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Methadone maintenance and cancer risk: An Israeli case registry study

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ABSTRACT

Objectives: This study explored cancer incidence rates in a large cohort of Israeli (Jewish and Arab) opioid-dependent individuals receiving methadone maintenance treatment (MMT), and how the incidences vary by ethnicity and sex.
Method: The record linkage between the Israel National Addiction Registry (INAR) and the Israel National Cancer Registry (INCR) was performed. Information about the Israeli general population from the Central Bureau of Statistics was used for comparison to match sex and year of birth to the cohort under study. Age standardized incidence ratios (SIRs) and 95% confidence intervals (CIs) were calculated.
Results: Though the SIR values for aggregated cancer sites for both men and women on MMT did not differ significantly from the corresponding figures in the general population (0.88, 95% CI 0.76–1.00, and 1.06, 95% CI 0.76–1.36, respectively), the risks were substantially increased for lung (1.97, 95% CI 1.13–2.82), larynx (3.62, 95% CI 1.11–6.13) and liver (6.8, 95% CI 1.76–11.83) cancers among Jewish men and for cervix uteri cancer among Jewish women (2.41, 95% CI 0.99–3.84). By contrast, the SIR values for colorectal cancer among Jewish men (0.46, 95% CI 0.09–0.82) and for breast cancer among Jewish women (0.36, 95% CI 0.00–0.71) were significantly lower than expected.
Conclusions: The results suggest that the increased and reduced site-specific cancer risks are counterbalanced, resulting in the absence of the expected excess cancer risk for the entire cohort. The reduced risks for colorectal and breast cancers suggest a protective effect of MMT, warranting further investigation.

1. Introduction

Mortality rates among opioid-dependent people are higher than for the general population, with some differences between countries and ethnic-religious groups (Bargagli et al., 2006; Degenhardt et al., 2011) varying between 15 and 28 per 1000 persons per year (Frischer et al., 1997; Sanchez-Carbonell and Seus, 2000; Bargagli et al., 2001). Although the majority of deaths among opioid-dependent people occur from accidental poisonings (Oyefeso et al., 1999), deaths from medical causes, such as cancer, have increased (Gachupin-Garcia et al., 1992; Zaccarelli et al., 1994; Ferreros et al., 2008; Bjornaas et al., 2008; Shiels et al., 2010). Prospective cohort studies in the field are uncommon (Gossop et al., 2002), and even rarer is the opportunity to compare a cohort with well-defined background characteristics with the general population. Therefore, studies of excess morbidity and mortality among opioid-dependent individuals using data from a reliable national case registry would be useful for obtaining more specific information about this subgroup of substance use disorders.

The relationship between opioid dependence and cancer morbidity has not yet become an issue for epidemiological investigation, despite the bulk of risk factors noted in this population. For example, people with opioid dependence smoke heavily (Hser et al., 2001; Brooner et al., 1997; Strain, 2002; Xue et al., 2011) and may neglect health-related behaviors, such as help-seeking (Eland-Goossensen et al., 1997) and eating a balanced diet (Morabia et al., 1989; Zador et al., 1996; Nolan and Scagnelli, 2007). In addition, there are the increased morbidity and mortality of site-specific cancers associated with comorbid immunosuppressive/immunoproliferative infections often observed in injecting opioid users, such as human immunodeficiency virus (HIV) (Gachupin-Garcia et al., 1992; Shiels et al., 2010; Zaccarelli et al., 1994; Allardice et al., 2003), Hepatitis B virus and Hepatitis C virus (HBV/HCV) (Amin et al., 2006), and Human Papilloma virus (HPV) (Walboomers et al., 1999). This increased cancer mortality calls for examining cancer incidence among an opioid-dependent cohort.

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Our systematic search of comprehensive medical databases, such as MEDLINE and PSYCHINFO revealed no study using population-based case registers of opioid-dependent persons and cancer incidences, to examine their association. Taking into account the variety of factors that may differentially affect cancer rates in opioid dependent individuals at different time points and environments, we conducted a record linkage study exploring the relationship between opioid dependence and cancer morbidity among users of the mental health services specializing in the treatment of opioid-dependence in Israel.

The present study aimed (1) to explore the overall and site-specific cancer incidence rates in a large cohort of opioid-dependent individuals participating in MMT programs, and (2) to examine how cancer incidence varies by ethnicity and sex. Based on the reviewed literature, we hypothesized that overall and site-specific cancer incidence rates will be increased among the opioid-dependent people under MMT compared to the general population. Such a finding has implications for public health policy and may encourage early screening for cancer in subjects who abuse opioids.

2. Method

2.1. Study design

The study was designed as a record linkage between the two population-based case registers, the Israel National Addiction Registry (INAR) and the Israel National Cancer Registry (INCR). Common for both databases, a unique person identifier was used by researchers for linkage procedure in a way that precluded obtaining any identifying information. The study was approved by the Sha'ar Menashe Institutional Review Board and due to the anonymous analyses no informed consent was required.

2.2. Data sources

The INAR of the Ministry of Health included complete information on all cases of opioid dependence in all medical treatment settings since 1970. Approximately 3000 cases are recorded annually in specialized settings for treatment of opioid dependence. The databank contains sociodemographic (gender, age, etc.) and treatment information.

The INCR is considered to be one of the best databases of its kind worldwide (Grinshpoon et al., 2005), covering all public and private medical facilities in the country. The registry completeness is over 95%. Data on every resident in this registry are organized according to personal identification number, as in the methadone treatment register. In addition to the demographic information, the registry contents detailed tumor characteristics (location using the ICD-9 codes, histopathology, etc.). The number of Israeli residents who would have been diagnosed as suffering from cancer and who sought diagnosis and treatment abroad is likely limited, as medical services in Israel are adequate and free of charge, including for those in the terminal stages.

2.3. Study sample

From the INAR we identified all individuals born until 1976 who were ever hospitalized or received ambulatory treatment for opioid dependence since 1970 onward. All diagnoses coded as F11.2 in ICD-10 (304 in DSM-IV-TR) were included as cases to be followed up for cancer. (A few cases of co-occurrence with schizophrenia, schizoaffective, and bipolar disorders were excluded from analysis as potentially confounding cancer estimates) The sample consists of 18,659 individuals (87.4% male and 90.3% Jewish). This cohort was followed up for cancer by record linkage with the INCR. The person-years of exposure to cancer risk for the index cases were defined from entry date (age 15 or the beginning of year 1991) to termination date (diagnosis of cancer, death, emigration, or the end of year 2008; a total period of 17 years). The mean follow-up time for Jewish male and female cases was 10.1 ± 3.6 and 9.6 ± 3.1 years (median time 12 and 11 years, respectively), with corresponding figures for Arab male and female 11.9 ± 4.8 and 8.5 ± 4.5 years (median time 13 and 9 years, respectively).

2.4. Comparison group

The Israeli general population used for comparison in this study was comprised of individuals living in Israel and (if feasible) were not registered as patients in the INAR. Relying on information from the Central Bureau of Statistics, we reconstructed this population to match sex, year of birth, country of origin, and year of immigration to addict population.

Table 1
Person-years, mean and median follow-up time by age, gender, and population group (1991–2008).

Age (yr.)	Population group					
	Jewish		Arab		Total cohort	
	Male	Female	Male	Female	Male	Female
15–19	2707	1041	995	63	5796	1789
20–24	5824	1759	2213	102	11,951	2909
25–29	9970	2215	4252	123	20,019	3611
30–34	14,108	2527	5824	138	27,123	3907
35–39	15,872	2507	6299	102	29,400	3714
40–44	14,351	1955	5193	61	26,276	2925
45–49	9877	1241	3139	23	17,905	1906
50–54	5096	599	1529	5	9291	948
55–59	2091	178	685	3	4267	380
60–64	761	49	291	0	1341	78
65–69	258	14	87	0	450	25
70–74	100	5	27	0	152	12
75+	34	0	10	0	44	5
Total	81,050	14,088	30,545	619	154,013	22,207
Follow-up time (yr.)						
Mean (SD)	10.1 (3.6)	9.6 (3.1)	11.9 (4.8)	8.5 (4.5)	11 (4.2)	9.05 (3.8)
Median	12	11	13	9	12	10

2.5. Study variables

The outcome variable in this study was cancer diagnosis (incidence) and the independent variables were sex and population group. Demographic information included gender, year of birth, population group (Jewish and Arab) and date of death. Age was divided into subgroups with a-5-year interval as follows: 15–19, 20–24, 25–29, 30–34, 35–39, 40–44, 45–49, 50–54, 55–59, 60–64, 65–69, 70–74, and 75 and older. Clinical information included ICD-10 diagnosis of opioid dependence and concomitant mental disorders. For every primary neoplasm, the following variables were extracted: ICD-9 codes, date of diagnosis, and histological morphology. Neoplasms were classified into the following groups: lung cancer (code 162), larynx cancer (code 161), liver cancer (code 155), colorectal cancer (codes 173 and 174), breast cancer (codes 174 and 174), bladder/kidney cancer (codes 188 and 189), cervical/uterine cancer (code 180), and lymphoma (code 162).

2.6. Statistical analysis

Expected number of cancer cases (total and specific cancers as classified by primary site) during the observation period was obtained by multiplying the number of person years at risk times with the corresponding mean incidence rate of cancer in the general population of Israel during the same observation period. (In the case when more than one cancer diagnosis was observed in the same person, only the first one was used) Age-standardized incidence ratios (SIRs) were calculated by dividing the number of observed cancer cases in each group by the expected number of cases. Calculation of 95% confidence intervals (CIs) of SIRs was based on the assumption that the observed number followed a Poisson distribution. SIR greater than 1 indicates excess incidence in the sample compared to the general population. The statistical significance level was set at 0.05. All data were linked and analyzed using SAS 9.1.3 for Unix software (Cary, NC: SAS Institute Inc.).

3. Results

Table 1 shows the person years accumulated during the years of observation by gender, age group, and population group. As can be seen, there was above 176,000 person years for the entire cohort.

During the follow-up period, 184 of the 18,659 opioid-dependent individuals under MMT had developed cancer. Table 2 shows the raw number of observed cancer cases in the sample according to primary site, gender, and population group. As can be seen, the vast majority of cancer cases were observed among Jewish men ($n = 118$, 64%), while no case was ascertained among Arab women. By specific site, the most cases comprised lung cancer (18%), bladder/kidney cancer (13%) and lymphoma (11%) among Jewish men and cervix uteri cancer (33%) and larynx cancer (24%) among Jewish women. Among Arab men, the corresponding figures were 24% for lung cancer, 12% for lymphoma, and by 9% each for larynx, bladder/kidney and brain cancers.