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N-acetyltransferase 2: Slow, intermediate or fast? A booming question of the molecular epidemiology in cancer research

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ABSTRACT

Throughout history, humanity has referred to reactions occurring with food, plants and, recently, medicines or drugs. The increase in pulmonary tuberculosis cases and the availability of treatment showed that genetic human differences can interfere in the capacity to metabolize drugs. There are remarkable genetic polymorphisms of N-acetyltransferase 2 (*NAT*2) activity that have been associated with different levels of susceptibility to developing many kinds of cancers. This review considers the field as an open window for the application of molecular epidemiology tools that led to the development of pharmacogenomics. We cover historical data and the most recent knowledge about *NAT*2 genetic polymorphisms and its distribution in different populations, which is an important concept being incorporated in epidemiological studies of cancer risk. We present up to date information about these studies, including meta-analysis based on the *NAT*2 distribution in different types of cancer. A critical broad at advances in *NAT*2 research, highlighting recent studies related to *NAT*2 alleles in cancer susceptibility. Although there are multifactorial aspects involved in cancer risk, the variability in *NAT*2 allelic frequency can be related to carcinogenesis through alterations in the metabolic rate after exposure to carcinogens.

Keywords: Cancer; Ethnicity; Genetic Variants; N-Acetyltransferase 2

1. INTRODUCTION

N-acetyltransferase 2 (*NAT*2) is a crucial enzyme in clinical pharmacology. This enzyme and its gene play an important role in the metabolism of many drugs and xenobiotics (chemicals present in cigarette smoke, certain diets and in the environment) [1]. Historically, *NAT*2 has been associated with a different response to tuberculosis therapy [2,3]. The acetylators phenotypes profiles related to *NAT*2 were described about 60 years ago, and it was one of the earliest hereditary traits identified that altered the drug metabolism [4]. In fact, it has been observed that exposure to a particular drug or substance does not result in the same degree of risk for all individuals. Differences between individuals, for example, in the processing of changes and damage to DNA are fundamental.

One of the most important sources of variation is precisely the xenobiotic metabolism system, found mainly in the liver but also present in almost all tissues. The "phase I" metabolizing enzymes are mainly cytochrome P450 (CYP), whose main function is to convert to reactive electrophilic metabolites by oxidation. The ironic point is that many chemicals become carcinogenic only when they are converted to a reactive form by CYPs. The next stage of detoxification is often the conjugation of reactive compounds and endogenous molecules by "phase 2" metabolizing enzymes, which may or may not convert them into inactive compounds before elimination. Aromatic and heterocyclic amines require metabolic activation to form electrophilic intermediates that may initiate carcinogenesis. In this case, *NAT*2 (*NAT*2, EC 2.3.1.5) is an important "starting point" as it is a crucial enzyme in the biotransformation of carcinogens. In fact, *NAT*2 enzymes are related to the metabolism of heterocyclic aromatic amines and they are particularly active in the liver, gastrointestinal tract and bladder, among other organs and tissues [1,5,6]. In the metabolic scheme for these drugs and carcinogens, *NAT*2 catalyzes not only

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N-acetylation, but following N-hydroxylation also catalyzes subsequent O-acetylation and N,O-acetylation.

In fact, several studies have been published analyzing different genes that encode proteins involved in activation (Phase I) and/or detoxification (phase II) of chemical carcinogens such as those present in tobacco, and their influence in the development of lung and aerodigestive cancer [7]. Besides, it has been verified that the genetic profile of an individual metabolic allele has a role in determining the rate in which carcinogens are eliminated and therefore the extent and time of carcinogen exposure [6,8]. Individuals who have inherited alleles that result in greater carcinogen effect should have a higher risk of developing cancer when compared to those who have inherited the alleles associated with lower risk [1,9].

In view of the number of published reports on *NAT*2, xenobiotic metabolism and cancer, we have conducted this review to summarize the scientific advances of recent years using different sources such as the Medical Literature Analysis and Retrieval System Online (MEDLINE), Elsevier (ScienceDirect), EBSCOhost® (EBSCO) and Scientific Electronic Library Online (SciELO). We also evaluated the approaches using ethnicity, and genetic polymorphisms in this booming field of pharmacogenetics. Publication time was not the main consideration.

2. *NAT*2 NOMENCLATURE AND GENERAL MOLECULAR ASPECTS

NAT genes are found in prokaryotes and eukaryotes. In humans they are codified into two *loci*, as two polymorphic and functional genes: *NAT*1 and *NAT*2*,* and a third *loci*, comprising a pseudogene—*NATP* [10], located at chromosome 8p23.1 - p21.3 (*NAT*1) and 8p22 (*NAT*2). In other species three other loci may be found producing a functional enzyme, or only one 1 locus. The two isoenzymes *NAT*1 and *NAT*2, of 290 amino acids, present differences as tissue distribution, as well as to their substrates specificity profile and regulation. Both consist of a single open reading frame of 870 base pairs and present 81% of similarity in the amino acid sequence, while proteins differ in only 55 amino acids [11].

The location of the *NAT* gene was initially made by Blum *et al.* in 1990 [12], whereas the description was published in 1989 by Grant *et al.* [13], after the determination of the gene's location, finally the tissue distribution of the enzymes was performed in a few works. In 2000, Windmil *et al.* showed the presence of RNAm for the enzyme in the liver and in others extra hepatic tissues, especially bladder and intestinal tissues [14]. Its presence also in the lungs suggested that inhaled pollutants could be metabolized by these enzymes. Subsequently its presence was demonstrated in breast tissues without enzymatic activity, indicating that this could be the result of the low enzyme expression in these tissues [15].

NAT activity variability is recognizably an important factor for the determination of the individual susceptibility to toxic effects of drugs and carcinogens. After sequencing and cloning of various *NAT*2 genes, it was suggested that phenotypic differences were due to Single Nucleotype Polymorphisms (SNP) [10], that are inherited combined as alleles or haplotypes, and are unequally distributed between ethnic groups [16,17]. The deduction of low, intermediate or fast acetylator is based on the co-expression of alleles or haplotypes determined as fast or slow. However, this determination is not so simple, with several phenotypes with different degrees of acetylation velocity, suggesting that the various SNPs and haplotypes must result in different effects.

Indeed, several mutations in the coding region, with different results, have been described in the *NAT* genes. These are detailed at (http://Louisville.edu/medschool/pharmacology/consensus-human-arylamine-n-acetyltransferase-gene-nomenclature) [18]. In the human population more than 15 SNPs have been identified in the coding region of *NAT*1 and more than 25 SNPs in *NAT*2, with different effects [17]. To *NAT*2, the most common SNPs are: 191G > A, 282C > T, 341C > T, 481C > T, 590G > A, 803A > G, 857G > A. However, to understand the true role of these polymorphisms more functional studies are necessary. Besides, many findings are not consistent or reproducible [17].

Due to *NAT*'s functional role and its high genetic variability, many studies are being carried out to evaluate the association between alleles and some pathologies. However, due to the nomenclature difficulty, sometimes the interpretation and comparison of results was a complicated task [6]. In this way, it was difficult to accommodate the nomenclatures to other non-human species. In order to standardize and join the nomenclature, as well as to make the results comparable, in 1995 a consensus for *NAT* nomenclature was proposed and published, according to International Rules for Gene Nomenclature [19]. All proposed classification system is described in Vatsis *et al* [19]. Briefly, the root symbol was defined as: *NAT*, in uppercase Latin letters*,* and not *AT* or *ACT*, to represent acetyltransferase. The loci encoding proteins with similar functions were distinguished by Arabic numerals, and the asterisk placed after the symbols (all in italic): *NAT*1* and *NAT*2**.* The alleles were represented by Arabic numerals and capitalized letters, immediately after the asterisk. *NAT*1*4 and *NAT*2*4 were defined as wild type to *NAT*1 e *NAT*2, respectively. The nomenclature to genotype and phenotype also were described and organized.

Even with the determination of consensus, new alleles continued to be identified, with confusion regarding the

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nomenclature, especially for human alleles. Thus, new updates were necessary and in 1998, in an event carried out in Kuranda, Queensland, Australia, (http://www.pharm.uwa.edu.au/workshop/prog.html) the first Arylamine N-acetyltransferase Gene Nomenclature Committee was proposed [20]. Other workshops were also carried out every 3 years, after this first one, for the interchange between researchers of the field [21]. Subsequent events happened in Eynsham Hall, close to Oxford, UK, in 2001; Vancouver, Canada, in 2004 and Alexandropoulos, Greece, in 2007 [22,23]. The fifth workshop was recently carried out in Paris, France, in September 2010. Also in 2000, when the Arylamine N-acetyltransferase Gene Nomenclature Committee was created, a website (http://louisville.edu/medschool/pharmacology/consensus-human-arylamine-n-acetyltransferase-gene-nomenclature), was created where new identified alleles (independently of species) would still be classified according to the homology of the nucleotides' sequence, as per original rules and adequately included (this website is referenced by the website of Human Gene Nomenclature Committee for classification of *NAT*) [24].

During the workshop carried out in 2007, in Alexandropoulos, it was proposed that in 2008 a new website (http://www.mbg.duth.gr/non-humanNATnomenclature), linked to the first one, would be available to deal with the sequences in prokaryotes and eukaryotes—with the exception of humans and several selected non-human mammals. This proposal was due to the large amount of information generated in the *NAT* field. It was also proposed that the alleles of all species, with the exception of rats and mice would still be written with capital letters. For these two last cases the first letter is capitalized and the following letters are in lower case (Nat). Furthermore, the nomenclature became species-specific, with the inclusion of information about the functional effects in human alleles [25].

3. *NAT2* ALLELES AND POPULATION DISTRIBUTION

Complex diseases are the result of the interaction of genetic and environmental factors, and may be influenced by population ethnic diversity. Many recent studies have demonstrated the influence of the ethnic component in the genetic variation of *NAT2* gene polymorphism [26]. The characterization of the alleles is important to determine if these variants differ between evaluated groups and if they confer a protection or susceptibility effect to diseases in the ethnical group under consideration.

NAT2 gene is one of the most well-known genetic polymorphisms in humans and displays a large genetic variability among different ethnic groups. From the variation of alleles/haplotypes presented by *NAT2* gene it is possible to establish slow, intermediate and fast phenotypes, and genotypes that may be related to many diseases. Considering the ethnic variation in the distribution of mutant alleles in world populations (literature data, **Table 1**) [26,56] two major groups are clearly distinct, with higher incidence of the alleles *NAT2**5 and *NAT2**7. The frequencies of these two variants are very similar in Caucasians, Indians and Africans (>0.100 and <0.150). Populations of the Pacific and East Asia and native American populations from Panama also present higher homogeneity in the frequency of alleles *NAT2**5 and *NAT2**7, ranging from <0.099 to >0.04, respectively. Allele *NAT2**6 presents higher frequency in Caucasians and are defined as slow acetylators; in contrast, some Asians-Japanese, Koreans and Chinese—present intermediate frequencies of *NAT2**6 (**Table 1**). Allele *NAT2**14 appears to be characteristic of Sub-Sahara Africans and Afro-Americans (**Table 1**).

Table 1. *NAT2* allele frequencies in worldwide populations.

Etnic group/Country		*NAT2*4*	*NAT2*5*	*NAT2*6*	*NAT2*7*	*NAT2*12*	*NAT2*13*	*NAT2*14*	*Others*	Ref.
Caucasianos										
Hispanic US	65	0.390	0.320	0.190	0.100					[29]
Saami	20	0.350	0.350	0.150	0.150					[30]
Hispanics	245	0.314	0.363	0.222	0.076	0.014	0.010			[28]
Poland	316	0.260	0.437	0.288	0.015					[31]
Danish	242	0.254	0.473	0.250	0.023					[32]
French	20	0.250	0.300	0.450						[30]
Americans	372	0.250	0.450	0.280	0.020					[33]
North Carolina	523	0.240	0.470	0.270	0.020					[34]
Danish	1216	0.230	0.472	0.275	0.023					[35]
German	844	0.227	0.465	0.278	0.013		0.015	0.001		[36]
Non-Hispanics	490	0.224	0.441	0.308	0.024	0.010	0.001			[28]
Americans	266	0.220	0.470	0.280	0.003					[29]
Hispanic	504	0.216	0.442	0.256	0.012	0.037	0.019	0.015		[37]

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Continued

Etnic group/Country	n	*NAT2*4*	*NAT2*5*	*NAT2*6*	*NAT2*7*	*NAT2*12*	*NAT2*13*	*NAT2*14*	*Others*	Ref.
Portuguese	128	0.212	0.433	0.328	0.027					[38]
United Kingdom	63	0.210	0.470	0.310	0.020					[39]
Scottish	96	0.203	0.490	0.271	0.036					[40]
Swedish	70	0.194	0.507	0.278	0.021					[40]
European	62	0.194	0.435	0.339	0.032					[41]
Sardinians	12	0.167	0.583	0.250						[30]
Ashkenazi	20	0.100	0.400	0.500						[30]
Total n/range	**5574**	**0.100 - 0.390**	**0.300 - 0.583**	**0.150 - 0.500**	**0.003 - 0.150**	**0.010 - 0.037**	**0.001 - 0.019**	**0.001 - 0.015**		
Koreans										
Koreans	85	0.692	0.018	0.180	0.110					[29]
Japanese	2000	0.657	0.016	0.201	0.115	0.008	0.001		0.004	[42]
Polynesians	79	0.641	0.019	0.230	0.110					[29]
Chinese	25	0.600	0.040	0.340	0.020					[29]
Chinese	154	0.571	0.036	0.247	0.146					[43]
Taiwanese	441	0.523	0.060	0.305	0.112					[44]
Japanese	100	0.515	0.025	0.310	0.150					[29]
Hong Kong	96	0.510	0.010	0.281	0.114	0.073	0.011			[45]
Pacific Rim	70	0.473	0.057	0.310	0.160					[29]
Filipino	48	0.417	0.083	0.313	0.188					[41]
Taiwanese	100	0.395	0.065	0.360	0.180					[29]
Gujarati	235	0.381	0.038	0.326	0.205		0.051			[46]
Thai	20	0.300	0.300	0.350	0.050					[30]
Koreans	28	0.286	0.143	0.429	0.107		0.036			[30]
Total n/range	**3481**	**0.286 - 0.692**	**0.010 - 0.300**	**0180 - 0.429**	**0.020 - 0.205**	**0.008 - 0.073**	**0.001 - 0.051**		**0.004**	
Indians and Arabs										
Tunisian	125	0.516	0.436	0.020	0.028					[47]
Iranians	88	0.430	0.320	0.190	0.060					[48]
Central Asian	138	0.380	0.210	0.300	0.110	0.002				[49]
Iranians	229	0.299	0.314	0.380	0.007					[50]
Indians	61	0.257	0.330	0.380	0.033					[29]
Indians and Arabs										
Turkish	303	0.231	0.417	0.305	0.045	0.002				[51]
Egyptians	199	0.215	0.497	0.260	0.028					[52]
Emiratis	106	0.180	0.540	0.210	0.040					[53]
Total n/range	**1249**	**0.180 - 0.516**	**0.210 - 0.540**	**0.020 - 0.380**	**0.007 - 0.110**	**0.002**				
Africans										
Afro-Americans	214	0.430	0.295	0.230	0.045					[29]
North Carolina	307	0.380	0.270	0.260	0.030			0.050		[34]
Afro-Americans	128	0.360	0.300	0.220	0.020			0.090		[33]
Ancestry African	48	0.146	0.271	0.250		0.229	0.104			[41]
Bantu	20	0.150	0.550	0.100		0.100	0.050	0.050		[30]
Bakola	20	0.100	0.100	0.150		0.500	0.150			[30]
Sub-Sahara Afric.	117	0.094	0.359	0.274	0.022	0.119	0.064	0.068		[54]
Madenka	97	0.093	0.360	0.170	0.067	0.155	0.052	0.103		[55]
Total n/range	**951**	**0.093 - 0.430**	**0.100 - 0.550**	**0.100 - 0.274**	**0.020 - 0.067**	**0.100 - 0.500**	**0.050 - 0.150**	**0.050 - 0.103**		
Ngawbe										
Embera	105	0.724	0.024		0.233		0.019			[56]
Native Americans	136	0.610	0.099	0.037	0.228		0.026			[56]
Siberia	384	0.378	0.253	0.047	0.230	0.01	0.078		0.003	[57]
Ngawbe	72	0.319	0.209	0.236	0.153		0.042		0.042	[57]
Total n/range	**697**	**0.319 - 0.724**	**0.024 - 0.253**	**0.037 - 0.236**	**0.153 - 0.233**	**0.01**	**0.019 - 0.078**		**0.003 - 0.042**	
Brazilians	404	0.200	0.380	0.267	0.040	0.040	0.030	0.040	0.040	[58]

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Emphasis must be given to the high frequencies of alleles *NAT*2*7 and *NAT*2*12 among Native Americans and Sub-Sahara Africans, respectively; the first allele is defined as substrate-dependent slow acetylator and the second as fast acetylator (http://louisville.edu/medschool/pharmacology/consensus-human-arylamine-n-acetyl transferase-gene-nomencla-ture) [18]. Populations of the East Asia present higher proportion of allele *NAT*2*4 – among Koreans the frequency reaches almost 70% [27]— whereas populations of the African sub-Sahara present the lowest frequencies of allele *NAT*2*12, which is also defined as fast acetylator. According to Sabbagh *et al.* (2008) derived haplotypes related to fast acetylator phenotype (cluster *NAT*2*12), are found mainly in Africa and are particularly frequent in Baka and among Bakola pygmies that display a proportion of fast acetylators similar to East Asians (83% and 90%, respectively) [53].

Besides of being useful in association studies in case-control samples with complex diseases, these polymorphisms may be used for population studies which are still not common. The Brazilian population, resulting from five centuries of miscegenation among Amerindians, Africans and Europeans (mainly Portuguese), presents a particular picture of the world distribution as regards the variation of alleles frequencies (*NAT*2*5, *NAT*2*7, *NAT**12 and *NAT*2*14) of gene *NAT*2 [56,57]. This indicates that this polymorphism may also be used to characterize the intra- and inter-ethnic genetic diversity [58] and ancestry of recent populations. Indeed, as they are not selectively neutral (coding regions) they may be useful in evolution models to test the natural selection probably driven by lifestyle and dietary habits of the population [28,47,53].

Currently there are some limiting factors that restrict the use of this polymorphism. The first one concerns the obtaining method. In the future, the PCR/RFLP technique must be complemented with the sequencing, which will lead to a substantial increase of the number of variants in world populations. The second is the functional analysis which should be implemented to define the acetylation pattern of new variants.

4. *NAT*2 POLYMORPHISMS AND CANCER SUSCEPTIBILITY

The evaluation of genetic polymorphisms of xenobiotic metabolizing enzymes is an important tool in the cancer susceptibility study. In this context, some alleles or genotypes have been related with a higher or lower predisposition to the development of this morbidity. As previously stated, due to the biological role of *NAT*2, capacity of reacting with environmental carcinogens such as polycyclic aromatic hydrocarbons (PAHs), aromatic amines (AAs), heterocyclic amines (HAs) and nitrosamines (NAs), many studies have investigated the relation between different genetic polymorphisms in *NAT*2 and cancer. The genetic variation in the expression of this enzyme in different individuals has also been classified into several phenotypes, *i.e.*, slow, intermediate or fast acetylation, which may be relevant in the determination of susceptibility to diseases.

Important studies have been done in the determination in the formation level of DNA adducts, that may be used as a genotoxicity biomarker. The study conducted by Turesky *et al.*, (2009), for example, shows the influence of *Nat*2 genetic polymorphisms in the appearance of adduct 3',5'-diphosphate-*N*-(2'-deoxyguanosin-8-yl)-AαC (3',5'-pdGp-C8-AαC) formed in Chinese hamster ovary cells, after exposure to 2-amino-9*H*-pyrido[2,3-*b*]indole (AαC) [59]. This compound, formed in well-done meat and tobacco smoke, was the first genotoxic heterocyclic aromatic amine identified, showing the importance of the xenobiotic-gene interaction. In addition to the molecular/ genetic studies relating *NAT*2 and its antimutagenic role, it is worth noting the wide distribution of this enzyme in various human tissues, especially those in greater contact with xenobiotics [14].

Considering the aspects above, and in view of the practicality of collecting information on the association between the influence of genetic polymorphisms of metabolizing enzymes, as already done in reviews recently published [60], we will address here some types of cancer and possible associations with different phenotypes for *NAT*2. We will consider the following types: bladder, colorectal, head and neck, gastric, lung, breast and prostate cancer, since these are the most prevalent around the world and are also the most studied as to their relation with *NAT*2.

4.1. *NAT*2 Slow Phenotypes in Cancer Susceptibility

Several case-control works published in the last years showed that phenotype *NAT*2 slow acetylator, alone or in combination with other polymorphic genes such as *CYP*, *NAT*1, *GST* and p53, among others, is more prevalent in individuals with different types of cancer, such as bladder [45,61-70], colorectal [71], head and neck [7,29, 72-78], gastric [79], lung [80-86], breast [87-92], and prostate cancer [93-95].

Overall, as expected by the biological activity of *NAT*2, most association studies find a positive correlation between slow acetylators and a higher genetic predisposition to the development of cancers. However, lifestyle seems to be extremely important for risk evaluation. Besides, the studies have used several methodologies and evaluated number and populations with dif-

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ferent backgrounds, making it difficult to compare data. In 2000, Hein *et al.*, showed that the phonotypical analysis of different *NAT*2 genotypes is complex. Authors also discuss which N-acetyltransferase activity reduction mechanisms are associated with the substitution of nucleotides present in several *NAT*2 alleles and that the ability to distinguish acetylation phenotypes is complex and depends on sensitivity and specificity of the phenotyping method [6]. Frazier *et al.* (2001) also suggest that there might be differences on slow acetylation phenotypes produced by different *NAT*2 genotypes, depending on the substrate [71]. Thus, further studies—especially functional ones—are needed to clarify these issues.

Besides of the positive association of *NAT*2 slow acetylators with different types of cancer, showed in various works, other works also verified the association between *NAT*2 slow acetylators with occupational and environmental exposure to carcinogens. Undoubtedly lung cancer (LC) is related to the direct contact with carcinogens present in cigarette smoke or environmental pollutants dispersed in the air, such as oral, head and neck cancer. *NAT*2 slow acetylator increased risk to lung cancer among Caucasian Swedes, Japanese and Indians [82,84,85]. mainly related to smoking habit in bladder cancer risk [61,62,66,68,69,96-105], or colorectal cancer related to smoking or higher meat intake [106,107-110], gastric cancer with high consumption of cigarettes [111], similarly, active smoking there is a slight increase of breast cancer risk among slow acetylators [26,87,89,90, 92,112-115], and to prostate cancer [93-95].

Moreover, the evaluation of the consumption of certain beverages such as coffee and alcohol, and eating food such as red meat, fruits and cruciferous, in association with *NAT*2 polymorphisms has been related to risk of development of BC. On the other hand, the regular intake of alcohol proved to be an additional risk factor for *NAT*2 slow acetylator individuals, as observed by Lu *et al.*, 2005 (OR = 18.04; 95%CI = 2.28 - 142.8) [116].

Some recent studies also show that the intake of products such as dark-green, yellow-orange and cruciferous vegetables, besides of citrus fruits/juices and tomato products function as protection factors against the development of BC [117-121], even for *NAT*2 slow acetylator individuals. During a study in Belgium, Kellen *et al.* (2006) observed that even smoking individuals that consumed a high amount of fruits presented lower risk in relation to smoking individuals that consumed a low amount of fruit (OR = 2.15; 95%CI = 1.15 - 4.05; and OR = 4.23; 95%CI = 1.91 - 9.4; respectively) [122]. Consistent with this hypothesis, slow/intermediate acetylators have a decreased capacity to detoxify dietary carcinogen to reactive metabolites that initiate DNA adducts and tumors, compared to rapid acetylators [111].

Based on the studies presented above we may conclude, in a general but not unanimous way, that *NAT*2 slow acetylator individuals appear to present higher susceptibility to the development a different types of cancer, and that the exposure to carcinogenic substances increase this risk. On the other hand, the maintenance of healthy habits such as not smoking and consuming adequate amounts of fruits and cruciferous, can mitigate this effect.

4.2. *NAT*2 Fast Phenotypes in Cancer Susceptibility

The data are controversial as regards about *NAT*2 fast phenotypes and the development different kinds of cancer. Some authors observed relation between phenotypes and/or genotypes *NAT*2 of fast acetylation and a higher risk of CRC development [123-127]. We may highlight the meta-analysis conducted by Ye & Parry (2002) that included 4,431 cases and 4,547 controls and observed that, for *NAT*2 fast phenotype individuals, there was a risk of 1.51 (95%CI = 1.07 - 2.12) for CRC, while no relation was observed for *NAT*2 fast genotype individuals [128].

Some studies also suggest an increased CRC risk related to smoking and/or intake of red meat, associated to a higher frequency of *NAT*2 alleles of fast acetylation [106,107,125,126,129-136]. When the risk association measure included smoking exposure and intake of alcohol, fast or intermediate *NAT*2 acetylator individuals (separately analyzed or in combination with other polymorphic genes), are more prevailing among patients with head and neck cancer [137-141]. On the other hand, only one study observed the association with fast acetylator and LC [142] and other one found a risk association between PC with fast acetylators individous [141].

However, fast acetylators show higher risk LC among Caucasian Americans and Taiwanese [142,143]. It is worth highlighting the studies by Chang-Claude *et al.* (2002) and Conlon *et al.* (2010), who observed increase associations as regards acetylator *NAT*2 and breast cancer. While Chang-Claude observed an association between passive smoking and fast acetylators [113], an association was observed between fast acetylators and heavy smokers ($p = 0.005$), thus showing the difficult in establishing a definitive association between *NAT*2 polymorphisms and breast cancer [92].

4.3. *NAT*2 Phenotypes Not Show Association in Cancer Susceptibility

However, studies with individuals of different ethnicities showed association of *NAT*2 slow, intermediate or fast acetylate, some studies also suggest an no significant difference between case and control in different types of cancer. Is an example, bladder cancer along [69], or in

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association with occupational and environmental exposure to carcinogens, mainly related to smoking habit [64,144,145-147]. In the same way CRC along [80,106, 148-158], related to smoking and/or intake of red meat [123,125,129,130,149,158-161] or cigarette smoking and prostate cancer [162].

The case of head and neck cancer, some studies also suggest an no significant difference in *NAT*2 slow, intermediate or fast acetylate [7,29,72-78,163]. By analyzing a sample of American Caucasians, Chen, *et al.* (2001) also showed that the risk of developing oral cancer is important, regardless of being fast, intermediate or slow acetylator individual, if the amount of cigarettes (>20 pack/years) or alcohol (>15 drinks/week) intake is high [164]. Moreover, we may find some studies in which no association was observed with *NAT*2 alleles and LC [7,81,83,165-167], and breast cancer, even when associated to smoking or red meat intake [92,113,168-176], or prostate cancer [177-180].

As well as, it is worth highlighting that recently a meta-analysis performed by Zhong *et al.* (2010) was published; in this study 2391 GC cases and 3237 health controls were included and no association was observed between different *NAT*2 acetylators [181] like others works [79,182,183].

5. CONCLUSIONS

The initial hypotheses on the reasons for cancer have postulated endogenous and/or exogenous pathways. While the first was intrinsically related to genetic influence, the other would depend on the environment, habits and behavior in a social and cultural context. However, new evidence has shown that the intersection between these two sources is much broader than the sum of their separate universes.

With relation to genetic influence, new approaches based on phases I and II enzyme genes involved in xenobiotics and endobiotics metabolism, such as *NAT*, is completely relevant. In fact, *NAT*2 has been associated with cancer and this could be explained by its roles in the bioactivation and detoxification of heterocyclic aromatic amine carcinogens [7,184,185]. However, several studies have been unable to establish consistent evidence [8,93,129,137,167,178]. Besides that, the majority of the studies had used genotyping results to determine the phenotype (phenotypes slow, intermediate and fast are based on the determination of SNPs).

To observe the real relevance of *NAT*2 in cancer development, more structural and functional studies with different alleles are needed. In this field, recombinant expression systems have been used to characterize *NAT*2 variants. Human recombinant *NAT*2*5, *NAT*2*6, *NAT*2* 7, and *NAT*2*14 clusters yield variable reductions in catalytic activity associated with slow acetylation phenotype, while human recombinant *NAT*2*12, and *NAT*2*13 clusters catalyze N-, O- and N,O-acetyltransferase activities at levels comparable to the rapid acetylator *NAT*2*4 [186,187], indicating that these experiments must be useful tools to correlate genetic and functional aspects.

In addition, the molecular homology modeling techniques, including SNP locations and computational docking of substrates, have increased the understanding of the *NAT*2 protein structure-function relationship [22,188,189] The released crystal structure of human *NAT*2 made it possible to evaluate its structure-function without the particular limitation of the molecular homology modeling. Thus, increased pharmacogenomic understanding may enable huge advances. It will be possible, for example, to add genetic information related to susceptibility to disorders, such as different kinds of cancer, to the individualized drug treatment protocol. Finally, public health authorities need to understand the complexities of personalized medicine and be ready to apply this knowledge. In this context, the epidemiological, laboratory-based experiments and genetic haplotype map may represent complementary strands that link preventive and curative modern medicine.

Perhaps the small sample size of these studies published in the last years, as well as the small number of analyzed alleles, may be a main reason for this differences and divergence of the results. More studies are necessary, with higher ethnic diversity, so that the true role of *NAT*2 as regards susceptibility to cancer could be clarified. They also show that the development of cancers is multifactorial, depending of the genetic susceptibility, but also and principals of eating habits, smoking and alcohol intake or pollutions exposure.

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