16.2)	80 (18.8)	715	7.68 (3.72–14.6)
Age at cohort entry (years)						
<25	16 266 (35.8)	166 503	9.48 (5.83–14.0)	139 (32.6)	1176	7.38 (3.87–13.0)
25–30	14 680 (32.3)	171 073	11.3 (6.26–17.4)	120 (28.2)	1027	7.96 (3.75–11.7)
≥31	14 466 (31.9)	144 361	9.46 (4.86–14.4)	167 (39.2)	1308	7.25 (2.83–12.7)
Year of cohort entry						
1985–1989	8476 (18.7)	161 566	20.4 (18.7–21.8)	75 (17.6)	887	10.2 (6.02–19.2)
1990–1995	11 220 (24.7)	152 938	14.1 (12.7–15.7)	140 (32.9)	1479	12.8 (5.99–14.8)
1996–2001	15 302 (33.7)	133 232	8.84 (7.35–10.4)	122 (28.6)	908	8.00 (6.33–9.65)
2002–2007	10 414 (22.9)	34 200	3.44 (1.88–4.81)	89 (20.9)	237	2.72 (1.22–3.89)

Table 1b Characteristics of NSW opioid substitution therapy registrants, by BBV notification status, 1993–2007

	Entire sub-cohort			No BBV infection			HBV monoinfection			HCV monoinfection			HBV/HCV co-infection			HIV infection[†]		
		Person-years			Person-years			Person-years			Person-years			Person-years			Person-years	
	No. (%) of registrants[*]	Total	Median	No. (%) of registrants	Total	Median	No. (%) of registrants	Total	Median	No. (%) of registrants	Total	Median	No. (%) of registrants	Total	Median	No. (%) of registrants	Total	Median
Total	29 613 (100)	213 008	7.28	23 650 (100)	109 313	3.53	598 (100)	2608	3.56	14 892 (100)	94 331	6.36	898 (100)	5249	6.02	234 (100)	1504	6.20
Sex																		
Men	20 348 (68.7)	144 932	7.19	16 352 (69.1)	76 495	3.64	436 (72.9)	1918	3.60	9793 (65.8)	61 378	6.29	643 (71.6)	3782	6.10	204 (87.2)	1355	6.55
Women	9265 (31.3)	68 076	7.51	7298 (30.9)	32 818	3.25	162 (27.1)	691	3.50	5099 (34.2)	32 953	6.47	255 (28.4)	1466	5.94	30 (12.8)	148	4.35
Age at cohort entry (years)																		
<25	11 674 (39.4)	87 088	7.60	9915 (41.9)	47 340	3.81	278 (46.5)	1282	3.96	5706 (38.3)	35 963	6.41	351 (39.1)	2130	6.27	61 (26.1)	373	6.08
25–30	8427 (28.5)	60 907	7.32	6771 (28.6)	31 905	3.56	169 (28.3)	770	3.18	4106 (27.6)	26 201	6.42	266 (29.6)	1534	5.79	68 (29.1)	494	7.73
>31	9512 (32.1)	65 013	6.74	6964 (29.4)	30 068	3.06	151 (25.3)	555	3.39	5080 (34.1)	32 167	6.23	281 (31.3)	1584	5.71	105 (44.9)	637	5.17
Year of cohort entry																		
1993–1997	10 212 (34.5)	111 454	11.7	8944 (37.8)	54 619	4.76	158 (26.4)	981	5.08	3563 (23.9)	36 132	11.2	129 (14.4)	1298	10.9	84 (35.9)	754	10.7
1998–2002	11 655 (39.4)	81 399	7.36	8962 (37.9)	42 095	5.35	290 (48.5)	1304	5.12	6958 (46.7)	47 049	7.05	475 (52.9)	3167	6.80	82 (35.0)	573	7.55
2003–2007	7746 (26.2)	20 155	2.70	5744 (24.3)	12 599	2.11	150 (25.1)	323	2.01	4371 (29.4)	11 150	2.55	294 (32.7)	784	2.75	68 (29.1)	177	2.71

[*] Category numbers will not sum to total numbers for the sub-cohort as individuals were followed-up in a time-dependent manner, allowing an individual to contribute person-years to multiple groups as their BBV notification status changed over the period of observation.

[†] With or without HBV or HCV notification.

Table 2 Risk of any cancer and the most frequently occurring cancers in NSW opioid substitution therapy registrants, by sex and current age (1985–2007)

Cancer type	Obs.	Exp.	SIR	95% CI
All cancer				
Men	536	431	1.24	1.14–1.35
Women	283	285	0.99	0.88–1.11
<40 yrs	282	295	0.96	0.85–1.07
40–49 yrs	357	282	1.27	1.14–1.40
≥50 yrs	180	139	1.30	1.12–1.50
Liver				
Men	51	6.92	7.37	5.49–9.69
Women	12	0.91	13.2	6.80–23.0
<40 yrs	4	1.62	2.47	0.67–6.33
40–49 yrs	26	3.96	6.57	4.29–9.63
≥50 yrs	33	2.26	14.6	10.1–20.6
Trachea, bronchus, and lung				
Men	82	19.8	4.15	3.32–5.11
Women	28	7.59	3.69	2.45–5.33
<40 yrs	15	4.11	3.65	2.04–6.02
40–49 yrs	58	13.0	4.46	3.41–5.71
≥50 yrs	37	10.2	3.61	2.57–4.90
Melanoma				
Men	64	91.2	0.70	0.54–0.89
Women	37	48.7	0.76	0.54–1.03
<40 yrs	48	71.6	0.67	0.50–0.88
40–49 yrs	37	51.4	0.72	0.51–0.98
≥50 yrs	16	16.9	0.95	0.56–1.49
Female breast				
<40 yrs	15	32.5	0.46	0.27–0.74
40–49 yrs	27	54.3	0.48	0.32–0.69
≥50 yrs	6	14.1	0.43	0.17–0.86
Cervical				
<40 yrs	21	11.0	1.90	1.20–2.84
40–49 yrs	14	4.67	3.00	1.64–5.03
≥50 yrs	2	0.63	3.19	0.39–11.5
Non-Hodgkin lymphoma				
Men	62	38.1	1.63	1.26–2.07
Women	13	11.5	1.13	0.62–1.86
<40 yrs	25	20.9	1.20	0.79–1.73
40–49 yrs	37	19.8	1.87	1.33–2.54
≥50 yrs	13	8.94	1.46	0.78–2.49

Obs=observed number of cancers. Exp=expected number of cancers. SIR=standardised incidence ratio. CI=confidence interval.

Table 3 Multivariable analysis of risk factors for common cancers among NSW opioid substitution therapy registrants, 1993-2007

	Lung Cancer				Non-Hodgkin lymphoma				Liver Cancer			
	n	**IRR***	**95%CI**	**P**	**n**	**IRR***	**95%CI**	**P**	**n**	**IRR***	**95%CI**	**P**
Current age†	27	1.19	1.15–1.24	<0.0001	23	1.06	1.01–1.11	0.025	13	1.20	1.13–1.27	<0.0001
Calendar year†	27	0.91	0.81–1.03	0.131	23	1.16	1.01–1.37	0.054	13	1.13	0.91–1.49	0.317
Sex												
Men	22	1.55	0.63–4.65	0.378	17	1.03	0.42–2.90	0.954	12	3.94	0.76–72.2	0.190
Women (ref)	5	1.00			6	1.00			1	1.00		
Notified HCV infection												
Yes	21	3.29	1.39–9.07	0.011	13	1.12	0.49–2.65	0.792	12	9.05	1.73–166	0.036
No (ref)	6	1.00			10	1.00			1	1.00		
Notified HBV infection‡												
Yes	2	1.59	0.25–5.42	0.531	0	-			3	4.63	1.03–15.4	0.021
No (ref)	25	1.00			23				10	1.00		
Notified HIV infection‡												
Yes	0	-			4	26.0	7.40–71.3	<0.0001	0	-		
No (ref)	27				19	1.00			13			

IRR=incidence rate ratio. CI=confidence interval. Ref=reference group in analysis.

*Adjusted for current age (years), calendar year, sex and time-dependent HCV notification status, HBV notification status and HIV notification status

†IRR refers to one year increase

‡IRRs could not be calculated if a cancer case did not occur in one of the binary groupings

Note: Infection groupings are not mutually exclusive

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CONTRIBUTORS

The study was conceived and designed by CMV, LB and LD. The data were obtained from data custodians by LM, NSM and CMV. All authors contributed to the analytical plans. The data were prepared and analysed by AS. AS, CMV and LD drafted the paper. All authors reviewed, revised and approved the final draft. CMV is the guarantor.

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COMPETING INTERESTS

All authors report no disclosures.

ETHICS APPROVAL

The study was reviewed and approved by all relevant ethics committees and the requirement for informed consent was waived because the researchers received only de-identified data.

DATA SHARING STATEMENT

There is no additional data available.

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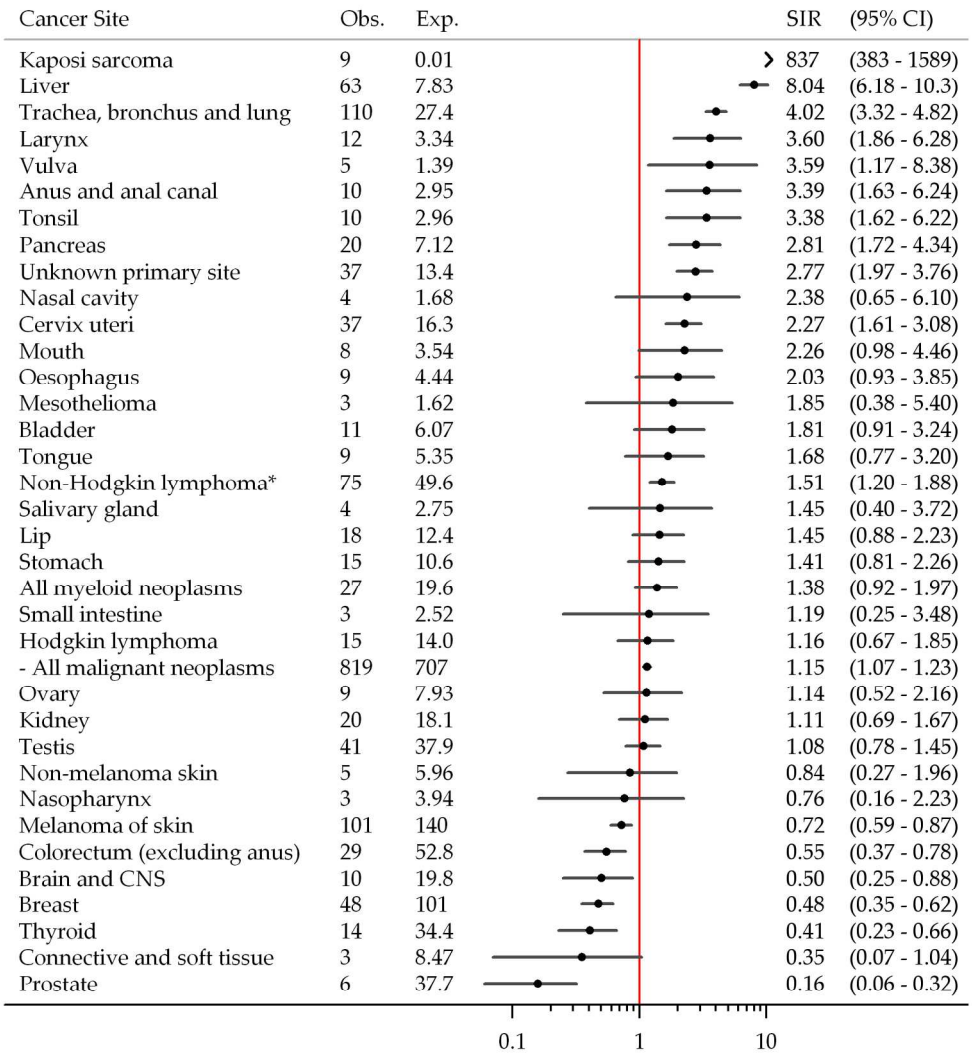

Figure 1 Risk of cancer among NSW opioid substitution therapy registrants, 1985–2007
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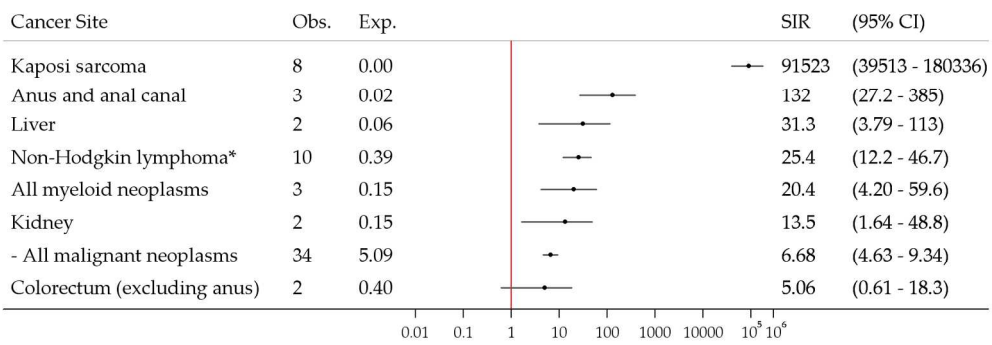

Figure 2 Risk of cancer in NSW opioid substitution therapy registrants with notified HIV infection, 1985–2007
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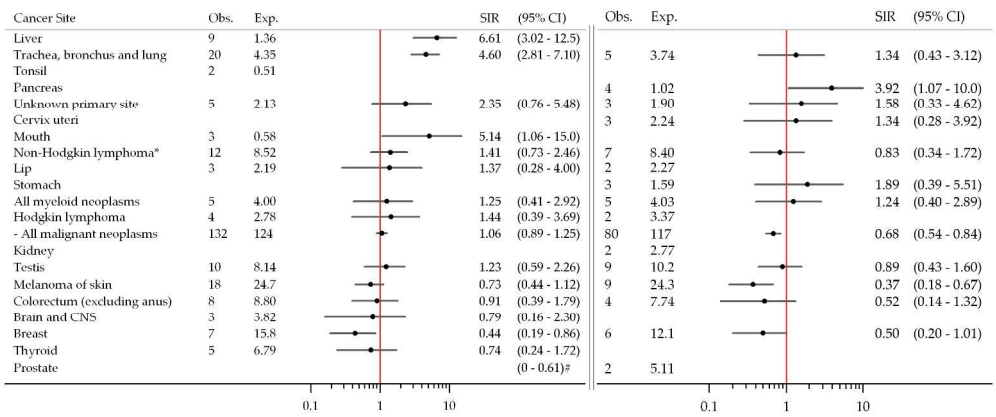

Figure 3 Risk of cancer among NSW opioid substitution therapy registrants with notified hepatitis C infection and registrants without notified hepatitis B, hepatitis C or HIV infection, 1993–2007
872x360mm (96 x 96 DPI)

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The importance of blood borne viruses in elevated cancer risk among opioid dependent people: a population-based cohort study

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The importance of blood-borne viruses in elevated cancer risk among opioid dependent people: a population-based cohort study

Alexander Swart[1], Lucinda Burns[2], Limin Mao[3], Andrew E. Grulich[4], Janaki Amin[4], Dianne L. O'Connell[5,6,7,8], Nicola S. Meagher[1], Deborah A. Randall[9], Louisa Degenhardt[2,10], Claire M. Vajdic[1]

1 Adult Cancer Program, Lowy Cancer Research Centre, Prince of Wales Clinical School, Faculty of Medicine at the University of New South Wales, NSW 2052, Australia.

2 National Drug and Alcohol Research Centre, Faculty of Medicine at the University of New South Wales, NSW 2052, Australia

3 National Centre in HIV Social Research, Faculty of Arts and Social Sciences at the University of New South Wales, NSW 2052, Australia

4 Kirby Institute, Faculty of Medicine at the University of New South Wales, NSW 2052, Australia

5 Cancer Research Division, Cancer Council NSW, NSW 2011, Australia

6 School of Medicine and Public Health, Faculty of Health, University of Newcastle

7 School of Public Health and Community Medicine, University of New South Wales, NSW 2052, Australia

8 Sydney Medical School – Public Health, University of Sydney, NSW 2006, Australia

9 School of Medicine, University of Western Sydney, NSW 2751, Australia

10 Centre for Health Policy, Programs and Economics, School of Population Health, University of Melbourne, Victoria 3010, Australia

Corresponding author

Claire M. Vajdic, Adult Cancer Program, Lowy Cancer Research Centre, University of New South Wales, NSW 2052, Australia. Phone (61-2) 9385 1424; fax (61-2) 9385 1430; email: claire.vajdic@unsw.edu.au

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ARTICLE SUMMARY

Article focus

- While opioids and opioid substitution therapies themselves are not known to be carcinogenic, opioid dependence is associated with exposure to a number of carcinogenic agents, including infection by the blood-borne viruses hepatitis B, hepatitis C, and HIV.
- The risk of cancer in opioid dependence has been examined in two studies with insufficient power to address risk for all cancer types.
- There is no prior evidence on the association between blood-borne virus infection and cancer risk in people who are opioid dependent.

Key messages

- People who are opioid dependent have an excess risk of a range of cancers compared with the general population.
- The excess cancer risk is predominantly restricted to those with blood-borne virus infection.
- Cancer incidence rates have increased dramatically over time, supporting use of the opioid substitution therapy setting to opportunistically implement targeted cancer prevention strategies.

Strengths and limitations

- The study is based on a large population-based cohort with infections and outcomes obtained from population-based registries.
- Misclassification of infection by blood-borne viruses is possible because not all OST recipients will have been routinely tested.
- Data on smoking, alcohol use, blood-borne virus treatment and vaccination are not available.

ABSTRACT

Objective To quantify cancer risk in opioid dependence and the association with infection by the oncogenic blood-borne viruses (BBVs) hepatitis C (HCV), hepatitis B (HBV), and HIV.

Design Cohort study.

Setting New South Wales, Australia.

Participants 45 412 adults aged 16 years or over registered for opioid substitution therapy (OST) between 1985 and 2007. Notifications of cancer, death, and infection with HCV, HBV, and HIV were ascertained by record linkage with registries.

Main outcome measures The ratios of observed to expected number of cancers, standardised incidence ratios (SIRs), and the average annual percent change (AAPC) in overall age and sex-standardised cancer incidence.

Results Overall cancer risk was modestly increased compared to the general population (SIR 1.15, 95% CI 1.07 to 1.23). Excess risk was observed for 11 cancers, particularly lung (4.02, 95% CI 3.32 to 4.82), non-Hodgkin lymphoma (1.51, 95% CI 1.20 to 1.88), and liver (8.04, 95% CI 6.18 to 10.3). Reduced risk was observed for six cancers, including prostate (0.16, 95% CI 0.06 to 0.32) and breast (0.48, 95% CI 0.35 to 0.62). Individuals notified with HCV or HBV had a markedly increased risk of liver cancer; lung cancer risk was also increased in those with HCV. HIV was associated with an elevated risk of liver, anus, and kidney cancer, non-Hodgkin lymphoma and Kaposi sarcoma. Cancer risk was not increased in individuals without a BBV notification, apart from pancreatic cancer (3.92, 95% CI 1.07 to 10.0). Cancer incidence increased significantly over time (AAPC 9.4%, 4.2 to 15%, p=0.001).

Conclusions BBVs play a major role in the cancer risk profile of opioid-dependent individuals registered for OST. To address the dramatic increasing trend in cancer incidence, the OST setting could be utilised for cancer prevention strategies.

INTRODUCTION

Opioid-dependent individuals are exposed to a multitude of carcinogens. People who inject drugs are more likely to have hepatitis C (HCV), hepatitis B (HBV) or human immunodeficiency virus (HIV).[1] Tobacco-smoking and hazardous alcohol use are extremely common,[2] as are risky sexual practices, resulting in high rates of infection with human papillomavirus (HPV).[3] Although it is an effective treatment for heroin and other opioid dependence,[4] opioid substitution therapy (OST) use is typically cyclic,[5] with relapse to drug injection a common occurrence.

In Australia, the long-standing and widespread availability of OST and public health initiatives such as needle and syringe programmes (NSPs) have extended the life expectancy of opioid-dependent people.[4, 6] In injecting drug users, the prevalence of HIV is low (<1% in heterosexuals), whereas the prevalence of hepatitis C is high (50-60%).[7] However one of the consequences of the increased longevity of opioid-dependent people is the attendant risk of age-related health conditions, including cancer.[8] The OST agents themselves are not considered risk factors for cancer as murine studies indicate they are not carcinogenic.[9, 10]

Despite evidence of exposure to multiple cancer risk factors and the public health impact that this may have upon ageing cohorts of opioid-dependent people, there has been no population-based study of the spectrum of cancer risk in this group and no study of this risk in relation to blood-borne virus (BBV) infection. We examined these associations among 45412 people who entered OST in New South Wales (NSW), Australia over a 23-year period, considering 1) overall and site-specific cancer incidence, 2) the cancer risk profiles of those infected with HCV, HBV, and HIV, and 3) trends in cancer incidence over time.

METHODS

Study population

We conducted a cohort study using record linkage between existing population-based health datasets. The study population comprised individuals registered on the Pharmaceutical Drugs of Addiction System, a record of all NSW Health Department authorities that administer methadone or buprenorphine to opioid-dependent people. Included were all adults (≥16 years) registered for OST between 1st January 1985, the date of inception of the system, and 31st December 2007, the latest date for which cancer diagnoses were available (n=45 483). Individuals were excluded from the cohort if information essential for record linkage was incomplete (n=10, 0.02%) or if the OST end date preceded the start date (n=61, 0.13%). Registrants diagnosed with cancer prior to commencing OST (n=183, 0.40%) were not excluded; however they did not contribute time at risk for that cancer.

HBV and HCV notification data were available for NSW residents only from 1993. Therefore our analyses of cancer risk in those with hepatitis notifications and those with no BBVs (no HCV, HBV, or HIV notification) were restricted to a sub-cohort of individuals registered for OST from 1st January 1993 (n=32 075). To limit the potential for under-ascertainment of hepatitis notifications, interstate OST registrants (n=2 462, 7.68%) were excluded and other OST registrants where censored when they moved interstate OST (n=2 297, 7.76%).

Data collection

In Australia, all deaths, newly diagnosed cancers (excluding basal and squamous cell carcinoma of the skin), and HCV, HBV, and HIV infections must be reported to government agencies by statute. Dates of death in OST registrants were ascertained by linkage with the National Death Index (1980–2007). The date of diagnosis, topography and morphology of

incident cancers were identified by linkage with the Australian Cancer Database, a register of incident primary invasive neoplasms (1982–2007). Solid cancers were classified according to the International Classification of Diseases (ICD), 10th revision while haematopoietic neoplasms and Kaposi sarcomas were classified according to the ICD for Oncology, 3rd edition. Dates of HIV and acquired immunodeficiency syndrome (AIDS) notifications were ascertained by linkage with the National HIV Database (1985–2007) and the National AIDS Register (1982–2007), respectively. Linkage with the NSW Health Notifiable Conditions Information Management System (1993–2007) identified dates of HBV and HCV notifications for the sub-cohort, based on detection of HBV surface antigen or HBV DNA and anti-HCV antibody or HCV RNA, respectively.

The name, sex, date of birth, date of death, and state of residence of registrants were used for record linkage. All linkages used probabilistic matching techniques except the HIV/AIDS linkage which used deterministic methods because only the first two letters of the given name and surname, not full name, were recorded on these registers.

Cancer incidence rates for the Australian population were obtained from the Australian Cancer Database by five-year age group, sex, calendar year, and state/territory, for 1985 to 2007.

Data analysis

Cancer incidence

Person-years of follow-up accumulated from the date of first OST registration and terminated at the first occurrence of cancer diagnosis, death, age 80, interstate transfer (for BBV analyses only), or 31st December 2007.

Crude and age/sex-standardised cancer incidence rates, standardised to the 1996 Australian population, and Poisson 95% confidence intervals (CIs) were calculated using annual Australian population estimates from the Australian Bureau of Statistics. To describe overall cancer incidence trends over time the average annual per cent change (AAPC) was estimated using Poisson regression.[11]

Relative risk of cancer

Risk of cancer overall and for each cancer type were examined in the full cohort (1985–2007) and the sub-cohort (1993–2007) using the standardised incidence ratio (SIR), the ratio of the observed and the expected numbers of cancers. The expected numbers of incident cancers were calculated by multiplying cohort person-years at risk by five-year age-, sex-, state-, and calendar year-specific population cancer incidence rates. The exception was Kaposi sarcoma, where 1982 population rates were used to avoid the impact of AIDS on the incidence of this cancer. The SIRs were computed for cancer overall and for the most frequently occurring cancers by sex and age at follow-up (<40, 40–49, ≥50years). In addition, SIRs were calculated by BBV notification status; HIV with or without HBV or HCV; HBV monoinfection; HCV monoinfection; HBV/HCV co-infection; and HBV/HCV/HIV uninfected. BBV infection was examined in a time-dependent manner, accounting for change in notification status over time.

For registrants with an AIDS notification only or an HIV notification occurring less than five years before the AIDS notification (n=59, 0.13%), the date of HIV infection was backdated to five years prior to the AIDS notification or to the date of cohort entry, whichever occurred later, to more accurately estimate the date of HIV infection. The resultant retrospectively

defined person-years were survival-adjusted by applying period-specific, all-age, sex-, and site-specific cancer survival rates to account for those individuals with HIV infection who may have developed cancer and subsequently died before being diagnosed with HIV.[12] A similar adjustment was performed as a sensitivity analysis for liver cancer risk in those notified with HCV, assuming a median age at infection of 25 years for injecting drug user (IDU)-acquired infection[13] and backdating HCV infection up to 15 years.

We compared patterns of cancer risk for the BBV subgroups but could not compare SIRs statistically because of the heterogeneity in subgroup age and sex distributions.[14]

Within-cohort risk factors were examined for the most frequently occurring cancers in the sub-cohort (1993–2007); liver, lung, and non-Hodgkin lymphoma. Sex and the time-dependent factors—current age, calendar year, and HBV, HCV, and HIV notification—were *a priori* included in all multivariable models. Poisson regression was used to determine incidence rate ratios (IRRs) with 95% CIs.

Analyses were performed using SAS® software v9.2 (SAS Institute Inc., Cary, NC, USA) and Joinpoint Regression Program, v3.5 (Statistical Methodology and Applications Branch and Data Modeling Branch, Surveillance Research Program, National Cancer Institute). Person-years were calculated using the *%stratify* macro.[15]

RESULTS

After applying exclusion criteria, 45412 individuals registered for OST between 1985 and 2007 were included in the study cohort (Table 1a). This cohort accumulated 481936 person-

years of follow-up for cancer, a median of 9.9 person-years per registrant (interquartile range [IQR] 5.61 to 15.2; Table 1a). Two-thirds of the cohort was male. The median age at OST registration was 27 years and the median cumulative time on OST was 2.6 years (IQR 0.6 to 6.5). A total of 423 (0.8%) registrants were notified with a HIV/AIDS diagnosis prior to or after OST registration.

We observed 819 (1.8%) incident primary cancers (803 first, 16 second cancers) after OST registration and the median age at diagnosis of first cancer was 43 (IQR 37 to 49) years.

After applying further exclusion criteria, the sub-cohort with assessable hepatitis data comprised 29 613 participants entering OST between 1993 and 2007 (Table 1b). They were of similar age and sex as the full cohort (median age at OST registration, 26 years; 69% male). A total of 14 892 (50%) registrants were notified with HCV alone, 598 (2%) with HBV alone, and 898 (3%) with HBV and HCV. Over the 213 008 person-years of follow-up in the sub-cohort, 240 (0.8%) incident cancers were observed.

Cancer incidence

For the period 1985 to 2007 the crude cancer incidence rate was 170 per 100 000 person-years (95% CI 159 to 182). The age-standardised rate was 349 per 100 000 person-years (95% CI 337 to 361) and the annual age-standardised rate increased significantly between 1985 and 2007 (AAPC=9.4%, 95% CI 4.2 to 15%; p=0.001).

Cancer risk

Risk of cancer overall was slightly higher in OST registrants compared to the Australian population (SIR=1.15, 95% CI 1.07 to 1.23). SIRs were significantly greater than unity for

cancers of the tonsil, anus and anal canal, liver, pancreas, larynx, trachea bronchus and lung, vulva and cervix, Kaposi sarcoma, non-Hodgkin lymphoma and cancer of unknown primary site (Figure 1). Conversely, SIRs were significantly less than unity for melanoma and cancers of the colorectum, breast, prostate, brain and central nervous system and thyroid.

Risk of any cancer was significantly increased in men and in those more than 40 years of age (Table 2). Liver and lung cancer risk was increased in men and women; liver cancer risk was significantly increased only for those more than 40 years of age, while lung cancer risk was increased regardless of attained age. Similarly, women of all ages experienced half the risk of breast cancer.

Blood-borne viruses and cancer risk

Thirty-four cancers were observed in registrants notified with HIV (irrespective of infection with other BBVs), with an SIR of 6.68 (95% CI 4.63 to 9.34; Figure 2). SIRs were significantly greater than unity for several cancers, including Kaposi sarcoma, non-Hodgkin lymphoma, and anal cancer.

In those notified with HCV monoinfection, the overall risk of cancer was not significantly different from that of the general population (SIR=1.06, 95% CI 0.89 to 1.25; Figure 3) but the SIR for liver cancer was 6.61 (95% CI 3.02 to 12.5). After adjusting for an assumed age of HCV infection of 25 years and for survival, the SIR for liver cancer increased to 13.1 (95% CI 6.00 to 24.9). Risk of lung cancer and mouth cancer were also elevated. On the other hand, breast cancer risk was decreased and while six prostate cancers were expected, none were observed. Few cancers were observed in those notified with HBV (one case) or HBV-

HCV co-infection (18 cases). The risk of liver cancer in individuals notified with HBV-HCV co-infection was markedly elevated (SIR=35.9, 95% CI 7.41 to 105).

Registrants without a notification of BBV infection were at decreased risk of cancer overall (SIR=0.68, 95% CI 0.54 to 0.84; Figure 3) and melanoma. In this subgroup, no infection-related cancers occurred at rates significantly different to the general population; however the risk of pancreatic cancer was significantly elevated.

In multivariable analyses adjusting for age, calendar year, sex and HCV, HBV, and HIV notification status, age was an independent risk factor for the most frequently occurring cancers (Table 3). Notification of HBV and HCV infection predicted risk of liver cancer, and notification of HIV infection predicted risk of non-Hodgkin lymphoma. Notification of HCV infection independently predicted risk of lung cancer.

DISCUSSION

We found that cancer risk in opioid-dependent people registered for OST was significantly increased for a number of cancers causally related to infection with oncogenic viruses, smoking, and alcohol consumption. The excess cancer risk was almost entirely restricted to those notified with a BBV infection, except for pancreatic cancer. The most common cancers for which there was an excess risk were independently associated with increasing age and infection by one or more BBVs; liver cancer (HCV, HBV), lung cancer (HCV), and non-Hodgkin lymphoma (HIV). Cancer incidence also increased significantly over time, highlighting cancer as an emerging public health concern for this population.

Strengths and weaknesses

The strengths of this study include the large population size and the lengthy follow-up, which provided the statistical power to improve upon sparse knowledge of the cancer risk faced by the opioid dependent population. Additionally, use of national, population-based registers for ascertainment of cancer diagnoses, HIV/AIDS diagnoses, and deaths enabled unbiased and comprehensive follow-up of the cohort. On the other hand, although routine testing for BBV infection is recommended, it is likely that not all OST recipients were routinely tested, and use of the notification date in analysis underestimates the timing of the infection. We also lacked data on BBV treatment and HBV vaccination. Furthermore, it was not possible to determine serological clearance of HCV. Thus it is possible that we have misclassification with respect to BBV infection, meaning that we have under-estimated the association of chronic HCV infection with cancer in OST registrants.

In addition, this study was retrospective, relying upon linkage with routinely collected administrative data, and some false positive and negative linkages do occur. Nevertheless, quality assurance practices performed by the data linkage units can result in high sensitivity and specificity (e.g. hepatitis linkage sensitivity >99.9%, specificity 99.8%).[16] The lack of data on smoking and alcohol use of the OST recipients meant that we could not examine the contribution by these agents to the excess risk of liver and lung cancer in those with BBV infection. Given it is likely that around 50% of Australians with opioid dependence enter OST at some point,[17] our findings are likely to be generalisable to the broader opioid dependent population. Our cohort being a representative sample is supported by the similarity of BBV prevalence with NSP survey results.[7] With respect to other OST populations, our data may represent a conservative estimate of the public health burden given the markedly lower incidence of HIV infection in comparison to most other countries.[18]

Context

This is the first population-based study of cancer incidence among people who are opioid dependent, and the first study to examine cancer incidence in relation to BBV infection. Of the two prior studies measuring cancer incidence in opioid dependent individuals, one had very limited statistical power and examined a US cohort of mostly Hispanic injecting drug users with a high prevalence of HIV,[19] while the other studied Israeli OST recipients but did not link with a population-based death registry and examined risk for only eight cancer types.[20]

Explanations

Apart from Kaposi sarcoma, the strongest excess cancer risk in those registered for OST was observed for liver cancer. Stratification by BBV notification and within-cohort risk factor analyses showed that this excess risk occurred only in those with BBV infection, especially HCV alone or HCV/HBV co-infection. Surveillance bias did not strongly affect our risk estimates, as only one liver cancer was diagnosed within six months of commencing OST. Lung cancer risk was elevated in the cohort overall and in the subgroup with HCV. Whilst HCV notification independently predicted lung cancer risk, there is no evidence of a biological link and this result may indicate those with HCV smoke more heavily than those without HCV. Tobacco exposure may also explain the excess risk of mouth cancer in this subgroup. The excess risk of liver[20] and lung[19, 20] cancer is consistent with prior evidence.

An excess risk of Kaposi sarcoma, non-Hodgkin lymphoma, and anal cancer was observed in OST registrants overall, particularly those with HIV. These cancers have an established causal association with HIV-related immunosuppression and are likely to result from impaired immune surveillance in people with infection by Kaposi sarcoma-associated

herpesvirus, Epstein-Barr virus, and HPV, respectively.[21] An excess risk of five non-AIDS-defining malignancies was also observed, supporting evidence that these cancers are becoming increasingly important for those with HIV infection.[22]

A number of cancers occurred at rates significantly lower than in the matched general population. For melanoma, two explanations are suggested. Firstly, Aboriginal Australians, who experience one-tenth the risk of melanoma compared to non-Aboriginal Australians, are over-represented in the OST population compared to the general population (11% vs. 1.5–2.0%).[23] Secondly, 69% of a recent sample (n=154) of active IDUs in NSW reported a history of incarceration,[17] which limits sun exposure, an established risk factor for melanoma. Under-participation in population-based and other cancer screening programs may explain the reduced risk of breast, colorectal and prostate cancer in OST recipients. However, only 4% of the total follow-up time was contributed by individuals who were age-eligible for these programs, substantially weakening the case for attenuation in risk due to under-participation in screening. A reduced risk of colorectal and breast cancer was observed in Israeli OST recipients,[20] and there is some evidence that opioid use may impart a decreased risk of certain cancers. For example, a side-effect of chronic opioid use is hypogonadism, resulting in low oestrogen (women) and testosterone (men).[24] Low levels of these hormones may decrease premenopausal breast cancer and prostate cancer risk, however the evidence is inconclusive.[25, 26] Characteristics common to OST registrants, high parity and early age at first pregnancy,[17, 27] both considered protective for breast cancer,[28] as well as reduced prevalence of overweight and obesity,[29] may also contribute to the observed risk reduction.

Implications

The observed cancer risk profile strongly supports the implementation of targeted cancer prevention strategies in the OST setting. Given the concentration of excess risk among those with BBV notifications, and the high prevalence of HCV among this population, there is a clear need for interventions that reduce HCV incidence[4] and that treat people who have developed chronic infections.[1] NSPs are highly effective at reducing the rate of acquisition of BBVs.[4] Antiviral treatments for HCV and HBV infection induce regression of fibrosis and decrease liver cancer risk.[30] People with a history of injecting drug use respond positively to HCV therapies, with acceptable levels of sustained virological response[31] and antiviral therapy is also not contraindicated in people with HIV receiving OST. The issue, however, is one of coverage. Many physicians remain unwilling to provide such treatments to people who use illicit drugs in the face of evidence that they have similar levels of adherence to treatment as other patient groups.[32] Thus, despite HCV being one of the strongest risk factors for cancer in OST, very few people in OST have received treatment to address this risk.[1]

As the risks for cancers with established causal links to tobacco-smoking and alcohol use were elevated, namely lung, larynx, and pancreatic cancer (smoking), and liver, oral, larynx, and oesophageal cancer (alcohol), a reduction in these behaviours would similarly mitigate cancer risk. OST clients show strong interest in smoking cessation programs,[33] and they do not adversely impact OST,[34] but again few are offered such treatments in routine healthcare settings. The excess risk of cancer of the cervix, vulva and anus, cancers caused by chronic infection with HPV, may be reduced by safer sexual practices. The increased risk of cervical cancer also supports the need for greater participation in cervical screening.

Conclusions

Opioid-dependent people registered for OST face an excess risk of a variety of cancers compared to the general population, in particular cancers associated with infection by BBVs. The implementation of harm reduction strategies in the OST setting represents an evidently underutilised opportunity to respond to the escalating cancer burden facing this marginalised population.

LIST OF FIGURE LEGENDS

Figure 1 Risk of cancer among NSW opioid substitution therapy registrants, 1985–2007

Key

Obs=observed number of cancers. Exp=expected number of cancers. SIR=standardised incidence ratio. CI=confidence interval. CNS=central nervous system.

*Includes non-Hodgkin lymphoma not otherwise specified (International Classification of Diseases for Oncology, 3rd edition: 9590).

Non-melanoma skin cancer excludes diagnoses of basal cell and squamous cell carcinoma.

Figure 2 Risk of cancer in NSW opioid substitution therapy registrants with notified HIV infection, 1985–2007

Key

Obs=observed number of cancers. Exp=expected number of cancers. SIR=standardised incidence ratio. CI=confidence interval.

*Includes non-Hodgkin lymphoma not otherwise specified (International Classification of Diseases for Oncology, 3rd edition: 9590).

Figure 3 Risk of cancer among NSW opioid substitution therapy registrants with notified hepatitis C infection and registrants without notified hepatitis B, hepatitis C or HIV infection, 1993–2007

Key

*Includes non-Hodgkin lymphoma not otherwise specified (International Classification of Diseases for Oncology, 3rd edition: 9590)

†SIRs not estimated for cancers with less than 3 observed cases

Table 1a Characteristics of all NSW opioid substitution therapy registrants and those with notified HIV infection, 1985–2007

	Entire cohort			HIV infection		
		Person-years			Person-years	
	No. (%) of registrants	Total	Median (IQR)	No. (%) of registrants	Total	Median (IQR)
Total	45 412 (100)	481 936	9.94 (5.61–15.2)	426 (100)	3511	7.60 (3.66–12.4)
Sex						
Men	30 147 (66.4)	310 632	9.67 (5.31–14.8)	346 (81.2)	2796	7.58 (3.63–11.8)
Women	15 265 (33.6)	171 304	10.6 (6.30–16.2)	80 (18.8)	715	7.68 (3.72–14.6)
Age at cohort entry (years)						
<25	16 266 (35.8)	166 503	9.48 (5.83–14.0)	139 (32.6)	1176	7.38 (3.87–13.0)
25–30	14 680 (32.3)	171 073	11.3 (6.26–17.4)	120 (28.2)	1027	7.96 (3.75–11.7)
≥31	14 466 (31.9)	144 361	9.46 (4.86–14.4)	167 (39.2)	1308	7.25 (2.83–12.7)
Year of cohort entry						
1985–1989	8476 (18.7)	161 566	20.4 (18.7–21.8)	75 (17.6)	887	10.2 (6.02–19.2)
1990–1995	11 220 (24.7)	152 938	14.1 (12.7–15.7)	140 (32.9)	1479	12.8 (5.99–14.8)
1996–2001	15 302 (33.7)	133 232	8.84 (7.35–10.4)	122 (28.6)	908	8.00 (6.33–9.65)
2002–2007	10 414 (22.9)	34 200	3.44 (1.88–4.81)	89 (20.9)	237	2.72 (1.22–3.89)

Table 1b Characteristics of NSW opioid substitution therapy registrants, by BBV notification status, 1993–2007

	Entire sub-cohort			No BBV infection			HBV monoinfection			HCV monoinfection			HBV/HCV co-infection			HIV infection[†]		
		Person-years			Person-years			Person-years			Person-years			Person-years			Person-years	
	No. (%) of registrants[*]	Total	Median	No. (%) of registrants	Total	Median	No. (%) of registrants	Total	Median	No. (%) of registrants	Total	Median	No. (%) of registrants	Total	Median	No. (%) of registrants	Total	Median
Total	29 613 (100)	213 008	7.28	23 650 (100)	109 313	3.53	598 (100)	2608	3.56	14 892 (100)	94 331	6.36	898 (100)	5249	6.02	234 (100)	1504	6.20
Sex																		
Men	20 348 (68.7)	144 932	7.19	16 352 (69.1)	76 495	3.64	436 (72.9)	1918	3.60	9793 (65.8)	61 378	6.29	643 (71.6)	3782	6.10	204 (87.2)	1355	6.55
Women	9265 (31.3)	68 076	7.51	7298 (30.9)	32 818	3.25	162 (27.1)	691	3.50	5099 (34.2)	32 953	6.47	255 (28.4)	1466	5.94	30 (12.8)	148	4.35
Age at cohort entry (years)																		
<25	11 674 (39.4)	87 088	7.60	9915 (41.9)	47 340	3.81	278 (46.5)	1282	3.96	5706 (38.3)	35 963	6.41	351 (39.1)	2130	6.27	61 (26.1)	373	6.08
25–30	8427 (28.5)	60 907	7.32	6771 (28.6)	31 905	3.56	169 (28.3)	770	3.18	4106 (27.6)	26 201	6.42	266 (29.6)	1534	5.79	68 (29.1)	494	7.73
>31	9512 (32.1)	65 013	6.74	6964 (29.4)	30 068	3.06	151 (25.3)	555	3.39	5080 (34.1)	32 167	6.23	281 (31.3)	1584	5.71	105 (44.9)	637	5.17
Year of cohort entry																		
1993–1997	10 212 (34.5)	111 454	11.7	8944 (37.8)	54 619	4.76	158 (26.4)	981	5.08	3563 (23.9)	36 132	11.2	129 (14.4)	1298	10.9	84 (35.9)	754	10.7
1998–2002	11 655 (39.4)	81 399	7.36	8962 (37.9)	42 095	5.35	290 (48.5)	1304	5.12	6958 (46.7)	47 049	7.05	475 (52.9)	3167	6.80	82 (35.0)	573	7.55
2003–2007	7746 (26.2)	20 155	2.70	5744 (24.3)	12 599	2.11	150 (25.1)	323	2.01	4371 (29.4)	11 150	2.55	294 (32.7)	784	2.75	68 (29.1)	177	2.71

[*] Category numbers will not sum to total numbers for the sub-cohort as individuals were followed-up in a time-dependent manner, allowing an individual to contribute person-years to multiple groups as their BBV notification status changed over the period of observation.

[†] With or without HBV or HCV notification.

Table 2 Risk of any cancer and the most frequently occurring cancers in NSW opioid substitution therapy registrants, by sex and current age (1985–2007)

Cancer type	Obs.	Exp.	SIR	95% CI
All cancer				
Men	536	431	1.24	1.14–1.35
Women	283	285	0.99	0.88–1.11
<40 yrs	282	295	0.96	0.85–1.07
40–49 yrs	357	282	1.27	1.14–1.40
≥50 yrs	180	139	1.30	1.12–1.50
Liver				
Men	51	6.92	7.37	5.49–9.69
Women	12	0.91	13.2	6.80–23.0
<40 yrs	4	1.62	2.47	0.67–6.33
40–49 yrs	26	3.96	6.57	4.29–9.63
≥50 yrs	33	2.26	14.6	10.1–20.6
Trachea, bronchus, and lung				
Men	82	19.8	4.15	3.32–5.11
Women	28	7.59	3.69	2.45–5.33
<40 yrs	15	4.11	3.65	2.04–6.02
40–49 yrs	58	13.0	4.46	3.41–5.71
≥50 yrs	37	10.2	3.61	2.57–4.90
Melanoma				
Men	64	91.2	0.70	0.54–0.89
Women	37	48.7	0.76	0.54–1.03
<40 yrs	48	71.6	0.67	0.50–0.88
40–49 yrs	37	51.4	0.72	0.51–0.98
≥50 yrs	16	16.9	0.95	0.56–1.49
Female breast				
<40 yrs	15	32.5	0.46	0.27–0.74
40–49 yrs	27	54.3	0.48	0.32–0.69
≥50 yrs	6	14.1	0.43	0.17–0.86
Cervical				
<40 yrs	21	11.0	1.90	1.20–2.84
40–49 yrs	14	4.67	3.00	1.64–5.03
≥50 yrs	2	0.63	3.19	0.39–11.5
Non-Hodgkin lymphoma				
Men	62	38.1	1.63	1.26–2.07
Women	13	11.5	1.13	0.62–1.86
<40 yrs	25	20.9	1.20	0.79–1.73
40–49 yrs	37	19.8	1.87	1.33–2.54
≥50 yrs	13	8.94	1.46	0.78–2.49

Obs=observed number of cancers. Exp=expected number of cancers. SIR=standardised incidence ratio. CI=confidence interval.

Table 3 Multivariable analysis of risk factors for common cancers among NSW opioid substitution therapy registrants, 1993-2007

	Lung Cancer				Non-Hodgkin lymphoma				Liver Cancer			
	n	**IRR***	**95%CI**	**P**	**n**	**IRR***	**95%CI**	**P**	**n**	**IRR***	**95%CI**	**P**
Current age†	27	1.19	1.15–1.24	<0.0001	23	1.06	1.01–1.11	0.025	13	1.20	1.13–1.27	<0.0001
Calendar year†	27	0.91	0.81–1.03	0.131	23	1.16	1.01–1.37	0.054	13	1.13	0.91–1.49	0.317
Sex												
Men	22	1.55	0.63–4.65	0.378	17	1.03	0.42–2.90	0.954	12	3.94	0.76–72.2	0.190
Women (ref)	5	1.00			6	1.00			1	1.00		
Notified HCV infection												
Yes	21	3.29	1.39–9.07	0.011	13	1.12	0.49–2.65	0.792	12	9.05	1.73–166	0.036
No (ref)	6	1.00			10	1.00			1	1.00		
Notified HBV infection‡												
Yes	2	1.59	0.25–5.42	0.531	0	-			3	4.63	1.03–15.4	0.021
No (ref)	25	1.00			23				10	1.00		
Notified HIV infection‡												
Yes	0	-			4	26.0	7.40–71.3	<0.0001	0	-		
No (ref)	27				19	1.00			13			

IRR=incidence rate ratio. CI=confidence interval. Ref=reference group in analysis.

*Adjusted for current age (years), calendar year, sex and time-dependent HCV notification status, HBV notification status and HIV notification status

†IRR refers to one year increase

‡IRRs could not be calculated if a cancer case did not occur in one of the binary groupings

Note: Infection groupings are not mutually exclusive

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CONTRIBUTORS

The study was conceived and designed by CMV, LB and LD. The data were obtained from data custodians by LM, NSM and CMV. All authors contributed to the analytical plans. The data were prepared and analysed by AS. AS, CMV and LD drafted the paper. All authors reviewed, revised and approved the final draft. CMV is the guarantor.

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COMPETING INTERESTS

All authors report no disclosures.

ETHICS APPROVAL

The study was reviewed and approved by all relevant ethics committees and the requirement for informed consent was waived because the researchers received only de-identified data.

DATA SHARING STATEMENT

There is no additional data available.

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The importance of blood-borne viruses in elevated cancer risk among opioid dependent people: a population-based cohort study

Alexander Swart[1], Lucinda Burns[2], Limin Mao[3], Andrew E. Grulich[4], Janaki Amin[4], Dianne L. O'Connell[5,6,7,8], Nicola S. Meagher[1], Deborah A. Randall[9], Louisa Degenhardt[2,10], Claire M. Vajdic[1]

1 Adult Cancer Program, Lowy Cancer Research Centre, Prince of Wales Clinical School, Faculty of Medicine at the University of New South Wales, NSW 2052, Australia.

2 National Drug and Alcohol Research Centre, Faculty of Medicine at the University of New South Wales, NSW 2052, Australia

3 National Centre in HIV Social Research, Faculty of Arts and Social Sciences at the University of New South Wales, NSW 2052, Australia

4 Kirby Institute, Faculty of Medicine at the University of New South Wales, NSW 2052, Australia

5 Cancer Research Division, Cancer Council NSW, NSW 2011, Australia

6 School of Medicine and Public Health, Faculty of Health, University of Newcastle

7 School of Public Health and Community Medicine, University of New South Wales, NSW 2052, Australia

8 Sydney Medical School – Public Health, University of Sydney, NSW 2006, Australia

9 School of Medicine, University of Western Sydney, NSW 2751, Australia

10 Centre for Health Policy, Programs and Economics, School of Population Health, University of Melbourne, Victoria 3010, Australia

Corresponding author

Claire M. Vajdic, Adult Cancer Program, Lowy Cancer Research Centre, University of New South Wales, NSW 2052, Australia. Phone (61-2) 9385 1424; fax (61-2) 9385 1430; email: claire.vajdic@unsw.edu.au

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ARTICLE SUMMARY

Article focus

- While opioids and opioid substitution therapies themselves are not known to be carcinogenic, oOpioid dependence is associated with exposure to a number of carcinogenic agents, including infection by the blood-borne viruses hepatitis B, hepatitis C, and HIV.
- The risk of cancer in opioid dependence has been examined in two studies with insufficient power to address risk for all cancer types.
- There is no prior evidence on the association between blood-borne virus infection and cancer risk in people who are opioid dependent.

Key messages

- People who are opioid dependent have an excess risk of a range of cancers compared with the general population.
- The excess cancer risk is predominantly restricted to those with blood-borne virus infection.
- Cancer incidence rates have increased dramatically over time, supporting use of the opioid substitution therapy setting to opportunistically implement targeted cancer prevention strategies.

Strengths and limitations

- The study is based on a large population-based cohort with infections and outcomes obtained from population-based registries.
- Misclassification of infection by blood-borne viruses is possible because not all OST recipients will have been routinely tested.
- Data on smoking, alcohol use, blood-borne virusBBV treatment and vaccination are not available.

ABSTRACT

Objective To quantify cancer risk in opioid dependence and the association with infection by the oncogenic blood-borne viruses (BBVs) hepatitis C (HCV), hepatitis B (HBV), and HIV ~~infection~~.

Design Cohort study.

Setting New South Wales, Australia.

Participants 45 412 adults aged 16 years or over registered for opioid substitution therapy (OST) between 1985 and 2007. Notifications of cancer, death, and infection with HCV, HBV, and HIV were ascertained by record linkage with registries.

Main outcome measures The ratios of observed to expected number of cancers, standardised incidence ratios (SIRs), and the average annual percent change (AAPC) in overall age and sex-standardised cancer incidence.

Results Overall cancer risk was modestly increased compared to the general population (SIR 1.15, 95% CI 1.07 to 1.23). Excess risk was observed for 11 cancers, particularly lung (4.02, 95% CI 3.32 to 4.82), non-Hodgkin lymphoma (1.51, 95% CI 1.20 to 1.88), and liver (8.04, 95% CI 6.18 to 10.3). Reduced risk was observed for six cancers, including prostate (0.16, 95% CI 0.06 to 0.32) and breast (0.48, 95% CI 0.35 to 0.62). Individuals notified with HCV or HBV had a markedly increased risk of liver cancer; lung cancer risk was also increased in those with HCV. HIV was associated with an elevated risk of liver, anus, and kidney cancer, non-Hodgkin lymphoma and Kaposi sarcoma. Cancer risk was not increased in individuals without a BBV notification, apart from pancreatic cancer (3.92, 95% CI 1.07 to 10.0). Cancer incidence increased significantly over time (AAPC 9.4%, 4.2 to 15%, p=0.001).

Conclusions BBVs play a major role in the cancer risk profile of opioid-dependent individuals registered for OST. To address the dramatic increasing trend in cancer incidence,

the OST setting ~~sh~~could be utilised for cancer prevention ~~targeted~~ strategies. ~~including BBV prevention and treatment~~.

INTRODUCTION

Opioid-dependent individuals are exposed to a multitude of carcinogens. People who inject drugs are more likely to have hepatitis C (HCV), hepatitis B (HBV) or human immunodeficiency virus (HIV).[1] Tobacco-smoking and hazardous alcohol use are extremely common,[2] as are risky sexual practices, resulting in high rates of infection with human papillomavirus (HPV).[3] Although it is an effective treatment for heroin and other opioid dependence,[4] opioid substitution therapy (OST) use is typically cyclic,[5] with relapse to drug injection a common occurrence.

In Australia, the long-standing and widespread availability of OST and public health initiatives such as needle and syringe programmes (NSPs) have extended the life expectancy of opioid-dependent people.[4, 6] In injecting drug users, the prevalence of HIV is low (<1% in heterosexuals), whereas the prevalence of hepatitis C is high (50-60%).[7] However one of the consequences of their increased longevity of opioid-dependent people is the attendant risk of age-related health conditions, including cancer.[8] The OST agents themselves are not considered risk factors for cancer as murine studies indicate they are not carcinogenic.[9, 10]

Despite evidence of exposure to multiple cancer risk factors and the public health impact that this may have upon ageing cohorts of opioid-dependent people, there has been no population-based study of the spectrum of cancer risk in this group and no study of this risk in relation to blood-borne virus (BBV) infection. We examined these associations among 45412 people who entered OST in New South Wales (NSW), Australia over a 23-year period, considering 1) overall and site-specific cancer incidence, 2) the cancer risk profiles of those infected with HCV, HBV, and HIV, and 3) trends in cancer incidence over time.

METHODS

Study population

We conducted a cohort study using record linkage between existing population-based health datasets. The study population comprised individuals registered on the Pharmaceutical Drugs of Addiction System, a record of all NSW Health Department authorities that administer methadone or buprenorphine to opioid-dependent people. Included were all adults (≥16 years) registered for OST between 1st January 1985, the date of inception of the system, and 31st December 2007, the latest date for which cancer diagnoses were available (n=45 483). Individuals were excluded from the cohort if information essential for record linkage was incomplete (n=10, 0.02%) or if the OST end date preceded the start date (n=61, 0.13%). Registrants diagnosed with cancer prior to commencing OST (n=183, 0.40%) were not excluded; however they did not contribute time at risk for that cancer.

HBV and HCV notification data were available for NSW residents only from 1993. Therefore our analyses of cancer risk in those with hepatitis notifications and those with no BBVs (no HCV, HBV, or HIV notification) were restricted to a sub-cohort of individuals registered for OST from 1st January 1993 (n=32 075). To limit the potential for under-ascertainment of hepatitis notifications, interstate OST registrants (n=2 462, 7.68%) were excluded and other OST registrants where censored when they moved interstate OST (n=2 297, 7.76%).

Data collection

In Australia, all deaths, newly diagnosed cancers (excluding basal and squamous cell carcinoma of the skin), and HCV, HBV, and HIV infections must be reported to government agencies by statute. Dates of death in OST registrants were ascertained by linkage with the

National Death Index (1980–2007). The date of diagnosis, topography and morphology of incident cancers were identified by linkage with the Australian Cancer Database, a register of incident primary invasive neoplasms (1982–2007). Solid cancers were classified according to the International Classification of Diseases (ICD), 10th revision while haematopoietic neoplasms and Kaposi sarcomas were classified according to the ICD for Oncology, 3rd edition. Dates of HIV and acquired immunodeficiency syndrome (AIDS) notifications were ascertained by linkage with the National HIV Database (1985–2007) and the National AIDS Register (1982–2007), respectively. Linkage with the NSW Health Notifiable Conditions Information Management System (1993–2007) identified dates of HBV and HCV notifications for the sub-cohort, based on detection of HBV surface antigen or HBV DNA and anti-HCV antibody or HCV RNA, respectively.

The name, sex, date of birth, date of death, and state of residence of registrants were used for record linkage. All linkages used probabilistic matching techniques except the HIV/AIDS linkage which used deterministic methods because only the first two letters of the given name and surname, not full name, were recorded on these registers.

Cancer incidence rates for the Australian population were obtained from the Australian Cancer Database by five-year age group, sex, calendar year, and state/territory, for 1985 to 2007.

Data analysis

Cancer incidence

Person-years of follow-up accumulated from the date of first OST registration and terminated at the first occurrence of cancer diagnosis, death, age 80, interstate transfer (for BBV analyses only), or 31st December 2007.

Crude and age/sex-standardised cancer incidence rates, standardised to the 1996 Australian population, and Poisson 95% confidence intervals (CIs) were calculated using annual Australian population estimates from the Australian Bureau of Statistics. To describe overall cancer incidence trends over time the average annual per cent change (AAPC) was estimated using Poisson regression.[11]

Relative risk of cancer

Risk of cancer overall and for each cancer type were examined in the full cohort (1985–2007) and the sub-cohort (1993–2007) using the standardised incidence ratio (SIR), the ratio of the observed and the expected numbers of cancers. The expected numbers of incident cancers were calculated by multiplying cohort person-years at risk by five-year age-, sex-, state-, and calendar year-specific population cancer incidence rates. The exception was Kaposi sarcoma, where 1982 population rates were used to avoid the impact of AIDS on the incidence of this cancer. The SIRs were computed for cancer overall and for the most frequently occurring cancers by sex and age at follow-up (<40, 40–49, ≥50years). In addition, SIRs were calculated by BBV notification status; HIV with or without HBV or HCV; HBV monoinfection; HCV monoinfection; HBV/HCV co-infection; and HBV/HCV/HIV uninfected. BBV infection was examined in a time-dependent manner, accounting for change in notification status over time.

For registrants with an AIDS notification only or an HIV notification occurring less than five years before the AIDS notification (n=59, 0.13%), the date of HIV infection was backdated to five years prior to the AIDS notification or to the date of cohort entry, whichever occurred later, to more accurately estimate the date of HIV infection. The resultant retrospectively defined person-years were survival-adjusted by applying period-specific, all-age, sex-, and site-specific cancer survival rates to account for those individuals with HIV infection who may have developed cancer and subsequently died before being diagnosed with HIV.[12] A similar adjustment was performed as a sensitivity analysis for liver cancer risk in those notified with HCV, assuming a median age at infection of 25 years for injecting drug user (IDU)-acquired infection[13] and backdating HCV infection up to 15 years.

We compared patterns of cancer risk for the BBV subgroups but could not compare SIRs statistically because of the heterogeneity in subgroup age and sex distributions.[14]

Within-cohort risk factors were examined for the most frequently occurring cancers in the sub-cohort (1993–2007); liver, lung, and non-Hodgkin lymphoma. Sex and the time-dependent factors—current age, calendar year, and HBV, HCV, and HIV notification—were *a priori* included in all multivariable models. Poisson regression was used to determine incidence rate ratios (IRRs) with 95% CIs.

Analyses were performed using SAS® software v9.2 (SAS Institute Inc., Cary, NC, USA) and Joinpoint Regression Program, v3.5 (Statistical Methodology and Applications Branch and Data Modeling Branch, Surveillance Research Program, National Cancer Institute). Person-years were calculated using the *%stratify* macro.[15]

RESULTS

After applying exclusion criteria, 45 412 individuals registered for OST between 1985 and 2007 were included in the study cohort (Table 1a). This cohort accumulated 481 936 person-years of follow-up for cancer, a median of 9.9 person-years per registrant (interquartile range [IQR] 5.61 to 15.2; Table 1a). Two-thirds of the cohort was male. The median age at OST registration was 27 years and the median cumulative time on OST was 2.6 years (IQR 0.6 to 6.5). A total of 423 (0.8%) registrants were notified with a HIV/AIDS diagnosis prior to or after OST registration.

We observed 819 (1.8%) incident primary cancers (803 first, 16 second cancers) after OST registration and the median age at diagnosis of first cancer was 43 (IQR 37 to 49) years.

After applying further exclusion criteria, the sub-cohort with assessable hepatitis data comprised 29 613 participants entering OST between 1993 and 2007 (Table 1b). They were of similar age and sex as the full cohort (median age at OST registration, 26 years; 69% male). A total of 14 892 (50%) registrants were notified with HCV alone, 598 (2%) with HBV alone, and 898 (3%) with HBV and HCV. Over the 213 008 person-years of follow-up in the sub-cohort, 240 (0.8%) incident cancers were observed.

Cancer incidence

For the period 1985 to 2007 the crude cancer incidence rate was 170 per 100 000 person-years (95% CI 159 to 182). The age-standardised rate was 349 per 100 000 person-years (95% CI 337 to 361) and the annual age-standardised rate increased significantly between 1985 and 2007 (AAPC=9.4%, 95% CI 4.2 to 15%; p=0.001).

Cancer risk

Risk of cancer overall was slightly higher in OST registrants compared to the Australian population (SIR=1.15, 95% CI 1.07 to 1.23). SIRs were significantly greater than unity for cancers of the tonsil, anus and anal canal, liver, pancreas, larynx, trachea bronchus and lung, vulva and cervix, Kaposi sarcoma, non-Hodgkin lymphoma and cancer of unknown primary site (Figure 1). Conversely, SIRs were significantly less than unity for melanoma and cancers of the colorectum, breast, prostate, brain and central nervous system and thyroid.

Risk of any cancer was significantly increased in men and in those more than 40 years of age (Table 2). Liver and lung cancer risk was increased in men and women; liver cancer risk was significantly increased only for those more than 40 years of age, while lung cancer risk was increased regardless of attained age. Similarly, women of all ages experienced half the risk of breast cancer.

Blood-borne viruses and cancer risk

Thirty-four cancers were observed in registrants notified with HIV (irrespective of infection with other BBVs), with an SIR of 6.68 (95% CI 4.63 to 9.34; Figure 2). SIRs were significantly greater than unity for several cancers, including Kaposi sarcoma, non-Hodgkin lymphoma, and anal cancer.

In those notified with HCV monoinfection, the overall risk of cancer was not significantly different from that of the general population (SIR=1.06, 95% CI 0.89 to 1.25; Figure 3) but the SIR for liver cancer was 6.61 (95% CI 3.02 to 12.5). After adjusting for an assumed age of HCV infection of 25 years and for survival, the SIR for liver cancer increased to 13.1

(95% CI 6.00 to 24.9). Risk of lung cancer and mouth cancer were also elevated. On the other hand, breast cancer risk was decreased and while six prostate cancers were expected, none were observed. Few cancers were observed in those notified with HBV (one case) or HBV-HCV co-infection (18 cases). The risk of liver cancer in individuals notified with HBV-HCV co-infection was markedly elevated (SIR=35.9, 95% CI 7.41 to 105).

Registrants without a notification of BBV infection were at decreased risk of cancer overall (SIR=0.68, 95% CI 0.54 to 0.84; Figure 3) and melanoma. In this subgroup, no infection-related cancers occurred at rates significantly different to the general population; however the risk of pancreatic cancer was significantly elevated.

In multivariable analyses adjusting for age, calendar year, sex and HCV, HBV, and HIV notification status, age was an independent risk factor for the most frequently occurring cancers (Table 3). Notification of HBV and HCV infection predicted risk of liver cancer, and notification of HIV infection predicted risk of non-Hodgkin lymphoma. Notification of HCV infection independently predicted risk of lung cancer.

DISCUSSION

We found that cancer risk in opioid-dependent people registered for OST was significantly increased for a number of cancers causally related to infection with oncogenic viruses, smoking, and alcohol consumption. The excess cancer risk was almost entirely restricted to those notified with a BBV infection, except for pancreatic cancer. The most common cancers for which there was an excess risk were independently associated with increasing age and infection by one or more BBVs; liver cancer (HCV, HBV), lung cancer (HCV), and non-

Hodgkin lymphoma (HIV). Cancer incidence also increased significantly over time, highlighting cancer as an emerging public health concern for this population.

Strengths and weaknesses

The strengths of this study include the large population size and the lengthy follow-up, which provided the statistical power to improve upon sparse knowledge of the cancer risk faced by the opioid dependent population. Additionally, use of national, population-based registers for ascertainment of cancer diagnoses, HIV/AIDS diagnoses, and deaths enabled unbiased and comprehensive follow-up of the cohort. On the other hand, although routine testing for BBV infection is recommended, it is likely that not all OST recipients were routinely tested, and use of the notification date in analysis underestimates the timing of the infection. We also lacked data on BBV treatment and HBV vaccination. Furthermore, it was not possible to determine serological clearance of HCV. Thus it is possible that we have misclassification with respect to BBV infection, meaning that we have under-estimated the association of chronic HCV infection with cancer in OST registrants.

In addition, this study was retrospective, relying upon linkage with routinely collected administrative data, and some false positive and negative linkages do occur. Nevertheless, quality assurance practices performed by the data linkage units can result in high sensitivity and specificity (e.g. hepatitis linkage sensitivity >99.9%, specificity 99.8%).[16] The lack of data on smoking and alcohol use of the OST recipients meant that we could not examine the contribution by these agents to the excess risk of liver and lung cancer in those with BBV infection. Given it is likely that around 50% of Australians with opioid dependence enter OST at some point,[17] our findings are likely to be generalisable to the broader opioid dependent population. Our cohort being a representative sample is supported by the similarity

of BBV prevalence with NSP survey results.[7] With respect to other OST populations, our data may represent a conservative estimate of the public health burden given the markedly lower incidence of HIV infection in comparison to most other countries.[18]

Context

This is the first population-based study of cancer incidence among people who are opioid dependent, and the first study to examine cancer incidence in relation to BBV infection. Of the two prior studies measuring cancer incidence in opioid dependent ~~populations~~individuals, one had very limited statistical power and examined a US cohort of mostly Hispanic injecting drug users with a high prevalence of HIV,[19] while the other studied Israeli OST recipients but did not link with a population-based death registry and examined risk for only eight cancer types.[20]

Explanations

Apart from Kaposi sarcoma, the strongest excess cancer risk in those registered for OST was observed for liver cancer. Stratification by BBV notification and within-cohort risk factor analyses showed that this excess risk occurred only in those with BBV infection, especially HCV alone or HCV/HBV co-infection. Surveillance bias did not strongly affect our risk estimates, as only one liver cancer was diagnosed within six months of commencing OST. Lung cancer risk was elevated in the cohort overall and in the subgroup with HCV. Whilst HCV notification independently predicted lung cancer risk, there is no evidence of a biological link and this result may indicate those with HCV smoke more heavily than those without HCV. Tobacco exposure may also explain the excess risk of mouth cancer in this subgroup. The excess risk of liver[20] and lung[19, 20] cancer is consistent with prior evidence.

An excess risk of Kaposi sarcoma, non-Hodgkin lymphoma, and anal cancer was observed in OST registrants overall, particularly those with HIV. These cancers have an established causal association with HIV-related immunosuppression and are likely to result from impaired immune surveillance in people with infection by Kaposi sarcoma-associated herpesvirus, Epstein-Barr virus, and HPV, respectively.[21] An excess risk of five non-AIDS-defining malignancies was also observed, supporting evidence that these cancers are becoming increasingly important for those with HIV infection.[22]

A number of cancers occurred at rates significantly lower than in the matched general population. For melanoma, two explanations are suggested. Firstly, Aboriginal Australians, who experience one-tenth the risk of melanoma compared to non-Aboriginal Australians, are over-represented in the OST population compared to the general population (11% vs. 1.5–2.0%).[23] Secondly, 69% of a recent sample (n=154) of active IDUs in NSW reported a history of incarceration,[17] which limits sun exposure, an established risk factor for melanoma. Under-participation in population-based and other cancer screening programs may explain the reduced risk of breast, colorectal and prostate cancer in OST recipients. However, only 4% of the total follow-up time was contributed by individuals who were age-eligible for these programs, substantially weakening the case for attenuation in risk due to under-participation in screening. A reduced risk of colorectal and breast cancer was observed in Israeli OST recipients,[20] and there is some evidence that opioid use may impart a decreased risk of certain cancers. For example, a side-effect of chronic opioid use is hypogonadism, resulting in low oestrogen (women) and testosterone (men).[24] Low levels of these hormones may decrease premenopausal breast cancer and prostate cancer risk, however the evidence is inconclusive.[25, 26] Characteristics common to OST registrants, high parity and early age at

first pregnancy,[17, 27] both considered protective for breast cancer,[28] as well as reduced prevalence of overweight and obesity,[29] may also contribute to the observed risk reduction.

Implications

The observed cancer risk profile strongly supports the implementation of targeted cancer prevention strategies in the OST setting. Given the concentration of excess risk among those with BBV notifications, and the high prevalence of HCV among this population, there is a clear need for interventions that reduce HCV incidence[4] and that treat people who have developed chronic infections.[1] NSPs are highly effective at reducing the rate of acquisition of BBVs.[4] Antiviral treatments for HCV and HBV infection induce regression of fibrosis and decrease liver cancer risk.[30] People with a history of injecting drug use respond positively to HCV therapies, with acceptable levels of sustained virological response[31] and antiviral therapy is also not contraindicated in people with HIV receiving OST. The issue, however, is one of coverage. Many physicians remain unwilling to provide such treatments to people who use illicit drugs in the face of evidence that they have similar levels of adherence to treatment as other patient groups.[32] Thus, despite HCV being one of the strongest risk factors for cancer in OST, very few people in OST have received treatment to address this risk.[1]

As the risks for cancers with established causal links to tobacco-smoking and alcohol use were elevated, namely lung, larynx, and pancreatic cancer (smoking), and liver, oral, larynx, and oesophageal cancer (alcohol), a reduction in these behaviours would similarly mitigate cancer risk. OST clients show strong interest in smoking cessation programs,[33] and they do not adversely impact OST,[34] but again few are offered such treatments in routine healthcare settings. The excess risk of cancer of the cervix, vulva and anus, cancers caused by chronic infection with HPV, may be reduced by safer sexual practices. The increased risk of cervical cancer also supports the need for greater participation in cervical screening.

Conclusions

Opioid-dependent people registered for OST face an excess risk of a variety of cancers compared to the general population, in particular cancers associated with infection by BBVs. The implementation of harm reduction strategies in the OST setting represents an evidently underutilised opportunity to respond to the escalating cancer burden facing this marginalised population.

LIST OF FIGURE LEGENDS

Figure 1 Risk of cancer among NSW opioid substitution therapy registrants, 1985–2007

Key

Obs=observed number of cancers. Exp=expected number of cancers. SIR=standardised incidence ratio. CI=confidence interval. CNS=central nervous system.

*Includes non-Hodgkin lymphoma not otherwise specified (International Classification of Diseases for Oncology, 3rd edition: 9590).

Non-melanoma skin cancer excludes diagnoses of basal cell and squamous cell carcinoma.

Figure 2 Risk of cancer in NSW opioid substitution therapy registrants with notified HIV infection, 1985–2007

Key

Obs=observed number of cancers. Exp=expected number of cancers. SIR=standardised incidence ratio. CI=confidence interval.

*Includes non-Hodgkin lymphoma not otherwise specified (International Classification of Diseases for Oncology, 3rd edition: 9590).

Figure 3 Risk of cancer among NSW opioid substitution therapy registrants with notified hepatitis C infection and registrants without notified hepatitis B, hepatitis C or HIV infection, 1993–2007

Key

*Includes non-Hodgkin lymphoma not otherwise specified (International Classification of Diseases for Oncology, 3rd edition: 9590)

†SIRs not estimated for cancers with less than 3 observed cases

Table 1a Characteristics of all NSW opioid substitution therapy registrants and those with notified HIV infection, 1985–2007

	Entire cohort			HIV infection		
		Person-years			Person-years	
	No. (%) of registrants	Total	Median (IQR)	No. (%) of registrants	Total	Median (IQR)
Total	45 412 (100)	481 936	9.94 (5.61–15.2)	426 (100)	3511	7.60 (3.66–12.4)
Sex						
Men	30 147 (66.4)	310 632	9.67 (5.31–14.8)	346 (81.2)	2796	7.58 (3.63–11.8)
Women	15 265 (33.6)	171 304	10.6 (6.30–16.2)	80 (18.8)	715	7.68 (3.72–14.6)
Age at cohort entry (years)						
<25	16 266 (35.8)	166 503	9.48 (5.83–14.0)	139 (32.6)	1176	7.38 (3.87–13.0)
25–30	14 680 (32.3)	171 073	11.3 (6.26–17.4)	120 (28.2)	1027	7.96 (3.75–11.7)
≥31	14 466 (31.9)	144 361	9.46 (4.86–14.4)	167 (39.2)	1308	7.25 (2.83–12.7)
Year of cohort entry						
1985–1989	8476 (18.7)	161 566	20.4 (18.7–21.8)	75 (17.6)	887	10.2 (6.02–19.2)
1990–1995	11 220 (24.7)	152 938	14.1 (12.7–15.7)	140 (32.9)	1479	12.8 (5.99–14.8)
1996–2001	15 302 (33.7)	133 232	8.84 (7.35–10.4)	122 (28.6)	908	8.00 (6.33–9.65)
2002–2007	10 414 (22.9)	34 200	3.44 (1.88–4.81)	89 (20.9)	237	2.72 (1.22–3.89)

Table 1b Characteristics of NSW opioid substitution therapy registrants, by BBV notification status, 1993–2007

	Entire sub-cohort			No BBV infection			HBV monoinfection			HCV monoinfection			HBV/HCV co-infection			HIV infection[†]		
		Person-years			Person-years			Person-years			Person-years			Person-years			Person-years	
	No. (%) of registrants[*]	Total	Median	No. (%) of registrants	Total	Median	No. (%) of registrants	Total	Median	No. (%) of registrants	Total	Median	No. (%) of registrants	Total	Median	No. (%) of registrants	Total	Median
Total	29 613 (100)	213 008	7.28	23 650 (100)	109 313	3.53	598 (100)	2608	3.56	14 892 (100)	94 331	6.36	898 (100)	5249	6.02	234 (100)	1504	6.20
Sex																		
Men	20 348 (68.7)	144 932	7.19	16 352 (69.1)	76 495	3.64	436 (72.9)	1918	3.60	9793 (65.8)	61 378	6.29	643 (71.6)	3782	6.10	204 (87.2)	1355	6.55
Women	9265 (31.3)	68 076	7.51	7298 (30.9)	32 818	3.25	162 (27.1)	691	3.50	5099 (34.2)	32 953	6.47	255 (28.4)	1466	5.94	30 (12.8)	148	4.35
Age at cohort entry (years)																		
<25	11 674 (39.4)	87 088	7.60	9915 (41.9)	47 340	3.81	278 (46.5)	1282	3.96	5706 (38.3)	35 963	6.41	351 (39.1)	2130	6.27	61 (26.1)	373	6.08
25–30	8427 (28.5)	60 907	7.32	6771 (28.6)	31 905	3.56	169 (28.3)	770	3.18	4106 (27.6)	26 201	6.42	266 (29.6)	1534	5.79	68 (29.1)	494	7.73
>31	9512 (32.1)	65 013	6.74	6964 (29.4)	30 068	3.06	151 (25.3)	555	3.39	5080 (34.1)	32 167	6.23	281 (31.3)	1584	5.71	105 (44.9)	637	5.17
Year of cohort entry																		
1993–1997	10 212 (34.5)	111 454	11.7	8944 (37.8)	54 619	4.76	158 (26.4)	981	5.08	3563 (23.9)	36 132	11.2	129 (14.4)	1298	10.9	84 (35.9)	754	10.7
1998–2002	11 655 (39.4)	81 399	7.36	8962 (37.9)	42 095	5.35	290 (48.5)	1304	5.12	6958 (46.7)	47 049	7.05	475 (52.9)	3167	6.80	82 (35.0)	573	7.55
2003–2007	7746 (26.2)	20 155	2.70	5744 (24.3)	12 599	2.11	150 (25.1)	323	2.01	4371 (29.4)	11 150	2.55	294 (32.7)	784	2.75	68 (29.1)	177	2.71

[*] Category numbers will not sum to total numbers for the sub-cohort as individuals were followed-up in a time-dependent manner, allowing an individual to contribute person-years to multiple groups as their BBV notification status changed over the period of observation.

[†] With or without HBV or HCV notification.

Table 2 Risk of any cancer and the most frequently occurring cancers in NSW opioid substitution therapy registrants, by sex and current age (1985–2007)

Cancer type	Obs.	Exp.	SIR	95% CI
All cancer				
Men	536	431	1.24	1.14–1.35
Women	283	285	0.99	0.88–1.11
<40 yrs	282	295	0.96	0.85–1.07
40–49 yrs	357	282	1.27	1.14–1.40
≥50 yrs	180	139	1.30	1.12–1.50
Liver				
Men	51	6.92	7.37	5.49–9.69
Women	12	0.91	13.2	6.80–23.0
<40 yrs	4	1.62	2.47	0.67–6.33
40–49 yrs	26	3.96	6.57	4.29–9.63
≥50 yrs	33	2.26	14.6	10.1–20.6
Trachea, bronchus, and lung				
Men	82	19.8	4.15	3.32–5.11
Women	28	7.59	3.69	2.45–5.33
<40 yrs	15	4.11	3.65	2.04–6.02
40–49 yrs	58	13.0	4.46	3.41–5.71
≥50 yrs	37	10.2	3.61	2.57–4.90
Melanoma				
Men	64	91.2	0.70	0.54–0.89
Women	37	48.7	0.76	0.54–1.03
<40 yrs	48	71.6	0.67	0.50–0.88
40–49 yrs	37	51.4	0.72	0.51–0.98
≥50 yrs	16	16.9	0.95	0.56–1.49
Female breast				
<40 yrs	15	32.5	0.46	0.27–0.74
40–49 yrs	27	54.3	0.48	0.32–0.69
≥50 yrs	6	14.1	0.43	0.17–0.86
Cervical				
<40 yrs	21	11.0	1.90	1.20–2.84
40–49 yrs	14	4.67	3.00	1.64–5.03
≥50 yrs	2	0.63	3.19	0.39–11.5
Non-Hodgkin lymphoma				
Men	62	38.1	1.63	1.26–2.07
Women	13	11.5	1.13	0.62–1.86
<40 yrs	25	20.9	1.20	0.79–1.73
40–49 yrs	37	19.8	1.87	1.33–2.54
≥50 yrs	13	8.94	1.46	0.78–2.49

Obs=observed number of cancers. Exp=expected number of cancers. SIR=standardised incidence ratio. CI=confidence interval.

Table 3 Multivariable analysis of risk factors for common cancers among NSW opioid substitution therapy registrants, 1993-2007

	Lung Cancer				Non-Hodgkin lymphoma				Liver Cancer			
	n	IRR*	95%CI	P	n	IRR*	95%CI	P	n	IRR*	95%CI	P
Current age†	27	1.19	1.15–1.24	<0.0001	23	1.06	1.01–1.11	0.025	13	1.20	1.13–1.27	<0.0001
Calendar year†	27	0.91	0.81–1.03	0.131	23	1.16	1.01–1.37	0.054	13	1.13	0.91–1.49	0.317
Sex												
Men	22	1.55	0.63–4.65	0.378	17	1.03	0.42–2.90	0.954	12	3.94	0.76–72.2	0.190
Women (ref)	5	1.00			6	1.00			1	1.00		
Notified HCV infection												
Yes	21	3.29	1.39–9.07	0.011	13	1.12	0.49–2.65	0.792	12	9.05	1.73–166	0.036
No (ref)	6	1.00			10	1.00			1	1.00		
Notified HBV infection‡												
Yes	2	1.59	0.25–5.42	0.531	0	-			3	4.63	1.03–15.4	0.021
No (ref)	25	1.00			23				10	1.00		
Notified HIV infection‡												
Yes	0	-			4	26.0	7.40–71.3	<0.0001	0	-		
No (ref)	27				19	1.00			13			

IRR=incidence rate ratio. CI=confidence interval. Ref=reference group in analysis.

*Adjusted for current age (years), calendar year, sex and time-dependent HCV notification status, HBV notification status and HIV notification status

†IRR refers to one year increase

‡IRRs could not be calculated if a cancer case did not occur in one of the binary groupings

Note: Infection groupings are not mutually exclusive

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CONTRIBUTORS

The study was conceived and designed by CMV, LB and LD. The data were obtained from data custodians by LM, NSM and CMV. All authors contributed to the analytical plans. The data were prepared and analysed by AS. AS, CMV and LD drafted the paper. All authors reviewed, revised and approved the final draft. CMV is the guarantor.

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COMPETING INTERESTS

All authors report no disclosures.

ETHICS APPROVAL

The study was reviewed and approved by all relevant ethics committees and the requirement for informed consent was waived because the researchers received only de-identified data.

DATA SHARING STATEMENT

There is no additional data available.

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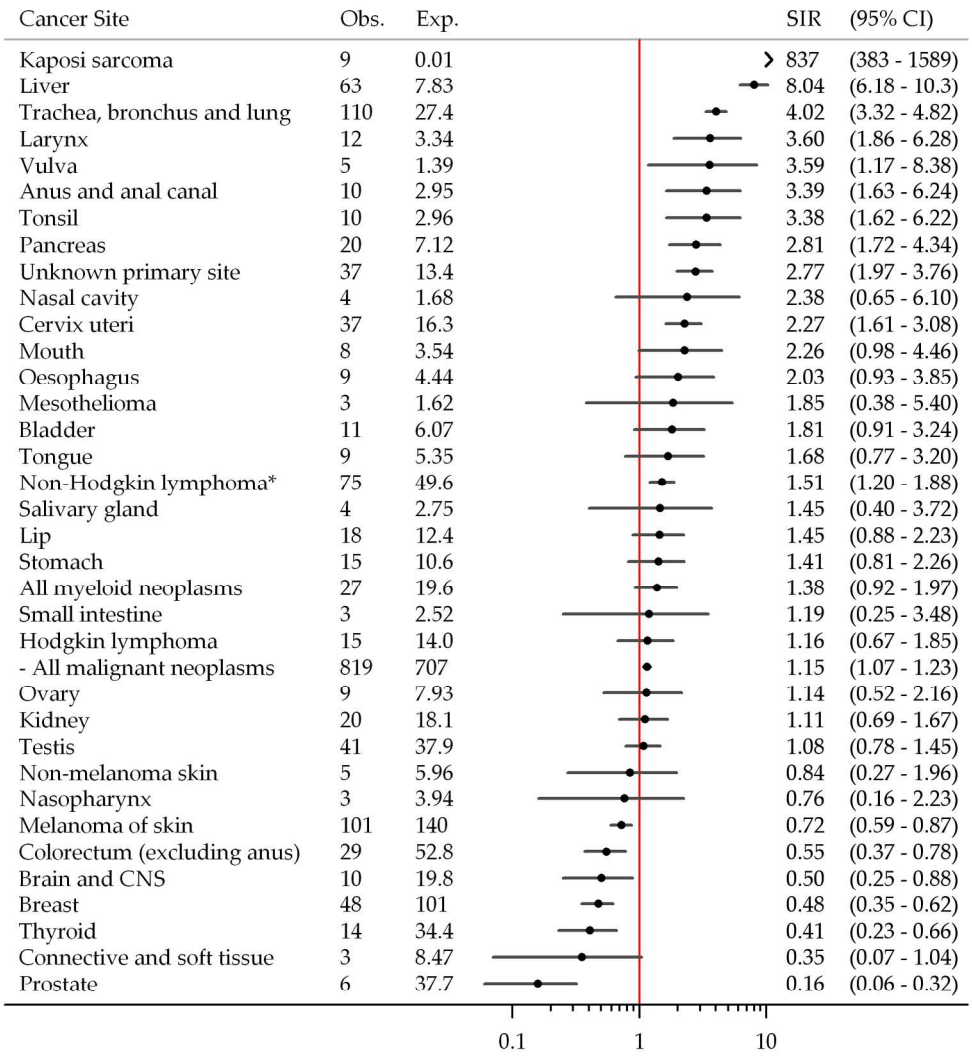

Figure 1 Risk of cancer among NSW opioid substitution therapy registrants, 1985–2007
529x587mm (96 x 96 DPI)

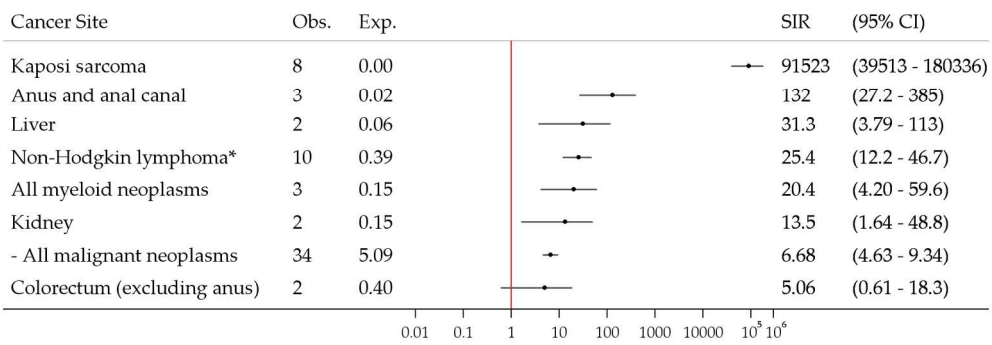

Figure 2 Risk of cancer in NSW opioid substitution therapy registrants with notified HIV infection, 1985–2007
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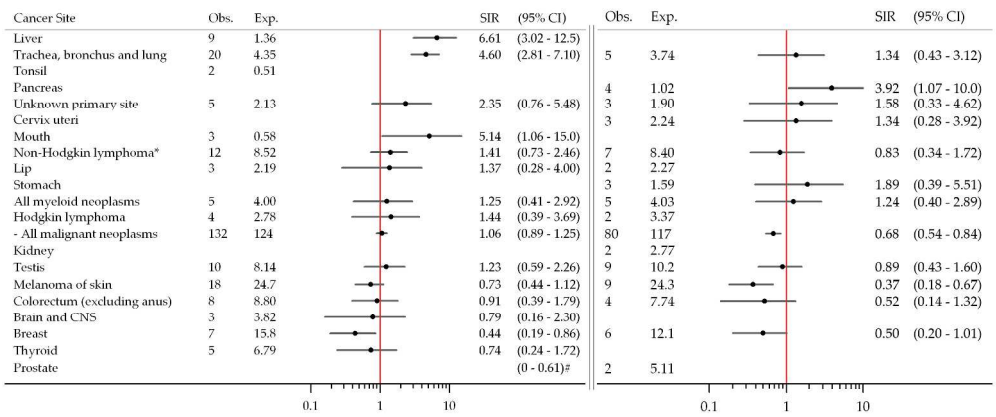

Figure 3 Risk of cancer among NSW opioid substitution therapy registrants with notified hepatitis C infection and registrants without notified hepatitis B, hepatitis C or HIV infection, 1993–2007
872x360mm (96 x 96 DPI)