

〔Risk Factors of Arsenicosis〕

It is mentioned that all the members of a family are consuming arsenic through same source of drinking water and foodstuff but all do not show skin manifestations. One or two of them show skin manifestations. The reason is not clear. Therefore, researchers are trying to identify risk factor(s) for arsenicosis. Better understanding of the risk factor(s) could help to reduce the number of cases of arsenicosis. The studied factors are age, gender, nutritional status, tobacco smoking, alcohol, betel nut use, exposure to sunlight, pesticide or fertilizer, liver dysfunction, keratosis or Bowen's disease.

2.1 Age

Early non-malignant skin manifestations of arsenicosis are not uncommon in children below 10 years. Approximately 90% of children below 11 years of age living in arsenic endemic areas show hair and nail arsenic level above the normal level. The youngest arsenic poisoned patient detected in Bangladesh was an 1.5 years old child. In the Antofagasta region of Chile, cases of non-malignant skin lesion of arsenicosis have been described in children as young as 2 years of age (Rosenberg, 1974; Zaldivar & Guillier, 1977). In Taiwan, the youngest patient drinking arsenic contaminated water who developed melanosis was 3 years old (USEPA, 1988).

Children appear to have a higher body burden than adults despite fewer dermatological manifestations (Rahman et al., 2001). The status of mental development in children is affected in the age group of 1-5 years (Akhtar et al., 2007) and 9.5-10.5 years (Wasserman et al., 2004).

Studies on arsenic-induced health effects in Matlab, Bangladesh, showed that the highest prevalence of arsenic-induced skin lesions occurred in middle-aged men (Rahman et al., 2006).

There are inconsistent results associated with age and arsenic metabolism.

2.2 Gender

Gender issue may be considered on the basis of incidence and severity of arsenicosis as well as geographical variation.

About incidence, conflicting results are obtained from different studies. Some researchers reported that males and females are equally affected (Ahsan et al.,

2000; Hadi and Parveen, 2004) whereas others showed higher incidence in males (Tseng 1977; Guha Mazumder et al., 1998; Tondel et al., 1999; Ferreccio et al., 2000; Watanabe et al., 2001; Kadono et al. 2002; Sinha and Misbahuddin, 2003; Chen et al., 2003; Rahman et al., 2006; Table 2.1). However, another study shows females are more affected than males (Ahmad et al., 1999). These conflicting findings are due to improper study design and low number of cases. Even the same researcher group conducted studies in two different areas show inconclusive results.

However, gender-related exposure to arsenic is clearly interpreted in certain industries, e.g., mining and smelting operation (mainly men), wood preservation (mainly men), and electronic industries which are using gallium and indium arsenide (often women; Vahter et al., 2007).

About severity, keratosis and pigmentation changes may be worsen for women than for men, particularly in poor families (Alam et al., 2002).

Considering mean lifetime arsenic exposure, males had twice the risk of obtaining skin lesions as females in the highest exposure quintile (Rahman et al., 2006).

Higher incidence and severity of skin lesions in males may be due to more sunlight exposure, smoking habit, large volume of water intake and genetics. An involvement of hormone interactions is possible, because arsenic has been shown to interact with estrogen (Kitchin & Wallace, 2005) which affects all the cell types of importance for skin physiology (e.g., epidermal keratinocytes, dermal fibroblasts, melanocytes). In addition, differences between the sexes in the metabolism of arsenic might have influenced the likelihood of developing skin lesions. Women have higher arsenic methylation efficiency than men, but only in childbearing age, supporting an influence of sex hormones (Lindberg et

al., 2008).

Table 2.1 *Some examples of incidence of male and female patients of non-malignant skin lesions.*

Study	Country	Clinical manifestation	Incidence (n)	
			Male	Female
Tondel et al. 1999	Bangladesh	Melanosis with or without keratosis	279	151
Ahsan et al., 2000	Bangladesh	Melanosis with or without keratosis	50%	50%
Hadi and Parveen, 2004	Bangladesh	Melanosis with or without keratosis	26	22
Seow et al., 2012	Bangladesh	Melanosis with or without keratosis	340	210
Milton et al., 2004	Bangladesh	Melanosis with or without keratosis	59	79
Sinha et al., 2003	Bangladesh	Melanosis with or without keratosis	11	1
Ahmad et al., 2007	Bangladesh	Melanosis with or without keratosis	600	524
Guha Mazumder et al., 1992	India	Melanosis with or without keratosis	25	28
Hsueh et al., 1997	Taiwan	Skin cancer	24/275	9/379

However, the males and females have similar urine arsenic concentrations (Rahman et al., 2006). Compared with females, males often have a higher fraction of the MMA in urine (Hopenhayn-Rich et al., 1996), which has been associated with increased risk of arsenic-related skin lesions, including skin cancer (Chen et al., 2003; Del Razo et al., 1997).

Higher hemoglobin levels are significantly protective against the presence of skin lesions among Bangladeshi males but no such effect is seen in females (Breton et al., 2006).

2.3 Nutritional Status

Nutritional status of arsenicosis and unexposed normal volunteers is assessed

based on Body Mass Index (BMI), 24-recall or 3 days recall of major dietary contents. When BMI is lower than 18.5, then it is considered as malnutrition. However, BMI is not the only indicator for measuring nutritional status.

One study conducted in Bangladesh shows that BMI was lower than 18.5 in 57 (41.31%) out of 138 cases of arsenicosis and 31 (21.53%) out of 144 unexposed normal individuals. The crude prevalence ratio (or risk) was 1.92 for poor nutritional status among the arsenicosis cases compared to the unexposed population (Milton et al., 2004). In Bangladesh, more than 75% of the total populations suffer from anemia. Therefore, it is natural to think that millions of Bangladeshi should have non-malignant skin lesions of arsenicosis instead of thousands.

The prevalence of keratosis in West Bengal, India is 1.6 fold higher in poor nutritional status group (Guha Mazumder et al., 1998). Arsenic affected people of South Western Taiwan (Tseng 1977; Hsueh et al., 1995) and the Antofagasta region in Northern Chile (Borgono et al., 1977; Zaldivar & Guillier, 1977) were reported to have a low socio-economic status and poor nutritional status.

Skin lesions have been reported in well-nourished populations in Chile (Smith et al. 2000). Yang and Blackwell (1961) conducted a study of the diet and environmental conditions of a group of families in the arsenic endemic blackfoot area of Taiwan. Fish was the only notable source of animal protein in most cases studied. The researchers concluded that, in general, the diet was adequate with respect to calories, high in carbohydrate, low in protein, and extremely low in fat. Undernourishment in the Taiwan population was marked by a high consumption of dried sweet potato, a staple food that was significantly associated with an increased prevalence of arsenic-induced skin cancer (Hsueh et al., 1995).

In Taiwan blackfoot-disease was associated with undernourishment (high intake of sweet potatoes, low intake of rice and vegetables) (Chen et al., 1988). Low serum β -carotene concentration was associated with a higher prevalence of arsenic-related skin-cancer (Hsueh et al., 1997) and ischemic heart disease (Hsueh et al., 1998).

Hemoglobin concentration was not associated with non-malignant skin lesions (Heck et al., 2008). However, anemic rats are more prone to develop arsenic poisoning following chronic ingestion of high content of arsenic (Paul et al., 2002).

Deficiency in some nutritional factors may increase the risk of non-malignant skin lesions of arsenicosis. The strongest evidence was for low intake of animal protein, calcium, fiber, folate, and vitamin C (Mitra et al., 2004).

It has been reported that subjects with a poor nutritional status have a lower capacity for methylation and arsenic detoxication (Vahter & Marafante, 1987).

However, it is quite surprising that there was no study designed in such a way that all the family members of a case of arsenicosis were screened for malnutrition and found that poor nutriated family member was affected by arsenicosis.

2.4 Smoking

A positive correlation between ingestion of inorganic arsenic and lung cancer in humans was found in Chile (Ferrecio et al., 2000). It is already known that cigarette smoking is a main risk factor for lung cancer, but the researchers found that cigarette smoking plus ingestion of arsenic from drinking water had a synergistic effect (Ferrecio et al., 2000).

A study conducted in USA shows that there is an elevated risk of bladder

cancer in smokers that are exposed to arsenic in drinking water near 200 µg/L, compared with smokers consuming lower arsenic levels (Steinmaus et al., 2003). Arsenic is synergistic with smoking at relatively high arsenic levels (200 µg/L). The latency of arsenic exposure causing bladder cancer can be very long (more than 40 years). The risks were lower than those in Taiwan with high arsenic exposure (Morales et al., 2000).

There was a significant dose-response trend of ingested arsenic on lung cancer risk, which was more prominent among cigarette smokers. The risk assessment of lung cancer induced by ingested arsenic should take cigarette smoking into consideration (Chen et al., 2004).

A meta-analysis of studies on occupational arsenic exposure via inhalation found a synergistic effect of cigarette smoking and arsenic on lung cancer, and 30% to 54% of lung cancer cases were attributable to both exposures (Hertz-Picciotto et al., 1992). This effect was found to be stronger among those who smoked cigarettes, and the risk could be as high as more than 10-fold.

A study conducted in Bangladesh shows synergistic effect between the highest level of arsenic exposure (>113 ppb) and tobacco smoking on risk of skin lesions in men (Chen et al., 2006).

Smoking consumption might be associated with a poorer methylation capacity.

2.5 Alcohol

An alcoholic person may be exposed to arsenic contaminated water or alcohol sometimes contaminated with arsenic. Formar is applicable in arsenic endemic area where a person is used to drink alcohol. Peripheral vascular disease and cardiomyopathies were seen in a group of German vintners in the

1920s who drank wine fermented from grapes treated with arsenical fungicides (Engel et al., 1994). Arsenic was also found in sweet little Gabonese palm wine (Mavioga et al., 2009). Arsenic contaminated whiskey (moonshine) was found to cause cardiovascular diseases in Georgia, USA (Gerhardt et al., 1980).

Co-exposure of arsenic and ethanol elevates more significantly the activities of serum transaminases and induces more liver lesions than arsenic or ethanol alone (Flora et al., 1997). Alcohol consumption might be associated with a poorer methylation capacity.

2.6 Exposure to Sunlight

A study conducted in Bangladesh shows that the risk of skin lesions associated with any given level of arsenic exposure was greater in men with excessive sun exposure (Chen et al., 2006). Another study conducted in an arsenic-exposed area in Taiwan shows that skin cancer patients reported greater sunlight exposure than controls (Chen et al., 2003).

If sunlight exposure plays an important role, then there must be the chance of developing more skin lesions in the unexposed part of the body than the exposed part. Melanosis and leucomelanosis mainly present in the unexposed part of the body.

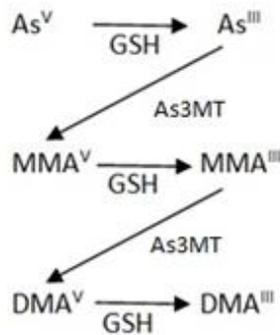
2.7 Exposure to Pesticide and Fertilizer

Most of the Bangladeshi consuming arsenic contaminated water are living at rural areas. A large percentage of them are either directly involved in cultivation or indirectly exposed to pesticides and fertilizers. Some of the pesticides are arsenic based (for example, Fudanon 10G in Bangladesh; Green plaster in West

Bengal, India). Foodstuffs are contaminated with these substances. A study conducted in Bangladesh shows that there is no influence of pesticide use in the relation between arsenic exposure and risk of skin lesions (Chen et al., 2006).

2.8 Liver Dysfunction

The main organ for arsenic metabolism is the liver. Methylation capacity might reduce with increasing dosage of arsenic exposure.



2.9 Melanosis and Cancer

A significant association between melanosis and liver cancer is not observed.

2.10 Keratosis and Cancer

A 67% increase in liver cancer risk is observed among subjects with skin cancers and keratoses, suggesting that a higher incidence of liver cancer should be expected among people with such skin signs.

Keratosis is significantly associated with an increased lung cancer risk. A significant interactive effect on lung cancer risk between keratosis and cigarette

smoking was identified, which suggests that patients with keratoses who have been exposed to arsenic should cease smoking (Hsu et al., 2013).

2.11 Bowen's Disease and Cancer

A significant association of Bowen's disease and nonmelanoma skin cancer with an increased lung, urinary tract, prostate, and other gastrointestinal cancer risk, but not with liver cancer. Keratosis is associated with increased lung cancer risk. The strong interaction between cigarette smoking and keratosis with or without skin cancer appeared to increase the risk of lung cancer significantly.

2.12 Questions to be Raised

1. Is there any relationship between nutritional status and the development of arsenicosis?
2. Whether poor nutritional status increases the susceptibility to arsenicosis, or alternatively that arsenicosis may be responsible to develop poor nutritional status.

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⊙ Arsenicosis: A Global Issue

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*** Myth 1**

Children are free from developing arsenicosis.

*** Myth 2**

Melanosis is due to high exposure to sunlight.