RESEARCH COMMUNICATION

Estimating the Incidence of Leukemia Attributable to Occupational Exposure in Iran

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Abstract

Objective: The aim this study was to estimate the fraction of leukemia incidence in Iran attributable to occupational exposure to benzene, ionizing radiation, and ethylene oxide. Methods: Nationwide exposure to each of these leukemogens was estimated using workforce data available at the ILO (International Labor Organization) website. The prevalence of exposure to leukemogens in each industry was estimated using exposure data from the CAREX (CARcinogen EXposure) database. The magnitude of the relative risk of leukemia for each leukemogen was from published literature. Using the Levin's population attributable risk (incidence), fractions of leukemia incidences attributed to workplace leukemogens were then estimated. Results: The total workforce in Iran according to the 1995 census included 12,488,020 men and 677,469 women. Agriculture was the largest sector with 24.5% of the males and 0.27% of the females, and the electricals-related sector was the smallest with 1.16% of the males and 0.66% of the females. After applying the CAREX exposure estimates to each sector, the proportion exposed to leukemogens was 0.016% for male workers and 0.02% for female workers. Estimating a relative risk of 3.6 (95% CI of 3.2–4.2) for high exposure and 1.9 (95% CI 1.7–2.1) for low exposure and employing the Levin's formula, the fraction of leukemia attributed to leukemogens in the workplaces among females was 3.6% (95% CI of 3.1-4.5) and among males was 7.6% (95% CI of 6.4-9.2). These fractions corresponded to estimated incidences of 0.60 (95% CI of 0.50-0.70) and 0.22 (95% CI of 0.16-0.23) cases of leukemia per 100,000 populations for males and females, respectively. Conclusion: The incidence of leukemia due to occupational exposure is very low in Iran, although males are at greater risk than females.

Key Words: Iran - leukemia - environmental carcinogens - benzene, ionizing radiation, ethylene oxide

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Introduction

With the rise in the incidence of leukemia due to occupational exposure, information is increasingly available for developing countries to use as a tool to combat the preventable causes of this disease. One source of such information is the CAREX (CARcinogen EXposure) international database on occupational exposure to known and suspected carcinogens. Constructed with the support of the program Europe Against Cancer of the European Union, CAREX provides selected exposure data and documented estimates of the number of exposed workers organized according to carcinogen and industry. Another source, the International Agency for Research on Cancer (IARC) (2002), has classified 87 agents as carcinogenic to humans (Group 1), the majority of which have been associated with leukemia. Among the many carcinogens in IARC Groups 1 and 2A, benzene, ionizing radiation, and ethylene oxide are very common in work place and there are sufficient exposure and risk data available in the literature related to them. Lack of sufficient exposure or risk data for other workplace leukemogens excludes them from population studies of this kind. Epidemiologic studies of exposure to benzene, ionizing radiation, and ethylene oxide have reported high and moderate magnitudes of relative risk for leukemia among workers exposed to each of these workplace carcinogens.

In general, determining what fraction of cancer incidences is due to workplace exposure to known carcinogens has been a challenging issue since late 1970, when scientists of the National Cancer Institute, the National Institute of Environmental Health Sciences, and the National Institute for Occupational Safety and Health of the United States estimated that up to 40% of all cancers were the result of occupational exposures (Bridbord et al., 1978). In 1981, Doll and Peto estimated that the fraction of cancer in the United States attributable to occupational exposure ranged between 2% to 8%, a very sharp difference from that of the previous estimate. Since

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then, several authors have estimated the impact of exposure to carcinogens in the workplace on the total burden of cancer in several countries, using different methodologies. Among these methodologies, the attributable risk concept (the fraction of disease occurring in a given population that would not have occurred had the factor of interest been absent), introduced by Levin (1953), has been of prime interest to epidemiologists and public health scientists. Attributable risk can be measured either among the exposed or in the general population (population attributable risk or PAR) (Miettinen, 1974; Bruzzi et al., 1985; Benichou, 2001). The PAR depends on the magnitude of the association between an exposure and a disease as well as on the prevalence of the exposure in the population.

The incidences of leukemia in the general population in Iran are reported to be 8.5 and 6.1 cases per 100,000 populations for males and females, respectively (Mohagheghi and Mosavi-Jarrahi, 2002). Using published figures regarding the relative risk of leukemia associated with exposure to the major workplace leukemogens (benzene, ionizing radiation, and ethylene oxide) and the proportion of exposed workers in different sectors, this study aimed to estimate the fraction of leukemia incidence attributed to occupational exposures in Iran. This study is the first to publish estimates of a nationwide incidence of occupational leukemia in the Middle East.

Materials and Methods

The methodology basically involves four main steps: 1) estimating the prevalence of exposure at any time in the workforce for the leukemogens of interest (benzene, ionizing radiation, and ethylene oxide); 2) estimating the magnitude of relative risk of leukemia associated with the exposure to the leukemogens of interest; 3) calculating the attributable fraction using Levin's formula; 4) estimating the fraction of leukemia attributed to occupational exposure from the reported incidences in population-based cancer registries.

To estimate the prevalence of exposure in the Iranian population to the three abovementioned leukemogens, the number of workers (both male and female, over 15 years of age) employed in each economic sector was obtained from the International Labor Organization (ILO) online workforce database (2006). The CAREX estimated proportions of exposed workers for each industry and leukemogens of interest (1998; 1999) were applied to the numbers of male and female workers in each industry. Since the number of workers in each industry was based on the 1995 national census, the proportion of workers who had ever been exposed was obtained by multiplying the proportion of those currently exposed by the national occupational turnover rate (the annual replacement of workers in a given job) as well as the rate of the economically active population. The average worker turnover in Iran is estimated to be 4 and the rate of the economically active population is estimated as 74.4% for males and 28.6% for females.

The reported relative risk of leukemia for exposure to the leukemogens of interest is estimated to be 1.9 (95% CI: 1.7–2.1) for low-level exposures, and 3.6 (95% CI 3.2–4.2) for high-level exposures (Driscoll et al., 2004). As recommended by World Health Organization in estimating global burden diseases, a partition factor of 0.5 was used to divide the number of exposed workers into low and high level of exposure, since in developing countries a higher proportion of the workforce receives a higher level of exposure due to compromise in workplace safety standards, the recommended partition factor for the level of exposure is 0.9 and 0.1 for high and low levels, respectively (Driscoll et al., 2004). The attributable fraction or attributable incidence fraction (AIF) was calculated using Levin's equation:

Table 1. Number and Proportion of Iranian Workers in Each Economic Sector According to Sex*

Sector	Male		Female	
Agriculture	3,062,798	24.53	1,827	0.27
Mining	115,185	0.92	4014	0.59
Manufacturing	1,968,806	15.77	24,000	3.54
Electrical	145,239	1.16	4,475	0.66
Construction	1,634,682	13.09	1,413	0.21
Trade	1,804,143	14.45	4,143	0.61
Transportation	955,271	7.65	9,258	1.37
Finance	139,286	1.12	12,111	1.79
Services	2,662,610	21.32	616,228	90.96
Total	12,488,020	100.0	677,469	100.0

*based on the 1995 census, ILO 2006

$$AF= \sum P_iRR_i-1 / \sum P_iRR_i$$

where AF is the attributable fraction; P_i is the proportion for exposure category '$_i$'; and RR_i is the relative risk of the exposure category '$_i$' compared to the reference category. To estimate the fraction of leukemia incidence attributed to occupational exposure, the incidence of leukemia, as reported by the Tehran Population-Based Cancer Registry, was multiplied by the estimated AIF.

Results

A total of 944 patients treated by radiotherapy in the afoA total of 12,488,020 males and 677,469 females were employed in different industrial sectors of Iran in 1995. Close to 25% of males were employed in agriculture sector and 91% of females were employed in the service sector. Table 1 presents the number and proportion of males and females in each industrial sector based on the 1995 census data. The CAREX estimate of the proportion of workers exposed to the three major workplace leukemogens in each industry is presented in Table 2. Applying the matrix of the carcinogen and exposure proportions to the number of workers in each industry provided the proportions of the workforce exposed to each leukemogens for each sex (Table 3). In total, 1.6% of the male's workforce and 2% of female's were exposed to the leukemogens of interest. Application of the national turnover and the growth rate of the economically active population to the proportions of exposed, considering 50% partition factor for low and high level exposure, indicated that 2.3% of males and 1.1% of females received low-level exposure and the same

Table 2. Percentages of Workers Occupationally Exposed to Leukemogens According to Industry*

Leukemogens	Agriculture	Mining	Manufacturing	Electrical	Construction	Trade	Transportation	Finance	Services
Benzene	0.001	0.002	0.003	0.001	0.001	0.010	0.005	0.000	0.020
Ionizing radiation	0.000	0.001	0.001	0.000	0.000	0.000	0.000	0.000	0.001
Ethylene oxide	0.011	0.000	0.034	0.000	0.000	0.004	0.000	0.000	0.000

*Based on the CAREX database estimates, FIOSH, 1998.

Table 3. Percentages of Workers Occupationally Exposed to Leukemogens According to the Economic Sector

Leukemogens	Agriculture	Mining	Manufacture	Electrical	Construct	Trade	Transport	Finance	Services	Total
Males										
Benzene	0.00025	0.00002	0.00047	0.00001	0.00013	0.00144	0.00038	0.00000	0.00426	0.00697
Ionizing radiation	0.00003	0.00001	0.00009	0.00000	0.00004	0.00000	0.00000	0.00000	0.00012	0.00030
Ethylene oxide	0.00270	0.00000	0.00536	0.00000	0.00000	0.00058	0.00000	0.00000	0.00000	0.00864
Females										
Benzene	0.00000	0.00001	0.00011	0.00001	0.00000	0.00006	0.00007	0.00000	0.01819	0.01845
Ionizing radiation	0.00000	0.00001	0.00002	0.00000	0.00000	0.00000	0.00000	0.00000	0.00052	0.00055
Ethylene oxide	0.00003	0.00000	0.00120	0.00000	0.00000	0.00002	0.00000	0.00000	0.00000	0.00126

proportion received high-level exposure. Employing the prevalence of those who have ever received low- and high-levels of exposure and their corresponding risk ratios, the Levin formula produced estimated fractions of leukemia incidence attributed to the leukemogens of interest to be 7.6% and 3.6% for males and females, respectively. Applying the attributable fraction to the actual estimate of leukemia incidences revealed a workplace-related incidence of leukemia of 0.60 (95% CI 0.50-0.70) per 100,000 population for males and 0.22 (95% CI of 0.16-0.23) per 100,000 population for females, Table 4.

Discussion

Our study estimated the portion of leukemia incidence in Iranian workers attributed to major workplace leukemogens. The carcinogenicity and the magnitude of association between the leukemogens of interest and the incidence of leukemia have been subject of several reviews. Benzene is a gasoline additive and it is used in chemical, pharmaceutical, rubber, printing, and shoe production industry. A systematic review of epidemiological investigations (Lynge et al., 1997) has estimated a relative risk of 2.0 (95% CI: 1.8-2.2) for low exposure and a relative risk 4.0 (95% CI: 3.6-4.4) for high exposure to benzene in workplaces. Ionizing radiation exposing mainly radiologists, nuclear planet workers, radium-dial workers, painters, underground miners, and aircraft crews is well established leukemogen with high magnitude of association (IARC, 2000; 2002). Ethylene oxide is another established leukemogen used mainly as a sterilizing agent in hospitals, spice fumigation, and other chemical industries (Siemiatycki et al., 2004). Pooled epidemiologic studies have estimated relative risk of 1.1 to 3.5 for leukemia among workers exposed to ethylene oxide (Driscoll et al., 2005).

Table 4. Estimated Attributable Fraction and Corresponding Leukemia Incidences for Each Sex

Incidence*	Fraction (95%CI)	Incidence (95%CI)
8.5	7.6% (6.4-9.2)	0.60 (0.50-0.70)
6.1	3.6% (3.1-4.5)	0.22 (0.16-0.23)

* Total, based on the Tehran Population-Based Cancer Registry; CI, confidence intervals

Our study estimated that 7.6% of the leukemia incidence among males and 3.6% among females were attributed to workplace exposure of the Iranian population to the leukemogens of interest. Although there are no published estimates for the incidence of occupational leukemia in Middle Eastern countries (ours is the first reported attempt), the World Health Organization (WHO) global burden of disease series has estimated an attributable fraction of 8% for males and 2% for females for countries in the regions of western Asia and northern Africa (Driscoll et al., 2004; 2005).

There have been many local and international efforts in different countries to estimate the proportion of cancers attributable to occupational exposures, resulting in estimates from 3% to 26% in South Australia (Weiss, 1999), 29% in Finland (Carbone et al., 2002), and another estimate of 29% for men and 5% for women in Finland (Nurminen and Karjalainen, 2001). In Britain, 4.9% of cancer deaths among men and 1.5% among women were estimated to be attributed to work-related carcinogens for cancers of bladder, lung, non-melanoma skin, nasopharyngeal cancers, leukemia and mesothelioma (Rushton et al., 2008). The estimated attributable fraction of leukemia incidence in our population for both males and females is consistent with the published estimates from other countries. The low prevalence of exposure or small number of economically active women (as is the case in conservative countries of the Middle East), accounts for the low attributable fraction in this sex.

Although there is some heterogeneity across studies in the exposure assessments and classifications, a sizeable fraction of the variations seen in the estimates reported from different population might be due to uncertainties incorporated into the estimates resulting from the methodology used and the nature of the exposure to carcinogens in different populations. The methodology used in our study has been widely used in different populations. It basically relies on the principles of estimating attributable risk frequently used by epidemiologist. The attributable risk estimate is a function of exposure prevalence and the magnitude of the association between an exposure and a disease. The prevalence of exposure in our study was estimated based on the CAREX database, which includes data on 139 agents evaluated by the IARC (all agents in Groups 1 and 2A, and selected agents in Group 2B) and displayed across the 55 industrial classes of the International Standards of Industrial Classification System (ISIC, rev. 3). Specific to occupational exposure among Finnish and US workers, the CAREX database has been used by several epidemiologists and the WHO to estimate the global burden of occupational cancer (Ezzati et al., 2002; Nelson et al., 2002; Concha-Barrientos, 2004; Driscoll et al., 2005), and as a basis to estimate the exposure prevalence for different countries after adjusting for population specificities using expert opinions (Timonen et al, 2000).

In the present study, the use of the CAREX exposure matrix may have introduced some degrees of uncertainty resulting from the differences in the industrial substructure of Iran compared to those of Finland and the US, such as the issue of asbestos for construction materials banned in early 1980 in Iran and smoking in the workplace, which is not yet regulated in our population. Another uncertainty in our estimation originates from the fact that the level of exposure was arbitrarily chosen as above 50% being high exposure and below 50% being low exposure. Determining what percent of the workforce receives high-level exposures depends on the regulations, standards, the safety and exposure monitoring practices as well as the technology used to minimize the exposures or monitor its quantity and quality. As a developing country, Iran is in the midst of transformation from a primarily agricultural society to a more industrial society, and may experience varying degrees of ambiguity in its workforce regulation and industrial exposure management policy. Another uncertainty built into this kind of analysis is the industrial classifications used in the study as there are lots of ambiguities in different labor classifications in various countries. Our data was obtained from the ILO web site where conversion of the local workforce data into the ISIC is performed by expert reviews rather than at the point of data collection. The use of international classifications of local data in epidemiological studies has been extensively practiced and its advantages and disadvantages well addressed (Mannetje and Kromhout, 2003).

Another parameter that plays an important role in our estimate is the relative risks used for the association of leukemia with carcinogens of interest. The relative risk estimates used in our study was based on pooled relative risk published in literature and used in World Health Organization in assessing the environmental burden of diseases. As the magnitude of association between an exposure and outcome theoretically depends on the dose-response relationship between the exposure and the outcome, the source of any uncertainty would be the partitioning factor used to divide the exposed into low and high levels of exposure.

In conclusion, our study utilized international exposure data and estimated the fraction of leukemia incidences among males and females attributed to major workplace leukemogens. Further studies are now needed to validate our estimates utilizing locally obtained exposure data.

References

Benichou J (2001). A review of adjusted estimators of attributable risk. *Stat Methods Med Res*, **10**, 195-216

Bridbord K, Decoufle P Fraumeni JF. Estimates of the fraction of cancer in the United States related to occupational factors. 1978. Prepared by NCI, NIEHS, and NIOSH.

Bruzzi P, Green SB, Byar DP, Brinton LA, Schairer C (1985). Estimating the population attributable risk for multiple risk factors using case-control data. *Am J Epidemiol*, **122**, 904-14.

Carbone M, Kratzke RA, Testa JR (2002). The pathogenesis of mesothelioma. *Semin Oncol*, **29**, 2-17.

Concha-Barrientos M (2004). Selected occupational risk factors. In: Ezzati M LAMC (ed.), Comparative Quantification of Health Risks: Global and Regional Burden of Disease Attributable to Selected Major Risk Factors. World Health Organization, Geneva.

Doll R, Peto R (1981). The causes of cancer: quantitative estimates of avoidable risks of cancer in the United States today. *J Natl Cancer Inst*, **66**, 1191-308

Driscoll T, Steenland K, Prüssestün A, Imel-Nelson D, Leigh J (2004).Occupational carcinogens: assessing the environmental burden of disease at national and local levels. World Health Organization. Environmental Burden of Disease Series, No. 6.

Driscoll T, Nelson DI, Steenland K, et al (2005). The global burden of disease due to occupational carcinogens. *Am J Ind Med*, **48**, 419-31.

Ezzati M, Lopez AD, Rodgers A, Vander HS, Murray CJ (2002). Selected major risk factors and global and regional burden of disease. *Lancet*, **360**, 1347-60.

IARC (2000). Ionizing radiation, part 1: X- and Gamma radiation, and neutrons. Monograph 75 Lyon France.

IARC (2002). Monographs programme on the evaluation of carcinogenic risks to humans. Lyon, France.

International Labor Association. ILO, Labor Statistics. ILO. ILO . 2006. 2-2-2006.

Levin ML (1953). The occurrence of lung cancer in man. *Acta Unio Int Contra Cancrum*, **9**, 531-41.

Lynge E, Anttila A, Hemminki K (1997). Organic solvents and cancer. *Cancer Causes Control*, **8**, 406-1

Mannetje A, Kromhout H (2003). The use of occupation and industry classifications in general population studies. *Int J Epidemiol*, **32**, 419-28.

Miettinen OS (1974). Proportion of disease caused or prevented by a given exposure, trait or intervention. *Am J Epidemiol*, **99**, 325-32.

Mohagheghi M, Alireza Mosavi-Jarrahi. Cancer registry, Final Report. 2002. The Cancer Institute Research Center.

Nelson DI, Driscoll T, Prüssestün A, et al (2002). Exposure assessment for the global burden of occupational injuries. American Industrial Hygiene Conference and Exposition.

Nurminen M, Karjalainen A (. Epidemiologic estimate of the proportion of fatalities related to occupational factors in Finland. Scand.J.Work Environ.Health ; 27 (3):161-213

Rushton L, Hutchings S, Brown TP (2008). The burden of cancer at work: estimation as the first step to prevention. *Occup Environ Med*, **65**, 789-800.

Siemiatycki J, Richardson L, Straif K, et al (2004) Listing occupational carcinogens. *Environ Health Perspect*, **112**, 1447-59.

Timonen K, Kariniemi AL, Niemi KM, et al (2000). Vascular changes in erythropoietic protoporphyria: histopathologic and immunohistochemical study. *J Am Acad Dermatol*, **43,** 489-97.

Weiss W (1999). Asbestosis: a marker for the increased risk of lung cancer among workers exposed to asbestos. *Chest*, **115**, 536-49.