American Journal of Cancer Epidemiology and Prevention

American Journals of Cancer Epidemiology and Prevention
http://ivyunion.org/index.php/ajcep
Vol. 1, Article ID 201300081, 10 pages

Research Article

Organ Specific Cancer Incidence in an Industrial Sub-district: A Population-based Study with 12 Years Follow-up

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Abstract

Background: Although emissions from petrochemical industries have been recognized as a cause of an increased in cancer deaths, its contribution to specific organ cancer incidence has not been investigated in a cohort study with an adequate sample size.

Objectives: To assess the association between organ specific cancer incidence and living in industrial subdistrict compared to other areas in Israel after controlling for socio- demographic variables.

Methods: Retrospective cohort study using baseline measurements from the Central Bureau of Statistics 1995 census living in the Haifa subdistrict, which houses major industrial facilities in Israel, compared to the rest of Israel. The census database was linked with the Israel Cancer Registry for cancer data. Smoking prevalence data was obtained from the Central Bureau of Statistics 1996/7 and 1999/2000 health surveys.

Results: A total of 175704 persons were included with a total of 8034 cancer cases. The mean age was 31 years (range: 0-101 years). In the analysis including all the target population the hazard ratio to develop cancer comparing Haifa subdistrict to non-Haifa was 1.16 (95% CI: 1.11-1.21, $p<0.001$) after adjusted for age, gender, Jews vs. non-Jews and continent of birth. Compared to the incidence in the rest of Israel, the Haifa subdistrict population had an elevated hazard ratio of lung, head and neck, colorectal, gastric and esophagus, bladder and cervical carcinoma. In discrepancy with this observation, people in the Haifa sub-district do not smoke more than in the rest of Israel.

Conclusions: We report an increased risk of developing cancer in a heavily industrialized sub-district, mainly among sites which are very similar to cancer sites caused by smoking.

Keywords: cancer; incidence; industrial zone; cohort study; lung cancer

Abbreviations: CBS - Central Bureau of Statistics; ICR - Israel Cancer Registry; ICD-O - International Classification of Diseases for Oncology; HR - Hazard Ratio; INS - Israeli New Shekel; PM10 - Particulate Matter; SIR - Standard Incidence Ratio; NIS - Israeli New Shekel

Peer Reviewers: Reza Nuri, PhD, Department of Clinical Exercise Physiology, University of Tehran, Iran; Yan Wei, MD, PhD, Department of public health, Guiyang Medical University, China

Received: December 29, 2012; **Accepted**: March 8, 2013; **Published:** March 25, 2013

Funding: This work was supported by the Hadassah – Hebrew University Fund for Young Investigators.

Competing Interests: The authors have declared that no competing interests exist.

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Introduction

The Haifa subdistrict, in the Northern part of Israel, covers an area of 294 sq. km and includes the city of Haifa and suburbs, with a total population of approximately 400,000 people. The region also comprises an oil-fired power plant, fertilizer plant, petrochemical plant and refinery, electronic and metal industrial facilities. Based on point measurements from industrial sites in this area, it is estimated that hundreds to thousands of tons of metal were released to the air, with an amount of dust of up to 5-6 tons/km^2/year [1] which mainly derives from the combustion of heavy fuel oil [2].

An ecological study conducted by the Israeli Ministry of Health reported [3] that cancer incidence in the Haifa subdistrict is high relative to other areas in Israel. Recently, Eitan and his colleagues [4] have reported that chronic exposure to ambient PM10 concentrations in Haifa subdistrict appears to be associated with elevated lung cancer incidence rates in males.

The increased incidence of cancer in the Haifa subdistrict is not well understood, as there are a number of possible confounders. These include demographic and socio-economic factors such as population composition, healthcare access, and/or cancer susceptibility [5]. For example, non-Jews in Israel have a lower cancer incidence compared to the Jewish population [6] and Jews of European or American origin have a higher incidence of cancer than other Jewish immigrants to Israel [7]. Exposure to smoking [5,8] environmental tobacco smoke [9] and occupational hazards [10] could also affect the incidence of cancer.

Outdoor air pollution has been recognized as a cause of an increase of deaths from non-specified causes [11-19], cardiopulmonary disease [15,18,20], respiratory disease [11,19] and cancer [20]. Data linking death from lung cancer to air pollution is conflicting: some epidemiological studies support such an association [9,18,21] while in others it is not found [11,20].

To the best of our knowledge, the impact of living in industrial region on organ specific cancer incidence (for example: esophagus cancer rather than the total cancer burden) has not been investigated in a cohort study with an adequate sample size and ability to assess the elevated risk after adjusting for potential confounders.

Materials and Methods

Retrospective cohort study based which is based on data collected in the 1995 national census, carried out by the Central Bureau of Statistics (CBS) and including the entire population of Israel. The census was conducted by personal interviews, avoiding interviews of proxies or mailed questionnaire. A fifth of the population was randomly sampled according to geographical residency to complete a comprehensive questionnaire, which addressed a wide range of topics including demographic, occupational and socio-economic variables; this file encompasses 1,113,420 people. The exposed group in the current study included all the people who had completed the questionnaire, lived permanently in the Haifa subdistrict and were free of cancer until 1998. The unexposed group was the same number of people, randomly sampled from those who completed the questionnaire and did not reside in the Haifa subdistrict.

The census database was linked (Using the personal Identification number, names and other demographical data) with the Israel Cancer Registry (ICR) for cancer data, including date of cancer diagnoses up to December 2007 and International Classification of Diseases for Oncology (ICD-O - Version 3) topography and morphology. The ICR receives compulsory notification from numerous sources of data, including pathologic reports, discharge summaries and death certificates and has been archiving cancer cases since 1982. Completeness of the registry was found to be about 95% for solid tumors [22]. The entire cohort's data was merged with the Israeli Population Registry in order to obtain dates and causes of death.

Smoking prevalence data was obtained from the

CBS 1996/7 and 1999/2000 health surveys. Each survey was conducted by telephone interview and included nearly 29,000 people of ages 15 years and above. The survey addressed a wide range of topics including demographic, socio-economic and health variables. Specific questions addressing smoking included: do you smoke? At what age did you start smoking? How many cigarettes do you smoke a day?

The current data set was designed in order to detect a hazard ratio (HR) of 1.15 with 90% power and a two-sided alpha level of 0.05 when comparing the incidence of cancer among people living in the Haifa subdistrict to that of people living in the rest of Israel. The sample size of 80,000 people was calculated according to the life expectancy of the study population and the expected cancer incidence rates in men and women [6]. Given the above calculation, and the expected number of cancer cases, the dataset provided an adequate sample size for univariate analysis and allowed for multivariate analysis controlling for important covariates. For comparison of the study population characteristics, continuous variables were compared by ANOVA test and categorical variables were compared with chi-test. Univariate survival analysis using log-rank tests comparing individuals living in the Haifa subdistrict with those living in other subdistricts for time to cancer diagnosis was performed. Multivariate Cox proportional hazards models, while controlling for age, gender, ethnicity, continent of birth, education years and income per person, was carried out. For all analyses $p < 0.05$ was considered statistically significant. The SPSS program (15th version; Chicago, Illinois) was used for the statistical analysis.

Results

A total of 175,704 people were included in the current study after excluding people who were diagnosed with cancer at or before 1998. When compared to the rest of Israel, people living in the Haifa subdistrict were older (mean age: 33.9 years vs. 28.8 years, $p < 0.001$), with more females (51.2% vs. 50.4%, $p < 0.001$), more Jews (87.6% vs. 78.2%, $p < 0.001$), more of European origin (27.0% vs. 15.7%, $p < 0.001$), more literate (mean: 11.7 school years compared with 11.3 years, $p < 0.001$), higher rates of heavy metals and chemical workers (2.1% vs. 1.7%, $p < 0.001$) and with a higher salary (4837 NIS income per person/month vs. 4637 Israeli New Shekel NIS income per person/month, $p < 0.001$).

From 1998-2007, a total of 8,034 cancer cases were diagnosed in the study population. The characteristics of persons who developed cancer in the Haifa subdistrict were similar to the baseline characteristics of this population in the 1995's survey (Table 1). Among heavy metals and chemical workers only 174 cases of cancers were reported (2.1% of all cancer cases). An increased incidence of cancer among residents of the Haifa subdistrict versus the rest of Israel was found in all age groups. The increased risk was significant using a chi-squared test in all ages between 0-74, while a non-significant trend towards elevated rates was seen in age groups 75-84 years and above 85 years (Table 2).

Table 1 Characteristics of patients who developed cancer among residents of the Haifa subdistrict versus the rest of Israel

	Haifa n=4860	**Non Haifa n=3174**	***p* value**
	n (%[*])	n (%)	
Age (years, mean) ±standard deviation	58.7±16.0	56.4±16.5	<0.001
Males	2252 (46.3)	1505 (47.4)	0.3
Non-Jews	258 (5.3)	583 (8.9)	<0.001
Origin: Europe	2756 (56.7)	1383 (43.6)	<0.001
Education years (years, mean) ±standard deviation	11.2±4.4	10.8±4.6	0.002
Income (mean, NIS)*	5448	5152	0.03

[*]restricted to ages 25-65 years old

Table 2 Cancer incidence among residents of the Haifa subdistrict versus the rest of Israel according to age groups

Age	**Haifa**	**Non Haifa**	***p* value**
	n (%[*])	n (%[*])	
0-14	60 (0.4)	50 (0.2)	0.009
15-40	546 (1.9)	480 (1.6)	0.010
41-64	2226 (10.2)	1483 (8.1)	<0.001
65-74	1346 (19.4)	769 (17.4)	0.008
75-84	588 (18.0)	336 (16.3)	0.120
>85	94 (12.3)	56 (10.6)	0.350

[*]percentages of cancer cases in each age group.

The HR for cancer incidence in residents of the Haifa subdistrict versus residents in the rest of Israel was 1.16 (95% CI: 1.11-1.21, p < 0.001). Other statistically significant variables associated with increased risk of cancer were older age (HR=1.06 per year, p < 0.001), male gender (HR=1.12, p < 0.001) and Jews born in Europe (HR=1.14, p < 0.001) and America (HR=1.31, p=0.002) compared with Jews born in Israel. The non-Jewish population had a decreased risk of cancer (HR=0.72, p < 0.001) compared with Jews born in Israel.

Number of cases for specific types of cancer appearing in Table 3 and the HR's for incidence in residents of the Haifa subdistrict versus residents in the rest of Israel are appeared in Table 4. Compared to the incidence in the rest of Israel, the Haifa subdistrict population had an elevated HR of lung, head and neck, colorectal, gastric and esophagus, bladder and cervical carcinoma. No cancer was associated with statically significant decreased incidence in the Haifa subdistrict compared to the rest of Israel.

In order to adjust the results for education and income, we established a sub-group comparison, in which only individuals who were 25-65 years old in 1995 were analyzed. A total of 54,049 people were included, with 3049 cancer cases. The HR for developing cancer in the Haifa subdistrict versus in the rest of Israel was 1.13 (95% CI: 1.05-1.22, p=0.001). In addition, age (HR=1.07 per year, p < 0.001) and higher income (per 1000 NIS) (HR=1.003, p=0.015) were associated with increased risk of cancer incidence. In this specific group, male sex (HR=0.78, p < 0.001) and a non-Jewish Israeli origin (HR=0.77, p=0.001) were associated with decreased risk of cancer incidence.

Table 3 Cancer cases among residents of the Haifa subdistrict versus the rest of Israel in all population and according to sex

P value	Females n (%)		P value	Males n (%)		P value	All population n (%)		Organ
	Haifa n=44613	Non Haifa n=44632		Haifa n=40484	Non Haifa n=43975		Haifa n=87097	Non Haifa n=88607	
<0.001	2608 (5.8%)	1669 (3.7%)	<0.001	2252 (5.3%)	1505 (3.4%)	<0.001	4860 (5.6%)	3174 (3.6%)	**All cancer**
<0.001	135 (0.3%)	66 (0.1%)	<0.001	235 (0.6%)	149 (0.3%)	<0.001	370 (0.4%)	215 (0.2%)	**Lung**
<0.001	356 (0.8%)	202 (0.5%)	<0.001	348 (0.8%)	222 (0.5%)	<0.001	704 (0.8%)	424 (0.5%)	**Colorectal**
<0.001	720 (1.6%)	544 (1.2%)	0.4	13 (<0.1%)	10 (<0.1%)	<0.001	733 (0.8%)	554 (0.6%)	**Breast**
			<0.001	394 (0.9%)	289 (0.7%)				**Prostate**
0.07	58 (0.1%)	40 (0.1%)	<0.001	224 (0.5%)	119 (0.3%)	<0.001	282 (0.3%)	159 (0.2%)	**Bladder**
<0.001	50 (0.2%)	20 (<0.1%)	0.006	84 (0.2%)	54 (0.1%)	<0.001	134 (0.2%)	74 (0.1%)	**Kidney**
<0.001	69 (0.2%)	44 (0.1%)	<0.001	111 (0.3%)	63 (0.1%)	<0.001	207 (0.2%)	107 (0.1%)	**Esophagus and gastric**
0.001	36 (0.1%)	13 (<0.1%)	0.2	34 (0.1%)	26 (0.1%)	0.002	70 (0.1%)	39 (<0.1%)	**Hepatobiliary**
0.1	73 (0.2%)	56 (0.1%)	0.9	51 (0.1%)	52 (0.1%)	0.2	124 (0.1%)	108 (0.1%)	**Pancreas**
0.08	38 (0.1%)	24 (0.1%)	<0.001	91 (0.2%)	45 (0.1%)	<0.001	129 (0.1%)	69 (0.1%)	**Head and neck**
0.01	85 (0.2%)	55 (0.1%)	0.9	16 (<0.1%)	16 (<0.1%)	0.016	101 (0.1%)	71 (0.1%)	**Thyroid**
0.06	55 (0.1%)	37 (0.1%)	0.3	60 (0.1%)	50 (0.1%)	0.036	115 (0.1%)	87 (0.1%)	**Sarcoma**
0.028	109 (0.2%)	79 (0.2%)	0.2	71 (0.2%)	57 (0.1%)	0.009	180 (0.2%)	136 (0.2%)	**Brain**
0.007	92 (0.2%)	59 (0.1%)	0.4	87 (0.2%)	80 (0.2%)	0.016	179 (0.2%)	139 (0.2%)	**Non Hodgkin Lymphoma**
0.07	52 (0.1%)	35 (0.1%)	0.09	62 (0.1%)	46 (0.1%)	0.013	114 (0.1%)	81 (0.1%)	**Leukemia**
0.004	124 (0.3%)	83 (0.2%)							**Cervix**
0.002	123 (0.3%)	80 (0.2%)							**Uterus**
			0.6	19 (<0.1%)	17 (<0.1%)				**Testis**

Table 4 Hazard ratio to develop cancer comparing Haifa subdistrict with the rest of Israel after adjusting for demographic variables according to cancer site

Variable	HR (95.0% CI)	*p* value
Lung (n=585)	1.29 (1.09–1.54)	0.003
Head and neck (n=198)	1.48 (1.10–1.99)	0.010
Colorectal (n=1128)	1.16 (1.03–1.31)	0.017
Gastric and esophagus (n=314)	1.37 (1.08–1.73)	0.010
Bladder (n=441)	1.26 (1.04–1.54)	0.022
Cervix (female only, n=208)	1.42 (1.07–1.88)	0.014
Pancreas (n=232)	0.79 (0.61–1.02)	0.074
Hepatobiliary (n=109)	1.36 (0.91–2.03)	0.132
Renal (n=208)	1.30 (0.97–1.73)	0.081
Testicular (male only, n=36)	1.14 (0.59–2.20)	0.707
Sarcoma (n=202)	1.07 (0.81–1.42)	0.634
Breast (female only, n=1264)	1.06 (0.95–1.19)	0.308
Uterus (female only, n=203)	1.16 (0.87–1.54)	0.313
Thyroid (n=172)	1.27 (0.93–1.72)	0.133
Prostate (male only, n=685)	1.04 (0.89–1.22)	0.614
Brain tumor (n=316)	1.05 (0.84–1.32)	0.649
Leukemia (n=195)	1.07 (0.80–1.43)	0.658
Non Hodgkin Lymphoma (n=318)	0.98 (0.78–1.22)	0.825

Additional analyses were carried, included only persons who were born in the same town (n=98852). This subgroup was younger (mean age: 20.1 years) and revealed an increased risk of cancer (HR=1.30, 95% CI: 1.18-1.42, p < 0.001) after adjusted for age, gender, Jews vs. non-Jews and continent of birth.

Analysis of the 1996/7 and 1999 /2000 CBS health surveys demonstrates that in the Haifa subdistrict, 21.5% and 21.8% people smoked versus 23.3% and 23.2% in the rest of Israel (p=0.068 and p=0.192, respectively, using a chi-squared test).

Discussion

In this study we show an increased cancer risk (HR=1.16, 95% CI: 1.11-1.21, p < 0.001) in the Haifa subdistrict, perceived as the most polluted subdistrict in Israel, compared to other subdistricts after adjusting for several potential confounders, including age, gender, Jewish origin, continent of birth. An elevated hazard ratio was also observed for lung, head and neck, gastric and esophagus, cervical, bladder and colorectal cancer (Table 4).

Smoking is an etiological cause in most of these tumors and the absence of personal smoking data among the study population is the major limitation of the study. However, several findings suggest that smoking is not the etiological cause of increased cancer incidence in the Haifa subdistrict. Analysis of the 1996/7 and 1999/2000 CBS health surveys demonstrates lower prevalence of smoking in the Haifa subdistrict compared to the rest of Israel (21.5% and 21.8% compared to 23.3% and 23.2%, respectively). Second, a significant increased incidence of cancer in the current study is found in ages 0-74 years old, including children and adolescents (Table 2). Third, a correlation between the prevalence of smoking and socio-economic status was reported in previous studies [23-24]. This association may be mediated by several factors including parental smoking, friends' smoking, cigarette availability and depression [23]. In the current study, the increased hazard ratio was controlled for education and income to eliminate these confounding effects.

Decreasing health service utilization among Haifa subdistrics may explain the study's results. However, national health insurance program established in 1995 provide insurance coverage to all citizens and permanent residents in Israel. In spite of national coverage and copayment waivers, low socioeconomic groups in Israel face more barriers to specialty care than the rest of the population [25]. Higher salaries and more literate population in the Haifa subdistrict do not support this explanation. In addition, the results were controlled for socioeconomic variables.

Previous studies focused on the impact of air pollution on cancer incidence have been focused on the impact of several fine particles [14,18,29,26-27] rather than living in areas which comprises various potential of potential emission. Assessment of fine particles may underestimate the total effect of the mixture particles which are found at pollution zones. Difference occupational exposure may explain our results. However, only 2.1% of the population in the Haifa subdistrict worked in the heavy metals and chemicals industries. Furthermore, only 174 cases of cancers were reported (2.1% of all cancer cases) among heavy metals and chemicals among all the study population.

The association between air pollution and cancer was evaluated in several studies, including studies which focused on petrochemical industries areas. Most of the data focused on lung cancer incidence with conflicting results [9,11,18,20,21]. Numerous studies have focused on malignancies other than lung cancer and the results in the current study are consistent with the minimal data which has been published up to date. The SIR in town proximity to a petrochemical plant in North-West Italy showed a significant higher risk (SIR=1.21; 95% CI: 1.02-1.40) for all cancers combined among males [28]. Yet, adjustment for relevant variable was not done at this study due to its template. Liver cancer in males was the only cancer which was elevated in inhabitants living adjacent to petrochemical industrial counties in Taiwan [29] and in Sweden [30]. Vinyl chloride is known to be associated with Angiosarcoma of the liver and a possible relationship between vinyl chloride exposure and hepatocellular cancer has also been suggested [30]. In the current study, Hepatobiliary cancer was elevated in the industrial areas compared to other inhabitants in Israel, albeit non significant (HR=1.36, 95% CI: 0.91-2.03, p=0.132). Non significant elevation in leukemia and lymphoma were found in residents living within 1.5–3 km of a petrochemical plant in Wales [31]. On the other hand, a slightly lesser number of cases of brain tumors than expected were seen in a petrochemical industry area in Sweden [Axelsson G, 2010]. In our study, no associations between living in Haifa subdistric and hematological malignancies or brain tumors were seen .

An absence of family history of cancer is another limitation of the current study. However, family history is not a dominant risk factor of lung, head and neck, gastric and esophagus, cervical, or bladder cancers. Jews of European or American origin have a higher incidence of cancer than other Jewish or non-Jewish ethnic groups in Israel [7]. The models we used in the current study included ethnicity and continent of birth to correct for these findings.

Advanced age, males in ages 25-65 years old and higher salary were associated with an increased risk for cancer in the current study. The association between age and cancer is well established and the risk for cancer in elderly is about ten-fold greater than in the younger age groups [32]. In the analyses which include all the study population, males were at increased risk for cancer, opposed to ages 25-65.
Increased risk for cancer among males has been documented in other reports, including in the USA [33]. Differences in cancer incidence are influenced by various reasons, such as individual's interaction with environmental and experimental factors, as well as genetic and physiological constitutions [34]. It is seems that the dominant causes of cancer differences are environmental. Yet, the explicit of exposures underlying these differences remain to be elucidated [34]. On the other hand, males were less likely to

develop cancer among ages 25-65 years old. The propensity to develop cancer at this age group is higher in females due to relative frequent of breast cancer, compared to prostate cancer which is more common in the elderly. There is a complex relationship between cancer incidence and socioeconomic status and is conflicted and stratified by race and ethnicity [35]. Indeed, prostate cancer in the entire American population and breast cancer incidence rates among white, Hispanic, and Asian women are higher with increased socioeconomic status [35]. On the other hand, the association between socioeconomic status and colorectal and lung cancer is influenced by ethnicity [35]. Due to heterogeneity of the population in Israel (Jews vs. non-Jews, recent immigrant and old resident, ancestors from Europe vs. Africa and Asia) the underlying reasons for the mechanism between higher salary and cancer in the current study is not clear.

On the other hand, non-Jews population had a decreased risk for cancer. The reasons for the decreased risk for cancer in the non Jews population in the current study are probably due to environmental exposures. For example, in the 1980's the risk of colorectal cancer in the Jews population was about 4 times higher than in the non-Jews population [36]. However, in the 1990's, the risk of colorectal cancer more than doubled in non-Jewish population compared with increased by only less than 20% in Jewish population [36].

The current study has several strengths. The cohort design is not associated with recall bias, which is common in case-control designs. The data were collected from population-based data sources, which are valid and reliable and not biased towards the study at the time of collection. In addition, ascertainment bias was eliminated by linking the study populations with the ICR, a data source with high validity and nationwide coverage [22]. A separate analysis was done which included only persons who were born in the same town in order to correct for the "healthy migrant effect" [27] and in this particular case, for the massive immigration from the former Soviet Union in the early nineties. Using this large dataset allowed us to reveal a significant elevation in the HR of cancer incidence between residents of the Haifa subdistrict compared to other subdistricts and allow for multivariate analysis controlling for demographic and socio-economic confounders.

Our analysis shows that there is an elevated risk of cancer incidence in the Haifa subdistrict compared to the rest of Israel. The result of our study supports the already established, positive association between environmental exposure and cancer risk in polluted areas. Further studies are necessary to confirm this association in other industrial polluted zones, to determine factors that may influence cancer risk in this group and to assess the impact of notification on disease detection in this population.

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