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Glutathione S-Transferase, N-Acetyltransferase, Cytochrome P450 Polymorphisms in Patients with Basal Cell Carcinoma

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Abstract

Background: GST, NAT and CYP polymorphisms have been shown to influence the level of oxidative DNA damage. Also, there is a consensus that ROS play part in the epidermal carcinogenesis.

Aim: Our purpose was to investigate the GST, NAT and CYP polymorphism in patients with skin cancer.

Material and Methods: Ninety seven subjects, 34 women and 63 men, with basal cell carcinoma, and 117 healthy control subjects, 52 women and 65 men, were enrolled in the study. The polymorphisms of GSTT1, GSTM1, GSTP, NAT2*5A, NAT2*6A, NAT2*7A/B, NAT2*14A, CYPC9*2, CYP2C9*3 CYPC19*2, CYP2C19*3 were performed by real time PCR.

Results: Patients (51.5%) had a higher prevalence of the GSTM1 null genotype than the control group (33.3%) and we found a 2.12 fold increased risk of skin cancer in individuals with the GSTM1 null genotype when compared to the control group. In the patient group, the frequency of the NAT2*6A heterozygous genotype was higher in comparison with that of the control group and this increase was statistically significant (p=0,004 OR=3,70; 95% CI: 1,53-8,95). Patients with the NAT2*7A/B heterozygous genotype had a higher risk of skin cancer compared with individuals with the NAT2*7A/B wild genotype (p=0,001 OR = 0,17; 95% CI = 0,06-0,048). CYP2C9*3 heterezygous genotype was higher in patient group (p=0.015 OR=2.02; 95% CI: 1.14-3.57). Compared with the CYP2C19*2 wild genotype, CYP2C19*2 heterezygous genotype was associated with more than 2.8 fold increased risk of skin cancer (p= 0.001, 95% CI: 1.50-5.26). These varying enzyme activities are supposed to influence the individual metabolism of carcinogenic aromatic amines, thereby modifying the susceptibility to certain cancers.

Conclusion: In our study, the results from the patient group suggest that there may be a relation between GST, NAT and CYP gene polymorphisms and basal cell carcinoma.

Introduction

A large supergene family located at least on seven chromosomes encode the Glutathione - S - transferase (GST) enzymes. Approximately 16 genes encode the enzymes in the tissue cytosoles and products of the six genes of this supergene family are expressed in membranes [1]. GST enzymes catalyse the conju-

gation of glutathione (GSH) to a variety of endogenous and exogenous electrophilic substrates including reactive oxygen species (ROS) and polycyclic aromatic hydrocarbons and play an important part in their detoxification process [2]. Many GST genes show well-defined polymorphisms and GST mu (GSTM), theta (GSTT) and pi (GSTP) class genes have been on the focus for a while [3]. Human arylamine N- acetyltransferases (NAT) are known to exist as two isoenzymes, NAT1 and NAT2, with different though overlapping substrate specificity. NAT are the enzymes present in the cells of most mammalian species. Two different genes code these enzymes: NAT1 and NAT2. Gene NAT1 is expressed in the cells of the majority of tissues and organs, whereas gene NAT2 only in the liver and intestine. Acetylation polymorphism is an important step in the biotransformation of many drugs and other arylamine xenobiotics. One of the well-described and genetically determined polymorphic drug metabolism is the NAT2 acetylation polymorphism [4]. Acetylation polymorphism and resultant division into the fast and free acetylator is caused by the occurrence of wild allele NAT2 and its mutant forms. A given person shows the fast acetylation phenotype if at least one allele NAT2 is wild. The presence of mutation in both alleles NAT2 is manifested by the free acetylation phenotype (slow acetylator) [5]. Many members of the cytochrome P450 (CYP) family are responsible for the metabolism of endogenous substrates, dietary compounds and environmental toxins. Additionally, CYP are known to be involved in the metabolism of commonly used medication. Two known allelic variants CYP2C9*2 (C430T) and CYP2C9*3 (A1075C) differ from the wild type CYP2C9*1 by a single nucleotide substitution. Literature indicates that both allelic variants are associated with an impaired enzyme activity towards the respective substrate [6, 7].

GST, NAT and CYP polymorphisms have been shown to influence the level of oxidative DNA damage [2, 8, 9, 10]. Also, there is a consensus that ROS play part in the epidermal carcinogenesis [2]. These varying enzyme activities are supposed to influence the individual metabolism of carcinogenic aromatic amines, thereby modifying the susceptibility to certain cancers. Therefore GST, NAT and CYP enzymes take part in the defence mechanisms against skin cancers and polymorphism of these genes may influence the susceptibility of skin carcinogenesis in humans [11]. Human GST, CYP and NAT, which are encoded by the polymorphic GST, CYP and NAT genes respectively, have been shown to have wide interindividual variations in metabolic capacity and may be the potential modifiers of an individual's susceptibility to certain types of cancers [12,13,14]. Our purpose was to investigate the GST, NAT and CYP polymorphism in patients with basal cell carcinoma.

Materials and Methods

Subjects: Ninety seven subjects, 34 women and 63 men, with skin cancer, and 117 healthy control subjects (52 women and 65 men) were enrolled in the study. The mean (±SD) age was 60.00±13.64 in patients, and 49.35±13.14 in control subjects (**Table 1**).

The skin cancer group consisted of 97 patients who were diagnosed as basal cell carcinoma (BCC). All the diagnoses of BCC were confirmed by biopsies. This was a hospital-based case-control study conducted at the University of Mersin Hospital. The patients and controls were from the same geographic region and of the same ethnic origin. Also, cases and controls were unrelated. Control subjects were selected among people who had no history of cardiovascular disease, cancer, chronic degenerative neurological disease, chronic obstructive pulmonary disease, autoimmune diseases and hepatitis. This study was approved by the Ethics Committee of Mersin University, School of Medicine.

DNA extraction and genotyping of GST, NAT2, CYP2C9 and CYP2C19: Blood was collected in EDTA-containing tubes and DNA was extracted from the leucocytes by high pure template preparation kit (*Roche* Diagnostics, GmbH, Mannheim, Germany). The polymorphisms of GSTT1, GSTM1 and GSTP1 were performed by real time PCR with LightCycler instrument using hybridization probes in combination with the LightCycler DNA Master Hybridization Probes Kit

Table 1. Characteristics of the Study Population

	Patients (n: 97)	Controls (n: 117)
Age (years)	60.00±13.64	49.35±13.14
Sex		
Male	63 (64.95)	65 (55.6)
Female	34 (35.05)	52 (44.4)

(Roche Diagnostics). Both the PCR primers and hybridization probes were synthesized by TIB MOLBIOL (Berlin, Germany). NAT2*5A, NAT2*6A, NAT2*7A/B, NAT2*14A, CYPC9*2, CYP2C9*3 CYPC19*2, CYP2C19*3 alleles were detected by using Light Cycler- NAT2, CYP2C9 and CYP2C19 mutation detection kits by real time PCR with Light Cycler instrument (Roche diagnostics, GmbH, Mannheim, Germany; catalog no: 3113914).

Statistical analysis: Patient ages were compared with Student's t test. All values are represented as mean and standard deviation (SD). Chi-square or (Fisher's F) exact tests were used to evaluate the distribution of the GST, NAT2, CYP2C9 and CYP2C19 genotypes among patients and control subjects. The association between GST, NAT2, CYP2C9 and CYP2C19 genotypes and patients was estimated by computing odds ratios (ORs) and 95% confidence intervals (CIs) from logistic regression analyses. All statistical calculations were performed using the SPSS software package version (11.0 for Windows SPSS Inc., Chicago, IL). All tests were conducted at the $p<0.05$ level of significance.

Results

In the patient group, the frequency of the NAT2*6A heterezygous genotype was higher in comparison with that of the control group and this increase was significant (p=0,004 OR=3.70; 95% CI: 1.53-8.95). Patients with the NAT2*7A/B heterezygous genotype had a lower risk of skin cancer compared with individuals with the NAT2*7A/B wild genotype (p=0.001 OR = 0.17; 95% CI: 0.06-0.48). NAT2*5A, NAT2*14A polymorphisms were not significant risk factors for skin cancer. NAT2*5A, NAT2*6A and NAT2*14A mutant genotypes were related with 2.97, 4.15 and 1.5 fold increased risk but this was not statistically significant (p>0,05) (**Table 2**).

Patients (51.5%) had a higher prevalence of the GSTM1 null genotype than the control group (33.3%) and we found a 2.12 fold increased risk of skin cancer in individuals with the GSTM1 null genotype (p=0.008, 95% CI: 1.22-3.70) when compared to control group but this increase was not significant. Distributions of GST T1 present and null genotypes in patient and control group are 66%, 34%; 71.8%, 28.2% respectively. GST T1 null genotype were not significant risk factors for skin cancer (p=0.376). GSTP1 homozygous Val/Val genotype had a 0.40 fold increased risk of skin cancer when compared to control group (p= 0.03, 95% CI: 0.17-0.92), but this increase was not important (**Table 2**).

CYP2C9*2 was not significant (p=0.376), but CYP2C9*3 heterezygous genotype higher in comparison with that of the control group and this increase was significant (p=0.015 OR=2.02; 95% CI: 1.14-3.57). Compared with the CYP2C19*2 wild genotype, CYP2C19*2 heterezygous genotype was associated with more than 2.8 fold increased risk of skin cancer (p= 0.001, 95% CI: 1.50-5.26). All of patient and control group have CYP2C19*3 wild genotype (**Table 2**).

Discussion

It is an established fact that ultraviolet (UV) light plays a major role in the development of cutaneous malignancies [**15**]. UV radiation can damage cell DNA directly or indirectly [**16**]. Energy carried by the photons of ultraviolet radiation can be absorbed by other cromophores than DNA. These cromophores then transfer the absorbed energy to DNA or molecular oxygen. The latter way leads to reactive oxygen species (ROS) which are also capable of damaging cellular DNA. This indirect way is thought to play an important role in UVA carcinogenesis [**17**]. UVA is dependent on molecular oxygen for its biological activities [**16**]. An induction of anti-oxygen free radical mechanisms in skin cancer tissues has also been shown [**18**]. So, a variation, especially a homozygote deletion of the GST gene, and also NAT and CYP polymorphims can lead to an increased risk of skin carcinogenesis [**8, 9, 10, 19**].

GSTM1 null genotype and GSTP1 homozygous 105 Ile/Ile and Val/Val genotype prevelances were higher in our patients. *Kanetsky* et al observed that absence of both GSTM1 and GSTT1 were associated with increased risk for melanoma [**20**]. The relevance of GSTP1 to skin cancer risk is also shown in studies on mice lacking pi class GST genes [**18**]. *Ramsay* et al have previously shown that the frequency of GSTM1 null genotype is increased in a cohort of nontransplant patients with BCC and SCC in accordance with

Table 2. GST, NAT2, CYP2C9 and CYP2C19 Genotypes and the Risk of Developing Skin Cancer (*From conditional logistic regression. OR, Odds ratio; CI, confidence interval. n, number of sample.**Odds ratio can not be calculated)

		Skin cancer (n=97) N (%)	**Control** (n=97) N (%)				
				P	OR (%95 CI)*	Lower	Upper
GST M1				0.008			
	Present	47 (48.5)	78 (66.7)		1 (reference)		
	Null	50 (51.5)	39 (33.3)		2.12	1.223	3.701
GST T1				0.376			
	Present	64 (66)	84 (71.8)		1 (reference)		
	Null	33 (34)	33 (28.2)		1.31	0.733	2.349
GST P1							
	Ile/Ile	41 (42.3)	46 (39.3)	0.034	1 (reference)		
	Ile/Val	46 (47.4)	43 (36.8)	0.545	1.20	0.664	2.169
	Val/Val	10 (10.3)	28 (23.9)	0.032	0.40	0.174	0.924
NAT2*5A	Wild	37 (38.1)	51 (43.6)	0.091	1 (reference)		
	Heterezy-gous	45 (46.4)	58 (49.6)	0.998	0.99	0.432	2.310
	Mutant	15 (15.5)	8 (6.80)	0.081	2.97	0.875	10.08
NAT2*6A	Wild	52 (53.6)	66 (56.4)	0.013	1 (reference)		
	Heterezy-gous	39 (40.2)	44 (37.6)	0.004	3.70	1.537	8.950
	Mutant	6 (6.20)	7 (6.0)	0.068	4.15	0.924	18.71
NAT2*14A	Wild	66 (68.0)	66 (56.4)	0.874	1 (reference)		
	Heterezy-gous	30 (30.9)	50 (42.7)	0.644	123	0.507	2.995
	Mutant	1 (1.0)	1 (0.90)	0.776	1.50	0.089	25.53
NAT2*7A/B	Wild	75 (77.3)	70 (59,8)	0.003	1 (reference)		
	Heterezy-gous	21 (21.6)	44 (37,6)	0.001	0.17	0.060	0.483
	Mutant	1 (1.0)	3 (2.60)	0.081	0.10	0.009	1.316
CYP2C9*2				0.092			
	Wild	72 (80,3)	98 (78.8)		1 (reference)		
	Heterezy-gous	25 (19.7)	19 (21.2)		1.79	0.917	3.499
CYP2C9*3				0.015			
	Wild	54 (74.2)	84 (83.8)		1 (reference)		
	Heterezy-gous	43 (25.8)	33 (16.2)		2.02	1.149	3.577
CYP2C19*2				0.001			
	Wild	60 (61.9)	96 (82.1)		1 (reference)		
	Heterezy-gous	37 (38.1)	21 (17.9)		2.81	1.509	5.267
CYP2C19*3	Wild **	97 (100)	117 (100)	-	-	-	-

our study [**21**]. *Ramachandran* et al found that GST-M1 AB, and GSTT1 null genotypes were significantly associated with BCC [**14**]. *Shimizu* et al indicated the expression of placental-type glutathione S-transferase (GST-pi) in actinic keratosis and *Bowen*'s disease [**22**].

The relationship between NAT and CYP polymorhisms and incidence, clinicopathologic parameters and prognosis had been studied

in many cancers such as cholangiosarcoma, hepatic, gastric, lung, urinary, breast, prostate, and testicular tumors [**12, 23, 24, 25, 26, 27, 28, 29**]. *Katoh* et al suggested that the NAT1*10 allele could be a genetic determinant of oral SCC among Japanese people [**30**]. However, *Fronhoffs* et al found no significant association between the risk of SCC of head and neck and any of the NAT1 alleles in a caucasion population [**31**]. We observed that the presence of the NAT2*6A and 7A/B heterozygous alleles significantly increased the risk of skin cancer. There are numerous occupational and environmental carcinogens, such as arsenic and aromatic hydrocarbons, that predispose to SCC and BCC [**32,33**]. Exposure to insecticides and herbicides have also been associated with SCC [**34**]. Human metabolism of these carcinogenic compounds is complex and involves acetylation as an important pathway in order to mutate DNA and initiate carcinogenesis (**5**). In humans, two N-acetyltransferases (NAT1 and NAT2) have been identified, which catalyze detoxification and activation of various amines by N-acetylation and O-acetylation, respectively. Both NAT1 and NAT2 genes are known to be polymorphic in humans, corresponding to slow and rapid acetylator phenotypes. These varying enzyme activities are supposed to influence the individual metabolism of carcinogenic aromatic amines, thereby modifying the susceptibility to certain cancers [**31**]. CYP2C9*3 and CYP2C19*2 heterezygous genotypes were higher in our patients. This polymorphisms may lead to BCC because of imbalance of metabolism of endogenous substrates, dietary compounds, drugs and environmental toxins.

In our study, the results from the patient group suggest that there may be a relation between GST, NAT and CYP gene polymorphisms and skin cancer. But further studies on larger groups are needed to determine the prevalence of GST NAT and CYP polymorphisms in patients with BCC and to determine whether they constitute a major risk factor in the development of skin cancers.

References

1. Armstrong RN. Structure, catalytic mechanism and evolution of the glutathione transferases. Chem Res Toxicol 1997; 10: 2-18. PMID: 9074797
2. de Gruijl FR, van Kranen HJ, Mullenders LH. UV-induced DNA damage, repair, mutations and oncogenic pathways in skin cancer. J Photochem Photobiol B 2001; 63: 19-27. PMID: 11684448
3. Hayes JD, Strange RC. Glutathione-S-transferase polymorphisms and their biological consequences. Pharmacology 2000; 61: 154-166. PMID: 10971201
4. Sim E, Pinter K, Mushtag A, Upton A, Sandy J, Bhakta S, Noble M Arylamine N-acetyltransferases: a pharmacogenomic approach to drug metabolism and endogenous function. Biochem Soc Trans 2003; 31: 615-619. PMID: 12773167
5. Pompeo F, Brooke E, Kawamura A, Mushtaq A, Sim E. The pharmacogenetics of NAT: structural aspects. Pharmacogenomics 2002: 3: 19-30. PMID: 11966400
6. Aithal GP, Day CP, Kesteven PJL, Daly AK. Association of polymorphisms in the cytochrome P450 CYP2C9 with warfarin dose requirement and risk of bleeding complications. Lancet 1999; 353: 717-719. PMID: 10073515
7. Tassies D, Freire C, Pijoan J, Maragall S, Monteagudo J, Ordinas A, Reverter JC. Pharmacogenetics of acenocoumarol: cytochrome P450 CYP2C9 polimorphisms influence dose requirements and stability of anticoagulation. Heamatologia 2002; 87: 1185-1191. PMID: 12414349
8. Culp SJ, Roberts DW, Talaska G, Lang NP, Fu PP, Lay JO Jr, Teitel CH, Snawder JE, Von Tungeln LS, Kadlubar FF. Immunochemical, 32P-postlabeling, and GC/MS detection of 4-aminobiphenyl-DNA adducts in human peripheral lung in relation to metabolic activation pathways involving pulmonary N-oxidation, conjugation, and peroxidation. Mutat Res 1997; 1; 378: 97-112. PMID: 9288889
9. Lee SH, Lee SM. Suppression of hepatic cytochrome p450-mediated drug metabolism during the late stage of sepsis in rats. Shock 2005; 23: 144-149. PMID: 15665729.
10. Sipowicz MA, Chomarat P, Diwan BA, Anver MA, Awasthi YC, Ward JM, Rice JM, Kasprzak KS, Wild CP, Anderson LM. Increased oxidative DNA damage and hepatocyte overexpression of specific cytochrome P450 isoforms in hepatitis of mice infected with Helicobacter hepaticus. Am J Pathol 1997; 151: 933-941. PMID: 9327726
11. Phillipson RP, Tobi SE, Morris JA, McMillan TJ. UV-A induces genomic instability in human keratinocytes through an oxidative stress mechanism. Free Radical Biology & Medicine 2002; 32: 474-480. PMID: 11864787
12. Hung RJ, Boffetta P, Brennan P, Malaveille C, Hautefeuille A, Donato F, Gelatti U, Spaliviero M, Placidi D, Carta A, Scotto di Carlo A, Porru S. GST, NAT, SULT1A1, CYP1B1 genetic polymorphisms, interactions with environmental exposures and bladder cancer risk in a high-risk population. Int J Cancer 2004; 110: 598-604. PMID: 15122594
13. Lear JT, Smith AG, Bowers B, Heagearty AH, Jones PW, Gilford J, Alldersea J, Strange RC, Fryer AA. Truncal tumor site is associated with high risk of multiple basal cell carcinoma and is influenced by glutathione S-transferase, GSTT1, and cytochrome P450, CYP1A1 genotypes, and their interaction. J Invest Dermatol 1997; 108: 519-522. PMID: 9077484

14. Ramachandran S, Lear JT, Ramsay H, Smith AG, Bowers B, Hutchinson PE, Jones PW, Fryer AA, and Strange RC Presentation with Multiple Cutaneous Basal Cell Carcinomas: Association of Glutathione S-Transferase and Cytochrome P450 Genotypes with Clinical Phenotype. Cancer Epidemiology, Biomarkers & Prevention 1999; 8: 61-67. PMID: 9950241

15. Brash DE, Rudoph JA, Simon JA, Lin A, McKenna GJ, Baden HP, Halperin AJ, Ponten J. A role for sunlight in skin cancer: UV-induced p53 mutations in squamous cell carcinoma. Proc Natl Acad Sci USA 1991; 88: 10124-10128. PMID: 1946433

16. de Gruijl FR, Sterenborg HJ, Forbes PD, Davies RE, Cole C, Kelfkens G, van Weelden H, Slaper H, van der Leun JC. Wavelength dependance of skin cancer induction by ultraviolet irradiation of albino hairless mice. Cancer Res 1993; 53: 53-60. PMID: 8416751

17. Kielbassa C, Roza L, Epe B. Wavelength dependence of oxidative DNA damage induced by UV and visible light. Carcinogenesis 1997; 18: 811-816. PMID: 9111219

18. Henderson CJ, Smith AG, Ure J, Brown K, Bacon EJi Wolf CR. Increased skin tumorigenesis in mice lacking pi class glutathione-S-transferases. Proc Natl Acad Sci USA 1998; 95: 5275-5280. PMID: 9560266

19. Heagerty AH, Fitzgerald D, Smith A, Bowers B, Jones P, Fryer AA, Zhao L, Alldersea J, Strange RC. Glutathione S-tansferase GSTM1 phenotypes and protection against cutaneous tumours. Lancet 1994; 343: 266-268. PMID: 7905099

20. Kanetsky PA, Holmes R, Walker A, Najarian D, Swoyer J, Guerry DP, Halpern A, Rebbeck TR. Interaction of Glutathione S-transferase M1 and T1 Genotypes and Malignant Melanoma. Cancer Epidemiol Biomarkers Prev 2001; 10: 509-513. PMID: 11352862

21. Ramsay HM, Harden PN, Reece S, Smith AG, Jones PW, Strange RC, Fryer AA Polymorphisms in glutathione S-transferases are associated with altered risk of nonmelanoma skin cancer in renal transplant recipients: a preliminary analysis. J Invest Dermatol 2001; 117: 251-255. PMID: 11511301

22. Shimizu K, Toriyama F, Zhang HM, Yoshida H. The expression of placental-type glutathione S-transferase (GST-pi) in human cutaneous carcinoma in situ, that is, actinic keratosis and Bowen's disease, compared with normal human skin. Carcinogenesis 1995; 16: 2327-2330. PMID: 7586130

23. Chiu BC, Kolar C, Gapstur SM, Lawson T, Anderson JR, Weisenburger DD. Association of NAT and GST polymorphisms with non-Hodgkin's lymphoma: a population-based case-control study. Br J Haematol 2005; 128: 610-615. PMID: 15725081

24. Lilla C, Risch A, Kropp S, Chang-Claude J. SULT1A1 genotype, active and passive smoking, and breast cancer risk by age 50 years in a German case-control study. Breast Cancer Res 2005; 7: R229-237. PMID: 15743503

25. Prawan A, Kukongviriyapan V, Tassaneeyakul W, Pairojkul C, Bhudhisawasdi V. Association between genetic polymorphisms of CYP1A2, arylamine N-acetyltransferase 1 and 2 and susceptibility to cholangiocarcinoma. Eur J Cancer Prev 2005; 14: 245-250. PMID: 15901993

26. Suzuki S, Muroishi Y, Nakanishi I, Oda Y. Relationship between genetic polymorphisms of drug-metabolizing enzymes (CYP1A1, CYP2E1, GSTM1, and NAT2), drinking habits, histological subtypes, and p53 gene point mutations in Japanese patients with gastric cancer. J Gastroenterol 2004; 39: 220-230. PMID: 15064998

27. Tsukino H, Kuroda Y, Nakao H, Imai H, Inatomi H, Osada Y, Katoh T. Cytochrome P450 (CYP) 1A2, sulfotransferase (SULT) 1A1, and N-acetyltransferase (NAT) 2 polymorphisms and susceptibility to urothelial cancer. J Cancer Res Clin Oncol 2004; 130: 99-106. PMID: 14648207

28. Zhang XF, Bian JC, Zhang XY, Zhang ZM, Jiang F, Wang QM, Wang QJ, Cao YY, Tang BM. Are polymorphisms of N-acetyltransferase genes susceptible to primary liver cancer in Luoyang, China? World J Gastroenterol 2005; 14; 11:1457-1462. PMID: 15770721

29. Wadelius M, Autrup JL, Stubbins MJ, Andersson SO, Johansson JE, Wadelius C, Wolf CR, Autrup H, Rane A. Polymorphisms in NAT2, CYP2D6, CYP2C19 and GSTP1 and their association with prostate cancer. Pharmacogenetics 1999; 9: 333-340. PMID: 10471065

30. Katoh T, Kaneko S, Boissy R, Watson M, Ikemura K, Bell DA. A pilot study testing the association between N-acetyltransferases 1 and 2 and risk of oral squamous cell carcinoma in Japanese people. Carcinogenesis 1998; 19: 1803-1807. PMID: 9806162

31. Fronhoffs S, Bruning T, Ortiz-Pallardo E, Brode P, Koch B, Harth V, Sachinidis A, Bolt HM, Herberhold C, Vetter H, Ko Y. Real-time PCR analysis of the N-acetyltransferase NAT1 allele *3, *4, *10, *11, *14 and *17 polymorphism in squamous cell cancer of head and neck. Carcinogenesis 2001; 22: 1405-1412. PMID: 11532862

32. de Berker D, Ibbotson S, Simpson NB, Matthews JN, Idle JR, Rees JL. Reduced experimental contact sensitivity in squamous cell but not basal cell carcinomas of skin. Lancet 1995; 345: 425-426. PMID: 7853955

33. Phillips DH, Hewer A, Seidel A, Steinbrecher T, Schrode R, Oesch F, Glatt H. Relationship between mutagenicity and DNA adduct formation in mammalian cells for fjord- and bay-region diol-epoxides of polycyclic aromatic hydrocarbons. Chem Biol Interact 1991; 80: 177-186. PMID: 1934148

34. Li WM. The role of pesticides in skin disease. Int J Dermatol 1986; 25: 295-297. PMID: 2941381