REVIEW ARTICLE

Polymorphism of Cytochrome p450, Glutathione-S-Transferase and *N*-acetyltransferases: Influence on Lung Cancer Susceptibility

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Abstract

Lung cancer remains a major health challenge in the world. It is the commonest cause of cancer mortality in men, it has been suggested that genetic susceptibility may contribute to the major risk factor, with increasing prevalence of smoking. Lung cancer has reached epidemic proportions in India. Recently indoor air pollution and dietary factors have been implicated in the causation of lung Cancer development. Accumulating evidences have highlighted that several polymorphisms involve the metabolic activation or detoxification of carcinogens derived from cigarette smoke have been found to be associated with lung cancer risk. Many studies have focused on the relation between the distribution of polymorphic variants of different forms of the metabolic enzymes and lung cancer susceptibility, Few of human biotransformating enzymes (Phase I enzyme: Cytochrome p450 enzymes, and Phase II enzymes: Glutathione-s-transferases, N-acetyltransferases) have been implicated in the formation and scavenging of ultimate reactive metabolites. These enzyme families are known to catalyze detoxification of electrophilic compounds including carcinogens. The treatment and prevention of lung cancer are major unmet needs that can probably be improved by a better understanding of the molecular origins and evolution of the disease. This review will focus on major recent advances in the molecular study of the origins and biology of lung cancer.

Keywords: *Lung Cancer, Cytochrome p-450, Glutathione-s-transferase, N-acetyltransferases*

Date Accepted for Publication: 18th June 2010
NigerJMed 2010: 257 - 263

Introduction

Lung cancer is the most common malignancy worldwide and has the highest mortality rate among all cancers. In United State, approximately 1700,000 deaths per year were corresponding to one sixth of all cancer morality, every year 1.2 million new cases of lung cancer were found. It is typically diagnosed in the severe stage; the five year survival rate is less than 15 %. Worldwide the lung cancer has the highest incidence and mortality rates among all malignancies[1], and the risk increases with exposure over a lifetime[25] .The development of lung cancer is strongly associated with both active and passive cigarette smoking[2, 3] and other carcinogenic compounds (such as NNK, nicotine-derived nitrosamine ketone) found in tobacco smoke are also present in ambient air and diet[4,5], Smoking is known to be the primary cause[6]. Cigarette smoke contained several thousand chemicals, of which about 50 compounds are known carcinogens including polycyclic aromatic hydrocarbons, aromatic amines and N-nitroso compounds, Some of these compounds are reactive carcinogens, but most are procarcinogens, which need to be activated by Phase I enzymes such as those encoded by the cytochrome P450 supergene family and converted into reactive carcinogens. All these reactive carcinogens can bind to DNA and form DNA adducts capable of inducing mutations and initiating carcinogenesis. CYPs are a multigene super family of mixed function monooxygenases[7]. Although of much less influence than tobacco use, consumption of diets high in fruits and vegetables have been associated with a lower risk of lung cancer in many studies[8, 9], in nonsmokers , as well as in smokers[10]. Phase II enzymes such as glutathione S-transferase are responsible for detoxification of activated forms PAH epoxides. GSTs are constitutively found in a wide variety of tissues, with different characteristic patterns of GST isozymes. [11,].The major isoforms, which involve the metabolic activation of carcinogens derived from tobacco smoke or detoxification of those activated carcinogens [12,13].

In this review, we collect and discuss the evidence reported up to date on the relationship between lung cancer and genetic polymorphism of genes most frequently investigate in recent years: cytochrome p450, N-acetyltransferase (NAT), glutathione-s-transferases (GSTs).

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World wide status

There is great variation in the prevalence of lung cancer in different geographical areas. Almost 70% of all the new cases of lung cancer in the world occur in the developed countries. USA and Europe have the highest incidence (>50/ 10^5 population) followed by China, Ireland, Malta, Spain, Australia and New Zealand (non - Maori population) with a moderate incidence (35-50 /10^5 population) and low incidence (<35/ 10^5 population) countries include Utah (USA), Latin America, most Asian countries, Ice-land, Norway and Sweden. Lung cancer was initially considered to be sporadic in India[13, 14, 15] but it constitutes 14.4% of all cancers[16,17] . Lung cancer deaths may rise to three millions per year by the year 2010[18].

Risk Factor for Lung Cancer Development

Lung cancer remains a highly lethal disease. Mean cumulative five-year survival rates range from 13% to 21% in developed countries and from 7% to 10% in developing countries, with an estimated global mean of 11 %[19, 20]. There are various risk factors for lung cancer including asbestos, radon, occupational Smoking and genetic factors. However, the most significant factor is smoking which accounts for 80% of the attributed risk for men and 45% of the cases for women. The intensive research on the etiology of carcinogenesis in lung tissue have shown that around 60-70% of lung cancer cases might be associated with the exposure to environmental carcinogens, while 30-40% with dietary habits[21].

The causal relationship between smoking and lung cancer has been accepted since the 1950s, when case-control studies revealed a relative risk of 10. In cohort studies, it has been demonstrated that lung cancer mortality increases in proportion to the level of smoking, this factor being more significant than the tar and nicotine content of the tobacco[22]. Nicotine (Fig.1) is a natural ingredient in tobacco leaves where it acts as a botanical insecticide[23] When tobacco smoke reaches the small airways and alveoli of the lung, the nicotine is rapidly absorbed in the huge surface area of the alveoli and small airways and dissolution of nicotine in the fluid of the human lung, facilitates transfer across membranes[24], After absorption, nicotine enters the bloodstream .it is about 69% ionized and 31% unionized[25] , Than enzymes involved in the nicotine metabolism and factors affecting the inter-individual differences, such as the genetic polymorphisms[26]. Nicotine acts through nicotinic receptors. Nicotinic acetylcholine receptors (nAChRs) normal human bronchial epithelial cells (BEC) express and that form channels modulating Ca2+ metabolism and regulating cell adhesion and motility[27]. Afterward, it was shown the presence of saturable nicotinic binding sites and nAChRs in BEC[28].Investigators are working to identify factors these can predict individual susceptibility[29.] Single region of study is the family of enzymes responsible for carcinogen activation, degradation, and subsequent DNA repair [30]. These enzymes conceal gene deletions and polymorphisms which can affect enzyme activity. It has been hypothesized that an individual's enzyme profile is associated with lung cancer risk and the metabolic pathways they regulate have the potential to become targets for preventive agents. This profile could be used to recommend individuals and could be used to decide on high risk individuals for specific chemoprevention agents.

Table: I-Resposible Factor For The Development Of Lung Cancer

S.No.	Type	Factor	Role
1	Smoking	Cigarettes	Damage cells in lung
		Beedies	May become cancerous
		Cigars	Lung cancer
		Pipe	
2.	Environmental Tobacco Smoke	Passive Smoking	May be Lung cancer
3.	Minerals	Asbestos etc	Asbestos fibers in air
			Damaging cells
			May Lung cancer
4	Radioactive gases	Radon etc.	Occurs Naturally in Soil and Rocks
			Damage to the lungs
			May Lung cancer
5.	Lung Disease	Tuberculosis (TB),	May be lung cancer
6.	Personal Medical and Family History		A person have lung cancer once is more likely to develop a second lung cancer compared to a person who has never had lung cancer. Brothers, sisters and children of those who have had lung cancer have a slightly higher risk of lung cancer
7.	Other Mineral Exposures	People with silicosis and berylliosis	Increased risk of lung cancer

Tobacco Smoke as genetic susceptibility to Lung Cancer

Tobacco smoke contains more than 60 carcinogens and between these, more than 20 carcinogens are strongly associated with lung cancer development[31]. The most tarnished of these compounds include the polycyclic aromatic hydrocarbons and the tobacco-specific nitrosamine 4-(methylnitrsosamino) - 1-(3-pyridyl)-1-butanones, both of which lead to genetic mutations through DNA adduct formation[32]. There are two groups of enzymes that are involved in DNA adduct formation such as CYP P450 enzymes, encoded by CYP family genes and GSTs. The carcinogenes are metabolically activated by P450 enzymes and are either secreted or can bind to DNA and leading to DNA adduct formation.

By contrast, GSTs detoxify the intermediates of carcinogens thus protecting against adduct formation. In most of cases, these adducts compound are repaired but from time to time the damage is severe enough to cause apoptosis. Chronic exposure to these compounds often leads to mutations in critical genes such as *p53* or *RAS* which lead to the initiation or progression of the disease. 8-oxoguanine is a major oxidative lesion that causes G-to-T transversion, possibly leading to mutations in critical genes concerned during lung cancer pathogenesis. 8-oxoguanine is repaired by 8-oxoguanine DNA N-glycosylase 1 (*OGG1*) and thus polymorphisms in *OGG1* with its reduced enzymatic activity is possibly associated with increased risk for lung cancer. Although it is generally accepted that tobacco smoke causes lung cancer, not everyone who smokes develops lung cancer. Many studies have been examined the relationship between polymorphic variants of the genes involved in tobacco smoke metabolism and DNA repair pathways, including *P450* and *GST* family genes and *OGG1*and the risk for lung cancer, but the results of these studies have been inconclusive however, a case control study has shown that low activity of *OGG1* correlates with an increased risk of lung cancer and suggesting that person with low *OGG1* activity could be good candidates for smoking-cessation programs.

Benzo[a]pyrene, a carcinogen found in cigarette smoke is metabolically begun by the P450 family of hepatic enzymes (mainly *CYP1A1*)[33,34,35]. These intermediate metabolites are chemically active and they can bind to DNA and effect gene dysfunction. *GST*, epoxide hydrolase (EH) and *N*-acetytransferase (*NAT*) detoxify these products. Polymorphisms and/or gene deletions result in modified metabolic activity[36, 37,] . Various Studies have suggested that genetic alterations in each of these enzyme families can have the small affects on an individual's risk of developing lung cancer. Gene-diet interaction would be also requiring careful investigation, it suggested that low levels of vitamin E can increase the *GSTM1* associated risk[38]. Interactions with dietary enzyme factors such as folate and subsequent folate metabolism have also been documented[39].

Cytochromes P450

Human cytochromes P450 (*CYP*) is a monomeric heam containing enzymes. It is a large multigene family with the differing substrate specificity. It plays very important role for the activation of phase 1 reaction[40]. They are confined to smooth endoplasmic reticulum and mitochondrial membrane[41] with NADPH-P450 reductase provide as terminal oxidase in electron transport chain reaction. Presently there are at least 50 different genes encoding *CYPs* in human genome[42], 40% homology of the nucleotide sequences was reported for *CYPs* indicating the conservativeness of the enzyme regions masked in the lipid bilayer membrane (N-terminal) as well as those responsible for the binding of P450 reductase (C-terminal) and heam ring. Four families of cytochromes P450 involved in xenobiotic oxidative metabolism in lung tissue cells were identified: *CYP1*, *CYP2*, *CYP3* and *CYP4*. Most of the data concerning the role of *CYP* genes polymorphisms in relation to lung cancer susceptibility has been reported for cytochromes belonging to the *CYP1* and *CYP2* families[43].

CYP1 gene family

There are three genes - *CYP1A1*, *CYP1A2* and *CYP1B1* they all are belonging to the *CYP1* gene family and encoding cytochromes *P450 1A1, 1A2* and *1B1* respectively. *CYP1A1* and *CYP1B1* are included in this and called aryl hydrocarbon (AH) gene battery which undergoes expression in lung cells. It localized on chromosome 15q and its expression is regulated by cytoplasmic receptor for PAH (AHR; aryl hydrocarbon receptor). PAH once entered into cell binds to AHR and the activated AHR-PAH complex is then transported into nucleus. Where in the cooperation with specific nuclear translocator, it was binds to the regulatory sequence in the enhancer region of *CYP1A1* and other genes of the AH battery called xenobiotic responsive elements[44].

CYP1A1 and *CYP1A2* isoforms are characterized by high degree of homology in their nucleotide sequences but their cell and tissue distribution varies. *CYP1A1* and *CYP1A2* catalyzes in chemical reactions, substrates for which are polycyclic aromatic hydrocarbons (PAH) and dicyclic/heterocyclic aromatic amines respectively and thus resulting in the activation of these procarcinogens and formation of mutagenic and genotoxic metabolites[45]. For The activation of *CYP1* genes results in about 100-fold increase of the mRNA and enzyme concentration in the cell[46,47]. It was induced the expression of *CYP1A1* for the expression of *CYP* many concerning regulatory proteins that causes difficulties in the interpretation of the role of *CYP1A1* gene polymorphism in determination of the individual differentiation in PAH metabolism. Many of the single nucleotides polymorphisms have been identified in *CYP1A1* gene. It has localized on chromosome 15q22. An MspI polymorphic site (also referred to as m1) at the 3_ non-coding region of the gene, characterized by the T6235C transition, has been identified (*CYP1A1*2A* allele). Another *CYP1A1* polymorphism (m2), located in exon 7 was found to be associated with the A4889G

transition resulting in a synthesis of an enzyme with valine rather than isoleucine at position 462 (*Ile462Val; CYP1A1*2B allele*). Such amino acid exchange takes place in a region involved in heam binding and it may be associated with significant increase in enzyme activity and thus production of reactive genotoxic metabolites[48, 49]. Alleles *CYP1A1*2A* and *CYP1A1*2B* have been associated with the increased activity of respective enzyme isoforms. Some of studied shows *CYP1A1*2A CYP1A1*2B* allele have increased levels of PAH-DNA adducts and higher rate of *p53* mutations in person who were smoked[50, 51]. In Japanese population, *CYP1A1*2A* and *CYP1A1*2B* alleles was shown to cause a seven-fold increase in the susceptibility to squamous cell carcinoma (SqCC) of lung, especially in individuals less exposed to a tobacco smoke[52] also showed an increased rate of the mutant *CYP1A1* allele in patients suffering from lung cancer (21.2% in patients versus 10.6% in controls).Similar results were obtained in Indian population. The tobacco smoking dramatically increase the risk for SqCC development in carriers of at least one allele of *CYP1A1*2A* or *CYP1A1*2*[53].

N-acetyltransferases

N-acetyltransferases (NAT) are cytosolic enzymes present in liver and other tissues in majority of mammals. Only two isoforms of these enzymes were identified in human cells: *NAT1* and *NAT2*. Both enzymes are closely related although their substrate specificity is different. However, there is no substrate acetylated solely by one ore the other enzyme[54]. These enzymes were the non-intron gene group and both were mapped to chromosome 8p (*NAT1*: 8p23.1; *NAT2*: 8p22). A *NATP* encoding for none physiologically active protein has also been detected (at locus 8p22). *NAT1* undergoes expression in most of human tissues and *NAT2* expression takes place predominantly in liver, intestine and to a lower extent in lung[55], these xenobiotics containing aromatic amine (R-NH2) or hydrazine (R-NH-NH2) groups it was catalyzed and transformed into aromatic amides (R-NH-COCH3) and hydrazides (R-NH-NH COCH3). This reaction - the *N*-acetylation is the major biotransformation pathway of such compounds [56].

All-embracing research has revealed that these two acetylation phenotypes have different proportions within the human population depending on the geographical region about 70% of people living in Egypt, Saudi Arabia and Morocco were found to be slow acetylators, while in black Africans the proportion varies widely from 20 to 80%. In Caucasians and Asians the proportion is around 50 and 25%, respectively. The lowest frequency of slow acetylators was found in Eskimos (only 5%)[57, , 58].

NAT2- and *NAT1*- mediated *N*-acetylation of aromatic amine leads to either reduction or enhancement of their toxic potential. It might, on one side, result in production of less toxic respective amides, but on the other side, following the *CYP1A2*-mediated *N*-hydroxylation might result in production of highly genotoxic acetoxy esters and further into nitrenium and carbonium ions easily forming adducts with DNA[59,,60]. An assortment of mutations within the *NAT2* gene was identified. It was acetylase the product. It was divided into two groups one is fast acetylator and second is slow acetylator. *NAT2*4* at least one allele is of wild type which had performed fast acetylation and second have slow acetylation phenotype is underlined by a lower stability or activity of enzymatic product what is believed to be a consequence of three common mutations within *NAT2: G191A, C282T, T341C*. Contradictory data were obtained analyzing the relationship among the *NAT2* acetylator genotype and the risk of lung cancer. Increased risk of lung cancer in homozygotic carriers of *NAT2*4* allele (fast acetylators) was reported. Most of the studied documenting no effect of *NAT2* gene polymorphism on lung cancer risk in various groups, can also be found[61, 62]. Nevertheless, authors seem to confirm a modulatory effect of smoking status on *NAT2*-associated lung cancer risk. While in non-smokers, the slow acetylator phenotype determining genotypes seem to be associated with increased risk of lung cancer, among smokers; such genotypes are rather protective[63, 64].

Glutathione S-transferases:

The glutathione S-transferases (GSTs), forming a superfamily. In human cells, six classes of cytosolic isoforms - Alfa (GSTA), Mi (GSTM), Pi (GSTP), Theta (GSTQ), Zeta (GSTZ), Sigma (GSTS), Kappa (GSTK) and one microsomal isoform - GSTMic - can be found. The classification is based simplifies the differences in their primary structure. It catalyzes and detoxifies the wide range of electrophilic substrates, play a significant role in phase II biotransformation of xenobiotics. The detoxification is achieved by the conjugation of xenobiotics with glutathione, which eases the neutralization of their electrophilic centre by it has -SH group[11, 12].

GSTs-coding enzymes are expressed in all occurring cells of all tissues and organs, varies considerably. Even though it is regulated by cell-specific environmental, hormonal and genetic agents, and it is also effected by age, sex, past and present diseases and by various types of endogenous and exogenous chemicals and xenobiotics. Utmost *GST* expression

was shown in gonads, colon and liver, providing the maximum protection to germ line cells and cells constantly exposed to harmful effects of carcinogenic chemicals. Two allelic forms of *GSTM1*, differing in amino acid at position 172 but functionally identical, are distinguishable: *GSTM1*A* with lysine and *GSTM1*B* with asparagine at that position. A null genotype of *GSTM1* (*GSTM1*0*) associated with zero GSTM1 activity common in white Caucasian population of Europe (40-50%), is known to occur due to a complete deletion of the *GSTM1* DNA fragment in both copies[65]. Subjects with *GSTM1*0* genotype have been shown to be more susceptible to lung cancer in several studies[66, 67], our latest study results also showed that same data[68].

Conclusion and future Prospects

Taking care of lung cancer patients will remain a daily task for decades. It will be important to find out the different molecular diagnostic marker for the treatment of lung cancer as well as early predication. .

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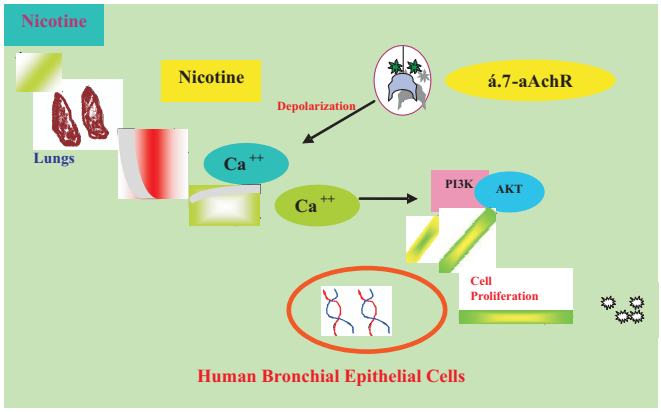
Fig. (1) Nicotine diffusion on human and lung and subsequent effects on Human Bronchial Epithelial Cells (BEC).



(Abstract)

Abbreviation:

Glutathione-s-transferases=GST
Cytochrome p450=CYP
N-acetyltransferase= NAT
Polycyclic aromatic hydrocarbons= PAHS
Nicotinic acetylcholine receptors= NACHRS
Human bronchial epithelial cells= BEC
Oxoguanine DNA N-glycosylase 1=OGG1
Epoxide hydrolase=EH
Squamous cell carcinoma= SQCC

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