

## RESEARCH COMMUNICATION

# DNA Damage Induction and Repair Inhibition Among Building Construction Workers in South India

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### Abstract

Construction industry workers are exposed to many known carcinogens in their complex occupational environment. Since there are no past studies on genotoxicity among this group in the Indian subcontinent, workers engaged in different construction sites at Coimbatore, Tamil Nadu, India, were assessed here. We enrolled 96 workers and 68 control subjects with similar mean age, smoking, tobacco chewing prevalence and alcohol consumption, for analysis of DNA damage in blood leucocytes by micronucleus (MN) and comet assays. DNA repair inhibition was also analyzed by assessing the XPD gene. Construction workers showed a significant increase in MN and comet tail length compared to controls with adjustment for smoking habits, tobacco chewing, alcohol consumption and years of exposure ( $P < 0.05$ ). The results indicated that chronic occupational exposure to cement during construction work could lead to increased levels of DNA damage and repair inhibition.

**Keywords:** Cement exposure - genotoxicity - micronucleus assay - comet assay - XPD gene polymorphism

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### Introduction

Construction Industry is one of the most booming industries in the whole world. Construction workers formed 4.97% of the total worker-force in India. Workers engaged in construction work are exposed to various hazardous substances. Portland cement is the most common type of cement in general usage, an important substance used in construction industry and it consists of many toxic constituents. Portland cement contain 0.75% insoluble residue. A fraction of these residues may be free crystalline silica. Respirable crystalline silica (quartz) can cause silicosis, a fibrosis of the lungs and possibly cancer (Brown et al., 1997; Hessel et al., 2000). There is evidence that exposure to respirable silica or the disease silicosis is associated with an increased incidence of Scleroderma, tuberculosis and kidney disorders. Carcinogenicity may be dependent on inherent characteristics of the crystalline silica or on external factors affecting its biological activity or distribution of its polymorphs (IARC, 1997).

Recent epidemiological surveys relate 2-8% of all cancer is due to exposure to carcinogens at the workplace and some studies have indicated that cement and concrete constituents might be carcinogenic. A case-control study in Denmark found that people working in concrete and cement manufacturing had an increased risk of laryngeal cancer (Olsen et al., 1984) and a Swedish cohort study reported an increased risk of colorectal cancer in cement exposed men (Jakobsson et al., 1993). An increased risk of lung cancer, gastrointestinal tumours and dermatitis were also reported in diverse studies (Vestbo and Rasmussen

1990; Jakobsson et al., 1993; Yang et al. 1996; Abu Dhaise et al., 1997; Noor et al., 2000; Algranti et al., 2001; Al-Neaimi et al., 2001; Laraqui et al., 2001; Stern et al., 2001).

Cement dust exposure occurs commonly in the cement production and construction industry. Most studies carried out in these industries, however, focus on silica exposure. On cement dust exposures in cement plants only inadequate data is available. There is no data published about genotoxicity among construction workers.

Millions of workers in India are potentially exposed each year to hazardous chemicals, dusts, or fibers in construction settings. Some of these agents are genotoxic and may cause genetic alterations in the somatic or germ cells of exposed workers. Such alterations may lead to the development of cancer. The risk of cancer is less easy to detect with traditional epidemiological methods in the construction industry than in other industrial sectors. It is not sufficient to rely upon broad epidemiological data to estimate the risk of cancer due chemicals in the construction industry (Järvholm, 2006).

The present study aimed to investigate the genotoxic effects associated with cement exposure on South Indian construction industry workers using the comet assay and the micronucleus (MN) test. The comet assay has been found to be a very sensitive, quick, reliable and fairly inexpensive way of measuring DNA damage (Schmid, 1975; Snow et al., 1989). It has a further advantage that the observations are made at the single cell level. Moreover, it is an invaluable tool for investigating DNA damage in human populations (Collins et al., 1997). To substantiate our results and to provide a cytogenetic parameter, the MN

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test was also carried out. This test allows the detection of both clastogenic and aneugenic agents (Salama et al., 1999). The influence of confounding factors like age, smoking, alcohol drinking, duration of exposure on the differences in DNA damage was also analyzed. The present study analysed the synergistic genotoxic effect of smoking, tobacco chewing and alcohol consumption among construction industry workers. The major pathway eliminating DNA base damage and helix distortion is the excision repair pathway, subdivided into nucleotide excision repair (NER) and base excision repair (BER). If the mutagenic potentials of certain compounds are rather weak, in contrast, they exert pronounced co-mutagenic effects, which may be explained by the inhibition of different DNA repair systems (Hartwig, 1998). Among the repair proteins, the XPD protein is interesting because it is a major player in the nucleotide excision repair pathway and is also involved in transcription initiation and in the control of the cell cycle and apoptosis. Mutations in the XPD gene can diminish the activity of transcription complexes giving rise to repair defects, transcription defects, abnormal responses to apoptosis and probably, hormonal dysfunctions. The XPD protein is a 5' 3' helicase with a molecular weight of 86.9 kDa and comprising 761 amino acids (Sarto et al., 1990). The genomic DNA of the XPD gene comprising 23 exons spans ~54.3 kb at 19q13.3 and almost 100 mutations have been mapped in this gene (Hengstler et al., 2003). Most of them are point mutations, indicating that the presence of a full-length XPD protein is necessary for life (Coin et al., 1998). The present study also aimed to analyze the incidence of polymorphisms in XPD DNA repair gene and thereby DNA damage evaluation by complementary genotoxic endpoints (MN assay and Comet assay) among South Indian building construction industry workers.

## Materials and Methods

### *Selection of subjects and collection of specimens*

The study populations composed of 96 building construction workers. The exposed group was further subdivided into smokers (48), tobacco chewers (50) and alcoholics (42) working at different construction sites located in the urban area of Coimbatore City, South India. The control group consisted of 34 smokers, 36 chewers and 33 alcoholics. Details of the type of work and materials with which they came in contact were recorded. Based on this, the study group included the following categories: masons and helpers. Masons were involved in skilled jobs like laying the bricks and paving and used cement as a basic ingredient in their work. Helpers were involved in unskilled jobs of mixing the cement, carrying it to construction sites, cleaning and helping masons. The workers had varying durations of exposure (10-30 years) and they were in the age group 21-60 years. The control group was selected from the general population with no history of occupational exposure to construction or any known physical or chemical agent in the workplace, but belonged to the same age group and socio-economic status as the construction workers. The selection criteria for the subjects were based on a questionnaire. The questionnaire

covered standard demographic questions (age, genetic disorders, number of X-ray diagnoses, vaccinations, medication, smoking, tobacco chewing, alcohol, etc.) and occupational questions (years of exposure). We ensured that the construction workers and the controls did not markedly differ from each other except for occupational exposure. We also ensured that all the subjects had not been taking any medicines nor had they been exposed to any kind of radiation for 12 months before sampling. The subjects who smoked >5 cigarettes/day at least for 1 year were considered as smokers and those who consumed >120gm of alcohol/day were considered as alcoholics in both groups. All subjects were informed of the objective of the study and gave their consent. The institutional review board approved the research procedures used in this study.

Venous blood (3ml) was collected from all subjects using heparinized syringes. The samples were transported on ice to the laboratory and were processed. MN assay and Comet assay were performed using the collected blood samples and the DNA isolated from the sample was used for gene polymorphism analysis.

### *Laboratory analyses*

**Micronucleus Assay:** Leukocyte cultures were set up by adding 0.5 ml whole blood to 4.5 ml RPMI 1640 medium supplemented with 15% heat-inactivated fetal calf serum, 1% antibiotics (penicillin and streptomycin) and L-glutamine (all obtained from Gibco). Leukocytes were stimulated by 1% phytohaemagglutinin (PHA; Gibco) and incubated for 72 h at 37°C. A final concentration of 6 µg/ml cytochalasin B (Sigma) was added to the cultures 44 h later to arrest cytokinesis. At 72 h of incubation, the cultures were harvested by centrifugation at 1000 rpm for 8 min and treated with a hypotonic solution (2–3 min in 0.075 M KCl at 4°C). Cells were centrifuged thereafter and a 3:1 (v/v) methanol: acetic acid solution was gently added. This fixation step was repeated twice and the resulting cells were resuspended in a small volume of fixative solution and dropped onto clean slides. Finally the slides were stained with Acridine orange (Merck) analyzed under a fluorescent microscope and scored.

**Comet assay:** An aliquot of 40 µl of whole blood was used to quantitate basal DNA damage. Cell viability determined by the trypan blue exclusion technique (Maxild et al., 1978) ranged from 90 to 95% (data not shown). Slides were prepared in duplicate per person according to Singh et al., (1988).

The cell suspension was centrifuged, the pellet obtained was mixed with 0.7% low melting agarose (LMA) and placed on fully frosted roughened slides previously coated with 1% normal melting point agarose. To the solidified agarose, a third layer of 0.1% LMA was applied and were immersed in freshly prepared ice cold lysis solution for 1 hour. The slides were then electrophoresed, neutralized, dried and stained with ethidium bromide.

A total of 100 randomly captured comets from each slide were examined at 400X magnification using an epifluorescence microscope (Zeiss) connected through a black and white camera to an image analysis system (Comet Assay II; Perceptive Instruments Ltd, UK). A

computerized image analysis system acquires images, computes the integrated intensity profiles for each cell, estimates the comet cell components and then evaluates the range of derived parameters. To quantify the DNA damage, tail length (TL) and tail moment (TM) were evaluated. Tail length (length of DNA migration) is related directly to the DNA fragment size and presented in micrometers. It was calculated from the centre of the cell. Tail moment was calculated as the product of the tail length and the fraction of DNA in the comet tail.

An undamaged cell resembles an intact nucleus without a tail and a damaged cell has the appearance of a comet. The length of the DNA migrated in the comet tail, which is an estimate of DNA damage, was measured.

**Restriction Fragment Length Polymorphism of XPD Gene:** Polymorphism of XPD gene was analyzed by a PCR-RFLP procedure with the following oligonucleotide primer: FP: 5'-GCCCGCTCTGGATTATACG-3' RP: 5'-CTATCATCTCCTGGCCCCC-3' which gave a 436 bp product. The PCR conditions were standardized as initial denaturation at 94°C for 3 min, followed by 38 cycles of denaturation at 94°C for 45 sec, annealing at 57°C for 45 sec, extension at 72°C for 60 sec and a final extension of 72°C for 7 min. A negative control without template DNA was used in each run. The amplified products were then resolved in 2% agarose gel stained with ethidium bromide.

The products were then digested with restriction endonuclease, PstI (Invitrogen Life Technologies), as recommended by the manufacturer. The fragments obtained were analyzed in a 1.2% agarose gel stained with ethidium bromide and photographed under UV light. The bands obtained were confirmed in triplicate along with undigested sample and DNA marker.

#### Statistical analysis

The samples were coded at the time of preparation and scoring. They were decoded before statistical analysis

**Table 1. Demographic Characteristics of Control and Experimental Subjects**

Characteristics		Exposed	Controls
n = 164		96	68
Age	Years	36.41±11.51	34.86±10.82
	Range	21-60	21-60
Duration of work Exposure	Years	13.33±9.60	-
	Range	10-30	-
Smoking	Yes	48	34
	No	48	34
Tobacco chewing	Yes	50	36
	No	46	32
Alcohol Consumption	Yes	42	33
	No	54	35

for comparison. Mean and standard deviation (SD) were calculated for each biomarker. The significance of the differences between control and exposed end-point means were analyzed using Student's t-test. Mean values and standard deviations were computed for the scores and the statistical significance (P<0.05) of effects were determined.

## Results

The effect of occupational exposure to cement on the levels of genetic damage in building construction workers and control subjects was assessed by the comet assay and MN assay. Table 1. represents the distribution of subjects with respect to age, years of exposure, smoking habits, tobacco chewing and alcohol consumption. The age, alcohol consumption and smoking status distributions were similar among exposed workers and controls. Among the smokers and alcoholics, the years of smoking/ alcohol consumption and daily cigarette/alcohol consumption were similar in the two groups. The mean age of the exposed group was 36.4±11.5, ranging from 21 to 60 years, and that of controls were 34.9±10.82.

Table 2 represents mean MN and DNA damage in

**Table 2. Micronucleus Frequency and Mean Comet Tail Length ( $\mu\text{m}$ ) with Respect to Age, Smoking, Tobacco Chewing Habit, Alcohol Consumption and Years of Exposure in Controls and Building Construction Workers**

Study group		n=164	MN (Mean $\pm$ SD)	Comet tail length (Mean $\pm$ SD)
Controls n = 68	Age	$\leq 40$	4.56±1.49	9.90± 0.92
		$\geq 41$	3.85±0.99	8.09±1.18
	Smoking	Yes	5.96±1.37	10.40 $\pm$ 2.42
		No	3.24±1.01	9.21±1.32
	Tobacco chewing	Yes	4.84±1.20	10.12±2.71
		No	2.98±0.96	8.85±2.33
Alcohol Consumption	Yes	3.95±0.82	9.96±2.44	
	No	3.12±1.13	9.23±2.30	
Workers n = 96	Age (years)	$\leq 40$	8.84±1.45	16.85±2.08 <sup>a</sup>
		$\geq 41$	8.92±1.71	14.12±2.33 <sup>a</sup>
	Smoking	Yes	9.64 $\pm$ 1.67 <sup>a,b</sup>	15.97±2.61 <sup>a</sup>
		No	6.70±2.13 <sup>a</sup>	13.71±2.89 <sup>a,b</sup>
	Tobacco chewing	Yes	7.74±1.83 <sup>a</sup>	15.71±2.34 <sup>a,b</sup>
		No	6.78±1.36 <sup>a</sup>	12.94±1.77 <sup>a</sup>
	Alcohol Consumption	Yes	8.28±1.23 <sup>a,c</sup>	14.05±2.59 <sup>a,c</sup>
		No	6.82±1.22 <sup>a</sup>	12.90±2.98 <sup>a</sup>
	Work exposure (years)	$\leq 10$	8.56 $\pm$ 1.88 <sup>a</sup>	14.36 $\pm$ 1.10 <sup>a</sup>
		$\geq 10$	10.97 $\pm$ 2.83 <sup>a,d</sup>	16.73±2.45 <sup>a,d</sup>

<sup>a</sup>Significantly different from controls (P<0.05); <sup>b</sup>Significantly different from the exposed never smokers (P<0.05); <sup>c</sup>Significantly

peripheral blood leukocytes with age, smoking, tobacco chewing, alcohol and exposure period of experimental and control subjects. The results of MN frequency of construction workers increased significantly, as compared with controls ( $P < 0.05$ ). The difference in MN frequency between  $\leq 40$  years and  $\geq 40$  year subgroups of exposed was insignificant (8.84 versus 8.92). Similar result was seen in control group also (4.56 versus 3.85). Duration of exposure to cement had a significant effect on MN frequency in lymphocytes of workers who had been working in building construction for  $\geq 10$  years over those who worked for  $\leq 10$  years (10.97 versus 8.56;  $P < 0.05$ ).

The comet tail length significantly increased in exposed group ( $P < 0.05$ ) than control groups. Subjects who were  $\leq 40$  years of age group showed a statistically significant increase in mean DNA damage than those who were  $\geq 40$  years in exposed group (16.85 versus 14.12,  $P < 0.05$ ). Similar result was seen in control group also (9.90 versus 8.09,  $P < 0.05$ ). The comet tail length significantly increased in exposed group with  $\geq 10$  years exposure than  $\leq 10$  years of exposure (16.73 versus 14.36,  $P < 0.05$ ).

Alcoholics of experimental subjects showed significant ( $P < 0.05$ ) amount of MN and DNA damage than alcohol users of control subjects and non alcohol users in experimental subjects. An increased level of DNA damage was observed in the workers with smoking habits when compared to controls with smoking habit. A clear and statistically significant ( $P < 0.05$ ) increase in DNA damage was observed in experimental group when compared to control groups. As analyzed smoking, tobacco chewing and alcohol differences shows that exposed subjects carry more number of MN and DNA damage than control subjects.

XPD gene (exon 23) was amplified by polymerase chain reaction using specific primer. The XPD gene exon 23 has an amplification product at 436bp. The XPD gene polymorphism was analyzed by PCR-RFLP. Bands of 227, 146 and 63bp products were observed for the presence of normal XPD gene. Samples with an altered gene failed to give bands at these sites. Our results also indicate an association between the frequencies of MN, mean comet tail length and polymorphisms in DNA repair gene (XPD, exon 23), involved in NER.

## Discussion

The main objective of the study was to evaluate if the exposure to complex mixture of chemicals in construction, induced increase in the level of genetic damage. The study was carried out in parallel with exposed and control group both from the same area and with similar individual characteristics. To evaluate the genetic damage two of the most common biomonitoring methods (MN assay and Comet assay) were chosen.

Biomarkers also permit enhanced analysis of health risk in humans exposed to carcinogens and because determinations are performed directly in human organism, uncertainties inherent in epidemiologic studies are avoided. There is no study available on the biomonitoring of construction workers. The current investigation reports

genotoxicity in building construction workers from South India.

Peripheral lymphocytes have been typically used for detecting genotoxic effects in a great number of studies since they are considered to be adequate for detecting general exposure (Murray and Edwards, 1999).

The MN assay and Comet assay test has been increasingly accepted as a reliable biomarker of genotoxicity in occupationally exposed groups (IARC, 1990).

The present investigation recommended that construction workers under their particular conditions of exposure (tobacco and alcohol) reveal clear evidence of genotoxicity in lymphocytes when evaluated by MN test. Our study revealed a significant induction of MN and Comet tail length in construction workers when compared to controls with respect to their age, years of exposure, smoking, tobacco chewing and alcohol consumption. Similarly, an increased incidence of chromosomal aberrations was observed in the cement factory workers with smoking habit (Shehla et al., 2001).

These results are in agreement with our previous study which reported an increased chromosomal aberration among cement factory workers (Jude et al., 2002) and an increased MN induction in cement exposed tobacco chewers (Sudha et al., 2009). An enhanced sister chromatid exchange and chromosomal aberration in peripheral blood lymphocytes of asbestos factory workers were reported by Fathima et al (2001) and also cement particulate extracts in invitro showed an increased chromosomal aberration (Hadnagy et al., 1989).

The building construction workers with smoking habits and tobacco chewing habit also shows more DNA damage, which shows tobacco has synergistic effect on inducing DNA damage. Some previous findings reported similar results on bidi, and smokeless tobacco users. In addition, the present study correlates with smoking and cement exposure. Smoking-related DNA adducts have been detected by a variety of analytical methods in the respiratory tract, urinary bladder, cervix and other tissues. On terms of biological activity, cigarette smokers and its conductors have been shown to form adducts with DNA protein and to induce chromosome aberrations (Sasikala et al., 2003; Manikantan et al., 2010).

The genetic susceptibility of cancer may result from inherited polymorphisms in the genes involved in carcinogen metabolism and DNA damage repair (Park et al., 2002). The DNA repair system plays an important role in protecting against mutagenesis and carcinogenesis. The defect of DNA repair often results from gene mutations and such defects in DNA repair causes several hereditary cancers.

DNA repair systems play a critical role in protecting the genome from insults caused by carcinogenic agents (Hoeijmakers, 1993). So far, over a hundred proteins implicated in DNA repair have been found in human cells. These proteins are concerned with four major DNA repair pathways, including nucleotide excision repair (NER), base excision repair (BER), double-strand break repair (DSBR) and mismatch repair (MMR) (Yu et al., 1999; Wood et al., 2001).



Polymorphisms in NER genes have also been associated with individual susceptibility to develop cancer. The *XPD* gene is abundant with polymorphisms (Claerkson et al., 2005). The *XPD* gene encodes an ATP-dependent DNA helicase involved in NER and in basal transcription as part of the transcription factor TFIIH (Laine et al., 2007). The presence of the variant alleles *312Asn* and *751Gln* of *XPD* have been associated with relatively high risk of cancer (Dybdahl et al., 1999; Sturgis et al., 2000; Hemminki et al., 2001). A recent meta-analysis concludes that the variant genotypes *312Asn/Asn* and *751Gln/Gln* are associated with lung cancer risk (Hu et al., 2004). Although *XPD* polymorphisms cannot be considered as a crucial factor for cancer susceptibility, our results suggested that *XPD* is a highly suspected candidate gene without considering the role of environmental factors cautiously.

In conclusion, biomonitoring studies of workers exposed to construction industry are rather vague because each population has a different life style factors but same occupation in different areas under different climatic and environmental conditions and are exposed to indistinguishable mutagen. Therefore, there is a need to educate those who work in construction sites about the potential hazard of occupational exposure and the importance of using protective measures. Since DNA damage is an important step in events leading from carcinogen exposure to cancer disease, our study represents an important contribution to the correct evaluation of the potential health risk associated with exposure.

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