RESEARCH COMMUNICATION

Cancer Morbidity among Methyl Isocyanate Exposed Long-Term Survivors and their Offspring: a Hospital-Based Five Year Descriptive Study (2006 - 2011) and Future Directions to Predict Cancer Risk in the Affected Population

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Abstract

The purpose of this study was to update both researchers and clinicians about the cancer incidence in methyl isocyanate (MIC) exposed long-term survivors and in their offspring, focusing on the etiological plausibility. In the time period 2006-2011, cancer morbidity was evaluated in the population surviving after exposure to (MIC) on December 3rd, 1984, in Bhopal. This descriptive study is based on hospital registration of 1261 cancer patients those are MIC gas victims and their subsequently born offspring. Morbidity status was studied on the basis of gender, age, organ and site with relative percentages. Cancers on specific sites, with special reference to breast (n=231) (18.31%), lung (n=103) (8.16%), tongue (n=103) (8.16%), buccal mucosa (n=94) (7.45%), cervix (n=72) (5.70%), and esophagus (n=68) (5.39%) were found in high proportions. Ovary (n=43) (3.40%), brain (n=42) (3.33%), larynx (n=40) (3.17%), non-Hodgkin's (n=31) (2.45%), gallbladder (n=29) (2.29%), stomach (n=28) (2.22%), head and neck (n=28) (2.22%), liver (n=27) (2.14%), acute lymphoid leukemia (n=24) (1.90%), rectum (n=20) (1.58%), colon (n=20) (1.58%), chronic myeloid leukemia (n=17) (1.34%), alveolus (n=17) (1.34%), Hodgkin's (n=14) (1.11%), uterus (n=14) (1.11%), multiple myeloma (n=14) (1.11%), and prostate (n=11) (0.87%) lesions were observed less frequently. Remarkably, gradual increase of cancers on different organs and sites were observed in the long-term survivors and their offspring. The present study observed some cancers which were not previously reported in this population. In addition, we also present the future research directions with systematic approaches to predict cancer risk in long-term survivors and their future generations. On the basis of this morbidity report, we suggest the need of biological surveillance through immune system biomonitoring and cytogenetic screening to predict the cancer risk in the MIC exposed population and their offspring.

Key words: Methyl isocyanate (MIC) - cancer morbidity - long-term survivors and offspring

Asian Pacific J Cancer Prev, **12**, 3443-3452

Introduction

Human carcinogenesis is markedly triggered by genetics as well as environmental factors (Schottenfeld, 1986). Environmental factors seem to play a definite role in cancer etiology as compared to genetics (Lichtenstein et al., 2000; Czene et al., 2002). Humans perceive cancers as an adverse effect on exposure to environmental and occupational chemicals (Huff, 1993). International Agency for Research on Cancer (IARC) is tirelessly evaluating the carcinogenic risks to humans through epidemiological and experimental evidence on the basis of occupational, accidental, and lifestyle (IARC, 1987; 1972 - 1992). Increasing evidence also suggest that cancer clusters and its burden are usually high in environmental chemical exposures. The first environmental chemical exposure induced human carcinogenesis was observed in the scrota of chimney sweeps and nasal carcinogenicity of snuff in 18th century (Cohen, 1991, Soussi, 2000). Moreover, we have also learned many cancer lessons from the episodes of Hiroshima and Nagasaki atom bombs (Ichimaru et al., 1991), Seveso dioxin (Bertazzi et al., 1998), Chernobyl nuclear reactor (Murbeth et al., 2004), and Minamata methyl mercury (Yorifuji et al., 2007).

Twenty seven years after its occurrence (3rd

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December, 1984), the Bhopal gas tragedy is the one still considered as a paradigm of world's worst chemical disaster. Methyl isocyanate (MIC), an intermediate chemical used in making pesticides (New Jersey HSFS, 2002) escaped as a suffocating gas with its toxic byproducts from Union carbide factory of Bhopal, killed 3600 individuals immediately and an estimated 2,00,000 was lethally exposed (Dhara and Kriebel, 1993).

Several animal and human studies conducted immediately after the exposure demonstrated the immunotoxic, genotoxic, and mutagenic effects of MIC (Luster, 1986; Tice et al., 1986; Naik et al., 1986; Karol et al., 1986; Kanhere et al., 1987; Schwetz et al., 1987; Conner et al., 1987; Varma et al., 1987). Ennever and Rosenkranz, (1987), predicted the carcinogenic effects of MIC in rodents and assumed that the chemicals carcinogenic to rodents are also potentially carcinogenic to humans. Many research investigations reported the persisting toxic effects in the exposed population (Kamat et al., 1992; Vijayan and Sankaran, 1996; Dhara and Dhara, 2002). A recent study published by Sarangi et al. (2011), well defined the clinical epidemiology, disease morbidity and long-term effects in the exposed survivors and offsprings.

Population based cancer registry established in 1986 by Indian council of Medical Research (ICMR) has highly contributed to the understanding of possible carcinogenic effects in gas exposed population of Bhopal. ICMR registry is dedicatedly registering all the cancer cases residing inside Bhopal. This registry studied the most common cancer sites like lung, oropharynx and oral cavity in relation to gas exposure from 1987 to 1992 and recommended that the effect of gas exposure on cancer must be studied in future (Dikshit and Kanhere, 1999). Recently, ICMR has encouraged and strengthened the biomonitoring studies by inviting the research proposal for studying the long-term effects in the MIC affected population after 27 years of exposure (ICMR, 2010).
As similar to this morbidity study, a previous research done by Ganesh et al. (2005), reported eight years (1994 – 2002) gender wise cancer pattern in MIC exposed population and their offsprings. After this preliminary report, the morbidity status of this population was not updated and limited due to the lack of investigations. This situation incited the necessity to present the cancer morbidity among MIC exposed population and their offspring.

Hence, the present study is aimed to aware the scientific community by emphasizing the five years cancer morbidity in the victims surviving after MIC exposure in 1984. This descriptive study is based on the data obtained from the hospital registry. This report is the first of its kind to forecast the gender wise - age specific cancer incidence from 2006 - 2011 in MIC exposed long-term survivors and their offsprings born aftermath. In addition, we also discuss the future research directions to predict cancer risk in the MIC exposed individuals and their future generations.

Materials and Methods

The Source of Data

Cancer morbidity was recorded from the registry of Jawaharlal Nehru cancer hospital and Research centre (JNCHRC), located in Madhya Pradesh State Capital Bhopal. JNCHRC is fully dedicated to cancer care for MIC victims as well as to the general population. According to the official notification of Government of Madhya Pradesh in 1994, all the cancer patients of the state especially MIC affected can avail the treatment from this hospital. This hospital registry provides much information about the patient's cancer type and its onset, course of the disease, previous illness, and treatment regime. Patients diagnosed with different type of cancers from all over India are registered in JNCHRC.

Data Extraction

We extracted only the five years data of cancer patients those are the victims surviving after the MIC exposure in 1984. These patients hold gas victim card as an evident during time of registration. Gas victim card was provided by the government to the victims those exposed to MIC gas. The general cancer population other than MIC victims registered from 2006 to 2011 in the same registry were not included or analyzed in this study.

From February 2006 to September 2011, overall 1381 MIC victims were registered in the hospital registry and 1261 was diagnosed with cancers after the appropriate diagnosis like histopathology, hematology, biochemical study and radiology. Their morbidity status was assessed by the analysis of their health records of the registry. The patients were grouped on the basis of gender and age to assess their cancer morbidity. Maximum age limit 0-75 years of males and females were analyzed. Additionally, Offsprings of the MIC exposed survivors reported with cancers were included in the study. The offsprings were < 26 years of age and born after MIC exposure. Life style, habit of tobacco chewing, Smoking and alcohol consumption status was blinded and not exactly known in this MIC affected cancer patients.

Data Analysis

Total percentage of cancer incidence on organs and sites were calculated according to gender with respective age groups of the survivors and offsprings. Data analysis was done using GraphPad InStat Ver.3.05. Paired-Samples T test were used to analyze the cumulative results in 95% confidence interval, at $p<0.05$ significance level.

Results

The frequency of cancers in relationship to gender, age, on specific sites and their results as percentage analysis on males (n=622) (49.32%) and females (n=639) (50.7) are shown in Table 1 and 2 respectively. The

Table 1. Relative Percentage of Cancer Morbidity in MIC Exposed Male Survivors and Male Offspring Born in the Aftermath (n=622)

Cancer Types and Sites	Age group								
	Male Offspring		Male Survivors						
	0-14	15-26	27-38	39-50	51-62	63-74	>75	Total	%
Oral Cavity & Pharynx									
Lip & Cheek	-	-	1	1	1	-	1	4	0.64
Salivary gland	-	-	2	-	-	1	-	3	0.48
Mouth, Throat, Tongue & Tonsil	-	2	16	27	24	13	2	84	13.5
Buccal mucosa	1	2	16	25	17	5	2	68	10.9
Pharynx & Oropharynx	-	-	-	-	-	1	-	1	0.16
Laryngo or Hypopharynx	-	-	-	-	1	-	-	1	0.16
Head & Neck	-	-	3	6	8	5	2	24	3.85
Digestive System									
Esophagus	-	-	1	6	17	10	3	37	5.94
Stomach, Duodenum & Abdomen	-	-	1	6	8	3	1	19	3.05
Colon	-	1	2	2	2	2	-	9	1.44
Rectum & Rectosigmoid	-	1	2	3	2	-	-	8	1.28
Anal canal & Anorectum	-	1	2	-	-	-	2	5	0.80
Liver	-	-	1	5	7	4	-	17	2.73
Gallbladder	-	-	3	1	5	2	-	11	1.76
Pancreas	-	-	1	4	1	1	-	7	1.12
Bile duct	-	-	-	-	4	1	-	5	0.80
Respiratory System									
Larynx &Vocal Card	-	1	2	7	8	13	4	35	5.62
Supraglotic & Epiglottis	-	-	-	2	2	5	1	10	1.60
Lung	-	1	3	10	29	32	12	87	14.0
Alveolus	-	-	-	4	4	1	1	10	1.60
Bone (Including Metastasis)	-	3	1	3	1	-	-	8	1.28
Soft Tissue	1	1	2	-	1	1	-	6	0.96
Skin & Melanoma	-	1	2	5	1	4	2	15	2.41
Male Breast	-	-	-	-	2	1	1	4	0.64
Male Genital System									
Prostate	1	-	-	1	3	2	4	11	1.76
Testis	-	5	-	1	1	-	-	7	1.12
Urinary System									
Bladder	-	-	-	2	-	1	2	5	0.80
Kidney & Renal Pelvis	2	-	-	4	1	-	-	7	1.12
Brain & Spine	3	4	5	4	5	5	1	27	4.34
Peripheral Nervous System	1	-	-	1	-	-	-	2	0.32
Endocrine System									
Thyroid gland	-	-	1	-	-	-	-	1	0.16
Lymphoma's									
Hodgkin's	3	-	2	1	-	-	-	6	0.96
Non-Hodgkin's	3	-	3	2	3	4	3	18	2.89
Multiple Myeloma	-	-	-	1	7	1	1	10	1.60
Plasmacytoma	-	-	1	-	1	-	-	2	0.32
Leukemia									
Acute lymphocytic	7	5	1	1	2	1	-	17	2.73
Chronic lymphocytic	-	-	1	-	-	2	1	4	0.64
Acute myeloid	-	1	-	-	2	2	-	5	0.80
Chronic myeloid	1	-	3	3	3	2	1	13	2.09
Multiple nodes	-	-	-	-	-	1	-	1	0.16
Glandular tissue	-	-	-	1	2	-	-	3	0.48
Others									
Eye	-	-	-	-	-	-	-	-	-
Ear & Nose	-	-	-	-	-	1	-	1	0.16
Thigh & Leg	-	-	-	-	1	2	-	3	0.48
Anemia	1	-	-	-	-	-	-	1	0.16
Total n=	24	29	78	139	176	129	47	622	
Age Specific (%)	(3.85)	(4.66)	(12.54)	(22.34)	(28.29)	(20.73)	(7.55)	(49.32)	
Group specific n (%)	53 (4.20)		569 (45.12)						

Table 2. Relative Percentage of Cancer Morbidity in MIC Exposed Female Survivors and Female Offspring Born in the Aftermath (n=639)

Cancer Types and Sites	Age group								
	Female Offspring		Female Survivors						
	0-14	15-26	27-38	39-50	51-62	63-74	>75	Total	Site (%)
Oral Cavity & Pharynx									
Lip & Cheek	-	-	-	-	1	1	-	2	0.31
Salivary gland	-	-	-	-	-	-	-	-	-
Mouth, Throat, Tongue & Tonsil	-	1	4	3	6	3	2	19	2.97
Buccal mucosa	-	-	2	8	8	6	2	26	4.06
Pharynx & Oropharynx	-	-	-	-	1	-	-	1	0.15
Laryngo or Hypopharynx	-	-	-	3	1	3	1	8	1.25
Head & Neck	-	-	-	3	-	-	1	4	0.62
Digestive System									
Esophagus	-	-	-	6	12	8	5	31	4.85
Stomach, Duodenum & Abdomen	-	1	-	4	2	2	-	9	1.40
Colon	-	-	1	2	4	4	-	11	1.72
Rectum & Rectosigmoid	-	2	-	5	2	2	1	12	1.87
Anal canal & Anorectum	-	-	-	1	-	1	-	2	0.31
Liver	-	1	1	6	1	-	1	10	1.56
Gallbladder	-	-	3	6	3	5	1	18	2.81
Pancreas	-	-	-	1	-	2	-	3	0.46
Bile duct	-	-	2	1	-	1	-	4	0.62
Respiratory System									
Larynx &Vocal Card	-	-	-	3	1	1	-	5	0.78
Supraglotic & Epiglottis	-	-	-	-	1	-	1	2	0.31
Lung	-	-	2	3	4	7	-	16	2.50
Alveolus	-	-	-	3	3	1	-	7	1.09
Bone (Including Metastasis)	2	7	-	-	-	-	-	9	1.40
Soft Tissue	1	1	-	-	1	2	-	5	0.78
Skin & Melanoma	-	-	-	2	2	-	1	5	0.78
Breast (Including in situ)	-	2	35	90	59	31	10	227	35.52
Female Genital System									
Cervix uteri	1	-	6	36	15	11	3	72	11.26
Ovary uteri	-	-	9	14	12	8	-	43	6.72
Vulva	-	-	-	-	-	1	-	1	0.15
Uterus & Endometrium	-	-	1	3	7	3	-	14	2.19
Urinary System									
Bladder	-	-	-	-	1	-	-	1	0.15
Kidney & Renal Pelvis	-	-	1	3	-	1	-	5	0.78
Brain & Spine	6	-	2	4	3		-	15	2.34
Peripheral Nervous System	-	-	-	1	-	-	-	1	0.15
Endocrine System									
Thyroid gland	-	-	2	2	2	-	-	6	0.93
Lymphoma's									
Hodgkin's	-	1	2	3	1	-	1	8	1.25
Non-Hodgkin's	1	1	2	-	5	4	-	13	2.03
Multiple Myeloma	-	-	-	-	1	1	2	4	0.62
Plasmacytoma	-	-	-	-	-	-	-	-	-
Leukemia									
Acute lymphocytic	1	-	3	1	2	-	-	7	1.09
Chronic lymphocytic	-	-	-	-	-	1	-	1	0.15
Acute myeloid	-	-	1	-	-	1	-	2	0.31
Chronic myeloid	-	-	-	3	1	-	-	4	0.62
Multiple nodes	-	-	-	-	1	-	-	1	0.15
Glandular tissue	-	-	-	1	-	-	1	2	0.31
Others									
Eye	1	-	-	-	-	-	-	1	0.15
Ear & Nose	-	-	1	-	-	1	-	2	0.31
Thigh & Leg	-	-	-	-	-	-	-	-	-
Total n=	13	17	80	221	163	112	33	639	
Age specific (%)	(2.03)	(2.66)	(12.5)	(34.6)	(25.5)	(17.5)	(5.16)	(50.7)	
Group specific n (%)	30 (2.37)		609 (48.29)						

Table 3. Morbidity Relationship between Males and Females (Both Offspring and survivors) (n=1261)

Gender	n (%)	Mean ± SD	Paired – Sample T test Significance
Males	622 (49.32)	88.8±59.6	
Females	639 (50.67)	91.2±79.1	t = 0.1805P = 0.8627
Total	1261		

overall cancer cases reported is (n=1261).

In offspring, cancer incidence was higher in the age group 15-26 male (n=29) (4.66%) and female (n=17) (2.66%) as compared to males of other age groups including pediatrics 0-14 males (n=24) (3.85%) and females (n=13) (2.03%). Overall, male offsprings (n=53) (4.20%) was reported with higher percentage of cancers as compared to the female offsprings (n=30) (2.37). But the trend is fully reversed in the case of higher age group survivors.

Female survivors (n=609) (48.29%) was reported with higher cancer incidence as compared to the male survivors (n=569) (45.12%). Females survivors of age group 39-50 were affected more among the over all population and around (n=221) (34.58) of cancers were observed. Female survivors of other age group 51-62 (n= 163) (25.5%), 63-74 (n=112) (17.52%), 27-38 (n=80) (12.51%), <75 (n=33) (5.16%) also shown an increased incidence of cancers.

In male survivors, the age group 51-62 (n=176) (28.29%) were observed with higher cancer incidence as compared to the other age group of males 39-50 (n=139) (22.34%), 63-74 (n=129) (20.73%), 27-38 (n=78) (12.54%), <75(n=47) (7.55%). Except the eye site, the males were reported with all type of cancers (Table 1), where the female are not reported with plasmacytoma,

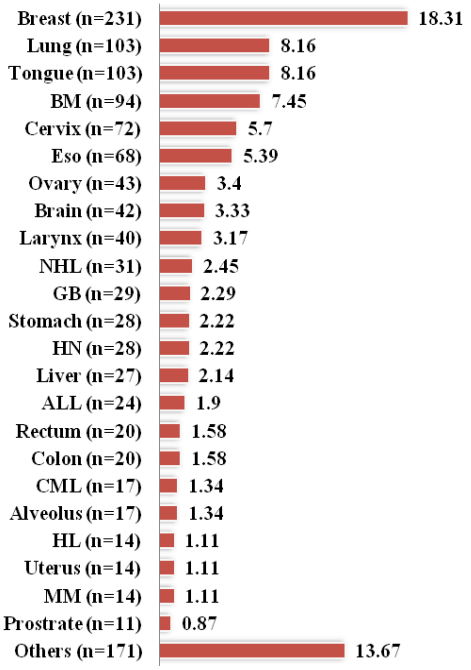

Figure 1. Relative Percentages of Cancers in the Affected Population (Both in Males and Females including Offspring)

anemia, and cancers of salivary gland, ear, nose, thigh, and leg (Table 2).

Although, the relative percentage of cancer morbidity was higher in females (n=639) (50.67) (91.2±79.1) as compare to males (622) (49.32) (88.8±59.6), there are no significant differences in morbidity status between males and females (t = 0.1805; P = 0.8627) (Table 3).

Among all the cancers, specific sites like breast (n=231) (18.31%), lung (n=103) (8.16%), tongue (n=103) (8.16%), buccal mucosa (BM) (n=94) (7.45%), Cervix (n=72) (5.70%), and esophagus (Eso) (n=68) (5.39%) were found in high proportions. Ovary (n=43) (3.40%), brain (n=42) (3.33%), larynx (n=40) (3.17%), non-Hodgkin's (NHL) (n=31) (2.45%), gallbladder (GB) (n=29) (2.29%), Stomach (n=28) (2.22%), head and neck (HN) (n=28) (2.22%), liver (n=27) (2.14%), acute lymphoid leukemia (ALL) (n=24) (1.90%), rectum (n=20) (1.58%), colon (n=20) (1.58%), chronic myeloid leukemia (CML) (n=17) (1.34%), alveolus (n=17) (1.34%), Hodgkin's (HL) (n=14) (1.11%), Uterus (n=14) (1.11%), multiple myeloma (MM) (n=14) (1.11%), and Prostate (n=11) (0.87%) were observed frequently (Figure 1).

Discussion

Our data provides a strong evidence of the association between MIC exposure and cancer in agreement with a previous study done by Ganesh et al. (2005), analyzed gas affected area specific exposed survivors and their offspring's registered in the same JNCHRC registry covering eight years cancer morbidity status from 1994 – 2002. In eight years, overall 17360 registered JNCHRC and among those, 637 were MIC gas affected. Eight years morbidity data revealed only gender wise cancer pattern and failed to analyze on age specific incidence. This study reported only 637 cancer cases in eight years, but the present study revealed 1261 MIC gas affected cancer cases within five years. The present study morbidity data shows that there is gradually increased risk of cancers in MIC affected population.

According to eight years morbidity study, the cancer incidence is higher in male survivors and male offsrings as compare to female survivors and female offsrings. Perhaps, the trend is totally contradictory to the findings of present study revealed that the overall cancer incidence is higher in female survivors as compare to males. But, the findings are in concordance with the pediatric age groups, observed higher cancer incidence in male offsprings as compared to females. However, the present study observed a manifold increase of previously reported cancers in the affected population. On the other hand, we also observed some of the cancers which were not previously reported in the affected population. Chronic lymphoid leukemia (CLL), Cancer of stomach, gall bladder, anal canal, glandular tissue's, sarcoma's were observed among the affected population in the present study which was not previously reported by

Ganesh et al.

Among all the observed cancers in MIC affected population, the frequently reported in high proportion was breast cancer. Ganesh et al., (2005) reported only 45 breast cancer cases in eight years, where as the present study observed (n=231) in five years. With respect to breast cancer, the female survivors and offsprings of the age groups ranging from 27-38 (n=35), 39-50 (n=90), 51-62 (n=59) and 63-74 (n=31) were observed at higher risk. In particular, the age group 27-38 was children's at the time of exposure. Much attention must be given in the present and future generations of the same age groups to determine their risk and vulnerability to breast cancers. Moreover, it is obvious to study the association of MIC exposure in breast cancer etiology in prior. Because, many investigations have explored the association of environmental contaminants, organic solvents and chemicals especially organochlorines and pesticides in breast cancer etiology (Blair et al., 1998; Ibarluzea et al., 2004; Engel et al., 2005; Newby and Howard, 2006).

MIC is used in making pesticides, polyurethane foams and plastics and directly targets the lungs on inhalation (New Jersey HSFS, 2002; Gupta, 1991). Lung cancers and NHL were common in pesticide exposed population (Burns, 2005). Mikoczy et al. (2004), studied the cancer incidence in chronic obstructive lung diseases in the Swedish polyurethane foam industry cohorts exposed to isocyanate and found an increased lung cancer risk among female workers. However, the study was unable to link isocyanate exposure with lung cancer risk. But, our observations were contrast to the findings of Mikoczy et al, we have observed (n=87) lung cancers in males and (n=16) in females of MIC exposed population.

Much type of cancers reported in MIC affected population have a strong association with chemical exposure and reported earlier as an evident in humans exposed to other chemicals and carcinogens. Astrocytoma, Glioblastoma and Glioma are evidenced in occupational chemical exposures (Thomas et al., 1987), Soft tissue Sarcoma's and lung cancers are frequently associated in dioxin exposure (IARC, 1997; Bodner et al., 2003), Lymphoma's and Lymphoprofilerative disorders like MM are linked with benzene exposures (Hayes et al., 2001), several aromatic amines has the etiology of bladder cancer as well as in lung cancers and the role of Aflatoxins are well known in liver cancers (Poirier, 2004), Breast, prostate, testicular, nervous system and brain cancers incidence in organochlorines and synthetic pesticide exposure are consistent (Newby and Howard, 2006; Rodvall et al., 2003). Pharynx, stomach and glandular tissue cancers such as Adenocarcinoma were reported in mustard gas (Alavian et al., 2009),

Although, cancers of breast, lung, tongue and buccal mucosa were frequently reported in MIC affected population, further experimental and epidemiological studies are needed to validate on those cancers as the response to earlier MIC exposure induced effect.

The present morbidity report may serve to emphasize the association of genotoxic chemical exposure in cancer etiology. Individual's susceptibility to cancer is also a matter of concern. The populations with cancer risk are characterized as oncodemes on the basis of relative contributions of environment and genetics. Individuals may develop cancer on the basis of environmental (Environmental carcinogens acting on normal people) and environmental or genetics (Environmental carcinogens acting on genetic susceptibility) are defined as oncodemes 2 and 3 respectively (Venitt, 1994). Most human cancers are common in oncodemes 2 and 3, due to their exposure to environmental chemicals and carcinogens.

Initiatively, we have projected the cancer morbidity in the affected population with possible explanation, in future additional research with large population-based case-control investigations are needed to validate the potential interaction of MIC in cancer etiology. The current study did not compare the cancer incidence of non-exposed general population with the MIC exposed, where the future must take in to consideration. The results from the present study suggest that the cancer risk in the MIC exposed population and their future generations must be adequately addressed by future epidemiological studies, which may provide more insights.

In summary, parental exposure to chemicals and carcinogens has been suspected in cancer risk in the offsprings since long time. Not only environmental factors, genetics shared by parents and offspring are also to play a definite role in cancer etiology. To minimize the cancer risk in the present and future generations of the affected population, it is essential to update the scientific knowledge of the persisting effects. Therefore, this type of report is highly needed to control the chemical exposure induced cancers in humans. Although this descriptive study has few limitations, for the first time it provides the gender wise - age specific cancer morbidity data that could be useful to both researchers and clinicians. Acknowledging the limitations never affects the quality of the study and does not nullify the data presented in this paper.

Nearing the 27th year aftermath, the insufficient biological evidence in the past and lack of biomonitoring in the present has invited the cancer incidence among the exposed survivors, which also burgeoned our scientific interest to present this future direction. However, the past was uncertain and harder to predict any risk in the affected population; the future can be validated with the use of predictive biomarkers.

Biomarkers of both exposure and effect provide support in human genotoxicant interactions assessment and indicate the future disease risk (Albertini et al., 1996). Hagmar et al. (2001), also reported the usefulness of below listed cytogenetic biomarkers as endpoints for predicting the environment-related cancer risk. With special reference to cancer risk predictors, we would like to discuss some of the novel cytogenetic biomarkers that predict cancer risk in the affected population. Although, many potential biomarkers are validated in the evaluation

of environmental chemical exposure induced biological disruption, here we discuss only few those frequently used with increasing confidence in cancer risk prediction.

While the immunotoxic and genotoxic effects of MIC are well-documented in animal models, less is known about the effects on human exposure. Many exposed survivors are now diagnosed with cancers on all sites, there is no need of any validation to prove the toxicity of MIC. While laboratory studies can provide direct evidence linking the chemical exposures to specific effects, biomonitoring studies are the only way to verify the cause-effect relationships and to validate the relevance to populations (Galloway, 2001).

The exposed population must be screened thoroughly by pedigree analysis to depict the exposure - response, complaint of late and early health effects. Pedigree will be a handful measure to explore the chances of disease, pre-existing medical impairments and inherited disorders. All the previous studies conducted in the affected population lacks of pedigree analysis. Through pedigree, not only the exposed, their future generations also predicted for health risk, if any.

Many evidence also suggested that the immune system is a possible target to industrial and environmental chemicals (Descotes et al., 1995). Lymphocytes are the moot pointers of immune system in human biomonitoring studies. Circulating lymphocytes are the functional indicators to evaluate any immunotoxic and genotoxic effects induced by chemical and radiation exposures. Even many cancers are due to lymphocyte-specific instability (Kirsch et al., 1994). Lymphocytes functioning as memory cells can act as a predictor in identifying the early immune system assaults. Such circulating memory cells can predict cancer and other major risks in the affected individuals. Exploring these lymphocytes, many chemical and biological endpoints can be monitored. This was made possible by a study, analyzed chromosomal aberrations as endpoints in the lymphocytes of atom bomb survivors of Hiroshima and Nagasaki after 40 years and evidenced the long-lived lymphocytes (Natarajan, 1993). So, there is every possibility to retrieve these MIC affected lymphocytes which may hopefully predict the cancer risk in the affected population. An earlier study conducted in MIC exposed population before two decades by Saxena et al, (1988), also observed suppressed T-cell counts with depressed cell mediated immunity and declared that MIC has residual effect on T-cell precursors.

Classical Chromosomal aberration analysis (CA), Micronucleus (MN) and Hypoxanthine-guanine phosphoribosyl transferase (HPRT) somatic mutation assays are the sensitive endpoints and validated biomarkers studied in human biomonitoring for genotoxic effects induced by carcinogens (Natarajan, 1993; Albertini et al., 2000). Hagmar et al. (1994) highlighted that cytogenetic assays in peripheral blood lymphocytes (PBL) have been used extensively to study the human exposure to genotoxic agents. Applying these biomarkers as endpoints is highly justifiable in determining DNA damage that predicts the cancer risk (Fenech, 2002). Validation of these biomarkers for DNA damage is well comprehensive for cancer risk prediction.

Several pivotal studies reported have shown the predictive value of these methods in cancer risk assessment and also made great contribution to our understanding in this regard. Hagmar et al. (1994), analyzed 3182 subjects in a Nordic study between 1970 and 1988 for CA, sister chromatid exchange (SCE) or MN in PBL and suggested an increased level of chromosome breakage appears to be a relevant biomarker of future cancer risk. Hagmar et al. (1998), reported in a European study updated data for 3541 subjects examined for CAs, 2703 for SCEs, and 1496 for MN. This pooled analysis results suggested that the frequency of CAs in PBL as a relevant biomarker for cancer risk in humans, which reflects either early biological effects of genotoxic carcinogens or individual cancer susceptibility. Liou et al., (1999) studied for the association CAs and cancer risk in the arsenic-exposed Taiwan population in Blackfoot Endemic Area and suggested that CAs are excellent biomarkers for the prediction of cancer development.

Bonassi et al. (2000), studied chromosomal aberrations for cancer predictivity in the case-control data from Nordic countries (cancer incidence data) and Italy (cancer mortality data). The data suggested that chromosomal damage is itself a casual factor involved in the pathway to cancer. Hagmar et al. (2001) also suggested that chromosomal mutations are causal events in the development of neoplasia, may reveal the enhanced cancer risk in occupational health surveillances. Hagmar et al. (2004) observed the impact of chromosome-type (CSAs) and chromatid-type aberrations (CTAs), in Nordic and Italian Cohorts for cancer risk. Findings of this study suggested that double-strand break and other initial DNA lesions responsible for CSAs and CTAs are associated with cancer risk. Boffetta et al. (2007), reported the association of CAs and cancer risk in 6,430 healthy individuals of Central Europe. The observation showed cancer incidence of 8.5 years, with 200 cancer cases. All these specific cancers were limited by small numbers, but the association was stronger for stomach cancer. Findings concluded the association between level of CAs and cancer risk in support to the Nordic-Italian cohort study conducted by Bonassi et al. (2000). Another study done by Rossner et al.(2005), also found stronger association between CA frequency and cancers of the digestive tract, especially in stomach cancer. A pooled cohort study of 22,358 subjects evidenced a link of CA frequency and cancer risk Bonassi et al. (2008).

The cytokinesis block micronucleus (CBMN) technique established by Fenech and Morley, (1985; 1986) developed a milestone in scoring MN in lymphocytes, buccal cells and erythrocytes. Znaor et al. (2003), analyzed the MN frequency in a cohort of 200 subjects occupationally exposed to genotoxic agents. This follow-up study observed the cancer incidence and

mortality through the Croatian National Cancer Registry and records of occupational medicine physicians. Owing the small number of cancer cases, the study was unable to estimate the predictive value of micronuclei in the Croatian cohorts.

Major contribution was made by HUman MicroNucleus project (HUMN), an international collaborative project by testing the hypothesis that an elevated MN frequency in human tissues predicts the cancer risk (Fenech et al., 1999; 2011). This hypothesis was widely accepted now, after the findings of Bonassi et al. (2007), in HUMN project revealed MN frequency in PBL is a predictive biomarker of cancer risk in healthy subjects. A recent report published by Bonassi et al. (2011), also suggested the use of MN frequency in cancer screening programmes. All these studies validated the frequency of MN as a predictive marker in cancer risk assessment.

Many environmental genotoxic agents and ionizing radiation induce mutational lesions and cancer in human somatic cells. Somatic cells undergo gene alterations such as point mutations, rearrangement, and amplification can facilitate several steps in carcinogenesis (Kyoizumi et al., 1989). Human cancers have direct link with somatic mutations. Although, somatic mutation are indicative and indirect predictors of cancer risk, but it is valid and applicable (Albertini, 1994). Such somatic cell mutations in vivo have both biological and toxicological relevance provides significant perceptive on genetic effects of environmental carcinogenic exposures in healthy populations and their disease mechanisms with increased cancer risk and other disorders (Albertini et al., 1990; 1993). Hackman et al. (2000), studied the mutational spectra at HPRT locus and suggested that the HPRT gene may be valuable as a reporter locus for somatic in vivo mutations that occur in the early steps of lung cancer development. Because, exposure - inhalation of MIC is known to cause hypersensitivity in the airways, pulmonary toxicity in the lungs with hypoxic condition and reduced cellular defence (Gupta, 1991).

Several cytogenetic studies done immediately after the MIC exposure also revealed higher frequency of CAs and SCE in exposed population when compared with the non-exposed population (Goswami, 1984; Goswami et al., 1986, 1990; Ghosh et al., 1990). It is important to point out here that there are no follow-up cytogenetic studies since two decades, in the exposed population.

Considering the aforementioned assay based experimental findings, we believe that cytogenetic monitoring will be worthwhile in cancer risk assessment. All the assays discussed in the context are apparent and suitable end point for predicting cancer risk.

According to the World Health Organization (WHO), global cancer rates may tend to increase as much as 50% by the year 2020 unless the further prophylaxis is put into practice (Frankish, 2003). Biological surveillance may provide the precise indications of any health hazards and cancers. Promoting the biological surveillance may predict the cancer risk in affected population and earlier screening may provide better prophylaxis in cancer prevention. Disease susceptibility and cancer risk in the MIC affected population may possibly predicted by the aforesaid biomarkers, which are needed as end points and can be utilized directly in design, method selection, and interpretation.

Scientifically, there is much space for biological surveillance in MIC affected population. Many researchers are conflicting the possibility of MIC induced long-term effects after 27 years of exposure. In Hiroshima and Nagasaki, the atom bomb survivors were diagnosed with cancers and other health problems after 40 years of the exposure, where the same situation prevailing still in Seveso and Chernobyl. Certainly, MIC exposure may also have the same type of cause-late effect relationship. Vulnerability of this population to cancer and a greater focus on this research is justified. Immune system monitoring and early cytogenetic screening may hopefully worthwhile in minimizing the cancer risk in long-term survivors and their future generations. This morbidity report suggests human biomonitoring studies to prevent the obscured health risk in the affected population and their probability associated with cancers.

Acknowledgements

The financial support of the Council of Scientific and Industrial Research (CSIR) to C. S. Senthilkumar (Senior Research Fellow) is gratefully acknowledged. The authors thank the management of JNCHRC especially Chairman Mr. Madan Mohan Joshi, Director Dr. K.V. Pandya, Asst. Director Mr. Rakesh Joshi, Research coordinator Mrs. Divya Parashar for long- standing support and encouragement. Special thanks to office staff Mr.Vineesh for the valuable assistance in data extraction.

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