**N-Acetyltransferase Polymorphism and Human Cancer Risk**

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**Abstract**

Because of the important role of N-acetyltransferase (NAT) enzymes in both metabolic activation and detoxification of certain precarcinogens, such as homo- and heterocyclic arylamines, extensive research in the past has focused on the relationship between the distribution of different variants of these enzymes and cancer susceptibility. In this context, we examined the relationship between the acetylator type of two NAT isoforms (NAT1 and NAT2) and cancer risk. It was shown that any independent overall association of those diseases with acetylation for either NAT1 or NAT2 is likely to be weak at most. Besides individual genetic profile, differences in the degree of exposure to environmental precarcinogens should also be considered. It was suggested that smoking and red meat intake were associated with both NAT1 and NAT2 genotype in the carcinogenesis. A gene-gene interaction, even linkage between NAT1 and NAT2 may also exist.

**Key words:** N-acetyltransferase, cancer risk, smoking, red meat intake

**Introduction**

The increased risk of cancer was related to the increased carcinogen exposure in the environment and workplace. In environmental exposures, lifestyle factors such as smoking and diet become the main attributable exposures. Since the majority of carcinogenic chemicals do not influence their biological effect directly, they require metabolic activation before they can react with cellular macromolecules and form covalent adducts \(^1\), which is generally regarded as a critical, initiating event in the multistep process of chemical carcinogenesis. Thus, the enzymes that are responsible for such bioactivation/detoxification should play an important role in the interaction between individuals and xenobiotics \(^2\). The relationship of carcinogen-DNA adduct level, acetyltransferase expression and human cancer susceptibility have been reviewed by Badawi \(^3\). The allelic variations of NAT1 and NAT2 were reviewed by Grant et al. \(^4\). The purpose of this review is to briefly summarize the current state of knowledge concerning NATs and cancer risk.

**General aspects of N-acetyltransferases**

There are two types of enzyme reactions involved in the metabolism of xenobiotics. Phase-I enzymes are involved in converting many compounds to reactive electrophilic metabolites, while phase-II enzymes usually act as inactivating enzymes. N-acetyltransferases (NAT), which belong to Phase-II enzymes, have two similar genes designated NAT1 and NAT2 \(^5,7\). Each gene is intronless, located on the short arm of chromosome 8 (8p22) and has an open reading frame of 870 bp \(^5,7\). There are two kinetically distinct isozymes, NAT1 and NAT2. NAT2 is expressed primarily in the liver, with lower activities present in the pancreas and the colon; while NAT1 is found in various extrahepatic tissues, including colon, bladder, lung and breast \(^8,9\).

The main carcinogens from cigarette smoke and fried red meat are aromatic amines (AA) and heterocyclic aromatic amines (HAA) such as 4-aminobiphenyl and 2-amino-1--methyl-6-phenylimidazo [4,5-b] pyridine (PhIP) \(^10,11\).

Hepatic NAT2 can compete with cytochrome P4501A2 (CYP1A2) which bio-activates (N-oxidation) arylamines by its detoxification (N-acetylation) reaction \(^12,13\). The arylamine metabolites can also enter the circulation and then be reabsorbed by the local tissues, where they could be further catalyzed by the NAT enzymes (O-acetylation and N, O-acetylation, predominantly NAT1 activity) \(^14\). The resulting unstable acetoxyl esters and N-acetyl-acetoxy esters can spontaneously decompose to electrophilic DNA- or protein-binding nitrenium ions \(^15\) (Fig. 1).

To date, nine NAT1 variant alleles and 15 NAT2 variant alleles have been described \(^16-20\). According to the distribution of the NAT enzyme metabolite ratio, two kinds of phenotypes (fast acetylator and slow acetylator) were determined. In NAT1, the 'mutant-type' NAT1*10 allele \(^21\) is associated with the fast acetylator; while in NAT2, the 'wild-type' NAT2*4 allele \(^9\) is associated with the rapid acetylator (Table 1.)
NATs polymorphism, cancer and precancerous diseases

Colorectal adenomatous polyps and colorectal cancer

Although only a small proportion of adenomatous polyps develop into malignancy, adenomas are generally considered precursors of most large-bowel cancers \(^{35,36}\). Therefore, inference can be made from polyps to colorectal cancer. Lang et al. \(^{30}\) reported an elevated but not significant risk in the fast acetylator; however, the association between the risk of polyps and the NAT2 acetylation has not yet been demonstrated by genotypic method \(^{37,39}\) (Table 2).

By phenotypic assay, Lang et al. \(^{40}\) and Ilett et al. \(^{41}\) firstly reported that a significantly higher proportion of fast acetylators in patients with a history of colorectal cancer was found. This relationship was supported by Kadlubar et al. \(^{42}\). However, the same result could not be obtained in Spain \(^{42}\). Because disease status or chemotherapeutic agents may affect acetylation, almost all of the studies were performed by genotypic assay rather than by phenotypic assay, after NATs genotypic polymorphism was found \(^{43}\). However, most of these genotypic studies failed to detect a significant role for NAT2 genotype \(^{26,44-46}\). Only two groups in Australia and Portugal respectively found consistent results with the hypothetical mechanism of food-contained arylamine activation by an NAT2-mediated O-acetyltransferase in the liver and colon. Accordingly, the slow acetylator phenotype should decrease the generation of critical intracellular concentrations of such ultimate carcinogens and consequent tumourigenesis upon environmental exposure to precursors \(^{39,40}\).

Comparison of NAT activity in cytosolic preparations from the human colon suggests that the NAT1 but not the NAT2 gene product is the predominant enzyme activity \(^{47}\). This implies that a previous association between the NAT2 polymorphism and colon cancer may arise partly as a result of differences in activity encoded by the NAT1 gene.

Probst-Hensch et al. \(^{30}\) reported that, in incident polyps, though the NAT2 phenotype had no effect on polyps, subjects with the NAT1 fast acetylator (homozygous or heterozygous for the NAT1*10 allele) were at an increased risk for developing colorectal adenomas (OR 2.92, 95% CI 1.23-4.24).

Bell et al. \(^{50}\) first showed a cancer risk associated with the NAT1 gene (Table 3). However, in a later prospective study, an independent overall association of colorectal cancer with NAT1 could not be observed \(^{46}\).

Bladder cancer

Studies that associate NATs to bladder carcinogenesis were begun with the observation that subjects with a history of arylamine-related occupational exposure history had higher prevalence of bladder cancer \(^{50}\). However, when the exposure condition was excluded, most of the studies failed to show that NAT polymorphism had any relation with the bladder cancer by either phenotypic or genotypic assay \(^{50-53}\). Only two groups reported a direct significant association between the NAT phenotype and bladder cancer \(^{54,55}\), however, the sample size of one study \(^{50}\) was small (Table 2). A study in Japan reported that the slow acetylator genotype of NAT2 was a significant risk factor for urothelial cancer patients \(^{56}\), in which 78% of the cases were bladder cancers.

NAT1 is also expressed at high levels in the bladder mucosa, and involvement of the NAT1*10 allele in the bioactivation of aromatic amines in bladder mucosa has been shown. For

Table 1: Association between NATs phenotypes and main genotype locus

<table>
<thead>
<tr>
<th>NAT1</th>
<th>NAT2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fast acetylator alleles</td>
<td>Slow acetylator alleles</td>
</tr>
<tr>
<td>NAT1*10</td>
<td>NAT1<em>4 (WT</em>)</td>
</tr>
<tr>
<td>NAT1*3</td>
<td>NAT1*11</td>
</tr>
<tr>
<td>NAT2*5A (M1)</td>
<td>NAT2<em>6A</em>5 (M2)</td>
</tr>
<tr>
<td>NAT2*7A (M3)</td>
<td>NAT2*14A (M4)</td>
</tr>
</tbody>
</table>

\(^{a}\) From Vatis et al. \(^{41}\), Grant et al. \(^{42}\).

\(^{b}\) In NAT1, both homozygote and heterozygote of NAT1*10 are fast acetylator genotypes, while all others are slow acetylator genotypes; In NAT2, both homozygote and heterozygote of NAT2*4 are fast acetylator genotypes, while all others are slow acetylator genotypes.

\(^{c}\) WT, wild type; M, mutant.
### Table 2: A summary of results from studies that evaluated the association of NAT2 polymorphism and cancer risk

<table>
<thead>
<tr>
<th>Diseases</th>
<th>Risk acetylator</th>
<th>Place of study</th>
<th>Subjects</th>
<th>Case</th>
<th>Control</th>
<th>Results (OR, 95% CI)</th>
<th>Notes</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colorectal adenomatous polyps</td>
<td>Fast</td>
<td>USA</td>
<td>41</td>
<td>205</td>
<td>1.92 (0.97-3.78)</td>
<td></td>
<td></td>
<td>36</td>
</tr>
<tr>
<td></td>
<td>Fast</td>
<td>USA</td>
<td>447</td>
<td>487</td>
<td>1.08 (0.83-1.40)</td>
<td>Total subjects</td>
<td></td>
<td>37</td>
</tr>
<tr>
<td></td>
<td>Fast</td>
<td>USA</td>
<td>441</td>
<td>484</td>
<td>1.10 (0.84-1.44)</td>
<td>Incident subjects within 23 years</td>
<td></td>
<td>38</td>
</tr>
<tr>
<td></td>
<td>Fast</td>
<td>USA</td>
<td>441</td>
<td>282</td>
<td>0.84 (0.53-1.32)</td>
<td>Incident cases within 5 years</td>
<td></td>
<td>41</td>
</tr>
<tr>
<td></td>
<td>Fast</td>
<td>Australia</td>
<td>89</td>
<td>110</td>
<td>1.1 (0.6-2.1)</td>
<td></td>
<td></td>
<td>39</td>
</tr>
<tr>
<td></td>
<td>Fast</td>
<td>Japan</td>
<td>234</td>
<td>329</td>
<td>0.83 (0.48-1.44)</td>
<td></td>
<td></td>
<td>40</td>
</tr>
<tr>
<td></td>
<td>Fast</td>
<td>USA</td>
<td>34</td>
<td>205</td>
<td>0.86 (0.41-1.80)</td>
<td></td>
<td></td>
<td>36</td>
</tr>
<tr>
<td></td>
<td>Fast</td>
<td>UK</td>
<td>202</td>
<td>112</td>
<td>1.1 (0.71-1.80)</td>
<td></td>
<td></td>
<td>26</td>
</tr>
<tr>
<td></td>
<td>Fast</td>
<td>UK</td>
<td>96</td>
<td>103</td>
<td>0.82 (0.45-1.49)</td>
<td></td>
<td></td>
<td>45</td>
</tr>
<tr>
<td></td>
<td>Fast</td>
<td>Australia</td>
<td>110</td>
<td>110</td>
<td>1.8 (1.0-3.3)</td>
<td></td>
<td></td>
<td>39</td>
</tr>
<tr>
<td></td>
<td>Fast</td>
<td>UK</td>
<td>174</td>
<td>174</td>
<td>0.95 (0.61-1.49)</td>
<td></td>
<td></td>
<td>40</td>
</tr>
<tr>
<td></td>
<td>Fast</td>
<td>Portugal</td>
<td>114</td>
<td>210</td>
<td>2.04 (1.28-3.24)</td>
<td></td>
<td></td>
<td>49</td>
</tr>
<tr>
<td></td>
<td>Fast</td>
<td>USA</td>
<td>114</td>
<td>210</td>
<td>3.46 (1.73-6.93)</td>
<td></td>
<td></td>
<td>17</td>
</tr>
<tr>
<td></td>
<td>Fast</td>
<td>USA</td>
<td>212</td>
<td>221</td>
<td>0.80 (0.53-1.19)</td>
<td></td>
<td></td>
<td>43</td>
</tr>
<tr>
<td>Bladder cancer</td>
<td>Slow</td>
<td>Denmark</td>
<td>71</td>
<td>74</td>
<td>1.74 (0.90-3.38)</td>
<td></td>
<td></td>
<td>50</td>
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<tr>
<td></td>
<td>Slow</td>
<td>Sweden</td>
<td>115</td>
<td>118</td>
<td>1.13 (0.65-1.98)</td>
<td></td>
<td></td>
<td>78</td>
</tr>
<tr>
<td></td>
<td>Slow</td>
<td>UK</td>
<td>111</td>
<td>95</td>
<td>1.52 (0.86-2.68)</td>
<td></td>
<td></td>
<td>51</td>
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<tr>
<td></td>
<td>Slow</td>
<td>Poland</td>
<td>67</td>
<td>22</td>
<td>2.82 (1.06-4.7)</td>
<td></td>
<td></td>
<td>56</td>
</tr>
<tr>
<td></td>
<td>Slow</td>
<td>China</td>
<td>66</td>
<td>15</td>
<td>0.3 (0.1-1.3)</td>
<td></td>
<td></td>
<td>52</td>
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<tr>
<td></td>
<td>Slow</td>
<td>UK</td>
<td>74</td>
<td>59</td>
<td>0.5 (0.1-1.8)</td>
<td></td>
<td></td>
<td>52</td>
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<tr>
<td></td>
<td>Slow</td>
<td>Germany</td>
<td>374</td>
<td>373</td>
<td>1.32 (0.97-1.80)</td>
<td></td>
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<td></td>
<td>Slow</td>
<td>Denmark</td>
<td>254</td>
<td>242</td>
<td>1.22 (0.92-1.62)</td>
<td></td>
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<td>54</td>
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<tr>
<td></td>
<td>Slow</td>
<td>USA</td>
<td>230</td>
<td>203</td>
<td>0.96 (0.68-1.36)</td>
<td></td>
<td></td>
<td>55</td>
</tr>
<tr>
<td></td>
<td>Slow</td>
<td>Japan</td>
<td>102</td>
<td>100</td>
<td>3.04 (1.22-7.60)</td>
<td></td>
<td></td>
<td>58</td>
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<tr>
<td>Breast cancer</td>
<td>Slow</td>
<td>Spain</td>
<td>160</td>
<td>132</td>
<td>1.10 (0.69-1.75)</td>
<td></td>
<td></td>
<td>59</td>
</tr>
<tr>
<td></td>
<td>Slow</td>
<td>USA</td>
<td>304</td>
<td>327</td>
<td>1.11 (0.80-1.54)</td>
<td>Total subjects</td>
<td></td>
<td>60</td>
</tr>
<tr>
<td></td>
<td>Slow</td>
<td>Spain</td>
<td>119</td>
<td>114</td>
<td>0.9 (0.7-2.0)</td>
<td>Premenopausal</td>
<td></td>
<td>61</td>
</tr>
<tr>
<td></td>
<td>Slow</td>
<td>UK</td>
<td>185</td>
<td>213</td>
<td>1.3 (0.8-1.9)</td>
<td>Postmenopausal</td>
<td></td>
<td>61</td>
</tr>
<tr>
<td></td>
<td>Slow</td>
<td>USA</td>
<td>465</td>
<td>466</td>
<td>0.9 (0.7-1.2)</td>
<td></td>
<td></td>
<td>61</td>
</tr>
<tr>
<td></td>
<td>Slow</td>
<td>USA</td>
<td>488</td>
<td>472</td>
<td>0.88 (0.68-1.14)</td>
<td>Total subjects</td>
<td></td>
<td>62</td>
</tr>
<tr>
<td></td>
<td>Slow</td>
<td>USA</td>
<td>236</td>
<td>213</td>
<td>1.1 (0.7-1.6)</td>
<td>Premenopausal</td>
<td></td>
<td>62</td>
</tr>
<tr>
<td></td>
<td>Slow</td>
<td>USA</td>
<td>303</td>
<td>317</td>
<td>0.87 (0.64-1.19)</td>
<td>Total subjects</td>
<td></td>
<td>63</td>
</tr>
<tr>
<td></td>
<td>Slow</td>
<td>USA</td>
<td>118</td>
<td>114</td>
<td>0.99 (0.58-1.70)</td>
<td>Premenopausal</td>
<td></td>
<td>63</td>
</tr>
<tr>
<td></td>
<td>Slow</td>
<td>USA</td>
<td>185</td>
<td>203</td>
<td>0.78 (0.52-1.18)</td>
<td>Postmenopausal</td>
<td></td>
<td>63</td>
</tr>
<tr>
<td>Lung cancer</td>
<td>Fast</td>
<td>UK</td>
<td>53</td>
<td>31</td>
<td>0.91 (0.37-2.21)</td>
<td></td>
<td></td>
<td>65</td>
</tr>
<tr>
<td></td>
<td>Fast</td>
<td>UK</td>
<td>126</td>
<td>273</td>
<td>1.20 (0.78-1.84)</td>
<td>Total subjects</td>
<td></td>
<td>66</td>
</tr>
<tr>
<td></td>
<td>Fast</td>
<td>Spain</td>
<td>108</td>
<td>243</td>
<td>0.98 (0.63-1.52)</td>
<td></td>
<td></td>
<td>67</td>
</tr>
<tr>
<td></td>
<td>Fast</td>
<td>Germany</td>
<td>389</td>
<td>657</td>
<td>1.05 (0.81-1.36)</td>
<td></td>
<td></td>
<td>71</td>
</tr>
<tr>
<td></td>
<td>Fast</td>
<td>UK</td>
<td>155</td>
<td>310</td>
<td>1.10 (0.73-1.65)</td>
<td></td>
<td></td>
<td>71</td>
</tr>
<tr>
<td></td>
<td>Fast</td>
<td>Japan</td>
<td>155</td>
<td>310</td>
<td>2.36 (1.05-5.32)</td>
<td></td>
<td></td>
<td>68</td>
</tr>
<tr>
<td></td>
<td>Fast</td>
<td>Sweden</td>
<td>124</td>
<td>376</td>
<td>0.75 (0.41-1.37)</td>
<td></td>
<td></td>
<td>69</td>
</tr>
</tbody>
</table>

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*The risk acetylator V5 the other acetylator; OR, odds ratio; CI, confidential interval
b b, phenotypic assay; all others were genotypic assay.
c Modified from the original paper
example, DNA adduct levels of 4-aminobiphenyl were found to
be 2-fold higher in individuals with the NAT1*10 allele. Preliminary
epidemiologic data suggest that the NAT1*10 allele is a risk factor for smoking-related bladder cancer (Table 3).

Breast cancer

The relationship of the risk of breast cancer with the NAT

*10 allele has been studied in a series of studies. However, no
current results indicate a direct association between them, no
matter whether a premenopausal or a postmenopausal condition
was considered (Table 2).

The expression of the human NAT1 in mammalian and
bacterial cells showed that NAT1 activates a broader class of
aromatic amines to compounds that can adduct to DNA, often
more efficiently than does NAT2. However, association
could not be found between the NAT1 genotype and breast cancer
risk when the environmental exposure was not considered (Table 3).

Lung cancer

Though the NAT fast acetylator phenotype was considered
as a risk factor for lung cancer susceptibility, most studies failed
to demonstrate it. Only Cascorbi et al. reported that the
relatively small subgroup of genetically homozygous fast
acetylators (NAT2*4/*4), which provide significantly higher
acetylation rates than heterozygotes, were at significantly
increased risk for lung cancer (Table 2). Though

NAT1 expression was also detected in all bronchial and lung samples, data concerning its genotypic polymorphism
and lung cancer risk are not available.

One explanation for the lack of relationship between the
acetylator polymorphism and the risk of the above malignancies
would be due to a lack of adequate carcinogens instead of the
absence of the enzymatic machinery that converts these
carcinogens into their active end products.

NATs polymorphism, smoking and cancer risk

One of the main routes of environmental exposure is
smoking, since smokers are exposed to numerous potent
carcinogens, including polycyclic aromatic hydrocarbons (PAHs),
tobacco-specific nitrosamines and arylamines. A well-recognized
heterocyclic amine, 2-amino-1-methyl-6-phenylimidazo [4,5-b]
pyridine (PhIP), typically found in fried beef, was also detected
in the urine of smokers and in the cigarette smoke condensate.

The high concentration of PhIP in fried meats has been suggested
to explain the increased risk of certain cancers that will be
discussed later. The metabolism of PAHs was suggested to be
affected by the cytochrome P4501A1 (CYP1A1) and the
 glutathione S-transferase M1 (GSTM1) pathway. However, the
arylamines, such as 2-naphthylamine and 4-aminobiphenyl, could
be either activated (N-oxidation) by the cytochrome P4501A2
(CYP1A2) or competitively detoxified (N-acetylation) by the
NATs enzymes (predominantly NAT2 activity) in the liver. The
arylamine metabolites can then enter the circulation, and be
reabsorbed into the target tissues. Further activation steps
may occur because NAT1 was suggested to be the major
pathway for acetylation here because NAT1 has a higher relative
activity for most of these compounds than NAT2.

The NAT1*NAT2 interaction is supported by a possible
metabolic mechanism. If an individual has a NAT2 fast allele,
arylamines may be rapidly detoxified in the liver so that little
hydroxylated arylamine may ever reach the bladder epithelium,
where NAT1 could act upon it. Consequently, if a person has a
NAT2 fast allele, his NAT1 genotype may have little effect on the
risk of bladder cancer. Conversely, if an individual has a NAT2
slow allele, detoxification in the liver may be incomplete, so that
excess hydroxylated arylamine reaches the bladder epithelium,
making the NAT1 genotype an important determinant of bladder
cancer risk. There are limited experimental data supporting such
a pathway; Badawi et al. found significantly higher arylamine
adduct levels in bladder epithelium among individuals with the
NAT2 slow and NAT1 rapid genotypes compared to other
genotypes tested. Ockels et al. indicated that the slow NAT1
and fast NAT2 genotype may be a protective genotype compared
with other genotype combinations. The existence of interaction
involving NAT1, NAT2 and smoking was further demonstrated
by Taylor et al. (Table 4).

The NAT smoking interaction has been well studied. However,
its results are still controversial (Table 5). Probst-Hensch
et al. observed that NAT2 Fast acetylator current smokers had
2.25 times higher risk for polyps than those slow acetylator never
smokers. This result was consistent with other studies that
reported a 1.5-3 times relative risk between cigarette smoking and
colorectal adenomas. As to colorectal cancer, smoking
increased the risk of NAT2 slow acetylators in one study.
Whereas, in a later research, a relatively higher risk was observed in past smokers who had intermediate/fast acetylators [76]. The discrepancy between these studies may be partly due to the complexity of the whole metabolic system, which includes other polymorphic enzymes such as CYP1A1, CYP1A2 and GSTM1. Secondly, usually information on diet factors, such as red meat intake, which also have an important effect on carcinogenesis, was unavailable. Thirdly, the misclassification of outcomes in colon cancer research might exist in that the controls used in studies of cancer may have colonic polyps, whereas in studies of adenomas, they do not. This is a consequence of adenoma studies including people who had had a colonoscopy, whereas carcinoma studies do not have that requirement. This type of misclassification bias would result in attenuated association seen in studies of cancer [77].

Bladder cancer has been more consistently associated with cigarette smoking than colon cancer. It was shown that genetically susceptible (NAT2 slow acetylators) individuals may have a higher risk by smoking cigarettes [54, 55, 56]. Though Taylor et al. [56] found no association between the NAT2 genotype and the risk of bladder cancer whether the genotype was considered alone or in combination with smoking, an increased risk for individuals carrying the NAT1*10 allele among smokers was demonstrated.

Most epidemiologic studies have not yet found a clear association between smoking and breast cancer risk [80], and the association between the NAT1 genotype, smoking and breast cancer is also not clear. Ambrosone et al. [80] demonstrated that, among postmenopausal women, slow acetylator and smoking increase breast cancer risk in a dose-dependent manner. Another study [81], which observed that the elevated risks for current smokers who had slow acetylators compared with never smokers who had fast acetylators were slightly stronger but not statistically significant among postmenopausal women, weakly supported that conclusion. However, The observation of Millikan et al. [82] was different from the former two studies. It indicated that, among postmenopausal women, ORs for smoking within the past 3 years were greater for women with the NAT2 rapid genotype (OR, 7.4; 95% CI, 1.6-32.6) than the NAT2 slow (OR, 2.8; 95% CI, 0.4-8.0) and greater for the NAT1*10 genotype (OR, 9.0; 95% CI, 1.9-41.8) than the NAT1-non*10 (OR, 2.5; 95% CI, 0.9-7.2). This result was supported by the observation that the NAT1 enzyme exhibits higher activity than NAT2 in the breast [79]. Since the etiology of breast cancer is largely unknown, it is impossible to give a clear explanation now. Anyway, the available data suggests that cigarette smoking might be a risk factor for post-, but not premenopausal breast cancer. In light of these evidences, it may be assumed that pre-menopausal and post-menopausal breast cancer have different etiologies [83].

Though no interaction between the NAT2 genotype, smoking and lung cancer risk was observed by Martinez et al. [79], study of Cascorbi et al. [81] found that NAT2*4*4 was statistically overrepresented in patients who had smoked heavily (OR, 3.22; 95% CI, 1.27-7.92). Moreover, Nyberg et al. [80] suggested that the NAT2 slow acetylator genotype may confer an increased risk among never-smokers, and that the fast acetylator genotype interacts with pack-year dose to produce a steeper risk gradient among smokers.

### NATs phenotype, red meat intake and cancer risk

Another main route of environmental exposure comes from eating red meat. This is because during the cooking of meats, the meat juices pyrolyze and form heterocyclic aromatic amines (HAA) [84]. HAA concentrations in meat increase with longer cooking times and higher temperatures [85-87]. These compounds are carcinogenic in animal tests [44, 88]. In some studies weak positive associations between colon cancer and consumption of "well-done" [89], "browned" [90], "barbecued" [91], or "red meat" [92] have been demonstrated. The cancer risk to humans exposed by HAAs in the diet may depend upon the extent to which the compounds are activated in vivo. HAAs need to be metabolically activated in order to act as mutagens or carcinogens [93]. The initial activation step is thought to be N-oxidation by CYP1A2 [94].

<p>| <strong>Table 4</strong> The NAT1 and NAT2 gene-gene interaction in carcinogenesis |</p>
<table>
<thead>
<tr>
<th><strong>Diseases</strong></th>
<th>Interaction found?</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colorectal adenomatous polyps</td>
<td>No</td>
<td>38</td>
</tr>
<tr>
<td>Colorectal carcinoma</td>
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<td>26</td>
</tr>
<tr>
<td>Bladder cancer</td>
<td>Yes</td>
<td>48</td>
</tr>
<tr>
<td>Breast cancer</td>
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<td></td>
</tr>
<tr>
<td>Lung cancer</td>
<td>Unknown</td>
<td></td>
</tr>
</tbody>
</table>

<p>| <strong>Table 5</strong> Interaction of NATs polymorphism and cigarette smoking in carcinogenesis |</p>
<table>
<thead>
<tr>
<th><strong>Diseases</strong></th>
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<th><strong>Risk acetylator</strong></th>
<th>Interaction found?</th>
<th>References</th>
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<tr>
<td>Colorectal carcinoma</td>
<td>NAT2</td>
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<td>Yes</td>
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<td>Weak*</td>
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<tr>
<td>Lung cancer</td>
<td>NAT2</td>
<td>Slow</td>
<td>Yes</td>
<td>58</td>
</tr>
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</table>
| **Note:** Weak, only weak correlation was found.
which also varies considerably among individuals 40, and which itself could be induced by HAAs 40. The N-hydroxy arylamine can be further O-acetylated by NATs to form an arylamine-DNA adduct in either the liver or the appropriate target organ where it is transported. Both NAT1 and NAT2 catalyze the O-acetylation of the N-hydroxy arylamine. However, NAT2 rather than NAT1 catalyzes the O-acetylation of HAAs such as N-hydroxy-Glu-P-1, N-hydroxy-PhIP and N-hydroxy-MelIQx almost exclusively 40. Since NAT2 is expressed primarily in the liver and NAT1 is expressed in extrahepatic tissues, it is thought that some N-hydroxy HAAs are O-acetylated by NAT2 mainly in the liver. However, other HAAs, such as PhIP which produces low DNA-adduct levels in the liver 40, are mainly transported in the blood to the various extrahepatic target tissues, where they are further O-acetylated by both NAT1 and NAT2 71-73.

Moreover, concerning red meat intake, a NAT1 * NAT2 interaction might also exist (Table 4). Bell et al. 20 also observed evidence of interaction between the variant allele of NAT1 and NAT2, such that a significantly increased risk of colorectal cancer among subjects with the NAT1*10 allele was even higher among NAT2 fast acetylators. In a later prospective study, it was found that the association of red meat intake with colorectal cancer was stronger among fast acetylators at NAT1 and NAT2 loci both separately and combined 41. However, this interaction was not observed by Probst-Hensch et al. 39 for colorectal adenomas. One reason for these inconsistencies is that data on cooking method preference were not or were imperfectly collected. Another reason is that the functional activity of the various NAT1 alleles has not been completely defined and the degree of acetylation activity of the NAT1*10 allele is still controversial.

The elevated risk of NAT2 rapid and red meat intake in carcinogenesis has also been demonstrated in colorectal adenomatous polyps and colorectal cancer 16, 39, 40, 41 (Table 6). Though in a study of breast cancer the same interaction could neither be found in premenopausal nor postmenopausal subjects, some likely measurement error in evaluation of sources of HAAs and the lack of data on CYP1A2 in that study might account for it 40.

In summary, NATs polymorphism only has a secondary effect on the carcinogenesis of cancers. Its relevance to carcinogenesis could be modified either by the dosage and variety of environmental exposure, or by other polymorphic enzymes. A gene-gene interaction, even linkage between NAT1 and NAT2 may also exist.

References

14) Felton JS, Knize MG, Shen NH, et al. The isolation and

Table 6 Interaction of NATs polymorphism and red meat intake in carcinogenesis

<table>
<thead>
<tr>
<th>Diseases</th>
<th>NAT type</th>
<th>Risk acetylator</th>
<th>Interaction found?</th>
<th>References</th>
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<td>Colorectal adenomatous polyps</td>
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<td>Unknown</td>
<td>63)</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>NAT2</td>
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<td></td>
</tr>
<tr>
<td>Lung cancer</td>
<td>Unknown</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>
identification of a new mutagen from fried ground beef: 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine (PhIP).


29) Matas N, Thygensen P, Stacey M, Risch A, Sim E. Mapping \( AAC1 \), \( AAC2 \) and \( AACP \), the genes for arylamine \( N \)-acetyltransferases, carcinogen metabolising enzymes on human chromosome 8p22, a region frequently deleted in tumours. Cyogenet Cell Genet 1997; 77:290-5.


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7:1079-84.