Health effects among a cohort exposed to low-level arsenic in a geothermal area of Tuscany, Italy

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Abstract

Background Studies on low-level As exposure have not found an association with cancer, while increased risks were reported for skin lesions, respiratory and cardiovascular diseases and reproductive outcomes. Prospective observational studies with individual exposure measures are needed to study low-level As exposure effects. In a geothermal area in Southern Tuscany (Italy), characterized by a natural presence of As in drinking water (< 50 µg/l), As urinary concentrations were measured in a survey in 1998 and cohort members were followed to evaluate the effects on health.

Methods Around 900 subjects (20–55 years old) randomly sampled in 4 municipalities of the area (Monte Amiata), have been followed from 1999 to 2015, by hospitalisation and mortality registries. Standardized Hospitalisation Ratios (SHRs) were performed, compared to a reference area. Competing-risks regression models were performed to test the association between As urinary concentration and risk of first hospitalisation.

Results SHRs show various increased risks, more frequently among males. Internal analyses show a positive association between As and skin diseases in the general population, the Hazard Ratio (HR) for 1 µg/l increase of As urinary concentration is 1.06 (90%CI 1.01–1.11) and in males, HR 1.08 (90%CI 1.02–1.14), between As and circulatory system diseases in males, HR 1.03 (90%CI 1.01–1.05).

Conclusions The results suggest an effect on skin diseases and circulatory system diseases and, considering the relative young age of cohort members, they could be considered also as predictive of future severer diseases.

Keywords Arsenic · Low-level exposure · Cohort · Metal

Introduction

Inorganic Arsenic (As), a natural element found in foods and environment, is classified as a Class 1 human carcinogen by the International Agency for Research on Cancer (IARC 2012). For this reason the World Health Organization limits at 10 µg/l the allowable As presence in drinking water for human consumption. This limit had been adopted by Italy too, through the Legislative Decree No. 31 of 2 February 2001, implementing the European Union Council Directive 98/83/EC of 3 November 1998 on the quality of water intended for human consumption. Epidemiologic studies on As exposure have shown carcinogenic effects on bladder, lung, skin, kidneys, prostate and liver, and non-carcinogenic effects on skin (Bates et al. 2004; Celik et al. 2008; Hopenhayn-Rich et al. 1998; Yuan et al. 2010; Lewis et al. 1999; Wadhwa et al. 2011), cardiovascular and respiratory diseases, diabetes and reproductive system diseases (Navas-Acien et al. 2006; Moon et al. 2012; Sanchez et al. 2016). This evidence has been observed in countries such as Bangladesh, Taiwan, Chile and Argentina with a high-level As concentration in drinking water (> 300 µg/l). Instead, other studies based on low/moderate-level exposure have not confirmed the association of As exposure with cancer of the skin,

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bladder and lung and with diabetes (Baastrup et al. 2008; Mink et al. 2008; Maull et al. 2012). Increased risks were reported for skin lesions (Chen et al. 2009), respiratory diseases (Parvez et al. 2010), cardiovascular diseases and reproductive outcomes (miscarriage and stillbirths) (Moon et al. 2012; Myers et al. 2010). In summary, effects of low/moderate-level As exposure are not well understood (Chen et al. 2009; Myers et al. 2010; Begum et al. 2015). This may depend on the aggregate rather than individual nature of measures used in these studies with a consequent non-differential misclassification of exposure that might introduce a bias toward the null hypothesis in relative risk estimates. Moreover, in many studies showing small risk increases results were affected by low statistical power (small sample size due to few expected cases). As a consequence, prospective observational studies with individual exposure measures are needed to effectively study the association between low/moderate-level As exposure and risk for human health.

In the geothermal area of Monte Amiata in Southern Tuscany (Italy), (Fig. 1) characterized by a natural presence of As and other metals in drinking water and geothermal fluids, As urinary concentrations were measured in a survey at the end of 1998. One of the aims of that survey was to evaluate the impacts of the exposure to As in drinking water.

In this study, cohort members were followed during the 17 years after the bio-monitoring survey to evaluate the effects of low-level As exposure (< 50 µg/l) on health.

Methods

Setting

In the volcanic area of Monte Amiata an extensive cinnabar mining activity for the production of mercury (Hg) was active for centuries. The mines were abandoned in the late 1970s, causing an intense socio-economic collapse in the local population. Today in this area 5 geothermal plants are active in this area. They produce more than 25 percent of the electricity produced in Tuscany together with another 27 plants situated in different Northern area of this region. Main air emissions from geothermal plants in the area include carbon dioxide (85%), hydrogen sulfide (1–2%) and methane (< 1%) (Environmental Protection Agency of Tuscany 2014) Other lesser emissions are composed of nitrogen, hydrogen, ammonia, boric acid, radon, rare gases and volatile forms of trace elements such as mercury, arsenic and antimony. As and other metals are also naturally present in springs used as drinking water supplies. After officially introducing the reduction of As limit in drinking water (lowered to 10 µg/l), many municipalities of this area did not succeed in conforming to this and were obliged to derogate to levels greater than 10 µg/l. Only since 2010, thanks to the installation of As filters in water systems, As levels in drinking water have been respecting regulatory limits.

In 1998 the Local Health Unit (LHA) and the Italian Istituto Superiore di Sanità (ISS) conducted a human biomonitoring campaign in 4 municipalities of the Amiata area, two of which in its geothermal area (Abbadia San

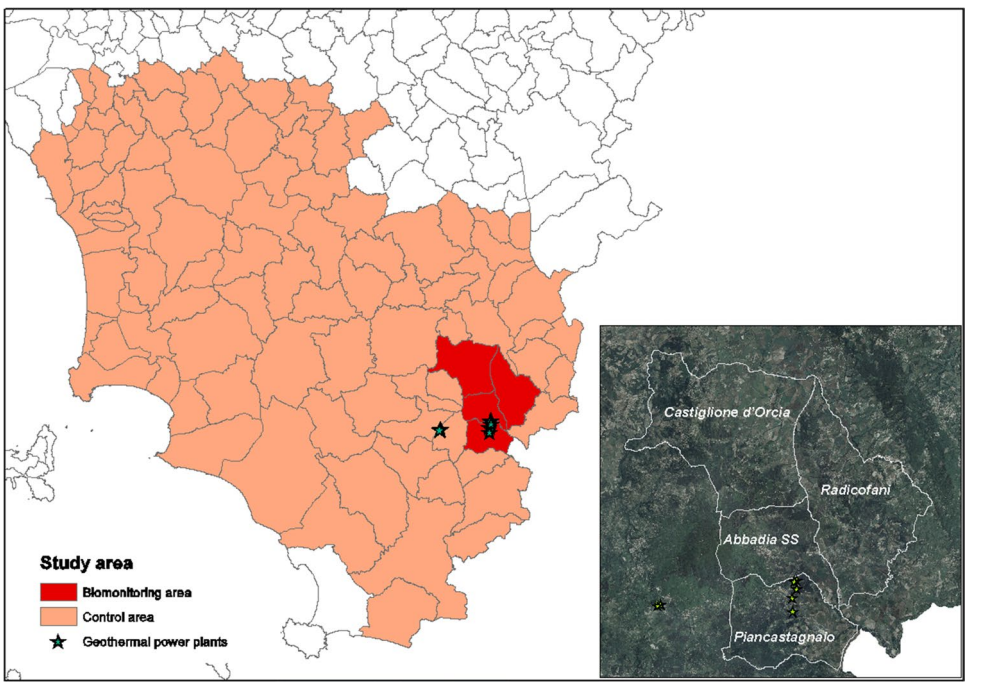

Fig. 1 Study area and control area in Southern Tuscany, Italy

Salvatore, Piancastagnaio) and two outside (Radicofani, Castiglione d'Orcia), chosen as controls.

As urinary concentrations were measured and a questionnaire about lifestyles and daily activities was developed to evaluate exposure determinants or potential confounders.

The institutional review committee approved the protocol and an informed consent by subjects was obtained in 1998.

Cohort

The original sample was composed by 906 subjects (approximately 1 every 50 inhabitants), all between 20 and 55 years old in 1998, randomly sampled from the municipalities' population registers. Children, elderly and people with a direct occupational exposure to metals were excluded.

The survey was conducted between June and December 1998. The final study cohort includes 889 participants, after excluding 17 people with an incorrect personal identifier, necessary to link the cohort with regional health administrative data.

Measurements

Arsenic exposure

Urine was sampled by Local Health Authorities (LHA) nurses to measure As concentration. The technique used allows the determination of the levels of inorganic As and mono and dimethylated forms (As_i+MMA + DMA) related to occupational or environmental exposure (Bavazzano et al. 1996). Trimethylated forms, related to fish consumption, are not detectable.

Urine samples, acidified by hydrochloric acid and subjected to reduction by potassium iodide, are extracted with toluene. After a re-extraction from organic phase by a 1% nitric acid solution, the sample was analyzed by electrothermal atomic absorption method (ETAAS) with Zeeman background correction. The parameter for the acceptability of the dilution is defined on the basis of creatinine. In this regard, the WHO criteria is used (creatinine > 0.3 g/l and < 3 g/l) (WHO 1996), samples out of this range have been eliminated from the case series.

All analyses were submitted to quality control by the German Society for Occupational Medicine and Environmental Medicine.

BIO-RAD reference materials had been used for the measurement of As in urine, in which analytes concentration is not certified, but it comes from an analysis conducted by three laboratories with a great experience in this type of measurement.

Outcomes

First hospital admissions for natural and other specific causes were considered. The following ICD9CM codes were used to identify outcomes:

All natural causes (traumatic injury and poisoning excluded: 800–999)
Benign neoplasms (210–229)
Malignant neoplasms (140–209, 230–239)

- Lip, oral cavity, pharynx (140–149)
- Stomach (151)
- Colon rectum (153–154)
- Trachea, bronchus and lung (162)
- Skin (172–173)
- Breast (174)
- Uterus (179, 180, 182)
- Ovary (183)
- Prostate (185)
- Bladder (188)
- Kidneys (189)
- Lymphatic and hematopoietic tissue (200–208)

Endocrine, nutritional and metabolic diseases (240–279)
Blood diseases (280–289)
Nervous system diseases (320–389)
Circulatory system diseases (390–459)

- Ischemic heart disease (410–414)
- Cerebrovascular disease (430–438)
- Heart failure (428)

Respiratory system diseases (460–519)
Digestive system diseases (520–579)
Urinary system diseases (580–599)
Skin and subcutaneous tissue diseases (680–709)
Musculoskeletal and connective tissue system diseases (710–739)

Cohort participants were linked to the health regional administrative data by an anonymous identifier code. Hospitalisation causes were extracted from the primary diagnosis code (ICD9CM code) reported in discharge forms.

Other covariates

Other covariates were collected by the questionnaire to investigate potential sources of metal exposure (chewing gum consumption, contact lenses, dental fillings, fish and local vegetables consume) and potential confounders.

In particular, the following potential confounders were used in our analyses:

- High alcohol consumption (high consumer vs other), defined as > 40 g alcohol per day for men and > 20 g per day for women.
- Smoking habits (current smoker and ex-smoker since less than 1 year vs never smoker and ex-smoker since more than 1 year).
- Overweight (overweight or obese vs other), identified by body mass index value, based on self- reported height and weight. Overweight/obese have a body mass index ≥ 25.

All variables used in the analyses are referred to the baseline time (1 January 1999).

Statistical analyses

Descriptive analyses were performed at baseline for age, gender, smokers, high alcohol consumers, overweight people and As urinary concentration level.

All participants were followed from the baseline (1 January 1999) until death, emigration from Tuscany or 31 December 2015, whichever came first. Standardized Hospitalisation Rates (SHRs) were performed, using all municipalities in a 50 km range from the geothermal area centre as reference area. SHRs were standardized for age, gender and calendar year.

Internal analyses were performed to test the association between exposure and outcomes by competing-risks regression models (Fine and Gray 1999). Death was considered a competing event. Two different adjusted models were performed for each outcome: adjustment for age and gender only (Mod1), adjustment for age, gender, alcohol, smoking and overweight (Mod2). Exposure was tested as a continuous variable. All internal analyses were stratified by gender.

Individuals with a disease history at baseline were excluded from the corresponding analysis. Disease history was defined observing primary diagnosis in hospitalisation during the previous period, since 1996.

All analyses were performed using Stata software V.12.0 (StataCorp).

Results

As urinary concentration has a log-normal distribution and the 5°–95° percentile range is 1.8–15.5 µg/l. Arithmetic average is 7.0 (standard deviation: 6.5), geometric average is 5.8 (SD: 1.9). Around 43% of cohort members are smokers or stopped during last year, 12% are high alcohol consumers and 38% are overweight. Males have worse lifestyles than females and As urinary concentration average is slightly higher among females than males (Table 1).

Among cohort participants, 9 (1%) left Tuscany before the end of 2015 and 41 (4.6%) died.

SHRs show a higher risk for natural causes, malignant neoplasms, lung cancer, stomach cancer, blood diseases, circulatory system diseases, digestive system diseases, urinary system diseases, musculoskeletal diseases (Table 2).

Table 1 Descriptive analyses at baseline

	Total sample (*n*: 889)		Men (*n*: 437)		Women (*n*: 452)		*p* value
	N	%	*N*	%	*N*	%	
Age group (year)							
20–29	174	19.6	86	19.7	88	19.5	0.415
30–39	270	30.4	124	28.4	146	32.3	
40–55	445	50.0	227	51.9	218	48.2	
Lifestyles							
Smoking	379	42.6	225	51.5	154	34.1	< 0.001
High alcohol consumer	103	11.6	88	20.1	15	3.3	< 0.001
Overweight	337	37.9	212	48.5	123	27.2	< 0.001
Arsenic urinary concentration values (µg/l)							
AM (ASD)	7.0 (6.5)		6.4 (4.7)		7.6 (7.8)		0.006
GM (GSD)	5.8 (1.9)		5.5 (1.8)		6.2 (1.9)		0.003
1° pct	0.0		0.0		0.0		
5° pct	1.8		1.8		1.8		
25° pct	3.8		3.7		4.0		
50° pct	5.7		5.4		6.2		
75° pct	8.6		7.6		9.3		
95° pct	15.5		14.6		16.8		
99° pct	26		25.6		28.2		

Table 2 Cases observed, Standardized Hospitalisation Ratio (SHR) and 90% confidence interval, for each hospitalisation outcome, stratified for gender

Causes	Total		Men		Women	
	N	SHR (90% CI)	*N*	SHR (90% CI)	*N*	SHR (90% CI)
Natural causes (traumatic injury and poisoning excluded)	441	1.7 (1.6–1.9)†	201	1.6 (1.4–1.8)†	240	1.8 (1.7–2.1)†
Benign neoplasms	53	1.0 (0.8–1.3)	10	1.0 (0.6–1.6)	43	1.1 (0.8–1.4)
Malignant neoplasms	87	1.4 (1.2–1.7)†	47	2.0 (1.6–2.5)†	40	1.0 (0.8–1.3)
Ovary					3	1.7 (0.7–4.5)
Colon rectum	8	1.4 (0.8–2.6)	8	2.8 (1.6–5.1)†	0	
Trachea, bronchus, lung	8	2.3 (1.3–4.1)†	5	2.4 (1.2–5.1)†	3	2.0 (0.8–5.3)
Uterus					1	0.4 (0.1–2.0)
Breast					8	0.5 (0.3–1.0)
Prostate			6	3.7 (1.9–7.3)†		
Bladder	3	1.0 (0.4–2.7)	1	0.5 (0.1–2.4)	2	2.8 (0.9–9.0)
Stomach	4	2.7 (1.2–6.2)†	3	3.4 (1.3–8.8)†	1	1.7 (0.3–8.9)
Kidneys	4	1.4 (0.6–3.3)	3	1.6 (0.6–4.1)	1	1.2 (0.2-6.0)
Skin	6	1.8 (0.9–3.5)	3	1.7 (0.7–4.5)	3	1.8 (0.7–4.7)
Lip, oral cavity, pharynx	3	1.8 (0.7–4.7)	3	2.7 (1.1–7.0)*	0	
Lymphohematopoietic	5	1.3 (0.6–2.6)	4	1.9 (0.8–4.3)	1	0.5 (0.1–2.8)
Endocrine	32	1.2 (0.9–1.6)	9	1.0 (0.6–1.7)	23	1.3 (0.9–1.8)
Blood	14	1.6 (1.0–2.4)*	7	2.6 (1.4–4.9)†	7	1.1 (0.6–2.1)
Nervous system	60	1.1 (0.9–1.4)	24	1.0 (0.7–1.5)	36	1.2 (0.9–1.6)
Circulatory system	135	1.4 (1.2–1.6)†	71	1.3 (1.1–1.6)†	64	1.5 (1.2–1.9)†
Ischemic heart	24	1.0 (0.7–1.4)	21	1.1 (0.8–1.6)	3	0.6 (0.2–1.4)
Cerebrovascular	18	1.2 (0.8–1.8)	9	1.1 (0.6–1.9)	9	1.4 (0.8–2.5)
Heart failure	7	1.8 (1.0–3.4)	4	1.5 (0.6–3.4)	3	2.6 (1.0–6.7)
Respiratory system	55	1.1 (0.9–1.4)	31	1.1 (0.8–1.4)	24	1.2 (0.8–1.6)
Digestive system	152	1.3 (1.1–1.4)†	92	1.4 (1.1–1.6)†	60	1.1 (0.9–1.4)
Urinary system	45	1.8 (1.4–2.3)†	24	1.6 (1.1–2.2)†	21	2.0 (1.4–2.9)†
Skin and subcutaneous	18	1.2 (0.8–1.7)	12	1.6 (1.0–2.5)	6	0.8 (0.4–1.5)
Musculoskeletal, connective	142	1.3 (1.1–1.5)†	75	1.4 (1.1–1.6)†	67	1.3 (1.0–1.6)†

*p value < 0.10, †p value < 0.05

Gender stratified analyses show a higher risk for all natural causes, malignant neoplasms, colon-rectum cancer, lung cancer, prostate cancer, stomach cancer, lip and oral cavity cancer, blood diseases, circulatory system diseases, digestive system diseases, urinary system diseases, musculoskeletal diseases in males. All natural causes, circulatory system diseases, urinary system diseases and musculoskeletal diseases SHRs show increased risks in females.

Internal analyses show a positive association between As urinary concentration level and skin diseases in the general population (adjusted HR 1.06, 90% CI 1.01–1.11, p 0.039) and in males (adjusted HR 1.08, 90% CI 1.02–1.14, p 0.030), between As urinary concentration and circulatory system diseases in males (adjusted HR 1.03, 90% CI 1.01–1.05, p 0.041). An increased risk has been shown also in lip and oral cavity cancer (adjusted HR 1.10, 90% CI 1.05–1.14, $p < 0.001$) and in skin cancer among males (adjusted HR 1.05, 90% CI 1.10–1.10, p 0.059), but these results are based only on 3 events observed (Table 3).

Discussion

Arsenic measurements

This study is one of the few existing examples of prospective studies with an individual exposure measure in low-level As exposure areas. Other studies have demonstrated that As urinary concentration levels do not fluctuate so much in time (Chen et al. 2009). The Sepias project, an Italian study on health effects of As exposure in four Italian areas carried out in 2010, collected 50 samples for As urinary determination in one of four municipalities of this study (Abbadia San Salvatore), obtaining a similar range

Table 3 Hazard Ratio (HR) of first hospitalisation and 90% confidence interval for continuous exposure, adjusted by Mod2[a], stratified for gender

Causes	HR (90% CI) for 1 µg/l increase of As urinary concentration	HR (90% CI) for 1 µg/l increase of As urinary concentration	HR (90% CI) for 1 µg/l increase of As urinary concentration
	Total	Total	Total
Natural causes (traumatic injury and poisoning excluded)	0.99 (0.98–1.01)	1.00 (0.98–1.02)	0.99 (0.97-1.00)
Benign neoplasms	0.99 (0.95–1.04)	0.92 (0.79–1.06)	1.00 (0.95–1.05)
Malignant neoplasms	0.96 (0.92–1.01)	0.98 (0.93–1.04)	0.94 (0.88-1.00)
Ovary			1.06 (0.97–1.16)
Colon rectum	0.94 (0.81–1.08)	0.94 (0.81–1.08)	NC
Trachea, bronchus, lung	0.89 (0.74–1.07)	0.89 (0.71–1.11)	0.90 (0.70–1.16)
Uterus			NC
Breast			0.97 (0.87–1.08)
Prostate		0.93 (0.80–1.09)	
Bladder	0.85 (0.72–1.00)	NC	NC
Stomach	1.00 (0.89–1.12)	1.02 (0.93–1.12)	NC
Kidneys	0.96 (0.84–1.10)	0.95 (0.78–1.15)	NC
Skin	0.97 (0.84–1.13)	1.05 (1.01–1.10)*	0.73 (0.53–1.02)
Lip, oral cavity, pharynx	1.10 (1.05–1.14)†	1.10 (1.05–1.14)†	NC
Lymphohematopoietic	0.87 (0.68–1.12)	0.93 (0.75–1.17)	NC
Endocrine	1.00 (0.97–1.04)	1.05 (0.99–1.11)	0.98 (0.94–1.03)
Blood	1.01 (0.93–1.09)	0.89 (0.69–1.15)	1.06 (1.00–1.12)
Nervous system	0.97 (0.94–1.01)	0.93 (0.85–1.01)	0.99 (0.96–1.03)
Circulatory system	1.02 (1.00–1.04)	1.03 (1.01–1.05)†	1.00 (0.97–1.04)
Ischemic heart	0.97 (0.91–1.03)	0.97 (0.90–1.04)	0.98 (0.90–1.05)
Cerebrovascular	0.97 (0.92–1.03)	0.98 (0.89–1.08)	0.97 (0.88–1.06)
Heart failure	0.92 (0.82–1.03)	0.87 (0.69–1.09)	0.94 (0.86–1.03)
Respiratory system	1.02 (0.98–1.06)	1.02 (0.98–1.07)	1.00 (0.93–1.08)
Digestive system	0.98 (0.94–1.01)	0.99 (0.96–1.03)	0.95 (0.90–1.00)
Urinary system	0.97 (0.92–1.02)	0.99 (0.91–1.09)	0.95 (0.91–0.99)
Skin and subcutaneous	1.06 (1.01–1.11)†	1.08 (1.02–1.14)†	1.03 (0.96–1.11)
Musculoskeletal, connective	0.99 (0.97–1.01)	1.00 (0.97–1.04)	0.97 (0.94–1.01)

NC not calculable, *p value < 0.10, †p value < 0.05

[a]Model adjusted for age, gender, smoking, alcohol, overweight

value (Bustaffa et al. 2014). The same study reported as principal exposure sources to be considered in the area, excluding direct work exposure, public drinking water supply and local food. Past mining activities and increased soil exploitation by geothermal plants might have increased the As level in local water. As urinary concentration levels in our cohort members are close to the reference values published by the Italian Society of Reference Values (SIVR) in 2011, that assesses 5°–95° percentile reference values for urinary concentration of arsenic, elemental and soluble inorganic compounds, between 2 and 15 µg/l.

A limit of this measurement procedure can be represented by the lack of As speciation to distinguish inorganic As (in arsenite or arsenate forms), MMA and DMA contributes to the total urinary concentration value.

Inorganic As mainly derives from contaminated drinking water exposure. In general, inorganic As are more toxicologically relevant than organic species (arsenobetaine or arsenocholine), that mainly derive from seafood consumption. Inorganic As methylation was described for a long time as a detoxification process by human metabolism, but recent studies showed that methylated metabolites are of greater toxicity in various systems (Agency for Toxic Substances and Disease Registry 2007; Hartwig and MAK Commission 2016). The measurement techniques used in this study did not allow us to obtain detailed values of different As species, we can only suppose that DMA is the prevalent form contained in urine, relying on data showed by Sepias project about Amiata cohort members sampled,

among which 51% of total As_i+DMA + MMA was DMA, 27% MMA, 22% inorganic As (Bustaffa et al. 2014).

Main results

SHRs show known excesses, also showed in other studies on this area (Minichilli et al. 2012). Observed excesses are coherent, considering the age range of cohort members too, with another epidemiological observational study conducted on the population resident in this area in 2012, that had showed increased mortality and hospitalisation risks with respect to the same reference area (Minichilli et al. 2012).

Internal analyses show an effect of As urinary concentration on circulatory system diseases in males, and on skin diseases in males and in both gender.

The exclusion of people aged over 55 years from the survey might have limited cancer events observation during the follow-up period. At the same time we could hypothesize a relative recent exposure for these people and there may be more opportunities to implement chronic long-term events prevention actions, especially in the increased circulatory and skin diseases observed.

Cancer

Although limited by the small number of hospitalisations observed, SHRs showed an excess for malignant neoplasms, particularly in males, for all malignant neoplasms and some specific sites (colon-rectum, lung, prostate and stomach). In internal analyses with continuous exposure, associations were observed with lips and oral cave cancer (+ 10% for increase of 1 µg/l of As urinary concentration) and skin cancer (+ 5% for increase of 1 µg/l of As urinary concentration) in males, but these results should be cautiously interpreted, because they are based on only 3 observed events for each outcome. It is likely that a longer follow-up period is necessary to increase statistical power to measure these events. The number of cancers observed could be low due to the relatively young age of this cohort and to latency of malignant events. The evidence of the association between low-level As exposure and cancer present in literature mainly derives from observational or case-control studies, frequently without individual exposure measurements. Although several studies have found an association with skin cancer (Leonardi et al. 2012), bladder cancer (Bates et al. 2004; Hopenhayn-Rich et al. 1996; Kurttio et al. 1999), and respiratory system cancer (Ferreccio et al. 2000), many other studies did not show any association or, in some cases, they observed a protective effect of these cancer sites (Baastrup et al. 2008; Chen et al. 2010; Han et al. 2009). In conclusion, the current evidence is insufficient to affirm that an association between these cancer sites and low-level As exposure exists.

Non-cancerous diseases

Hospitalisation excesses were observed for blood, digestive system and urinary system diseases only in males, while excesses for all natural causes, circulatory system, urinary system and musculoskeletal/connective system diseases were observed in both gender. Internal comparisons confirm in males a positive association between As urinary concentration and circulatory system diseases and skin diseases. Other studies report the association between long term low-level As exposure and skin diseases (Guha Mazumder et al. 1998; McDonald et al. 2007; Xia et al. 2009; Ahsan et al. 2006; Argos et al. 2011), mainly hyperkeratosis, hyper- or hypopigmentation, more frequently in males (Rahman et al. 2006), and suggest that skin diseases might be considered as a predictive factor of future malignant skin diseases. The results of this study are coherent with this hypothesis, also considering the young age of the cohort and the relative short period of follow-up to develop malignant diseases. Among the 18 cases observed in our cohort, no pigmentation cases were observed. Different skin inflammations and infections had occurred, but few cases for specific subgroups do not allow us to analyse each one separately.

Also results for circulatory system diseases find confirmations in other studies. Systematic reviews report that some studies have limits in exposure and outcome measurements, and often conclude hoping for future prospective studies with an individual exposure measurement to obtain more solid evidence (Moon et al. 2012). The lack of association between low-level As exposure and cardiovascular endpoints, such as stroke or myocardial infarction, suggests that increased risk might regard less severe circulatory system diseases, in line with other studies that had showed effects on hypertension, atherosclerosis, and in general on risk factors and initial steps along a history of cardiovascular disease (Moon et al. 2012; Stea et al. 2016; Engel and Smith 1994; Lisabeth et al. 2010; Medrano et al. 2010; Islam et al. 2012). An internal subgroup analysis is not even possible for circulatory diseases, because many different diseases were observed, with a few cases for each one. Among the 71 cases observed in males, excluding 21 ischemic heart diseases, 9 strokes and 4 heart failures, arrhythmia and arteries and veins diseases were mainly observed.

Internal analyses showed significant increased risks only among males, but our data can hardly explain these differences between the two gender. We could only consider the possible presence of a residual bias due to other not measured lifestyles, such as diet or physical activity habits, assuming that males have worse habits than females, more frequently in people with high As urinary concentration levels.

Limitations and strengths of the study

The exclusive use in this study of administrative data from hospital discharges to measure outcomes may have underestimated the number of events, because only diseases that need a hospital admission have been considered. In addition, the estimate of hospitalisation rates and ratios, which implies the inclusion in the numerator only of new events and the exclusion of prevalent conditions, may have been incomplete since the registry of hospitalisations was available only since 1996, therefore, a retrospective assessment of previous diseases based on the hospitalisation registry was limited to 3 years (1996–1998). Furthermore, upon enrolment no questions were asked to the subject about specific diagnoses he/she may have received previously. Another limitation could be due to the lack of As speciation which may have indicated the origin of As (whether from water, rice or seafood) and the lack of new exposure measurements and other covariates during the follow-up period.

On the other hand, individual exposure measurements represent a strong point of this study, and the linkage with administrative data will allow us to increase the follow-up period in the future, to investigate cancer diseases and mortality with more statistical power.

Conclusions

In this study, we found an association between low-level As exposure and hospitalisation for circulatory system diseases in males (+3% for 1 µg/l increase of As urinary concentration). There was also an association with skin diseases in males (+8% for 1 µg/l increase of As urinary concentration) and in the general population (+6% for 1 µg/l increase of As urinary concentration). These results suggest a low-level As exposure effect on these diseases and, considering the relative young age of cohort members, they could be considered also as predictive of future severer diseases. To confirm these hypotheses and to repeat these analyses considering a longer latency period for cancer diseases, an update of follow-up is recommended.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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