Environmental effects on copd

Chronic Obstructive Pulmonary Disease (COPD) is an obstructive airway disorder characterized by the slowly progressive and irreversible decrease in forced expiratory volume in one second (FEV_1), accompanied by emphysema and chronic bronchitis (Rabe et al. 2007; Cazzola et al. 2015); it develops with decreasing lung function as a function of age in the normal population (Ito and Barnes, 2009). Despite the heritability of 40-77%, a host of other influences can also exacerbate this condition (Young et al., 2009). Rather the development and progression of COPD involves multiple genes, gene-gene and gene-environment interactions (Å½idzik et al. 2008; de Jong et al. 2015). Smoking exposure is considered as the most important risk factor for the development of COPD (Chan-Yeung et al. 2007; Kurmi et al. 2015) with mild and moderate COPD cases having a three- fold risk of developing lung cancer within ten years, which increases to a ten-fold risk with severe COPD compared to the smokers with normal lung function (El-Zein et al. 2012). There also however exists COPD-associated increased mortality from lung cancer in non-ever smokers (Turner et al. 2007; Kiri et al. 2010; Aldrich et al. 2015).

Despite quarrying and mining activities as important occupational set-ups inducing COPD (Jhoncy et al. 2011; Iftikhar et al. 2009), yet work-place identification of this occupational disease has not come to attention on pursuing literature related to COPD. Also there is uncertainty in prognosis of COPD although a number of validated indices exist (Briggs et al. 2008). As these indices require in-puts from patients and the interpretation by the care-giver/physician, these may not be able to cater to disease-identification in the field. In the present study, the on-site disease-identification using the

recommended spirometry evaluation (Briggs et al. 2008; Shiota et al. 2015) to recognize COPD cases at stone-crushing units (dust exposure) was carried out. Such an identification at the workplace gains importance as 50-80% of COPD are missed-out on the basis of misdiagnosis/co-current diagnosis due to relying on reported symptoms which are not sufficiently sensitive and / or because of failure of persons to report to the health provider (Levy et al. 2009).

The effect of various environmental stressors from occupational exposures needs to be assessed for prediction of cancer outcome(s) (Fenech, 2002) as 90% of cancer is environmental in origin (Hemminki et al. 2006). COPD has also been identified as an independent risk factor for lung cancer with inflammation as the pathophysiologic factor for high risk of its progression (Sin et al. 2006; Hillas et al. 2015) and smoking- induced COPD associated with lung cancer has also been documented (Koshiol et al. 2009). While mechanisms governing the risk of developing neoplastic disease are not well known (Barreiro, 2008), of the various theories, oxidative stress may be playing a pivotal role in its manifestation. In COPD, oxidative stress has been observed as ensuing from decreased FEV_1 (Kluchová et al. 2007), substantial inflammatory response increasing cytokines as triggered by exogenous dust particles (Yang et al. 2011) and decreased antioxidants because of depletions of glutathione peroxidase, superoxide dismutase (SOD), catalase, ascorbic acid and vitamin E (Borm et al. 2004).

The impaired oxidant-antioxidant status can cause cellular damage; DNA damage can result from the action of reactive oxygen species (Jackson and Loeb, 2001) and is the underlying cause of mutations leading to cancer

(Bernstein, 2012). Chromosomal damage (increased micronuclei frequency) in peripheral blood lymphocytes has been extensively used for predicting risk of cancer (Fenech et al. 2011) and oxidative DNA damage is also implicated in carcinogenesis, ageing and age-related neurodegenerative diseases (Fortini et al. 2003, Nishigori et al. 2004). The major form of oxidative DNA damage is 8-hydroxy-2`-deoxyguanosine (8-OHdG) resulting from G→T and A→C base substitutions. It may lead to mutagenesis if unrepaired and is directly correlated with lung carcinogenesis (Gackowski et al. 2006). The lesion 8-OHdG is an established biomarker of oxidative stress/oxidative DNA damage and being potentially mutagenic, it is useful as an intermediate marker of a disease end-point like cancer (Cheng et al. 1992). Therefore in the present study, 8-OHdG level was assessed as a pre-lesion of neoplasia in peripheral blood leukocytes (PBL) of COPD- identified cases at stone-crushing units. Although the leukocytes are not the direct target of the exposure at this workplace, they may possibly be affected by the accumulated unmetabolized toxic compound(s) in the lung (Gackowski et al. 2003). This hence prompted the assessment of oxidative DNA damage in the peripheral blood leukocytes and also because of the non- accessibility of the target (lung) cells.

The biomarkers of exposure and effect, and clinical disease (cancer) may further be influenced by susceptibility genotypes and their gene products as pre-dispositional factors (Their et al. 2003). Also as DNA damage and DNA repair have a major role in carcinogenesis and from occupational settings, the susceptible metabolic genotypes (gene products) may inherently be associated in causing genetic damage. Therefore genotyping of the

occupational workforce was carried out for glutathione-S-transferase (*GST*) gene variants (both for disease susceptibility and genetic damage) since *GST* alleles have been documented to have an association with COPD (Young et al. 2011). Furthermore, a reduced expression of these alleles has also been observed in the air passage of COPD patients (Imboden et al. 2001; Lakhdar et al. 2011) and hence the expression of glutathione-s-transferases was also estimated. Association of the *Val/Ala* variants of manganese superoxide dismutase (*MnSOD*) with lung cancer (Wang et al. 2001) further justified the genotyping of this allele and assessing its expression. Variant forms of these susceptible genes are generally common in the population. Due to their specificities for substrates they interact with during environmental exposures, they can increase the risk for disease-causation (Lan et al. 2000). Incidentally, *GST* and SOD enzymes are also involved in the metabolic and oxidative stress pathways (Borm et al. 2004), and since stone-crushing is an inflammation-triggering occupation (Vallyathan et al. 1995), the assessment of the amounts of these enzymes was thought appropriate.

The purpose of the present study was two-fold. On one hand to identify COPD cases from workplace exposure (occupation-related disease) and hence assist in identifying ‘ missing’ COPD cases using recommended (spirometry) measurements (Briggs et al. 2008, Young et al. 2011) and COPD categorizations (GOLD, 2003). The other (main) purpose was to determine the propensity (Prognostic Index/score) for genetic damage and by extension an increased likelihood for carcinogenesis as ensuing from the combined effects/interactions of prognostic (risk) factors in COPD cases (the workers exposed to industrial-type prevalent conditions) at stone-crushing units. This

entailed the evaluation for the presence of oxidative stress (GSH and SOD) and oxidative DNA damage in workers at stone-crushing units genotyped for the *GST* and *MnSOD* genes.