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The risk of cancer among persons with a history of injecting drug use in Sweden – a cohort study based on participants in a needle exchange program

Authors

Anton Reepalu[a], Marianne Alanko Blomé[a], Jonas Björk[b], Anders Widell[c], and Per Björkman[a]

From the [a]Department of Clinical Sciences, and [c]Department of Clinical Microbiology, Skåne University Hospital, Lund University, SE-205 02 Malmö, Sweden, and from the [b]Competence Centre for Clinical Research, Skåne University Hospital, SE-221 85 Lund, Sweden.

Correspondence to Anton Reepalu, Department of Clinical Sciences, Skåne University Hospital, Lund University, S-205 02 Malmö, Sweden.

Tel: +46 707 471575; Fax: +46 40 191166; e-mail: reepalu@gmail.com

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Running title

The risk of cancer among injecting drug users.

Abstract

Background

Injecting drug use (IDU) may lead to exposure to a range of carcinogenic agents. We investigated the risk and distribution of cancers among individuals with a history of IDU in Sweden.

Material and Methods

The cancer incidence in a cohort of longitudinally followed participants in a needle exchange program (NEP), recruited between 1987 and 2007, was compared to that in the Swedish general population, matching for age group and gender. Baseline demographic and drug use data were collected and longitudinal testing of serological markers for HIV, hepatitis B and C virus was performed during NEP participation. Standardized incidence ratios (SIR) for types of cancer found in the study cohort were calculated, using data from the Swedish National Cancer Registry for reference.

Results

The mean follow-up time for the 3 255 participants was 11.8 years, constituting 38 419 person years at risk, The mean age at end of follow-up was 42.7 years, and 75% of participants were men. Seventy-eight cases of cancer were observed (SIR 1.1 [95% CI = 0.9-1.4]). The SIR was significantly increased for 5 cancer types among men; primary liver, laryngeal, lung, oropharyngeal and non-melanoma skin cancer (respective SIR 12.8 [95% CI = 4.2-30.0], 9.2 [95% CI = 1.9-26.8], 3.2 [95% CI = 1.5-6.1], 7.3 [95% CI = 1.5-21.2], and 3.5 [95% CI = 1.1-8.2]), and for cancers of endocrine organs among women (5.3 [95% CI = 1.7-12.4]).

Conclusion

Although the standardized overall cancer incidence in this relatively young IDU cohort was similar to that in the general population, the risk of specific types of cancer was significantly

increased, suggesting that IDU confers elevated risks for certain malignancies. These findings prompt further studies to investigate causative factors and suggest the need for surveillance among persons with a history of IDU.

Introduction

The etiology of cancer is complex and a multitude of factors, both genetic and environmental, may be involved. Injection drug users (IDUs) are at risk of frequent exposure to carcinogens, in particular toxic substances in narcotic drugs and blood-borne viruses (HIV, hepatitis B and hepatitis C viruses) [1-3]. Furthermore, environmental factors known to be associated with cancer, such as tobacco, alcohol and micronutrient deficiencies, may be more common in IDUs [4, 5]. The distribution of cancer types occurring with higher frequency among IDUs could also suggest the presence of hitherto unknown mechanisms in carcinogenesis, and direct targeted investigations for causative agents.

Few studies have examined the cancer risk related to injection drug use (IDU), and most have focused on cancer among HIV-infected IDUs [1, 6]. Since IDUs are at an overall increased risk of death, it is possible that any biological impact of IDU on cancer development could be obscured by premature death from other causes, such as trauma, intoxication and acute infections [7-9]. Detection of cancer among IDUs may also be reduced, due to lower access to screening and diagnostic investigations for suspected cancer than in the general population [10].

We hypothesized that IDU could predispose to a long-term increased risk of cancer. Cancer incidence among persons exposed to IDU is difficult to investigate due to the lack of representative cohorts that may be followed over time. In this study we have compared the overall incidence of cancer and the distribution of cancer types among Swedish IDUs with those in the Swedish general population, matching for age group and gender. For this purpose, we have followed an unselected cohort of IDUs participating in a needle exchange program (NEP), using national identity numbers for linking to national registries.

Setting

The Malmö NEP was initiated in 1987 as a targeted intervention to prevent HIV transmission, and provides clean needles and syringes to active IDUs, as well as a package of medical and social services. It is based in the Department of Infectious Diseases, Skåne University hospital, Malmö, the third largest city in Sweden with 286 000 inhabitants. All services are provided free of charge. Criteria for participation in the NEP are age above 20 years and signs of venepuncture as evidence of ongoing IDU. The number of heavy drug addicts (mostly IDUs) in Malmö was estimated to be around 1 600 in 1998 [11]. In that year 1 136 persons visited the NEP, suggesting that about 70% of the heavy drug addicts in Malmö are registered in the NEP.

At registration, a structured interview is conducted by an experienced nurse or staff nurse and a detailed questionnaire concerning personal data, drug habits and social conditions is completed. For serosurveillance purposes, blood samples are obtained at approximately three monthly intervals. Participants are longitudinally tested for serological markers of HIV, hepatitis B and C virus (HBV and HCV) for as long as they remain negative for the respective infection. Testing for HIV is required for participation, but can be done under code. In contrast, testing for viral hepatitis is voluntary, but must be done under national identity number. All collected data is coded and entered into a computerized database.

For this study, all participants registered with correct national identity numbers in the NEP between 1987 and 2007 were included. No exclusion criteria were applied.

Methods

The NEP database was first matched with a national death and emigration registry from Statistics Sweden to obtain dates for possible deaths or emigrations from Sweden among the

participants. The database was then matched to the National Cancer Registry from the National Board of Health and Welfare.

The National Cancer Registry is based on the registration of malignant tumours, and 99% of the reported tumors are histopathologically confirmed. The most recent assessment of the Swedish cancer registry, published in 2009, reported a high degree of coverage of malignant tumors in Sweden [12]. The data obtained from these registries included all registrations until 31-12-2007. **The seventh and ninth International Classification of Diseases (ICD-7 and ICD-9) were used for categorization of different cancer types.**

To calculate standardized incidence ratios (SIR) for different cancer types found in the study cohort, a method using person-years at risk was chosen. SIR:s were calculated for all cancer types found in the IDU cohort. The time period a participant in the NEP was considered to be at risk for cancer was from the year of entry in the NEP until the year of death, emigration, or the end of study follow-up. From the National Board of Health and Welfare gender, age and calendar year specific cancer incidence data were obtained for all reported cancers in Sweden. To avoid influence of natural fluctuations in incidence during the follow-up period the mean incidence from 1988 until 2007 was used.

Data on HIV, HBV and HCV serological markers was obtained from the available test results in each participant case record.

Statistical analysis

The data was divided into five year age groups starting from 10 until 79 years of age. For each cancer type diagnosed in the cohort an expected number was computed based on the mean incidence data mentioned above. The 95% confidence intervals (CI) for the SIR were determined assuming Poisson distribution for the observed cases [13]. For the statistical

analysis and matching of the database to the different registries SPSS statistics 17.0 and Microsoft Office Excel 2007 were used.

Ethics

The study was approved by the Ethics Committee at the University of Lund. All information in the database that could be used to identify individual subjects, including the national identity numbers, were removed prior to statistical analysis.

Results

Study population

The database from the NEP contained 4 139 individuals during the study period. National identity numbers were missing from 882 subjects, and two individuals appeared in the death and emigration registries prior to their enrollment in the NEP. Thus, a total of 3 255 individuals (79%) could be included (Fig 1). Comparing several baseline variables among the excluded individuals with those included in the study revealed minor non-significant differences between the two groups, with the exception that participants without accessible national identity number were to a larger extent one-time visitors in the program (Table 1). The mean age of the study participants at the end of follow-up was 42.7 years. Male and female participants had similar age distributions, but the median age of women at the end of follow-up was lower than that of male participants (41 vs. 44 years) (Fig 2).

Standardized incidence ratios for cancer among IDUs

The follow-up time at risk for the entire cohort was 38 419 years, yielding a mean follow-up time of 11.8 years. Ninety cases of cancer were detected, 12 of which had been registered

prior to the year of entry in the NEP, resulting in a total of 78 cases of cancer for SIR analysis (Table 2). The mean age at cancer diagnosis was 49.7 years (men 50.8 years; women 47.2 years).

The overall cancer incidence in the NEP cohort was not significantly increased (SIR 1.1 [95% CI = 0.9-1.4]). However, among male participants, the SIR was increased for primary liver cancer (12.8 [95% CI = 4.3-30.0]), laryngeal cancer (9.2 [95% CI = 1.9-26.8]), cancers of trachea, bronchus and lung (3.2 [95% CI = 1.5-6.1]), oropharyngeal cancer (7.3 [95% CI = 1.5-21.2]) and non-melanoma skin cancer (3.5 [95% CI = 1.1-8.2]). Among women, a significantly increased SIR was found for cancers of endocrine organs (5.3 [95% CI = 1.7-12.4]. This group included 2 thyroid cancers, 1 parathyroid cancer, 1 cancer of the pituitary gland and 1 cancer of the aortic body.

Serological results for HIV, HBV and HCV are presented in table 3. HIV prevalence has remained low among participants, whereas a majority of IDUs have markers of HCV infection ([14, 15]). Data on HBV markers were missing from several participants.

Discussion

Although an overall increased risk of cancer was not detected among injection drug users in this longitudinal study, we did observe elevated risks for certain types of cancer with regard to gender. Men with a history of IDU were at higher risk for developing cancers of the liver, respiratory tract and skin, whereas an increased risk of cancers in various endocrine organs was found among women.

The reason for the gender differences observed could depend on gender-specific risk exposures or biological factors. Furthermore, the small number of female participants could explain why the high SIR:s for certain cancer types failed to reach statistical significance.

HIV infection is common in many IDU populations, and has strong associations with the development of several types of cancer [16], but its impact in our cohort was negligible. This is in contrast to most other published studies on this subject, which have focused on the specific role of HIV in this context [1].

The association between hepatocellular carcinoma (HCC) and chronic viral hepatitis is well established [17]. Since exposure to HCV was nearly universal in our cohort (87%) and data on HBV markers were lacking from 28% of participants, we were unable to determine particular risk factors for HCC development. In a recent Swedish study investigating the incidence of HCC among persons notified with hepatitis C in Sweden between 1990-2004, the reported SIR was higher than in our cohort (35 [95% CI of 31-40]) [3]. The most common route of infection reported for HCV-infected subjects in that study was IDU (57%), and the mean age at diagnosis was 60 years. In our cohort, the corresponding age was 42 years, suggesting that the incidence of HCC is likely to rise over time with aging of the cohort, in accordance with recent observations from cohorts of veterans in USA [18]. Similar phenomena might occur for other types of malignancies associated with HCV, such as lymphoproliferative malignancies [19].

We also detected increased SIR:s among men for oropharyngeal, laryngeal and lung cancers. An increased risk of lung cancer was observed among French and Italian IDUs, both for those with and without HIV infection [1], and an association between cannabis use and lung cancer has been reported [20]. Cigarette smoking – a recognized risk factor for these malignancies [21, 22] - was reported at baseline by 97% of participants in our cohort from whom this information was available. We did not have access to accurate data on alcohol use during follow-up, which could contribute to the increased risk of oropharyngeal carcinoma [23]. The

presence of potential carcinogenic substances in narcotic drugs could account for an increased cancer incidence among persons exposed to IDU; however, scientific information on this is extremely scarce [20].

Interestingly, several of the cancer types with elevated SIR **in this cohort, such as non-melanoma skin cancer, oropharyngeal cancer and cervical cancer,** are known to be associated with human papillomavirus (HPV) infection [24, 25], although an increased risk of HPV has not been clearly linked to IDU.

Our finding of an increased incidence of various cancers of endocrine organs among women has not been reported previously; the reasons for this are unknown and merit further investigation.

Our study was limited by a relatively small cohort size, with a low proportion of women. The real risk of cancer related to IDU may have been underestimated both due to premature death from drug-related causes, and a mean follow-up time of 11.8 years, which could have been insufficient to detect differences in incidence for other types of cancer. For these reasons, we were unable to investigate risk factors for cancer development among participants and to perform stratification relating to age group and duration of IDU.

All IDUs in our uptake area were not included in the cohort, which therefore might not be fully representative of this population. However, we believe that the design of this study has advantages, by using unselected inclusion of participants during active IDU with longitudinal follow-up and linking to high-quality national registers. IDUs may be of special relevance for studying cancer incidence and identification of potential carcinogenic agents – both toxic substances, as well as unrecognized blood-borne viruses that may be implicated in carcinogenesis [24]. The linking of data from the National Cancer Registry with participant

data from NEP demonstrate a new and promising way to further assess the long-term risk of cancer related to IDU exposure.

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Tables and figures

Figure 1

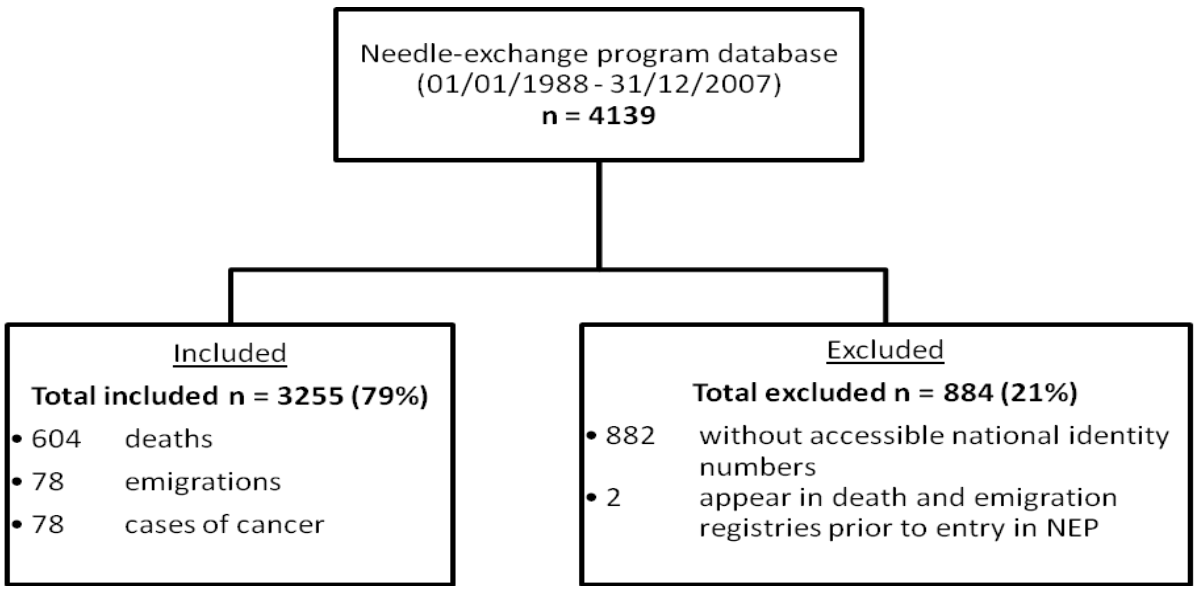

Figure 2

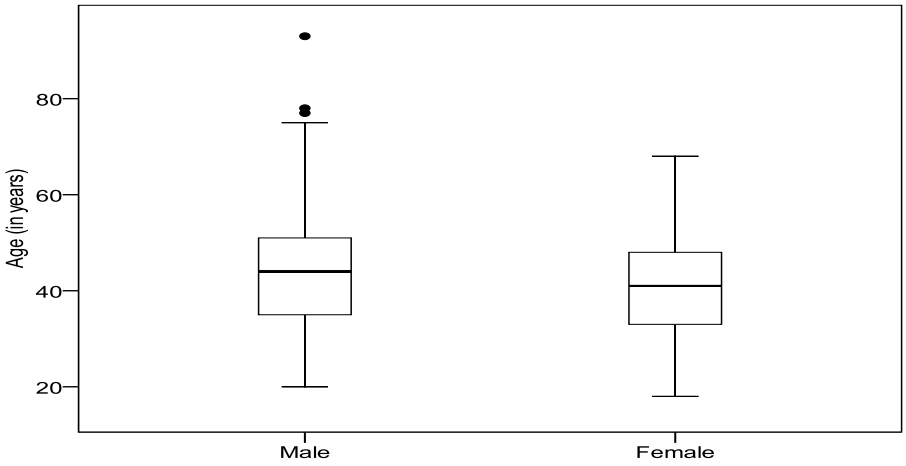

Table 1. Baseline characteristics of needle-exchange program participants

	Included	Excluded
Number in each group	3255	884
Mean birth year	1964	1963
Percentage men	75 %	81 %
Percentage born in Sweden	85 %	82 %
Mean year of NEP registration	1996	1996
Median number of visits to NEP	70	1
Mean year of starting amphetamine injection use	1985	1984
Mean year of starting heroin injection use	1991	1990
Amphetamine injection use	88 %	85 %
Heroin injection use	66 %	56 %

Table 2. Observed and expected number of cancer cases, standardized incidence ratios, and 95% confidence intervals among 3 255 injecting drug users in a needle exchange program in Malmö, Sweden (follow-up until 12-31-2007)

		Male (number)				Female (number)			
Cancer site	ICD-9*	Observed	Expected*	SIR*	95% CI*	Observed	Expected*	SIR*	95% CI*
*Oropharyngeal**	*144,146*	*3*	*0,41*	*7,3*	*1,5-21,2*	1	0,04	22,7	0,6-126,6
Digestive tract									
Esophagus	150	1	0,42	2,4	0,1-13,4	0	-	-	-
Stomach	151	1	1,00	1,0	0,0-5,6	1	0,17	5,9	0,2-32,6
Colon	153	2	2,18	0,9	0,1-3,3	1	0,55	1,8	0,1-10,1
Rectum	1541	1	1,50	0,7	0,0-3,7	1	0,28	3,6	0,1-20,1
Anus	1542	1	0,09	10,6	0,3-59,3	0	-	-	-
Liver, primary	*1550*	*5*	*0,39*	*12,8*	*4,2-30,0*	1	0,05	18,5	0,5-12,5
Respiratory									
Larynx	*161*	*3*	*0,33*	*9,2*	*1,9-26,8*	0	-	-	-
Trachea, bronchus, lung	*162*	*9*	*2,81*	*3,2*	*1,5-6,1*	2	0,58	3,5	0,4-12,5
Skin									
Melanoma	172	3	3,40	0,9	0,2-2,6	0	-	-	-
Non-melanoma	*173*	*5*	*1,42*	*3,5*	*1,1-8,2*	0	-	-	-
Breast	174	0	-	-	-	2	6,43	0,3	0,0-1,1
Female genital organs									
Cervix uteri	180	0	-	-	-	4	1,16	3,5	0,9-8,8
Corpus uteri	182	0	-	-	-	1	0,48	2,1	0,1-11,7
Male genital organs									
Prostate	185	4	5,12	0,8	0,2-2,0	0	-	-	-
Testis	186	2	2,52	0,8	0,1-2,9	0	-	-	-
Urinary organs									
Bladder	188	4	2,13	1,9	0,5-4,8	1	0,18	5,7	0,2-31,8
Kidney	189	3	1,36	2,2	0,5-6,5	1	0,19	5,3	0,1-29,6
Other and unspecified									
Brain	191	1	2,82	0,4	0,0-2,0	0	-	-	-
*Endocrine organs**	*193,194*	0	-	-	-	*5†*	*0,94*	*5,3*	*1,7-12,4*
Unknown site	199	2	1,13	1,8	0,2-6,4	0	-	-	-
Blood and lymphatic									
Non-Hodgkin lymphoma	200	3	1,93	1,6	0,3-4,6	1	0,36	2,8	0,1-15,5
Hodgkin's disease	201	1	0,60	1,7	0,0-9,4	0	-	-	-
Multiple myeolma	203	1	0,51	2,0	0,1-10,9	0	-	-	-
Myeloid leukaemia	205	1	0,64	1,6	0,0-8,7	0	-	-	-
All sites		56	49,79	1,1	0,9-1,5	22	18,72	1,2	0,7-1,8
All sites, entire cohort (male and female)		78	68,50	1,1	0,9-1,4				

ICD-9, International Classification of Diseases, Ninth Revision; Expected, number of cancer cases expected using age group, sex and calendar year-specific incidence rates from the Swedish Cancer Registry; SIR, standardized incidence ratio; CI, confidence interval; Oropharyngeal, floor of mouth and oropharynx; Endocrine organs, the thyroid and other endocrine glands and related structures;
†2 thyroid cancers, 1 parathyroid cancer, 1 cancer of the pituitary gland and 1 cancer of the aortic body

Table 3. Prevalence of serological markers for HIV, HBV and HCV

	All			Male			Female		
	Positive	Negative	Missing	Positive	Negative	Missing	Positive	Negative	Missing
Hepatitis C virus	87%	7%	6%	87%	7%	6%	87%	7%	6%
Hepatitis B virus	47%	25%	28%	49%	25%	26%	42%	26%	32%
Human immunodeficiency virus	1%	96%	3%	1%	96%	3%	1%	96%	3%

For HCV: anti-HCV antibodies; for HBV: anti-HBV core antibodies; for HIV: anti-HIV antibodies

Positive denotes subjects who ever tested positive for the respective marker; negative denotes subjects with no known positive test result for the respective marker; Missing, no data available.

Legend for figures

Figure 1

Flow diagram of the potential participants in the study, reasons for exclusion and outcomes for the included participants.

Figure 2

Box plots showing the age distribution among study participants, divided into male and female.