Research Article

Polymorphisms in COMT and SULT1A1 Genes and Chronic Lymphocytic Leukemia Risk in Estonia

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Abstract

Objectives: Studies investigating associations between common polymorphisms in phase II metabolic enzymes COMT and SULT1A1 and the risk of various cancer types have revealed inconsistent and controversial results, with no attention turned to date to the most common adult leukemia type, i.e., chronic lymphocytic leukemia.

Methods: In this small case-control study with 47 cases and 50 controls, the role of two functional polymorphisms, Val158Met in COMT gene and Arg213His in SULT1A1 gene affecting the activity level of respective enzymes, was studied on the susceptibility to chronic lymphocytic leukemia in an Estonian cohort.

Results: Although statistically non-significant (p>0.05), the suggestive reduction in disease risk observed with low activity enzyme variants could indicate the involvement of O-methylation and sulfation of various endogenous and exogenous substances in the process of leukemogenesis. The odds ratio (OR) for Met158Met genotype of COMT was 0.60 with 95% confidence interval (95% CI) 0.20-1.82 compared to the wild type Val158Val genotype and the OR for His213His genotype of SULT1A1 was 0.58 with 95% CI 0.20-1.71 compared to the wild type Arg213Arg genotype.

Conclusion: Further large-scale studies are highly needed to confirm or disprove the findings of the present study and determine genetic risk factors for chronic lymphocytic leukemia.

Keywords: Chronic lymphocytic leukemia, O-methylation, phase II enzyme, single nucleotide polymorphism, sulfate conjugation

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Chronic lymphocytic leukemia (CLL) is a heterogeneous malignancy with a high variability in clinical presentations affecting mainly the elderly with mean age at diagnosis of nearly 70 years.[1, 2] With annual incidence of 3-5 cases per 100000 persons, CLL is the most common leukemia in adults of the Western world revealing about two-fold higher incidence rate in males than females.[3, 4] This disease is characterized by the clonal proliferation of the mature CD5/CD19 lymphocytes in the bone marrow, blood, and lymphoid tissues, such as lymph nodes and spleen.[2] De-

spite several efforts made in the last decades in evolution of new treatment strategies, including development of anti-CD20 antibodies-based immunochemotherapy options, Bruton`s tyrosine kinase inhibitors and phosphoinositide 3-kinase inhibitors, CLL is still considered an incurable disease.[1, 2, 4] Therefore, seeking further and more effective approaches are highly needed to attain the eventual goal of curing CLL. In parallel, development of strategies to select at-risk individuals using appropriate biomarkers is also important.

It has been previously suggested that genetic changes in metabolic enzymes can be potentially important in carcinogenesis process and certain polymorphisms in genes encoding these enzymes might be considered as disease biomarkers. However, only very few association studies are still focused on hematological malignancies.[5, 6]

Catechol-O-methyltransferase (COMT, EC 2.1.1.6) is a phase II enzyme that metabolizes various compounds with catecholic structure.[6] Dr. Julius Axelrod described this enzyme first in 1958[7] and nowadays it is generally accepted that COMT plays an important role in the O-methylation and detoxification of various catechols, including endogenous catechol estrogens and catecholamines, but also catechol-containing exogenous substances.[8–11] This enzyme catalyzes the transfer of a methyl moiety from S-adenosylmethionine to one of the hydroxyl groups on catechol compound.[12, 13] A single COMT gene encodes two forms of COMT enzymes, a membrane-bound protein with 271 amino acid residues and a soluble cytoplasmic protein with 221 amino acid residues, whereas the majority of COMT is present in the soluble form in human tissues apart from brain where COMT exists in membranous variant.[14–16] Although expression of COMT is highest in kidney and liver, it can be detected practically in all human tissues.[12, 17] In 1995, a genetic change of guanine (G) to adenine (A) in the exon 4 of COMT gene was described by Lotta et al resulting in amino acid replacement of valine (Val) to methionine (Met) in codon 158 in membrane-bound variant and at position 108 in soluble enzyme form.[18–21] This single nucleotide polymorphism (SNP; rs4680) was found to control the activity of COMT enzyme inducing high-, intermediate- and low-activity enzyme phenotypes, whereas the change Val158Met has been related to two- to fivefold reduction in the activity level of COMT.[15, 20, 22, 23] Thus, subjects carrying two Met alleles (Met158Met) exhibit considerably reduced ability to O-methylate various catechols resulting in an increase in circulating catechol-containing substances compared to the wild type individuals with two Val alleles (Val158Val); heterozygotes (Val158Met) have intermediate enzyme activity.[12, 17, 24, 25]

Sulfotransferase (SULT) 1A1 (EC 2.8.2.1) is another phase II enzyme that mediates sulfation of various compounds with phenolic structure.[5] This enzyme catalyzes the transfer of sulfonyl group from 3`-phosphoadenoside-5`-phosphosulfate to a wide variety of phenolic substances, including endogenous estrogens and thyroid hormones, but also different exogenous agents.[5, 26] The SULT1A1 enzyme is a 295 amino acid protein being expressed in the majority of human tissues.[26–28] The most common polymorphic change in SULT1A1 (rs9282861) consists of G to A nucleotide transition at position 638 in exon 7 leading to an arginine (Arg) to

histidine (His) replacement at amino acid 213.[29–31] At that, subjects homozygous to variant His alleles (His213His) reveal only approximately 15% of enzyme activity compared to those with wild type SULT1A1 form (Arg213Arg).[28, 31, 32] As sulfation results in more polar compounds with promoted elimination from the human body, this process is generally considered a detoxification pathway.[33, 34]

To investigate the possible involvement of metabolic enzymes in development of chronic lymphocytic leukemia, a small-scale case-control study on association between functional polymorphisms in COMT and SULT1A1 enzymes and the risk of CLL was performed in Estonian population.

Methods

Study Subjects

This case-control study was conducted in Tartu, Estonia. Cases were individuals (n=47) with clinically confirmed diagnosis of CLL treated in the Clinic of Hematology and Oncology, Tartu University Hospital. Controls (n=50) were recruited from medical staff as well as healthy subjects visiting the same hospital for examination of hereditary cancer risk. All participants were older than 45 years in the time of blood collection and were recruited during 2011-2016. The research protocol was approved by the Research Ethics Committee of the University of Tartu (Approval 245/T-4). A written informed content was obtained from each subject.

Isolation of Peripheral Blood Mononuclear Cells (PBMC), B Cells and Non-B Cells

Peripheral blood samples (10 ml) were collected from all CLL patients and healthy volunteers. Mononuclear cells were isolated from heparinized venous blood by density-gradient centrifugation by using Ficoll separation method. Ficoll-PaqueTM Premium was purchased from GE Healthcare Bio-Sciences AB (Uppsala, Sweden). Only freshly isolated normal PBMCs were used for further separation of B cells and non-B cells. B cells were isolated from PBMCs using the human B-CLL Cell Isolation Kit obtained from MACS Miltenyi Biotec (Auburn, CA, USA). At that, the fraction of non-B cells was also collected.

DNA Separation and Genotyping

As tumoral B cells can contain CLL specific genetic changes, the genomic DNA was isolated from non-B cell fraction of PBMCs using QIAamp DNA Mini Kit protocol (Qiagen, Inc., Chatsworth, CA, USA). The PCR reaction was carried out in the volume of 20 μl, containing 1 μl of genomic DNA, 4 μl of 5x HOT FIREPol Blend Master Mix Ready to Load (Solis Biodyne, Tartu, Estonia) and 0.8 μl of 10 μM primer solutions. A 111 bp fragment of COMT was amplified by using the fol-

lowing primers: forward 5´-GGCTCATCACCATCGAGATCAA-3´and reverse 5´-CCAGGTCTGACAACGGGTCA-3´. A 287 bp fragment of SULT1A1 was amplified by using the following primers: forward 5´-TTGGCTCTGCAGGGTTTCTA-3´and reverse 5´-GGAGATGCTGTGGTCCATGA-3´. PCR primers were synthesized in Metabion (Planegg/Steinkirchen, Germany). The PCR reaction was performed as follows: 1 cycle of 5 min predenaturation at 94 0C, then 45 cycles of 30 s at 95 0C, 30 s annealing at 61 0C, 30 s extension at 72 0C, and followed by 1 cycle of 5 min extension at 72 0C. The correctness of PCR products was analyzed by agarose gel electrophoresis and visualized by staining with ethidium bromide.

Amplified fragments of COMT and SULT1A1 were cleaved by Hin1II (NlaIII) and BfoI (HaeII) restriction enzymes, respectively (Thermo Fisher Scientific Inc., Lithuania). These reactions were performed in the volume of 30 µl containing 2 µl of 10x FastDigest Green Buffer (Thermo Fisher Scientific Inc., Lithuania), 10 µl amplified PCR product and 1 µl FastDigest restriction enzyme. Incubations were conducted at 37 0C for 1 hr and 37 0C for 30 min for Hin1II and BfoI with following inactivation at 80 0C for 5 min and 65 0C for 10 min, respectively. Products of restriction fragment lengths were separated on 2.4% agarose gel in TAE buffer (Tris-acetate-EDTA) at ambient temperature using GeneRuler 50 bp DNA ladder as marker (Thermo Fisher Scientific Inc., Lithuania).

DNA sequencing reactions were performed in the core laboratory of Estonian Biocentre by Sanger sequencing method using BigDye Terminator v3.1 enzyme mixture.

Examples of DNA genotyping for Val158Met in COMT gene and Arg213His in SULT1A1 gene are demonstrated in Figure 1 and Figure 2, respectively.

Statistical Analysis

The frequency distributions of polymorphic genotypes of COMT Val158Met and SULT1A1 Arg213His for CLL patients and healthy controls were calculated and tabulated. To determine differences in the genotypic distributions between cases and controls, Chi-square test was performed. For each polymorphic site, odds ratio values (ORs) along with 95% confidence intervals (95% CIs) were determined using unconditional logistic regression model. Subjects with wild type genotypes (COMT Val158Val, SULT1A1 Arg213Arg) were used as reference groups for comparison of risk allele containing genotypes. P value below 0.05 was considered statistically significant.

Results

The study population included 47 CLL cases and 50 controls that were all analyzed concerning the genotypes in
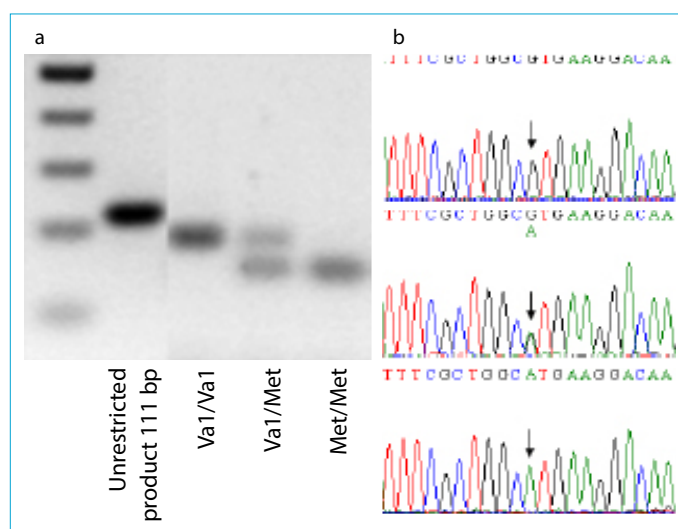

Figure 1. PCR-based RFLP analysis **(a)** and DNA sequencing **(b)** of COMT Val158Met (G>A) polymorphism. A 111 bp fragment of COMT was restricted by Hin1II (NlaIII) enzyme resulting in products with sizes of 89 bp for Val/Val; 89 and 71 bp for Val/Met and 71 bp for Met/Met genotypes.
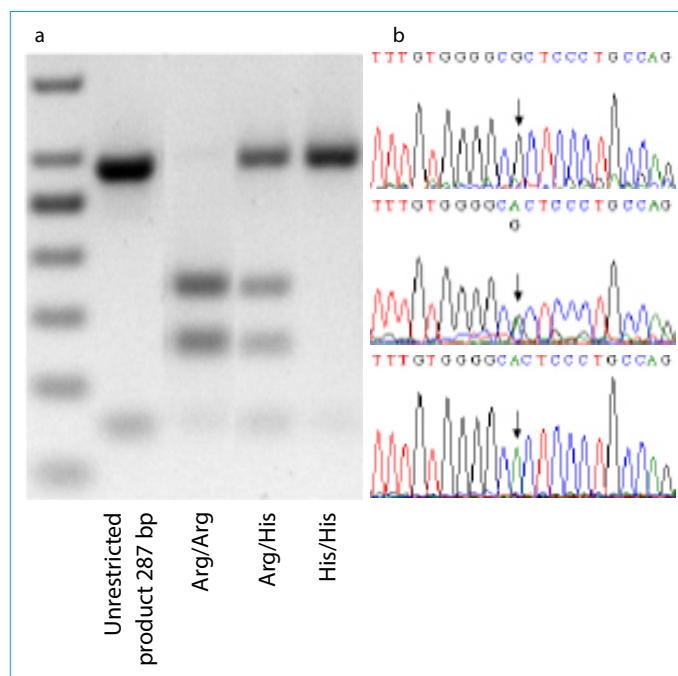

Figure 2. PCR-based RFLP analysis **(a)** and DNA sequencing **(b)** of SULT1A1 Arg213His (638G>A) polymorphism. A 287 bp fragment of SULT1A1 was restricted by BfoI (HaeII) enzyme resulting in products with sizes of 167 and 120 bp for Arg/Arg; 287, 167 and 120 bp for Arg/His and 287 bp for His/His genotypes.

COMT Val158Met and SULT1A1 Arg213His. There were 21 men (45%) and 26 women (55%) among cases, and 16 men (32%) and 34 women (68%) among controls. The mean age of cases was 70.7±8.4 and of controls 61.1±8.5 years with the respective age ranges of 52-89 and 45-82 years.

Table 1 represents the genotypic frequencies of COMT and SULT1A1 polymorphisms. These results showed the distribution of COMT Val158Met genotypes among CLL cases of Val/Val 30%, Val/Met 51%, Met/Met 19% and controls 28%, 42%, 30%, respectively. The distribution of SULT1A1 Arg213His genotypes among CLL cases were Arg/Arg 32%, Arg/His 47%, His/His 21% and among controls 28%, 40%, 32%, respectively. Although no statistically significant associations revealed, individuals with low methylation and sulfation activities exerted a suggestive inverse association with CLL risk (OR=0.60, 95% CI 0.20-1.82 for COMT Met158Met and OR=0.58, 95% CI 0.20-1.71 for SULT1A1 His213His), as compared to individuals carrying wild type genotypes, i.e., Val158Val for COMT and Arg213Arg for SULT1A1.

Discussion

Due to a small general population in Estonia, the number of CLL cases involved in this work was also rather limited being reflected in the odds ratio measures with wide confidence intervals. However, the distribution of COMT genotypes among controls (28% Val158Val, 42% Val158Met, 30% Met158Met) is similar to the values described previously for Caucasian subjects (~25% Val158Val, ~50% Val158Met, ~25% Met158Met) adding validity to the results of the current work.[6, 35]

One of the most important functions of COMT and SULT1A1 enzymes in the human body is metabolization of estrogen to methoxy estrogens and estrogen sulfates by inactivating the potentially harmful intermediate semiquinones and quinones formed from catechol estrogens during their oxidation.[6, 19, 36–38] Lowered activity of detoxification processes due to functional polymorphisms in COMT and SULT1A1 enzymes can lead to accumulation of mutagenic and carcinogenic catechol estrogens and therefore elevate the cancer risk.[6, 20, 35, 39] Indeed, experiments with the

Syrian hamsters revealed an increased renal tumorigenesis by suppressing the activity of COMT.[40] In this context, the results of the current work, showing a suggestive, still statistically non-significant, 40% and 42% decrease in CLL risk with low activity enzyme variants COMT Met158Met and SULT1A1 His213His respectively, are somewhat unexpected. Although it is possible that this outcome was caused by chance as the numbers of study subjects with corresponding genotypes were very small, the lowered risk can still be explained by several factors. First, albeit O-methylation of catechol estrogens is considered a detoxification pathway, elevated amounts of 2-methoxyestradiol has been recently found to produce breaks in chromosome and aneuploidy contributing thus to development of neoplasias.[41] Second, besides well-known function in detoxification of various cell-damaging substances, sulfation can also bioactivate several promutagens and carcinogens from food and environment, such as heterocyclic amines and polycyclic aromatic hydrocarbons, leading to a potential DNA damage.[5, 42–49] These dual actions can also provide some explanations to the inconsistent and controversial findings of epidemiological studies about associations between COMT Val158Met and SULT1A1 Arg213His genotypes and susceptibility to different cancer types indicating that these relationships can be much more complex and depend probably on numerous endogenous and exogenous determinants, such as age, gender, ethnicity, level of physical activity, obesity, menopausal status, age at menarche, number of full term pregnancies, family history of certain malignant disorders, but also exposure to contraceptives and hormone replacement therapy, tobacco smoke or other environmental pollutants.[5, 6, 9, 50–55] Unfortunately, the small number of study subjects in this work did not allow us to make any further stratification analyses for susceptibility to CLL.

Furthermore, several plant-derived dietary flavonoids, such as flavonols quercetin, myricetin and fisetin, flavone

Table 1. Genotype frequencies of COMT and SULT1A1 polymorphisms among cases and controls and their association with CLL				
	47 Cases (%)	50 Controls (%)	OR (95% CI)	p
COMT Val158Met				
Val/Val (high)	14 (30)	14 (28)	1 (Ref.)	
Val/Met (intermediate)	24 (51)	21 (42)	1.14 (0.44-2.94)	0.78
Met/Met (low)	9 (19)	15 (30)	0.60 (0.20-1.82)	0.37
Val/Met, Met/Met	33 (70)	36 (72)	0.92 (0.38-2.21)	0.84
SULT1A1 Arg213His				
Arg/Arg (high)	15 (32)	14 (28)	1 (Ref.)	
Arg/His (intermediate)	22 (47)	20 (40)	1.03 (0.40-2.65)	0.84
His/His (low)	10 (21)	16 (32)	0.58 (0.20-1.71)	0.32
Arg/His, His/His	32 (68)	36 (72)	0.83 (0.35-1.98)	0.67

luteolin and tea flavanols (catechin, epicatechin, epicatechin gallate, epigallocatechin, epigallocatechin gallate) also contain catecholic structure representing thus substrates for O-methylation by COMT.[56–60] These and other flavonoids with general polyphenolic structure are also metabolized by SULT1A1-catalyzed sulfation reaction in the small intestine and liver.[5, 61, 62] Dependent on the dietary habits, humans consume up to 1 g of flavonoids per day, presenting in fruits and vegetables, nuts, spices, medicinal herbs, but also plant-based beverages like cocoa and tea.[5, 56, 61] Numerous in vitro works with cell lines and in vivo studies with animal models have demonstrated that these plant secondary metabolites exert various anticancer properties, such as antioxidant, antiproliferative, proapoptotic, antiinvasive, antiangiogenic and antimetastatic effects.[63, 64] However, compared to the parent flavonoids originally present in plant-based food items, anticancer potential of their O-methylated or sulfated conjugates as the major metabolites entering bloodstream is reported to be considerably less efficient.[5, 6, 65–76] Although the current knowledge about anticancer action of COMT- and SULT1A1-mediated derivatives of flavonoids is still rather limited, it is possible that lower efficacy of O-methylation and sulfation processes caused by polymorphisms in these enzymes can provide somewhat higher levels of intact flavonoids entering circulation and reaching target tissues to exert more protection against initiation and development of chronic lymphocytic leukemia.

According to the best knowledge of authors, there are no studies performed to date about the role of COMT and SULT1A1 polymorphisms in susceptibility to CLL. For COMT Val158Met, Skibola et al. demonstrated a 1.6-fold increase in the risk of non-Hodgkin lymphoma among American women with two Met alleles (Met158Met) compared to their counterparts homozygous to Val alleles (Val158Val).[77] Concerning SULT1A1, no results about the possible role of Arg213His polymorphism on hematological malignancies have been reported.[5]

The strengths of the current work included ethnical homogeneity of the study population and obviating the possibility for detection of genetic changes formed in any stages during carcinogenesis as tumoral B cells were eliminated from peripheral blood mononuclear cells before separation of genomic DNA. Indeed, we have previously shown that Val158Met polymorphism in COMT gene can be specific for tumoral B cells and possibly involved in the progression of CLL.[78] However, this study had also several limitations, including small number of subjects and a possible selection bias. As controls, a mixed cohort of medical staff and healthy individuals visiting hospital for risk estimation of hereditary cancers was used. The possibility that distribution of COMT and SULT1A1 genotypes among people with family history of neoplasms might differ from general population can not be fully excluded. Also, we can not rule out the possibility that some unknown factors could play role in associations between studied gene variants and tumorigenesis risk.

This is the first study presenting results on associations between functional polymorphisms in COMT and SULT1A1 metabolic enzymes and the risk of CLL. Although statistically non-significant, the suggestive reduction of CLL risk related to low activity enzyme variants certainly needs further investigations with larger study cohorts allowing also stratifications by potentially important endogenous and environmental factors. At that, dietary choices and preferences of plant-based food products rich in natural flavonoids may prove to be crucial. In parallel, expansion of in vitro and in vivo studies on antileukemic action of methylated and sulfated metabolites of dietary polyphenols is equally important to delineate possibilities for possible prevention of CLL in the future.

Disclosures

Ethics Committee Approval: Ethics Committee Approval number is: 245/T-4

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Conflict of Interest: None declared.

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References

1. Voorhies BN, Stephens DM. What is optimal front-line therapy for chronic lymphocytic leukemia in 2017? Curr Treat Options Oncol 2017;18:12. [CrossRef]

2. Janroziak K, Pula B, Walewski J. Current treatment of chronic lymphocytic leukemia. Curr Treat Options Oncol 2017;18:5.

3. Robak T, Jamroziak K, Robak P. Current and emerging treatments for chronic lymphocytic leukaemia. Drugs 2009;69:2415–49. [CrossRef]

4. Parker H, Strefford JC. The mutational signature of chronic lymphocytic leukemia. Biochem J 2016;473:3725–40. [CrossRef]

5. Sak K, Everaus H. Sulfotransferase 1A1 as a biomarker for susceptibility to carcinogenesis: from molecular genetics to the role of dietary flavonoids. Curr Drug Metab 2016;17:528–41.

6. Sak K. The Val158Met polymorphism in COMT gene and cancer risk: role of endogenous and exogenous catechols. Drug Metab Rev 2017;49:56–83. [CrossRef]

7. Axelrod J, Senoh S, Witkop B. O-Methylation of catechol amines in vivo. J Biol Chem 1958;233:697–701.

8. Tian C, Liu L, Yang X, et al. The Val158Met polymorphism in the

COMT gene is associated with increased cancer risks in Chinese population. Tumour Biol 2014;35:3003–8. [CrossRef]

9. Zhang H, Zhang Z, Wu J, et al. Lack of association between COMT Val158Met polymorphism and prostate cancer susceptibility. Urol Int 2013;91:213–9. [CrossRef]

10. Zou LW, Xu XJ, Liu T, et al. No association between COMT Val158Met polymorphism and prostate cancer risk: a meta-analysis. Genet Test Mol Biomarkers 2013;17:78–84. [CrossRef]

11. Zhou Q, Wang Y, Chen A, et al. Association between the COMT Val158Met polymorphism and risk of cancer: evidence from 99 case-control studies. Onco Targets Ther 2015;8:2791–803.

12. Matos A, Castelao C, Pereira da Silva A, et al. Epistatic interaction of CYP1A1 and COMT polymorphisms in cervical cancer. Oxid Med Cell Longev 2016;2769804. [CrossRef]

13. Naushad SM, Pavani A, Rupasree Y, et al. Modulatory effect of plasma folate and polymorphisms in one-carbon metabolism on catecholamine methyltransferase (COMT) H108L associated oxidative DNA damage and breast cancer risk. Indian J Biochem Biophys 2011;48:283–9.

14. Moreno-Galvan M, Herrera-Gonzalez NE, Robles-Perez V, et al. Impact of CYP1A1 and COMT genotypes on breast cancer risk in Mexican women: a pilot study. Int J Biol Markers 2010;25:157–63. [CrossRef]

15. Yager JD. Catechol-O-methyltransferase: characteristics, polymorphisms and role in breast cancer. Drug Discov Today Dis Mech 2012;9:e41–6. [CrossRef]

16. Doyle AE, Yager JD. Catechol-O-methyltransferase: effects of the val108met polymorphism on protein turnover in human cells. Biochim Biophys Acta 2008;1780:27–33. [CrossRef]

17. Lin G, Zhao J, Wu J, et al. Contribution of catechol-O-methyltransferase Val158Met polymorphism to endometrial cancer risk in postmenopausal women: a meta-analysis. Genet Mol Res 2013;12:6442–53. [CrossRef]

18. Lotta T, Vidgren J, Tilgmann C, et al. Kinetics of human soluble and membrane-bound catechol O-methyltransferase: a revised mechanism and description of the thermolabile variant of the enzyme. Biochemistry 1995;34:4202–10. [CrossRef]

19. Pan W, Liao H. Correlations between the COMT gene rs4680 polymorphism and susceptibility to ovarian cancer. Genet Mol Res 2015;14:16813–8. [CrossRef]

20. Ghisari M, Eiberg H, Long M, et al. Polymorphisms in phase I and phase II genes and breast cancer risk and relations to persistent organic pollutant exposure: a case-control study in Inuit women. Environ Health 2014;13:19. [CrossRef]

21. Li K, Li W, Zou H. Catechol-O-methyltransferase Val158Met polymorphism and breast cancer risk in Asian population. Tumour Biol 2014;35:2343–50. [CrossRef]

22. Du JZ, Dong YL, Wan GX, et al. Lack of association between the COMT rs4680 polymorphism and ovarian cancer risk: evidence from a meta-analysis of 3940 individuals. Asian Pac J Cancer Prev 2014;15:7941–5. [CrossRef]

23. Peng S, Tong X, Liu S, et al. Association between the COMT 158 G/A polymorphism and lung cancer risk: a meta-analysis. Int J Clin Exp Med 2015;8:17739–47.

24. Liu JX, Luo RC, Li R, et al. Lack of associations of the COMT Val158Met polymorphism with risk of endometrial and ovarian cancer: a pooled analysis of case-control studies. Asian Pac J Cancer Prev 2014;15:6181–6. [CrossRef]

25. Wolpert BJ, Amr S, Saleh DA, et al. Associations differ by sex for catechol-O-methyltransferase genotypes and bladder cancer risk in South Egypt. Urol Oncol 2012;30:841–7. [CrossRef]

26. Daniels J, Kadlubar S. Sulfotransferase genetic variation: from cancer risk to treatment response. Drug Metab Rev 2013;45:415–22. [CrossRef]

27. Tsukino H, Kuroda Y, Nakao H, et al. 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. [CrossRef]

28. Lindsay J, Wang LL, Li Y, Zhou SF. Structure, function and polymorphism of human cytosolic sulfotransferases. Curr Drug Metab 2008;9:99–105. [CrossRef]

29. Xiao J, Zheng Y, Zhou Y, et al. Sulfotransferase SULT1A1 Arg213His polymorphism with cancer risk: a meta-analysis of 53 case-control studies. PLoS One 2014;9:e106774. [CrossRef]

30. Arslan S, Silig Y, Pinarbasi H. Sulfotransferase 1A1 Arg(213) His polymorphism and prostate cancer risk. Exp Ther Med 2011;2:1159–62. [CrossRef]

31. Liu K, Ye J, Huang Y, et al. Quantitative analysis of the association between sulfotransferase isoform 1A1 polymorphism and risk of urothelial carcinoma. Mol Clin Oncol 2015;3:93–100. [CrossRef]

32. Wang Z, Fu Y, Tang C, et al. SULT1A1 R213H polymorphism and breast cancer risk: a meta-analysis based on 8454 cases and 11800 controls. Breast Cancer Res Treat 2010;122:193–8. [CrossRef]

33. Yang G, Gao YT, Cai QY, et al. Modifying effects of sulfotransferase 1A1 gene polymorphism on the association of breast cancer risk with body mass index or endogenous steroid hormones. Breast Cancer Res Treat 2005;94:63–70. [CrossRef]

34. Wang Y, Spitz MR, Tsou AM, et al. Sulfotransferase (SULT) 1A1 polymorphism as a predisposition factor for lung cancer: a case-control analysis. Lung Cancer 2002;35:137–42. [CrossRef]

35. Baclig MO, Predicala RZ, Mapua CA, et al. Allelic and genotype frequencies of catechol-O-methyltransferase (Val158Met) and CYP2D6*10 (Pro34Ser) single nucleotide polymorphisms in the Philippines. Int J Mol Epidemiol Genet 2012;3:115–21.

36. Lajin B, Hamzeh AR, Ghabreau L, et al. Catechol-O-methyltransferase Val 108/158 Met polymorphism and breast cancer risk: a case control study in Syria. Breast Cancer 2013;20:62–6.

37. Tan X, Chen M. Association between catechol-O-methyltransferase rs4680 (G>A) polymorphism and lung cancer risk. Diagn Pathol 2014;9:192. [CrossRef]

38. Lavigne JA, Helslsouer KJ, Huang HY, et al. An association be-

tween the allele coding for a low activity variant of catechol-O-methyltransferase and the risk for breast cancer. Cancer Res 1997;57:5493–7.

39. Delort L, Chalabi N, Satih S, et al. Association between genetic polymorphisms and ovarian cancer risk. Anticancer Res 2008;28:3079–81.

40. Doherty JA, Weiss NS, Freeman RJ, et al. Genetic factors in catechol estrogen metabolism in relation to the risk of endometrial cancer. Cancer Epidemiol Biomarkers Prev 2005;14:357–66. [CrossRef]

41. Onay UV, Aaltonen K, Briollais L, et al. Combined effect of CCND1 and COMT polymorphisms and increased breast cancer risk. BMC Cancer 2008;8:6. [CrossRef]

42. Su CM, Chen MC, Lin IC, et al. Association between the SULT1A1 Arg213His polymorphism and the risk of bladder cancer: a meta-analysis. Tumour Biol 2014;35:7147–53. [CrossRef]

43. Chung YT, Hsieh LL, Chen IH, et al. Sulfotransferase 1A1 haplotypes associated with oral squamous cell carcinoma susceptibility in male Taiwanese. Carcinogenesis 2009;30:286–94.

44. Koike H, Nakazato H, Ohtake N, et al. Further evidence for null association of phenol sulfotransferase SULT1A1 polymorphism with prostate cancer risk: a case-control study of familial prostate cancer in a Japanese population. Int Urol Nephrol 2008;40:947–51. [CrossRef]

45. Liang G, Miao X, Zhou Y, et al. A functional polymorphism in the SULT1A1 gene (G638A) is associated with risk of lung cancer in relation to tobacco smoking. Carcinogenesis 2004;25:773–8. [CrossRef]

46. Tang D, Rundle A, Mooney L, et al. Sulfotransferase 1A1 (SULT1A1) polymorphism, PAH-DNA adduct levels in breast tissue and breast cancer risk in a case-control study. Breast Cancer Res Treat 2003;78:217–22. [CrossRef]

47. Tiemersma EW, Voskuil DW, Bunschoten A, et al. Risk of colorectal adenomas in relation to meat consumption, meat preparation, and genetic susceptibility in a Dutch population. Cancer Causes Control 2004;15:225–36. [CrossRef]

48. Kellen E, Zeegers M, Paulussen A, et al. Does occupational exposure to PAHs, diesel and aromatic amines interact with smoking and metabolic genetic polymorphisms to increase the risk on bladder cancer?; The Belgian case control study on bladder cancer risk. Cancer Lett 2007;245:51–60. [CrossRef]

49. Nowell S, Coles B, Sinha R, et al. Analysis of total meat intake and exposure to individual heterocyclic amines in a case-control study of colorectal cancer: contribution of metabolic variation to risk. Mutat Res 2002;506–7:175–85. [CrossRef]

50. Ashton KA, Meldrum CJ, McPhillips ML, et al. The association of the COMT V158M polymorphism with endometrial/ovarian cancer in HNPSS families adhering to the Amsterdam criteria. Hered Cancer Clin Pract 2006;4:94–102. [CrossRef]

51. Zienolddiny S, Campa D, Lind H, et al. A comprehensive analysis of phase I and phase II metabolism gene polymorphisms and risk of non-small cell lung cancer in smokers. Carcinogenesis 2008;29:1164–9. [CrossRef]

52. Zheng W, Xie D, Cerhan JR, et al. Sulfotransferase 1A1 polymorphism, endogenous estrogen exposure, well-done meat intake, and breast cancer risk. Cancer Epidemiol Biomarkers Prev 2001;10:89–94.

53. Roubalova L, Purchartova K, Papouskova B, et al. Sulfation modulates the cell uptake, antiradical activity and biological effects of flavonoids in vitro: an examination of quercetin, isoquercitrin and taxifolin. Bioorg Med Chem 2015;23:5402–9.

54. Rebbeck TR, Troxel AB, Wang Y, et al. Estrogen sulfation genes, hormone replacement therapy, and endometrial cancer risk. J Natl Cancer Inst 2006;98:1311–20. [CrossRef]

55. 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:R229–37. [CrossRef]

56. Sak K, Everaus H. Nanotechnological approach to improve the bioavailability of dietary flavonoids with chemopreventive and anticancer properties. In: Grumezescu A, ed. Nutraceuticals, vol. 4. Academic Press, 2016:427–79. [CrossRef]

57. Chen Z, Chen M, Pan H, et al. Role of catechol-O-methyltransferase in the disposition of luteolin in rats. Drug Metab Dispos 2011;39:667–74. [CrossRef]

58. Chen Z, Zheng S, Li L, Jiang H. Metabolism of flavonoids in human: a comprehensive review. Curr Drug Metab 2014;15:48–61. [CrossRef]

59. Zhu BT, Patel UK, Cai MX, et al. Rapid conversion of tea catechins to monomethylated products by rat liver cytosolic catechol-O-methyltransferase. Xenobiotica 2001;31:879–90. [CrossRef]

60. Zhu BT. Catechol-O-methyltransferase (COMT)-mediated methylation metabolism of endogenous bioactive catechols and modulation by endobiotics and xenobiotics: importance in pathophysiology and pathogenesis. Curr Drug Metab 2002;3:321–49. [CrossRef]

61. Jiang W, Hu M. Mutual interactions between flavonoids and enzymatic and transporter elements responsible for flavonoid disposition via phase II metabolic pathways. RSC Adv 2012;2:7948–63. [CrossRef]

62. Nakano H, Ogura K, Takahashi E, et al. Regioselective monosulfation and disulfation of the phytoestrogens daidzein and genistein by human liver sulfotransferases. Drug Metab Pharmacokinet 2004;19:216–26. [CrossRef]

63. Sak K. Cytotoxicity of dietary flavonoids on different human cancer types. Pharmacogn Rev 2014;8:122–46. [CrossRef]

64. Sak K. Site-specific anticancer effects of dietary flavonoid quercetin. Nutr Cancer 2014;66:177–93. [CrossRef]

65. Landis-Piwowar K, Chen D, Chan TH, Dou QP. Inhibition of catechol-omicron-methyltransferase activity in human breast cancer cells enhances the biological effect of the green tea polyphenol (-)-EGCG. Oncol Rep 2010;24:563–9. [CrossRef]

66. Wang P, Aronson WJ, Huang M, et al. Green tea polyphenols and metabolites in prostatectomy tissue: implications for cancer prevention. Cancer Prev Res (Phila) 2010;3:985–93. [CrossRef]

67. Forester SC, Lambert JD. Synergistic inhibition of lung cancer cell lines by (-)-epigallocatechin-3-gallate in combination with clinically used nitrocatechol inhibitors of catechol-O-methyltransferase. Carcinogenesis 2014;35:365–72. [CrossRef]

68. Lorenz M, Paul F, Moobed M, et al. The activity of catechol-O-methyltransferase (COMT) is not impaired by high doses of epigallocatechin-3-gallate (EGCG) in vivo. Eur J Pharmacol 2014;740:645–51. [CrossRef]

69. Landis-Piwowar KR, Wan SB, Wiegand RA, et al. Methylation suppresses the proteasome-inhibitory function of green tea polyphenols. J Cell Physiol 2007;213:252–60. [CrossRef]

70. Nicolini F, Burmistrova O, Marrero MT, et al. Induction of G2/M phase arrest and apoptosis by the flavonoid tamarixetin on human leukemia cells. Mol Carcinog 2014;53:939–50. [CrossRef]

71. Shi ZH, Li NG, Tang YP, et al. Biological evaluation and SAR analysis of O-methylated analogs of quercetin as inhibitors of cancer cell proliferation. Drug Dev Res 2014;75:455–62. [CrossRef]

72. Delgado L, Fernandes I, Gonzalez-Manzano S, et al. Anti-proliferative effects of quercetin and catechin metabolites. Food Funct 2014;5:797–803. [CrossRef]

73. Androutsopoulos VP, Spandidos DA. The flavonoids diosmetin and luteolin exert synergistic cytostatic effects in human hepatoma HepG2 cells via CYP1A-catalyzed metabolism, activation of JNP and ERK and P53/P21 up-regulation. J Nutr Biochem 2013;24:496–504. [CrossRef]

74. Barrajon-Catalan E, Taamalli A, Quirantes-Pine R, et al. Differential metabolomic analysis of the potential antiproliferative mechanism of olive leaf extract on the JIMT-1 breast cancer cell line. J Pharm Biomed Anal 2015;105:156–62. [CrossRef]

75. Vaidyanathan JB, Walle T. Glucuronidation and sulfation of the tea flavonoid (-)-epicatechin by the human and rat enzymes. Drug Metab Dispos 2002;30:897–903. [CrossRef]

76. Yang CH, Tang L, Lv C, et al. Sulfation of selected mono-hydroxyflavones by sulfotransferases in vitro: a species and gender comparison. J Pharm Pharmacol 2011;63:967–70. [CrossRef]

77. Skibola CF, Bracci PM, Paynter RA, et al. Polymorphisms and haplotypes in the cytochrome P450 17A1, prolactin, and catechol-O-methyltransferase genes and non-Hodgkin lymphoma risk. Cancer Epidemiol Biomarkers Prev 2005;14:2391–401. [CrossRef]

78. Sak K, Kasemaa K, Everaus H. Change of COMT Val158Met genotype in tumoral B cells of a chronic lymphocytic leukemia patient: a case report. Ann Hematol Oncol 2017;4:1130. [CrossRef]