HUMAN EXPOSURE TO ARSENIC RELATED CANCER EPIDEMIOLOGY AND RISK ANALYSIS 20 YEARS FOLLOW UP

V.Bencko*, **, P. Franìk*, M. Götzl***, J.Rameš*, **
*Charles University in Prague, First Faculty of Medicine & General University Hospital, Institute of Hygiene & Epidemiology, Prague, Czech Republic
**European Centre for Medical Informatics, Statistics and Epidemiology - Cardio, Prague, Czech Republic
***Department of Oncology District Hospital of Bojnice, Slovak Republic

SUMMARY

The subject of our analysis was a database of 1503 non-melanoma skin cancer cases (756 in men and 747 in women) and 1 117 lung cancer cases (1007 in men and 110 in women) collected from 1977 to 1996 in a region polluted by emissions of a power-plant rising from burning of coal with high arsenic content ranging between 900 to 1,500 g per metric ton of dry coal.

Exposure assessment of the local population of the district was based on biological monitoring. Determination of arsenic was done in groups of 10 year old boys as samples of non-occupationally exposed general population by analyzing of hair and urine samples at different localities situated up to the distances of 30 km from the local power plant.

Basic epidemiological data of the cancer cases were obtained in a questionnaire which covered basics of personal, family, residential and occupational history.

Over study base represent 1,328 thousands man/year and 1,334 thousands woman/year of a population of approximate size of 125 000 inhabitants. The age standardized incidence of non-melanoma skin cancer (each confirmed by histological examination) in non-occupational settings ranged from 45.9 to 93.9 in men and from 34.6 to 81.4 in women. Relevant data for lung cancer (each confirmed by biopsy or autopsy histological examination) ranged from 10.8 to 89.8 in men and from 1.1 to 10.1 in women per 100,000.

Analysis of our database reconfirms a positive correlation of human cumulative arsenic exposure with non-melanoma skin cancer risk.

A less pronounced relationship was noted between arsenic exposure and incidence of lung cancer. This is most likely to be due to the presence of confounding variables such as cigarette smoking.

Key words: cancer epidemiology, biological monitoring, arsenic toxicity, non-melanoma skin cancer incidence, and lung cancer incidence

INTRODUCTION

The trace elements contents of coal show marked geographic variations[1]. In a previous study[2,3] we examined the ecological as well as the human health hazards (e.g., neuro- and immunotoxicity) of environmental pollution due to emissions emitted from a power plant burning local coal with high arsenic content. At the time of their recruitment, all human subjects included in that study, referred to as above, had been living and/or working in the area surrounding the power plant. The subjects studied were collected up longitudinally over a period of 20-year to examine the trend in the incidence of non-melanoma skin cancer (NMSC) and lung cancer a most frequently related with exposure to arsenic[4-6]. Herein we summarize the data we gathered during this 20-year follow up period and we analyze non-melanoma skin cancer incidence and lung cancer incidence as important human health effects related to environmental arsenic exposure.

Our database consists of 1503 NMSC cases (756 in men and 747 in women) and 1 117 lung cancer cases (1007 in men and 110 in women) collected over a period from 1977 through 1996 from a region polluted by emissions of a power-plant that had been burning local coal with high arsenic content (ranging between 900 to 1,500 g per metric ton of dry weight) since mid 1950s.

MATERIAL & METHODS

Study Base: The database analysed was assembled over a 20-year period beginning 1977. During the study period, a population-based survey was conducted in the central Slovakian district of Prievidza. The aim of the survey was to study the trend in the incidence of all types of malignant diseases. Furthermore, a local cancer register for an entire administrative region was created comprising a population of about 125,000 inhabitants of this district. During the study period, the actual size of population in Prievidza district remained more or less stable as was evident during several censuses conducted by the government, and migration was very low.

As part of the study, any patient diagnosed or suspected as having a malignant lesion was referred to the district oncologist for final diagnosis and treatment. In all subjects included, the diagnosis of cancer was confirmed by the histological examinations of tissue samples obtained by biopsy or at autopsy. Structured questionnaires were used for collecting and recording data pertaining to the subjects' personal data, and residential, family and occupational histories. The data thus obtained were stored in a central database. The study base represents at the time of this analysis 1,335 thousand man/year and 1,337 thousand woman/year of a population of approximately 125 000 inhabitants.

Statistics: In case of suspected residential exposure to arsenic, the size of the population at risk was estimated[7] using census data and estimates released by the Slovak Statistical Bureau.

Estimation of demographic data: Denote by A_i^{1970}, A_i^{1980} and A_i^{1991} the sizes of *i*-th age group of the population of total size *A* as obtained from census data at three instances. Partially linear estimations of the number of person-years for the three time periods of our interest were calculated.

Incomplete census data were available for the exposed villages and the Prievidza district in the years 1992, 1993, 1994, 1995, 1996 and 1997. For some villages only the combined number of men and women (total number of inhabitants) were available for the years 1992, 1993 and 1994.

Furthermore, the age categories 0-4, 5-9, ..., 30-34 had been combined into a one age group in those additional census data. In order to keep consistency with the calculations in the previous periods the aggregate number *A* in the joined category 0-34 was subdivided into a set of age categories in one of the particular areas observed in the particular year 1995 and 1996 in the case of the villages, and in the particular years 1992–1996 in the case of the Prievidza district.

Having the values in the required age categories in the years 1991 (census data) and 1994 (census data combined with the estimation described above) the 1992, 1993 and 1994 values in the different age and sex categories were calculated using linear interpolation as described above for the first three periods. The approximate values obtained by this procedure were then multiplied by appropriate constants to match the known totals for men and women in these years.

In case of suspected occupational exposure to arsenic, the size of the population at risk was estimated using data recorded in the employees' registry maintained by the power plant authority. Therefore, a complete set of identification numbers of employees of the coal burning power station were with information on the required age categories for all observed years.

In addition to non-standardized incidence rates age-adjusted incidence rates (AIR) were evaluated using direct-standardisation methodology and the world standard population.

The AIR was determined for various subpopulations (e.g. defined by smoking and exposure status). The SMR 95% confidence interval was calculated as described before[7,8]. Both direct and indirect standardisations were used to cross-verify the results[9]. Not unexpectedly, the results of all three methods corresponded well with each other as long as each group contained a reasonably large number of persons-years. While this was the case in residential exposure, the variances of AIR were very large for the population of the power plant employees, presumably due to small number of person-years. Accordingly, the results of the three different methods varied in this subpopulation. Standard statistical software (MS Access 2000 and MS Excel 2000 Applications) was used for all statistical analyses.

Exposure assessment:

Exposure assessment of the local non-occupationally exposed general population of the district was based on biological monitoring of arsenic in hair and urine samples obtained from groups (n=20-25) of 10-year old boys from different localities situated up to a distance of 30 km from the local power plant. The district of exposure was divided into two areas marked off by a seven and a half-km circle around the power plant. The criterion for higher exposure included a mean arsenic concentration of > 3µg/g arsenic of hair. Close to 20% of the study subjects lived within 7.5-km radius of the exposed region (i.e., exposed area). The rest living outside this inner circle served as "control" population.

Hair was chosen as the most readily obtainable biological specimen for determining arsenic exposure. Our data lend further credence to the idea of using hair arsenic concentrations for monitoring environmental pollution due to arsenic. As the levels of arsenic in various biological specimens show marked individual variations, group-wise comparison of arsenic levels confirmed to be more meaningful[10]. The levels of arsenic in urine reflect the amount of arsenic that an individual has inhaled or ingested recently and was therefore not used as long-time exposure metric.

Although not universally accepted, an arsenic level of >3µg/g of hair should be considered as abnormally high, while values round 0.2µg/g indicate current range of environmental exposure to arsenic[5,10].

Results

The age-adjusted incidence of histologically confirmed NMSC in non-occupational settings ranged in the four time periods between 45.9 to 93.9/100,000 population in men and 34.6 and 81.4 in women. The age-adjusted incidence of histologically confirmed lung cancer ranged between 10.8 and 89.8 /100,000 population in men and 1.1 and 10.1 in women.

The prime objective of the present study was to examine whether environmental pollution due to arsenic would have any effect on the incidence of NMSC and lung cancer.

The data presented herein did, in fact, show that over the first ten-year period, there had been a dramatic increase in the incidence of NMSC in the most polluted region of Prievidza district (Tables 1 and 2) in the population living in the vicinity of the plant. This upward trend gradually went into a downhill course during the next five-year periods. In our opinion, this downward trend in the incidence of NMSC is most likely attributed to the measures taken by the plant authority to reduce the levels of arsenic emissions from the plant. We strongly feel that the downward trend in the incidence of non-melanoma skin cancer following reduction in the arsenic emissions from the power plant may suggest a dose-effect relationship between the degree of environmental pollution due to arsenic and NMSC incidence. The biological plausibility of such a notion is understandable, considering the fact that arsenic is a known inducer of p53 mutations in basal cells[11].

An expected difference of lung cancer incidence in environmental settings is demonstrated in Tables 3 and 4. In occupational settings[12] the development of lung cancer incidence follows a dramatically different pattern. The small numbers of cases represent a main problem.

DISCUSSION

The incidence of skin cancer showed an upward trend during the last five-year of the study in the region considered to be less polluted. Understandably, the individuals living in this area had been exposed to lower levels of arsenic over a prolonged period of time and so arsenic have a cumulative effect on the incidence of non-melanoma skin cancer.

We did not observe any sex-linked bias in the incidence of NMSC in our study population. The incidence of NMSC appeared to have been markedly influenced by exposure to arsenic in occupational settings[12]. This may not be surprising, as a recent study has noted that the levels of arsenic still often exceed the permissible levels in such industrial operations as maintaining and boiler cleaning.

Since industrial safety measures have been markedly improved as compared to those in place in the 60s and 70s, at present, we have focussed our attention to the long-term effects of arsenic exposure on human health in those occupational settings[13,14].

We carefully evaluated the history of smoking habits of all study subjects in both – environmental and occupational settings. This provided us an opportunity to examine the potential of arsenic exposure and cigarette smoking in the induction of malignant lesions in the lungs as well as in other body sites[15-17]. We have also studied the smoking habits in the general population[18] and its relevance to the study population. Until now we did not find reliable statistical tools to perform a relevant analysis which would enable us to assess the proportion of arsenic and smoking in our database. Parts of our dilemma of lung cancer originates in “soft” CINDY data useful only for a limited part of our study period, and attributable to difficulties in comparison with the registered data in our data base, which have been built very carefully.

Confounding:

Although debatable, cigarette smoking was not considered as an important risk factor for NMSC[19,20]. The possibility that the study cohorts differed in terms of the exposure to ultraviolet radiation1[11,21] is considered extremely unlikely. Due to an almost equal likelihood of the populations in more and less polluted areas of the study area to ultraviolet light, this confounding variable might not have any effect on the differences of incidences of non-melanoma skin cancer as noted between these populations.

CONCLUSION

Our data demonstrate a positive correlation between human cumulative exposure to arsenic and incidence of NMSC. This adds further confirmation to the long-held clinical and epidemiological experiences corroborating non-melanoma skin cancer and exposure to arsenic. A less pronounced relationship was noted between arsenic exposure and incidence of lung cancer. This is most likely to be due to the presence of confounding variables such as cigarette smoking.

ACKNOWLEDGEMENTS

This study was supported by EC INCO COPERNICUS EXPASCAN grant ERBBIC 15 CT98-0325. Statistical analysis was made in collaboration with EuroMISE Centre Cardio, supported by project LN00B107 Ministry of Education of the Czech Republic.

Table 1.: NON-MELANOMA SKIN CANCER INCIDENCE IN POPULATION LIVING IN THE VICINITY OF THE POWER-PLANT BURNING THE COAL OF HIGH ARSENIC CONTENT AND IN THE REST OF THE DISTRICT (MALES ONLY)

	1977-1981		1982-1986		1987-1991		1992-1996	
	Exp. Cases (p-years)	Non-exp. Cases (p-years)	Exp. Cases (p-years)	Non-exp. Cases (p-years)	Exp. Cases (p-years)	Non-exp. Cases (p-years)	Exp. Cases (p-years)	Non-exp. Cases (p-years)
Absolute number	44	125	32	134	30	142	27	222
Expected number	23.8		20.8		18.6		24.7	
Non-standardized rate	98.4	45.8	77.6	46.5	81.9	46.9	78.2	70.9
Age standardized rate	93.9	45.9	66.9	45.9	65.2	46.0	57.8	66.5
Person-years	(44 730)	(273 205)	(41 249)	(288 368)	(36 649)	(303 029)	(34 507)	(313087)
Statistical parameters (Confidence interval (p = 0.05))								
		Min - Max		**Min - Max**		**Min - Max**		**Min - Max**
RR	2.05	1.45-2.90	1.46	0.99-2.15	1.42	0.95-2.11	0.87	0.58-1.30
Mantel-Haenszel estimate	2.02	1.43-2.85	1.46	0.99-2.15	1.39	0.94 - 2.05	0.87	0.58-1.30
Chi- square	16.62		3.70		2.67		0.46	
Probability	<0.01	S	0.05	S	0.10	NS	0.50	NS

Table 2.: NON-MELANOMA SKIN CANCER INCIDENCE IN POPULATION LIVING IN THE VICINITY OF THE POWER-PLANT BURNING THE COAL OF HIGH ARSENIC CONTENT AND IN THE REST OF THE DISTRICT (FEMALES ONLY)

	1977-1981		1982-1986		1987-1991		1992-1996	
	Exp. Cases (p-years)	Non-exp. Cases (p-years)	Exp. Cases (p-years)	Non-exp. Cases (p-years)	Exp. Cases (p-years)	Non-exp. Cases (p-years)	Exp. Cases (p-years)	Non-exp. Cases (p-years)
Absolute number	46	118	32	134	22	165	25	205
Expected number	22.7		20.1		20.1		23.4	
Non-standardized rate	104.9	43.3	78.3	46.3	59.7	53.9	70.9	65.9
Age standardized rate	81.4	34.6	54.4	37.4	39.8	42.7	37.5	47.1
Person-years	(43869)	(272729)	(40869)	(289593)	(36870)	(306319)	(35263)	(311304)
Statistical parameters (Confidence interval (p = 0.05))								
		Min - Max		**Min - Max**		**Min - Max**		**Min - Max**
RR	2.35	1.67-3.34	1.45	0.98-2.17	0.93	0.59-1.48	0.80	0.52-1.22
Mantel-Haenszel estimate	2.25	1.60-3.16	1.47	1.00-2.15	0.88	0.57-1.38	0.89	0.59-1.35
Chi- square	22.81		3.84		0.29		0.31	
Probability	<0.01	S	0.05	S	0.59	NS	0.58	NS

Table 3: LUNG CANCER INCIDENCE IN POPULATION LIVING IN THE VICINITY OF THE POWER-PLANT BURNING THE COAL OF HIGH ARSENIC CONTENT AND IN THE REST OF THE DISTRICT (MALES ONLY)

	1977-1981		**1982-1986**		**1987-1991**		**1992-1996**	
	Exp. Cases (p-years)	Non-exp. Cases (p-years)	Exp. Cases (p-years)	Non-exp. Cases (p-years)	Exp. Cases (p-years)	Non-exp. Cases (p-years)	Exp. Cases (p-years)	Non-exp. Cases (p-years)
Absolute number	37	174	41	200	36	271	5	243
Expected number	29.7		30.2		33.1		24.6	
Non-standardized rate	82.7	63.7	99.4	69.4	98.3	89.5	14.5	77.5
Age standardized rate	77.7	66.1	85.1	69.9	78.5	89.8	10.8	73.2
Person-years	(44 730)	(273 205)	(41 249)	(288 368)	(36 649)	(303 029)	(34 507)	(313087)
Statistical parameters (Confidence interval (p = 0.05))								
		Min-Max		**Min - Max**		**Min - Max**		**Min - Max**
RR	1.17 0.82	-1.68	1.22	0.87-1.71	0.87	0.62 -1.24	0.15	0.06 - 0.36
Mantel-Haenszel estimate	1.19 0.84	-1.70	1.24	0.88-1.73	0.87	0.61 -1.23	0.15	0.06 - 0.36
Chi- square	0.94		1.55		0.65		24.46	
Probability	0.33	NS	0.21	NS	0.42	NS	<0.01	S

Table 4.: LUNG CANCER INCIDENCE IN POPULATION LIVING IN THE VICINITY OF THE POWER-PLANT BURNING THE COAL OF HIGH ARSENIC CONTENT AND IN THE REST OF THE DISTRICT (FEMALES ONLY)

	1977-1981		**1982-1986**		**1987-1991**		**1992-1996**	
	Exp. Cases (p-years)	Non-exp. Cases (p-years)	Exp. Cases (p-years)	Non-exp. Cases (p-years)	Exp. Cases (p-years)	Non-exp. Cases (p-years)	Exp. Cases (p-years)	Non-exp. Cases (p-years)
Absolute number	4	18	6	28	2	28	1	23
Expected number	3.1		4.2		3.2		2.4	
Non-standardized rate	9.1	6.6	14.7	9.7	5.4	9.1	2.8	7.2
Age standardized rate	5.3	5.8	10.1	7.5	3.1	7.3	1.1	6.0
Person-years	(43 869)	(272 729)	(40 869)	(289 593)	(36 870)	(306319)	(35 263)	(311 304)
Statistical parameters (Confidence interval (p = 0.05))								
		Min - Max		**Min - Max**		**Min - Max**		**Min - Max**
RR	0.92	0.31 - 2.73	1.34	0.53 - 3.39	0.43	0.10-1.83	0.19	0.03-1.42
Mantel-Haenszel estimate	1.25	0.42 - 3.67	1.31	0.54-3.15	0.48	0.11 -2.01	0.33	0.04 - 2.45
Chi- square	0.16		0.36		1.07		1.32	
Probability	0.67	NS	0.55	NS	0.30	NS	0.25	NS

REFERENCES

1. Thornton, I. and Farago, M. (1997) The Geochemistry of Arsenic. In Arsenic, Exposure and health effects, C.O. Abernathy, R.L. Calderon, and W.R. Chappell (Eds.), Chapman and Hall, New York, 1-16.

2. Bencko, V. (1997) Health aspects of burning coal with a high arsenic content: the Central Slovakia experience. In Arsenic, Exposure and health effects, C.O. Abernathy, R.L. Calderon, and W.R. Chappell (Eds.), Chapman and Hall, New York, pp. 84-92.

3. Bencko, V., Rameš, J., Götzl, M. (2001) Preliminary analysis of lung cancer incidence in arsenic exposed population. In: Arsenic Exposure and Health Effects IV, C.O. Abernathy, R.L. Calderon, and W.R. Chappell (Eds.), Elsevier, pp. 185-192.

4. ATSDR (2000) Toxicological Profile for Arsenic (update). Department of Health & Human Services, USA, p.428.

5. WHO (2000) Arsenic. In: Air quality guidelines for Europe, 2nd edition (WHO Regional Publications, European Series, No. 91) p. 273, Geneva.

6. Pleško, I., Severi, G., Obšitníková, A., Boyle, P. (2000) Trends in the incidence of non-melanoma skin cancer in Slovakia, 1978-95. *Neoplasma*, 47, 3, 137-42.

7. Breslow, N.E., Day, N.E. (1987) Statistical methods in cancer research (Volume II), Oxford University Press, New York.

8. Boyle, P., Parkin, D.M. (1991) Statistical methods for registries, In: Cancer Registration: principles and Methods, IARC Scientific Publications No. 95, International Agency for Research on Cancer, Lyon, pp.126-158.

9. Kahn, H. A. (1989) Statistical methods in epidemiology, Oxford University Press, New York.

10. Bencko, V. (1995) Use of human hair as a biomarker in the assessment of exposure to pollutants in occupational and environmental settings. *Toxicology*, 101, pp. 29-39.

11. Seidl, H., Kreimer-Erlacher, H., Back, B., Soyer, H.,P., Hofler, G., Kerl, H., Wolf, P. (2001) Ultraviolet exposure as the main initiator of p53 mutations in basal cell carcinomas from psoralen and ultraviolet A-treated patients with psoriasis. *J. Invest. Dermatol*., Aug., 117(2), 365-70.

12. Bencko, V., Fabiánová, E., Franìk, P., Götzl, M., Rameš, J. (2004) Non-melanoma skin and lung cancer incidence in relation to arsenic exposure – 20 years of observation. In press.

13. Buchancová, J., Klimentová, G., Kni•ková, M., Meško, D., Gáliková, E., Kubík, J., Fabiánová, E. and Jakubis, M. (1998) A health status of workers of a thermal power station exposed for prolonged periods to arsenic and other elements from fuel. *Centr. eur. J. publ. Hlth.*, 6, 29-36.

14. Fabiánová, E., Hettychová, L., Hrubá, F., Koppová, K., Marko, M., Maroni, M., Grech, G., Bencko, V. (2000) Health risk assessment for inhalation exposure to arsenic. *Centr. eur. J. publ. Health* 8**,** No. 1, pp.28-32.

15. Welch, K., Higgins, I., Oh, M., Burchfield, C. (1982) Arsenic exposure, smoking and respiratory cancer in copper smelter workers. *Arch. Environ. Health*, 1982, 387, pp.325-335.

16. Jarup, L., Pershagen, G. (1991) Arsenic exposure, smoking and lung cancer in smelter workers – a case control study. *Am. J. Epidemiol*., 134, pp.545-551.

17. Hertz-Picciotto, I., Smith, A.,H., Holtzman, D., Lipsett, M.,. Alexeeff, G. (1992) Synergism between occupational arsenic exposure and smoking in the induction of lung cancer. *Epidemiol.*, 3, pp.23-31.

18. CINDY (1990) Personal communication.

19. Nieuwenhuijsen, M.,J., Rautiu, R., Ranft, U., *et al*. (2001) Exposure to arsenic and cancer risk in central and east Europe. Final report, project EXPASCAN IC 15 CT98-0325. Brussels, Belgium, European Union, March 31

20. Pesch, B., Ranft, U., Jakubis, P., Nieuwenhuijsen, M.,J., Hergemoller, A., Unfried, K., Jakubis, M., Miskovic, P., Keegan, T. (2002) Environmental arsenic exposure from a coal-burning power plant as a potential risk factor for non-melanoma skin carcinoma: results from a case-control study in the district of Prievidza, Slovakia. *Am. J. Epidemiol.*, May 1, 155(9), 798-809.

21. Rossman, T.,G. (1999) Arsenic genotoxicity may be mediated by interference with DNA damage-inducible signaling. In: Arsenic Exposure and Health Effects, C.O. Abernathy, R.L. Calderon, and W.R. Chappell (Eds.), Elsevier, 233-241.

CORRESPONDING AUTHOR:
Prof. Vladimír Bencko, M.D., Ph.D.,
Institute of Hygiene & Epidemiology, First Faculty of Medicine,
Charles University in Prague,
Studnièkova 7, CZ 128 00 Praha 2,
Czech Republic.