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Review Article

Carcinogenic potential of arylamine N-acetyltransferase in Asian populations

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ABSTRACT

Arylamine N-acetyltransferase (NAT) is a phase II metabolizing enzyme, which belongs to the transferase family; specifically those acyltransferases which transfer various groups except aminoacyl. NATs are found in both prokaryotes and eukaryotes. They generally perform detoxification reactions; however they sometimes participate in the bioconversion of heterocyclic arylamines into electrophilic nitrenium ions, which are directly implicated in the process of tumor initiation. Several human metabolic enzymes are genetically polymorphic. Polymorphism in the *NAT1* and *NAT2* genes occurs through single nucleotide polymorphisms in a single exon coding region. The *NAT* enzymes add an acetyl group from the *O* to the *N* group of arylacetohydroxates, which causes the activation of arylamine carcinogens and the subsequent production of *N*-acetoxy-esters. Additional studies are required to determine the specific role of *N*- and *O*-acetylation in carcinogenesis, as at present there is limited literature available and no association has been reported between NAT genotype polymorphisms and cancer development within Asian populations.

1. Background

The arylamine N-acetyltransferase (NAT) enzyme is a phase II metabolizing enzyme with a functional role in conjugation reactions associated with drug metabolism. NATs generally perform detoxification reactions, however they can be carcinogenic by acting as a carrier for toxic compounds.[1] Several human metabolic enzymes are genetically polymorphic. These polymorphisms affect the activities of the enzymes, and have been previously studied worldwide to determine any associations with the development of various carcinomas.[2]

The systematic name of the NAT enzyme is “acetyl-CoA: arylamine N-acetyltransferase” and it belongs to the transferase family, specifically those acyltransferases which transfer groups other than aminoacyl. NATs are found in both prokaryotes and eukaryotes, where they transfer an acetyl group from acetyl coenzyme A to various arylamine and hydrazine xenobiotics. Humans encode two functional *NAT* genes (*NAT1* and *NAT2*) and one pseudogene.[3] The *NAT* enzymes add an acetyl group from the *O* to the *N* group of arylacetohydroxates, which results in the activation of arylamine carcinogens and the subsequent production of *N*-acetoxyesters. Polymorphisms in the *NAT1* and *NAT2* genes occur through single nucleotide polymorphisms (SNPs) in a single exon coding region. These polymorphic proteins are degraded following ubiquitation in proteasomes.[4] The genes for each of the isoenzymes are located at chromosome 8 (*NAT1*, 8p21.3–22; *NAT2*, near the centromere of chromosome 8 - usually 177 kb) with 87% nucleotide identity and 81% homology in translation.[5,6]

The association of N-acetylation activity with different types of cancer has been determined in different populations and ethnic groups. The N-acetylation activity of NAT is classified into slow, intermediate and rapid phenotypes based on the polymorphism of their genotype. The frequency of slow and fast NAT phenotypes varies markedly among different ethnic groups. An individual’s phenotype influences their sensitivity to different toxins and carcinogenic arylamines, and the incidence rate of particular mutations within the NAT loci largely depends on an individual’s ethnic and racial origin.[7] Individual variations may be due to the different frequencies of polymorphism in the slow acetylator phenotype, which are observed in different populations. Asian populations only have 10–30% slow acetylators, whereas the incidence of slow acetylator phenotypes ranges from 40 to 70% in

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Caucasians.[8,9] These ethnic differences are due to the frequency distribution of the NAT genotype, and its potential association with cancer emphasizes the need to study its relationship with major types of cancer in Asian populations.

2. Association of genetic polymorphism with cancer susceptibility

At present, 28 *NAT1* and 88 *NAT2* alleles have been identified, among them *NAT1*4* and *NAT2*4* are considered as wild type alleles.[10] Allelic variants of *NAT* determine whether an individual has a slow, intermediate or rapid phenotype.

The two NAT isoenzymes have different tissue specificity. The NAT1 enzyme is typically expressed in the majority of tissues with major activity in the extrahepatic tissues, whereas NAT2 activity is primarily confined to the liver and gastrointestinal tract.[11] NAT metabolic activity changes in individuals with an SNP in the NAT gene, as this causes allelic differences to their genotype and results in the expression of a different phenotype. The 'slow acetylator' is considered as expressed if the subject is homozygous for NAT polymorphisms. Individuals heterozygous for NAT polymorphisms are said to have the intermediate acetylator phenotype, and individuals who lack NAT2 polymorphisms have the rapid acetylator phenotype. The genotype polymorphism of some NAT alleles and their corresponding phenotypes are defined in Table 1.[9]

The N- or O-acetylation activity of NAT determines which phenotype is at the highest risk of developing certain types of cancer. For instance, the NAT2 slow acetylator phenotype is at higher risk when N-acetylation is a detoxification step, as in aromatic amine associated urinary bladder cancer. Whereas, the NAT2 rapid acetylator phenotype is at highest risk for cancers in which O-acetylation is an activation step, such as heterocyclic amine-related colon cancer.[12] Each of the enzymes has a preferred substrate; NAT1 has increased catalytic activity with 2-Aminofluorene, *p*-Aminobenzoic acid, *p*-Aminosalicylic acid, Sulfamethoxazole, and Sulfanilamide. Whereas, NAT2's preferred substrates include Aminoglutethimide, 2-Aminofluorene, Hydralazine and Procainamide. Whether activation or deactivation occurs depends on the nature of the substrate and its kinetic properties; however the tissue expression of NAT is also an important factor in determining cancer risk at specific sites.[13]

The acetylation genotype influences the acetylation of several carcinogens, thus demonstrating its association with several types of cancer. However, the racial and ethnic origin of individuals, as well as environmental factors are also involved in cancer predisposition.[14]

2.1. Urinary bladder cancer

Genetic predisposition, environmental factors, occupational exposure and cigarette smoking are the major risk factors for bladder cancer. Aromatic and heterocyclic amines are carcinogenic compounds, which increase an individual's risk of bladder cancer. These compounds are metabolized by several enzymes, including NAT. The genetic polymorphism of *NAT1* affects its detoxification activity against carcinogens.[15] NAT2 exhibits dual functionality as it can activate carcinogens and detoxify toxic compounds. Arylamines and other bladder carcinogens can undergo a detoxification reaction, either through N-acetylation by the liver NAT2 enzyme or through oxidation by the cytochrome P450 enzyme (CYP1A2T). The derivatives of these reactions are catalyzed by phase II metabolic enzymes, such as glutathione S-transferases and UDP-glucuronosyltransferases, and form stable metabolites which are eventually excreted from the body in the urine. Alternatively, the NAT2 enzyme activates the procarcinogens via an O-acetylation reaction. Initially, the metabolically active N-hydroxy compounds of procarcinogens are formed by hepatic CYP1A2T. Following their transportation into the lumen of the bladder, these compounds are O-acetylated by NAT2, which generates reactive oxygen species and causes DNA damage (Fig. 1).[16] Slow NAT2 acetylators are at an increased risk for developing cancer in which N-acetylation is involved in detoxification, such as urinary bladder cancer.[17]

A meta-analysis performed on one ethnic group within the Chinese population, revealed that the NAT2 slow acetylation phenotype was associated with an increased risk of bladder carcinoma in mainland China.[18] The results of a similar meta-analysis, which included different populations also reported a strong correlation between the NAT2 slow acetylation phenotype and an increased risk of bladder cancer in Asian and non-Asian populations.[19] The findings of other previous studies from Bangladesh, Japan and China are consistent with these results suggesting that there is a statistically significant positive correlation between the NAT2 slow acetylation phenotype and a higher risk of bladder carcinoma.[20–22] However, there have been conflicting; several recent studies (experimental and meta-analysis) reported no correlation between the *NAT1* or *NAT2* genotype and bladder cancer.[12,23,24]

2.2. Colorectal carcinoma (CRC)

The incidence rate of CRC is increasing among Asians and the highest prevalence rate is observed in the Chinese population. There has also been a reported increase in the prevalence of CRC in Japan, Taiwan, South Korea, Iran and Singapore over the past few decades.[25,26] Dietary heterocyclic amines, polycyclic aromatic hydrocarbons and the endogenous formation of N-nitroso compounds are all potential carcinogens of CRC.[27,28] Previous genotypic and phenotypic studies have cited several risk factors for CRCs, which include the genetic susceptibility of individuals, and certain environmental factors, such as the consumption of alcohol, fat and red meat. Red meat consumption is specifically associated with CRCs due to the release of fecopentanes, and heterocyclic amines.[29,30] NATs play a critical role in the metabolic activation of these carcinogens and present them for O-acetylation reactions to

Table 1
The NAT1 and NAT2 genotype corresponding to their phenotypes.

Normal phenotype		Slow phenotype		Unknown phenotype		Rapid phenotype	
NAT1 alleles	NAT2 alleles	NAT1 alleles	NAT2 alleles	NAT1 alleles	NAT2 alleles	NAT1 alleles	NAT2 alleles
NAT1*4	NAT2*4	NAT1*14	NAT2*5	NAT1*18	NAT2*10	NAT1*10	NAT2*12
NAT1*3		NAT1*15	NAT2*6	NAT1*20	NAT2*11	NAT1*21	NAT2*13
NAT1*5		NAT1*16	NAT2*7	NAT1*23	NAT2*18	NAT1*24	
NAT1*11		NAT1*17	NAT2*14	NAT1*26		NAT1*25	
		NAT1*19	NAT2*17	NAT1*27			
		NAT1*22	NAT2*19	NAT1*28			
				NAT1*29			

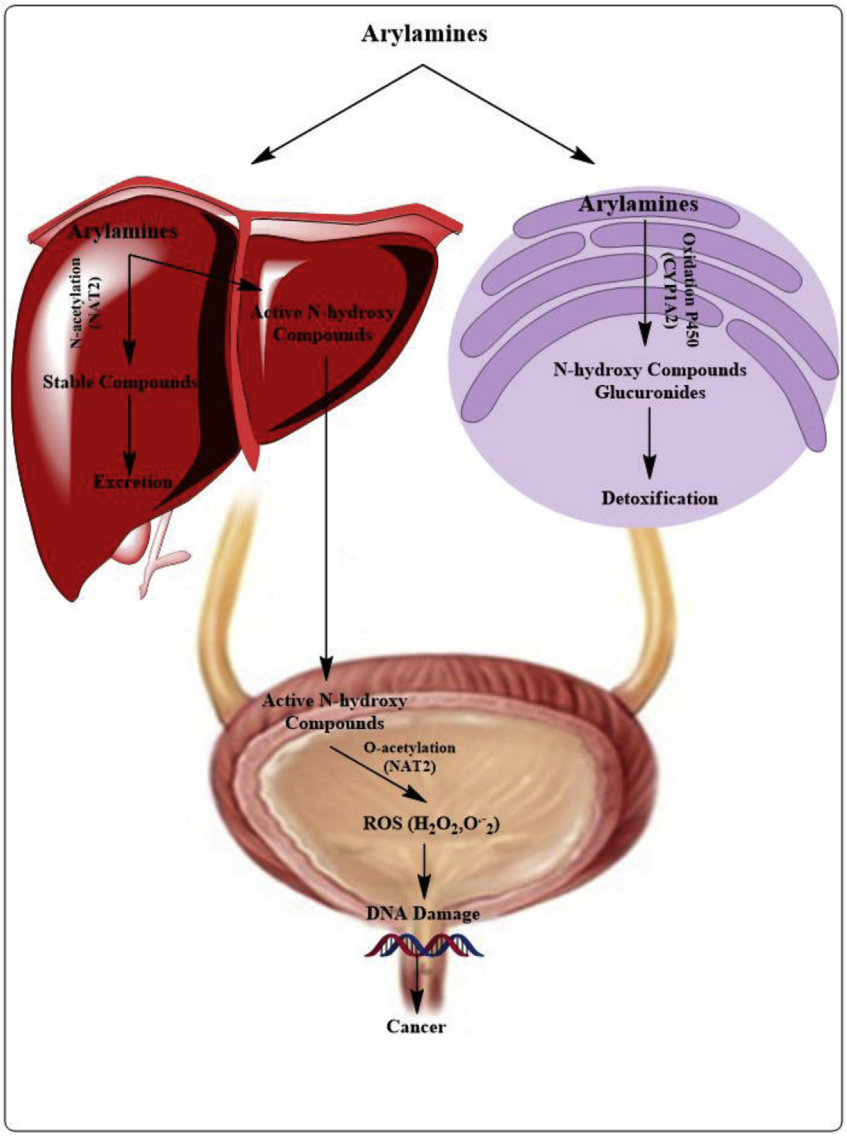

Fig. 1. The role of NAT2 enzyme in *N*- and *O*-acetylation. Arylamines from environmental sources can be *N*-acetylated by hepatic NAT2 function, or possibly oxidized by CYP1A2 in endoplasmic reticulum. The derivatives can form more stable metabolites and eventually excreted through urine. Alternatively, arylamines could be procarcinogens and form metabolically active *N*-hydroxy- compounds which are transported through circulation to the bladder lumen. These active *N*-hydroxy compounds can be *O*-acetylated by local NAT2 to generate ROS which cause the DNA damage and resulted mutations lead to cancerous process.

form N-acetoxyaryl amines. These derivatives may cause DNA damage by direct binding with the DNA. Individuals with a rapid NAT acetylator type have an increased risk of developing CR due to increased activation of these carcinogens.[31–33] In CRC and other cancers where O-acetylation is the activation step, individuals with the rapid NAT2 acetylator type are at highest risk of disease onset.[11] Asian populations are primarily composed of individuals with the rapid acetylor phenotype for the NAT2 enzyme.[8,34,35]

A large sample size meta-analysis performed on a Japanese population and African Americans (a population with a high risk of CRC) suggested an association between NAT2 phenotype and CRC. The risk of cancer was highest in Japanese individuals with the rapid NAT2 acetylator phenotype. A linear association was also found between the consumption of processed red meat and an increased risk of colorectal cancer.[36] Another study in Japan has reported no association between the NAT1*10 or NAT2 rapid acetylator genotypes with colorectal or gastric carcinoma. However, NAT1*10 was found to be associated with smoking induced gastric carcinoma.[37] A controlled study in Chinese individuals supported the findings that there is no significant correlation between the slow or rapid NAT acetylator phenotypes with the development of CRC. Among the ten genotypes of NAT2 identified within patients, one genotype (WT/M2) was observed more frequently and showed an association with CRC.[38] Conversely, the results of a controlled study conducted in Taiwan revealed an association between CRC and the rapid NAT2 phenotype, particularly in females. The results indicated a greater risk of disease onset in individuals with homozygous NAT2 acetylator genotype compared with individuals with the slow NAT2 genotype. Heterozygous genotypes showed no association with CRC.[39]

2.3. Prostate cancer

The well-known predisposing factors for prostate cancer are old age, family history, smoking and a western diet. In Asian Pacific Islanders the incidence rate of prostate cancer is 79.3 per 100,000

people.[40] According to 2008 data, 14% of all cases of worldwide prostate cancer were within the Asia-Pacific region and the majority of those cases were diagnosed in Japan, China and Australia.[35] Prostate cancer is extremely prevalent in Pakistan, where it is the third most common cancer in males. Incidence rates vary among different countries due to variations in genetic factors, diagnosis, treatment and lifestyle.[41] As epithelial cells of the prostate express NAT, they can activate heterocyclic amines, which have carcinogenic potential and are therefore associated with an increased risk of cancer.[42]

Hamasaki et al.[43] reported on the incidence of NAT2 polymorphism in Japanese men and its association with prostate cancer. They found a high frequency of the NAT2 acetylator type in patients with prostate cancer, and its expression was significantly increased in high-grade tumors. However, smoking was revealed to have a greater influence on the risk of prostate cancer.[33] A pilot study conducted in India by Srivastava and Mittal,[44] found a significant association between the *NAT2* rapid acetylator genotype and prostate cancer (C-aP) in tobacco users (OR = 3.43; 95% CI, 1.68–7.02; $P < 0.001$) compared with the controls.

2.4. Breast cancer

According to GLOBOCAN 2012 data, the highest prevalence rate of breast cancer in Eastern Asian countries occurs in Japan and South Korea, and among South-Eastern Asian countries it occurs in Singapore.[45] A study on a Lebanese population revealed no association between NAT2 polymorphisms and the risk of breast cancer. Two NAT slow acetylator genotypes were assessed; however no rapid NAT acetyaltor genotypes were tested against the risk of breast cancer. This was the first study conducted on a Lebanese population to investigate the correlation between dug metabolizing enzymes and the risk of breast cancer.[46] Many studies have linked NAT polymorphisms and the risk of breast cancer with smoking. In general, females with the slow acetylator type have an increased risk of developing cancer compared with females with the rapid acetylator type. A controlled study on Japanese women reported a correlation between the rapid acetylator genotype and breast cancer development, however no significant association was observed between the slow NAT acetylator genotype and disease onset. Smokers with the rapid acetylator phenotype had an increased risk of breast cancer compared with non-smokers. Smoking status did not show significant differences between the risk of breast cancer in females with slow acetylator genotypes. However, there was only a small amount of data on the slow acetylator genotype included in the study. This, together with other limitations of the study does not provide strong evidence of the increased risk of breast cancer associated with NAT phenotype.[47] Similarly, a study on Israeli-Arab women showed inconsistent results of the NAT2 phenotype being associated with an increased risk of breast cancer in passive smoking females. This study did not identify the NAT2 polymorphisms for the slow and rapid acetylator types.[48] Several other studies did not reveal any significant correlation between NATs and an increased risk of breast carcinoma.[47,49]

Overall a meta-analysis on data from several countries, including South Korea revealed no strong link between NATs and breast cancer.[49] However, Huang et al.[50] reported the onset of breast cancer caused by *NAT2* polymorphisms in Taiwan and China. The NAT2 slow acteylator phenotype was demonstrated to be associated with an increased risk of breast cancer in post-menopausal women, specifically women who were not on hormonal replacement therapy and who had lower body mass indexes. Interestingly, this association was not associated with women with rapid acetylator phenotypes and pre-menopausal women. The role of *NAT1* methylation in malignant, benign and normal breast tissues was also investigated in a study conducted in South Korea. In cancerous breast tissues the NAT1 gene was markedly hypomethylated compared with the normal breast tissues and less mRNA expression was observed. This indicates the role of DNA hypomethylation in the development of breast cancer tissue.[51]

2.5. Lung and other cancers

A previous study demonstrated that an increased susceptibility to lung cancer was associated with the NAT2 acetylator phenotype. The smoking status of Chinese women in Singapore was correlated with an increased risk of lung cancer as this is an environmental source of carcinogenic heterocyclic amines. The NAT2 slow acetylator phenotype was found to be associated with an increased risk of lung cancer in non-smokers, however not in smokers.[52] A previous study in a Japanese population was consistent with these findings. Non-smokers with the NAT2 slow acetylator phenotype and light smokers with intermediate NAT2 type were at greater risk of disease development.[53]

An association between NAT and disease development was also reported in other cancer types. Yu et al.[54] assessed the role of NAT in Hepatitis B associated hepatic cancer in smokers and non-smokers in Taiwan. The results of the study suggested that NAT2*4 plays a role in the development of hepatocellular carcinoma in patients with Hepatitis B. This association was positively associated with the patients smoking status. In non-smokers there was no correlation between NAT and hepatocellular carcinoma. However, *NAT1* alleles were found to have no association in both smokers and non-smokers. These results highlight the important role NAT2 plays in increasing the risk of hepatic cancer induced by tobacco smoke.

Malik et al.[55] revealed the impact of NAT2 polymorphisms on the development of esophageal and gastric cancers in the Kashmir valley, (India), which are the most prevalent types of carcinoma in that area. None of the three loci of *NAT2* studied were observed to influence the risk of esophageal or gastric cancer. However, the combination of haplotype in the NAT2 slow acetylator phenotype had some modulating effect in both types of cancer.

3. Conclusion

The association between NAT polymorphisms and acteylator type has been reported in a variety of different types of cancer. However, only limited studies are available in Asia and the findings of these studies are inconsistent and inconclusive. The variations in results may be due to individual differences in the metabolism of NAT activity against carcinogenic heterocyclic amines. Based on the published data, the current review does not support any association between NAT activity and the development of cancer within Asian populations. However, more studies should be conducted involving Asian populations to further our understanding of the relationship between NATs and cancer development, and to learn more regarding the differences in NAT activity between different ethnic groups.

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Conflicts of interest

The authors declare that they have no competing interests.

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