PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (see an example) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below. Some articles will have been accepted based in part or entirely on reviews undertaken for other BMJ Group journals. These will be reproduced where possible.

ARTICLE DETAILS

TITLE (PROVISIONAL)	The importance of blood borne viruses in elevated cancer risk among opioid dependent people: a population-based cohort study
AUTHORS	Vajdic, Claire ; Swart, Alexander; Burns, Lucinda; Mao, Limin; Grulich, Andrew; Amin, Janaki; O'Connell, Dianne; Meagher, Nicola; Randall, Deborah; Degenhardt, Louisa

VERSION 1 - REVIEW

REVIEWER	A.M. Ponizovsky, MD, PhD Mental Health Services Ministry of Health Jerusalem Israel I have no competing interests.
REVIEW RETURNED	31-Jul-2012

GENERAL COMMENTS	This is a well-written report on a rigorously performed study about the association between blood borne viruses' infections and cancer risk among opioid dependent population under opioid substitution treatment. The findings are sound and contribute substantially to some of the knowledge preexisting in the field. An additional value of the study is the replication of the results of previous studies concerning increased and decreased risks for the specific types of cancer in this population. I have only few minor points that should be addressed before the report can be published. Introduction. It seems to me that the word "success" is not very pertinent for cancer as one of consequences of the high prevalence of hepatitis C (p 6, para 2). Discussion. In the Context subsection (p.15, para 1), the authors somewhat illogically state that their work "is the first population-based study of cancer incidence among people who are opioid dependent… Of the two prior studies measuring cancer incidence in opioid dependent populations,…". Even though the previous studies cited had defined limitations (Does any study exist without them?), this does not cancel the fact that those preceded your study. Figure 2. There are the incorrect reporting expected cases (0.00), SIR (91523) and 95% CI (39513-180336) for Kaposi sarcoma (p.32).

REVIEWER	Daniel Wolfe, International Harm Reduction Development Program, Open Society

	Foundations. No conflicts of interest.
REVIEW RETURNED	12-Aug-2012

THE STUDY	my sense is that more could/should be done to convey that the increased risk of some cancers among OT patient have nothing to do with blood borne infections, and to clarify that increased risks of cancers associated with HIV infection are not necessarily particularly different among those on OST than others infected with HIV.
RESULTS & CONCLUSIONS	Would also add here that use of OST programs as a site for smoking cessation, HCV treatment, or other cancer reducing measures is one possibility, but that the conclusion is week.
GENERAL COMMENTS	While literature has documented increased risk of bloodborne infections associated with injecting of opioids, links between history of opioid use and cancers—and the argument that methadone or buprenorphine programs are settings that can be used to help to reduce cancer risk—have been less explored. The authors seek to assess the epidemiology of cancer among injecting drug users using a cohort of opioid substitution treatment patients, linking their records those of cancer registries to assess cancer risks relative to the general population, and arguing that elevated risk of cancers (particularly of the lung and liver) should provide an additional incentive to using opioid substitution treatment programs for smoking cessation, heptatitis C treatment, etc. to help reduce cancers. The study seems methodologically sound, though other reviewers would be better placed to assess statistical assumptions or the limitations of the cancer registries. In order to clarify or strengthen the arguments based on the findings, though, I would offer some thoughts for consideration by the authors. **Greater clarity about correlation/causation in the premises of the study, and in the conclusion, regarding cancers not directly linked to injecting drug use.** Some greater clarity could be brought by the authors about how they are conceiving of carcinogens, and how they accounted for confounding in the causal chain between opioid injection, exposure to carcinogens, and subsequent manifestation of cancers. This seems particularly important to clarify with lung cancer, anal cancer, etc, where the risk exposure of interest as demonstrated in previous studies (e.g., smoking, sexual contact leading to infection with human papilloma virus, etc) are not directly related to opiate use, and where other interventions (eg, smoking cessation, condom use and reduction of sexual partners, etc) have been shown to reduce incidence . The 'key message' that excess cancer risk is associated with OST patients may read differently once so contextualized (if it is the cigarettes, rather than the opioids, that are responsible for lung cancers in this group, would be good to say that; if smoking data were unavailable, it would be good to note in discussion the likelihood of this confounder as a primary weakness that limits the relevance of claims of an association)

Less importantly, but related, the authors also assert that HIV is a carcinogen. While it is of course true that those with HIV infection have increased rates of multiple cancers, including anal cancer, KS, non Hodgkin lymphoma, cervical cancer, etc, it is less clear whether these outcomes—the result of a combination of immune system damage and cancer-causing pathogens—can/should be attributed primarily to HIV, rather than to the viruses known to cause these cancers in those who are not immunocompromised.

These clarifications are also relevant for understanding the conclusions and recommendations of the study authors. While methadone and buprenorphine users may be more likely to smoke or to have more unprotected sex, it is not the authors' argument that opioid substitution treatment will significantly impact these behaviors, or that the carcinogenic effects of exposures would be mitigated by greater availability of OST. Instead, and appropriately, they argue for provision of smoking cessation at OST programs (and, one would assume, sexuality/STI education), but the "key message" that OST sites are key for cancer prevention may obscure the point. Similarly, the claim that OST settings can be used to target cancer prevention, is slightly confusing as phrased, since it is not really the OST, but rather the opportunity to reach a population more likely to drink, smoke, and have hepatitis C, that offers the opportunity. Some nuancing of messaging can address these issues.

The difficulty in justifying programmatic action based on correlations between receipt of OST and cancer risk is illuminated similarly by limitations to conclusions based on decreased risks of certain cancers among OST patients. The claim that incarceration may reduce exposure to sunlight and consequently result in decreased melanoma, for example, could arguably lead to the recommendation that prison is good for cancer prevention among opioid users. While this is not of course not the argument of the authors (happily, since incarceration has been associated with multiple adverse health outcomes among those on OST or receiving ART), it makes clear the limits of interpreting the data as a guide to action. It would be interesting to know if the authors have thoughts about mechanisms that would account for decreased rates of other cancers among OST patients, such as prostate cancer.

Greater clarity about claims of OST programs as a site for reduction of cancer risk even where cancer is directly associated with injection drug use. Apart from KS, which is well known to manifest itself in men with immune systems compromised by HIV infection, the greatest excess cancer risk observed by the authors was that for liver cancer. This is not surprising given the high rates of hepatitis C infection noted by the authors and in multiple other studies among injecting drug users, and the accelerated progression of liver disease among those with HIV/HCV co-infection. As authors assert, HCV treatment—which indeed can

	result in sustained virologic response and decreased risk of liver cancer—is indeed essential for those with HCV. It is not clear—beyond the fact that OST patients formed the sample of this study—that OST programs are the best or most appropriate sites for HCV treatment, or whether there are other places where HC V prevention and treatment might receive greater emphasis. It might also be useful to integrate OST into other clinical settings as has been done, for example, with HIV or TB. The core of this study—which examines rates of cancer among OST patients, noting increased risks of some and decreased risks of others—remains important and instructive. Clarification of the claims about the associations, and tighter scrutiny of the conclusions, would strengthen the piece further, and prevent misinterpretation by the many who may get no farther than the abstract and key messages and conclude, incorrectly, that use of opioids increases cancer risk, and that provision of OST may reduce them.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1: A.M. Ponizovsky, MD, PhD

Issue 1
Introduction. It seems to me that the word ''success'' is not very pertinent for cancer as one of consequences of the high prevalence of hepatitis C (p 6, para 2).

Response 1
Agreed. The word “success” has been removed and replaced with the more descriptive “increased longevity”.

Issue 2
Discussion. In the Context subsection (p.15, para 1), the authors somewhat illogically state that their work ''is the first population-based study of cancer incidence among people who are opioid dependent... Of the two prior studies measuring cancer incidence in opioid dependent populations,...''. Even though the previous studies cited had defined limitations (Does any study exist without them?), this does not cancel the fact that those preceded your study.

Response 2
We have revised our wording to “Of the two prior studies measuring cancer incidence in opioid dependent individuals…”. However, our study is the first truly population-based assessment of cancer risk in opioid dependent individuals. Grinshpoon et al. (2011) was not population-based as information on deaths was not obtained from a population-based deaths register. As such we have not altered the wording pertaining to the fact that our study ''is the first population-based study of cancer incidence among people who are opioid dependent…”

Issue 3
Figure 2. There are the incorrect reporting expected cases (0.00), SIR (91523) and 95% CI (39513-180336) for Kaposi sarcoma (p.32).

Response 3
The expected count for Kaposi sarcoma was 0.00009 so we rounded to two significant figures (0.00). The estimated SIR and 95% confidence interval have been checked and are correct. No change has been made in response to this comment.

Reviewer 2: Daniel Wolfe

Issue 1
Greater clarity about correlation/causation in the premises of the study, and in the conclusion, regarding cancers not directly linked to injecting drug use.
Some greater clarity could be brought by the authors about how they are conceiving of carcinogens, and how they accounted for confounding in the causal chain between opioid injection, exposure to carcinogens, and subsequent manifestation of cancers. This seems particularly important to clarify with lung cancer, anal cancer, etc, where the risk exposure of interest as demonstrated in previous studies (e.g., smoking, sexual contact leading to infection with human papilloma virus, etc) are not directly related to opiate use, and where other interventions (eg, smoking cessation, condom use and reduction of sexual partners, etc) have been shown to reduce incidence. The 'key message' that excess cancer risk is associated with OST patients may read differently once so contextualized (if it is the cigarettes, rather than the opioids, that are responsible for lung cancers in this group, would be good to say that; if smoking data were unavailable, it would be good to note in discussion the likelihood of this confounder as a primary weakness that limits the relevance of claims of an association)

Response 1
In response to the request for greater clarity regarding the potential for confounding, we have amended both the Article Summary and the Discussion (page 14) to include the lack of data on smoking and alcohol use as a limitation.

The reviewer suggests better clarity is needed to ensure readers are not falsely led into the suggestion that opioid/opiate use itself is directly causally associated with cancer risk. We agree that it would be unfortunate if this occurred as it is not our conclusion and there is certainly no evidence to support it. However we do not believe that readers will be vulnerable to this conclusion. For example, in the Discussion (page13) we open by mentioning the key finding of an increased risk of cancers "causally related to infection with oncogenic viruses, smoking, and alcohol consumption." In the final paragraph of the Discussion, we further highlight the true causal mechanisms in several cancers: "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)…" Nevertheless, we have amended the Article Summary to include the following in the first dot-point, '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".

Issue 2
Less importantly, but related, the authors also assert that HIV is a carcinogen. While it is of course true that those with HIV infection have increased rates of multiple cancers, including anal cancer, KS, non Hodgkin lymphoma, cervical cancer, etc, it is less clear whether these outcomes—the result of a combination of immune system damage and cancer-causing pathogens—can/should be attributed primarily to HIV, rather than to the viruses known to cause these cancers in those who are not immunocompromised.

Response 2

The International Agency for Research on Cancer (IARC) has assessed the evidence regarding carcinogenicity of HIV and have classified it as a Group 1 carcinogen (e.g. Bouvard et al Lancet 2009;10:321-2). We agree with the reviewer that the carcinogenic mechanism is indirect. We do specifically address this issue in the Discussion (page 15) by delineating the carcinogenic mechanism in the setting of HIV infection: “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.” To improve clarity, we have slightly amended the wording of the Article Summary and Abstract regarding HIV infection.

Issue 3
These clarifications are also relevant for understanding the conclusions and recommendations of the study authors. While methadone and buprenorphine users may be more likely to smoke or to have more unprotected sex, it is not the authors’ argument that opioid substitution treatment will significantly impact these behaviors, or that the carcinogenic effects of exposures would be mitigated by greater availability of OST. Instead, and appropriately, they argue for provision of smoking cessation at OST programs (and, one would assume, sexuality/STI education), but the “key message” that OST sites are key for cancer prevention may obscure the point. Similarly, the claim that OST settings can be used to target cancer prevention, is slightly confusing as phrased, since it is not really the OST, but rather the opportunity to reach a population more likely to drink, smoke, and have hepatitis C, that offers the opportunity. Some nuancing of messaging can address these issues.

Response 3
We agree with the reviewer and had recommended counselling for “safer sexual practices” (see page 17, Discussion).

We agree that our conclusions regarding OST settings could be improved by rephrasing and so we have amended the Key Message point as well as the Abstract conclusion.

Issue 4
The difficulty in justifying programmatic action based on correlations between receipt of OST and cancer risk is illuminated similarly by limitations to conclusions based on decreased risks of certain cancers among OST patients. The claim that incarceration may reduce exposure to sunlight and consequently result in decreased melanoma, for example, could arguably lead to the recommendation that prison is good for cancer prevention among opioid users. While this is not of course not the argument of the authors (happily, since incarceration has been associated with multiple adverse health outcomes among those on OST or receiving ART), it makes clear the limits of interpreting the data as a guide to action. It would be interesting to know if the authors have thoughts about mechanisms that would account for decreased rates of other cancers among OST patients, such as prostate cancer.

Response 4
On page 16 of the Discussion we had suggested possible reasons for our finding of a reduced risk of various cancers. For example, for prostate cancer we suggested that under-participation in screening may account for the reduced risk, as well as a more mechanistic suggestion, low testosterone levels in opioid-induced hypogonadism. No change has been made in response to this comment.

Issue 5
Greater clarity about claims of OST programs as a site for reduction of cancer risk even where cancer is directly associated with injection drug use.
Apart from KS, which is well known to manifest itself in men with immune systems compromised by

HIV infection, the greatest excess cancer risk observed by the authors was that for liver cancer. This is not surprising given the high rates of hepatitis C infection noted by the authors and in multiple other studies among injecting drug users, and the accelerated progression of liver disease among those with HIV/HCV co-infection. As authors assert, HCV treatment—which indeed can result in sustained virologic response and decreased risk of liver cancer—is indeed essential for those with HCV. It is not clear—beyond the fact that OST patients formed the sample of this study—that OST programs are the best or most appropriate sites for HCV treatment, or whether there are other places where HCV prevention and treatment might receive greater emphasis. It might also be useful to integrate OST into other clinical settings as has been done, for example, with HIV or TB.

Response 5
Our study was not designed to assess whether the OST setting is the best or most appropriate site for HCV treatment. We found however that a large proportion of cancers in OST clients are associated with HCV infection. This, coupled with the knowledge that HCV infection is exceedingly common in the IDU population (who regularly cycle in and out of OST), led to our conclusion that the OST setting would be an opportunistic way to target a population likely to benefit from such services. We have nevertheless amended our Abstract conclusion, including removing reference to blood-borne virus treatment in the OST setting.

Issue 6
The core of this study—which examines rates of cancer among OST patients, noting increased risks of some and decreased risks of others—remains important and instructive. Clarification of the claims about the associations, and tighter scrutiny of the conclusions, would strengthen the piece further, and prevent misinterpretation by the many who may get no farther than the abstract and key messages and conclude, incorrectly, that use of opioids increases cancer risk, and that provision of OST may reduce them.

Response 6
The main amendments in response to this reviewer's comments have involved the Article Summary section and Abstract as we agree that some readers may focus only on these sections.

We thank the reviewers for their insights.

VERSION 2 – REVIEW

REVIEWER	Daniel Wolfe, International Harm Reduction Development Program, Open Society Foundations. No conflicts of interest.
REVIEW RETURNED	23-Aug-2012

GENERAL COMMENTS	All my comments addressed satisfactorily, and abstract and key messages clarified, so can recommend publication.