Digestive and Liver Disease 51 (2019) 579–583

Contents lists available at ScienceDirect

Digestive and Liver Disease

journal homepage: www.elsevier.com/locate/dld

Oncology

A study of the association between UGT1A1*28 variant allele of *UGT1A1* gene and colonic phenotype of sporadic colorectal cancer

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ARTICLE INFO

Article history:
Received 15 August 2018
Received in revised form
25 November 2018
Accepted 27 November 2018
Available online 10 December 2018

Keywords:
Colonic phenotype
Colorectal cancer
UGT1A1
UGT1A1*28 variant

ABSTRACT

Introduction: The transcriptional activity of the *UGT1A1* gene is modulated by a variable number of repetitions of the dinucleotide (TA) within its promoter region. By comparison to the most common allele $(TA)_6$ (UGT1A1*1), decreased activity is observed with increasing TA repetitions. The aim of this study was to determine whether the presence of the variant allele UGT1A1*28, harbouring seven TA repetitions, $(TA)_7$, in the homozygous state, is associated with precancerous colonic lesions and/or with specific colorectal cancer characteristics.

Material and methods: All patients treated for colorectal cancer in a tertiary care centre, between January 2009 and December 2013, who had routine *UGT1A1* genotyping for irinotecan dose-adjustment were included. Data were retrospectively collected.

Results: 292 patients were enrolled, including 23 *UGT1A1**28/*28 homozygous (7.9%), 137 wild type homozygous (46.9%) and 132 heterozygous (45.2%). There were no significant differences in phenotypic colonic characteristics between homozygous and heterozygous patients carrying the UGT1A1*28 allele as compared to *1/*1 homozygous. Patients treated with aspirin were significantly more common in the *UGT1A1**28/*28 homozygous group than in the other groups (7/23 (30.4%) compared to 22/269 (8.2%), p = 0.001).

Conclusion: Dinucleotide polymorphism in the promoter region of the *UGT1A1* gene is not associated with a specific colonic phenotype in patients with sporadic colorectal cancer.

1. Introduction

According to the 2012 GLOBOCAN, colorectal cancer (CRC) is the third most common cancer in men (746,000 cases, 10.0% of the total) and the second in women (614,000 cases, 9.2% of the total) worldwide [1]. Some risk factors for colorectal cancer are well-known such as age, family history of CRC in the first degree, a body mass index (BMI) greater than 25 kg/m^2, tobacco usage, and red meat consumption [2].

Xenobiotics are exogenous substances (drugs, food components or environmental pollutants). Some of these are involved in colorectal carcinogenesis [3]. Xenobiotic metabolism, mainly operated by the liver, is based on the coordinated action of biotransformation enzymes and transporters expressed by the biliary membranes of hepatocytes. Phase I enzymes, mainly cytochrome P450 monooxygenases, ensure functionalization reactions, while phase II enzymes perform the conjugation reactions [4,5].

Uridine-diphospo glucuronosyltranferases (UGTs) catalyse the conjugation reactions of endogenous (e.g., bilirubin, bile acids, steroid hormones) and exogenous substrates with glucuronic acid.

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https://doi.org/10.1016/j.dld.2018.11.032
1590-8658/

This process favours the formation of hydrophilic compounds which are excreted through the bile ducts or urinary tract [6]. UGT1A1, one of nine human isoforms, is involved in the metabolism of carcinogens such as polycyclic aromatic hydrocarbons (PAH) or 2-amino-1-methyl-6-phenylimidazo (4,5-b) pyridine (PhIP) (reference). These carcinogens are involved in the development of colorectal, breast and prostate cancer [7,8].

The *UGT1A1* gene has over 60 different genetic polymorphisms [9]. Allelic variations have been described in the UGT1A1 gene, both in the promoter and in its 5th exon. The most common (wild-type) allele *UGT1A1*1* comprises six Thymine–Adenine (TA) dinucleotide repeats in the promoter region (in the vicinity of the TATA box). The number of TA repeats, ranging from five (*UGT1A1*36*, proficient allele) to eight (*UGT1A1*37*, deficient allele). *UGT1A1* 28* variant, contains 7 TA repeats, is a frequent variant associated with Gilbert's syndrome in the Caucasian population. It was the only variant investigated in this study. This insertion affects the promoter binding of the transcription factor IId (TFIId), which plays a major role in the initiation of transcription. Consequently, this polymorphism is associated with variations in the level of enzyme activity, which is inversely proportional to the number of (TA) replicates. Homozygous carriers for the *UGT1A1*28* allele have a 70% lower transcription rate, and a corresponding decreased enzyme activity, in contrast to *UGT1A1*1* [10]. We hypothesised that the reduced UGT1A1 enzyme activity observed in *UGT1A1*28* carriers, by reducing procarcinogen elimination, could influence the occurrence of precancerous colic lesions and/or the characteristics of colorectal cancer. It is now well-established that the location of the primitive tumour correlates with clinical outcome. Right-sided colorectal cancer is becoming increasingly frequent, and has particular clinical and biological characteristics, along with a poor prognosis [11]. A study by Van Der Logt et al. showed that UGT1A6 variants were associated with proximal CRCs whereas UGT1A7 variants were associated with distal CRCs [12]. These results suggest a potential role for UGTs in the colonic phenotype, though complementary data are needed. Besides their unique association with colorectal cancer risk, UGTs and other metabolizing enzymes are central to the metabolism of aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs). These agents have a protective effect on colon neoplasia and previous studies have shown that genetic polymorphisms of NSAID-metabolizing enzymes may modulate their chemopreventive effects [13–16].

This study aimed at evaluating a link between a common genetic polymorphism of *UGT1A1* and the colorectal phenotype of patients with sporadic colorectal cancer.

2. Materials and methods

This study was retrospective and conducted in a tertiary care hospital. All adult patients with histologically proven diagnosis of initial or secondary metastatic colorectal cancer, treated between January 2009 and December 2013, were included. Patients with Lynch syndrome, Familial adenomatous polyposis (FAP), inflammatory bowel disease and synchronous colorectal cancer were excluded. Data were retrospectively collected from electronic medical records.

All patients underwent UGT1A1*28 genotyping after information and written consent, in anticipation of a treatment with irinotecan. Data retrieved from medical records were gender, age at diagnosis, Body Mass Index (BMI), family history of colorectal cancer and daily aspirin use. Overweight was defined as a BMI greater than 25 kg/m^2 and obesity was defined as a BMI greater than 30 kg/m^2. Familial history included colorectal cancer history in a first-degree relative. The colorectal phenotype of patients was established from data obtained by colonoscopy at diagnosis and/or colonoscopies performed in the five years preceding or following diagnosis, as well as the study of surgical specimens if necessary. Data were thus collected from the primary tumour, including location, size, pathologic description (differentiation, mucinous component, presence of vascular emboli and/or perineural invasion), TNM (2017) stage and biological molecular data (MMR status, KRAS and BRAF status). MMR status was determined by microsatellite instability (MSI) testing. Genomic DNA was extracted from either paraffin-embedded tissues or frozen samples. MSI was assessed using five consensus nucleotide repeats (BAT-25, BAT-26, NR-21, NR-24 and NR-27), as recommended [17]. MSI was defined by the presence of instability affecting at least two markers. The same tumour DNA was used to determine KRAS mutation (codons 12 and 13) and BRAF mutation (V600E) status. Additional data were collected from the colorectal lesions: size, number, proximal or distal location, and pathological description. Right lesions were between the caecum and the left corner, left lesions were located between the left corner and the rectosigmoid junction, rectal location was separated. Different polyps were classified as adenomas (tubular, villous or tubulovillous) according to their degree of dysplasia (low or high grade) or hyperplastic polyps. Advanced adenomas were defined as adenomas whose size was $\geq$ 10 mm or with a villous component or high-grade dysplasia.

UGT1A1 genotyping assay

Genomic DNA was extracted from peripheral blood leukocytes. The promoter region of the *UGT1A1* gene containing the TATAbox was amplified by polymerase chain reaction (PCR) with a DNA thermal cycler, using the forward primer GCTCCACCTTCTTTATCTCTG and the fluorescent reverse primer FAM-CAGCATGGGACACCACTG. The PCR reaction was carried out in a total volume of 50 μL, containing 100 ng total DNA, 1 μL of each primer (10 μM), 5 μL Accuprime® PCR buffer II (10X), and 1 μL Taq polymerase (Invitrogen, Carlsbad, Calif, USA). The amplification protocol consisted of an initial denaturation step at 95 °C for 4 min, 22 thermocycling cycles (annealing at 55 °C for 60 s and primer extension at 72 °C for 30 s) and a final extension step at 72 °C for 10 min. The length of the PCR product generated depended on the number of Thymine-Adenine (TA) repeats in the promoter region. PCR products were separated by size using capillary electrophoresis on an Applied 3130XL DNA capillary sequencer (Applied Biosystems, Carlsbad, Calif, USA). The GeneScan™ 500 ROX™ Size Standard was used as a standard to extrapolate the size of the sample product peaks. The method has been previously validated in our laboratory against Sanger sequencing. Three different genotypes were defined: homozygous for the $(TA)_6/(TA)_6$ allele, homozygous for the *28 variant $(TA)_7/(TA)_7$ and heterozygous $(TA)_7/(TA)_6$. We used a simple calculator to determine whether observed genotype frequencies were consistent with Hardy-Weinberg equilibrium. We compared homozygous $(TA)_7/(TA)_7$ with heterozygous $(TA)_7/(TA)_6$ and homozygous patients $(TA)_6/(TA)_6$.

2.1. Statistical analysis

Descriptive data are described as means + standard deviation or percentages. Statistical analysis was performed using STATA 9 and ExcelStat software. The Chi^2 test was used to assess the association between UGT1A1 polymorphism and colorectal phenotype. The Student test was used for comparisons of means. $P < 0.05$ indicated statistical significance.

3. Results

3.1. Patients

Six hundred and fifty-three blood samples were taken for UGT1A1 genotyping between January 2009 and December 2013, of which 304 corresponded to a diagnosis of colorectal cancer. Among

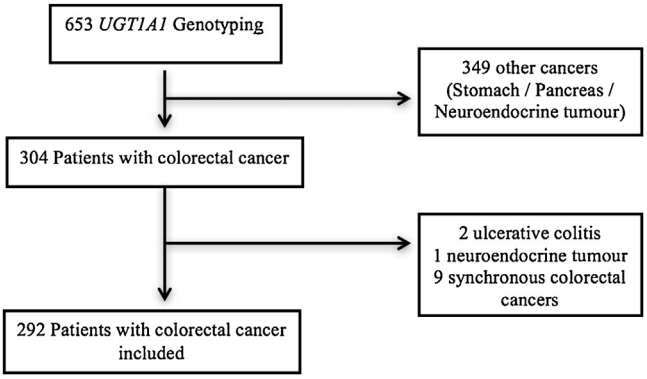

Fig. 1. Flow chart. Process used to select the patients to be analysed.

Table 1
Patient characteristics (n = 292).

	Number	%
Gender		
Female	136	46.6
Male	156	53.4
Age at diagnosis		
Average	65.4 years	
Median	65 years	
Min-Max	25–91 years	
Aspirin use	29	10
Familial history	32	11.0
BMI (n = 286)		
≥30	58	20.3
25 ≥ BMI > 30	90	31.5
<25	144	48.2
UGT1A1 status (n = 292)		
$(TA)_7/(TA)_7$	23	7.9
$(TA)_7/(TA)_6$	132	45.2
$(TA)_6/(TA)_6$	137	46.9

them, 12 were excluded (one patient had a cancer with a neuroendocrine component, 2 patients had ulcerative colitis (UC), and 9 had synchronous colorectal cancers). Of the 653 patients who benefited from *UGT1A1* genotyping during the study period, 292 patients were included (Fig. 1**)**. Most patients shared a Caucasian genetic background. There were no patients with FAP or Lynch syndrome. Patients were predominantly men (n = 156, 53.4%) and the mean age at diagnosis was 65.4 years. Fifty-eight (20.3%) were obese with a BMI greater than 30 kg/m^2. Aspirin use was not frequent (10%, n = 29) and was prescribed for secondary cardiovascular prevention, at a daily dose of 75 or 160 mg (Table 1**)**. The *UGT1A1* genotypes among patients were as follows: 7.9% (n = 23) were homozygous for the *UGT1A1*28* allele ($(TA)_7/(TA)_7$), 46.9% (n = 137) were homozygous for the common allele *UGT1A1*1* ($(TA)_6/(TA)_6$) and 45.2% (n = 132) were heterozygous $(TA)_7/(TA)_6$. Our observed genotype frequencies did not deviate from the Hardy-Weinberg equilibrium (p value 0.254409)

3.2. Colorectal phenotype

Among the 292 patients, 169 were metastatic at diagnosis (58.1%). When the disease was not metastatic, stage III accounted for nearly one third of patients (n = 85, 29.2%). Right location was observed in 31%, the remaining 69% having distal tumours. Microsatellite instability analysis was performed in 153 patients (79.7%). The tumour had a stable molecular phenotype (MSS) in 91.5% of cases (n = 140). Among the 13 cases with unstable phenotype (MSI), none had Lynch syndrome. When the KRAS status was requested, it was mostly of wild-type genotype (n = 154, 60.2%). BRAF mutation was detected in 17/23 (7.4%) of patients (Table 2**)**.

Table 2
Colorectal phenotype: cancer charateristics.

	Number	%
Stage at diagnosis (n = 291)		
Non metastatic	122	41.9
Metastatic	169	58.1
Stage I	6	2
Stage II	31	10.7
Stage III	85	29.2
Stage IV	169	58.1
Location (n = 292)		
Proximal	90	30.8
Distal	202	
Left-side	126	43.2
Rectum	76	26.0
Differentiation (n = 271)		
Well to moderately differentiated	216	79.7
Poorly differentiated	55	20.3
Mucinous component	57	20.65
Microsatellite instability (n = 153)		
MSS	140	91.5
MSI	13	8.5
KRAS (n = 256)		
KRAS wild-type	154	60.2
KRAS mutation	102	39.4
BRAF (n = 231)		
BRAF wild-type	214	92.6
BRAF mutation	17	7.4

Table 3
colorectal phenotype: adenomas and hyperplastic polyps.

	Number	%
Patients with a complete colonic exploration	212	72.6
No polyps/adenomas	110	51.9
Adenomas	89	42
Only proximal	29	32.6
Only distal	35	39.3
Proximal and distal	25	28.1
Advanced adenomas	51	57.30
Average number of adenomas	2.4/patient	(1–15)
Hyperplastic polyps	49	23.1
Only proximal	7	14.30
Only distal	37	75.5
Proximal and distal	5	10.2
Average number of hyperplastic polyps	2.4/patient	(1–8)
Proximal adenomas and/or hyperplastic polyps	58	27.36

Among the 292 patients, 212 (72.6%) underwent complete colon exploration, either at diagnosis by full colonoscopy, or during cancer surgery (surgical specimen and colonoscopy pre or post-operative) or within five years before or after the diagnosis. Patients who did not undergo complete exploration had either stenosing tumour with metastatic disease at the onset, contraindicating surgery, or died before the completion of examinations. About 51.9% of patients with a complete colonic exploration had neither hyperplastic polyps nor adenomatous polyps. Eighty-nine patients (42%) had adenomas, including 51 advanced adenomas. The average number of adenomas was 2.4 per patient, with a maximum of 15 adenomas per patient. Forty-nine patients (23.1%) had hyperplastic polyps. The average number of hyperplastic polyps per patient was also 2.4 (Table 3**)**.

Study according to UGT1A1 polymorphism

There was no significant difference in the colorectal phenotype characteristics of the cancer or polyp in homozygous patients for the variant *28, $(TA)_7/(TA)_7$, by comparison with carriers of the common allele (Table 4**)**. There was a significant difference in the proportion of patients treated with aspirin, with a higher prevalence in homozygous patients $(TA)_7/(TA)_7$ than in the group of $(TA)_6$ carriers with 7 of 23 patients (30.4%) and 22 of 269 patients (8.2%), respectively (p = 0.001).

Table 4
Comparison of homozygous patients $(TA)_7/(TA)_7$ with other patients. HP: hyperplastic polyps; A: adenomas.

	Number (%) $(TA)_7/(TA)_7$	Number (%) $(TA)_6/(TA)_7$ + $(TA)_6/(TA)_6$	p
Patients			
Female	9 (39.1)	127 (47.2)	NS
Age	65,3 ys	65.4 ys	
Aspirin use	7 (30.4)	22 (8.2)	0,001
Familial history	3 (13)	29 (10.9)	NS
BMI > 25	14 (60.9)	134 (51)	NS
Colorectal phenotype			
Cancers			
Proximal	6 (26.1)	84 (31.2)	NS
Metastatic	10 (43.5)	159 (59.1)	NS
MSS	10 (90.9)	130 (91.5)	NS
KRAS wild-type	9 (42.9)	145 (61.7)	NS
BRAF wild-type	17 (94.4)	197 (92.5)	NS
Mucinous component	6 (28.6)	51 (19)	NS
Adenomas	11 (55)	78 (40.6)	NS
Proximal adenomas	6 (54.5)	48 (61.5)	
Average number	2.8	2.3	
Hyperplastic polyps	6 (30)	43 (22.4)	NS
Proximal HP	0 (0)	12 (27.9)	NS
Advanced adenomas	4 (20)	48 (25)	NS
Proximal A et/or HP	6 (30)	52 (27)	NS

4. Discussion

This study was designed to evaluate a putative relationship between the *UGT1A1*28* polymorphism and the colorectal phenotype of patients with sporadic colorectal cancer. To our knowledge, this is the first study investigating this endpoint. Furthermore, other studies have evaluated the occurrence of polyps (adenomas or hyperplastic) with regard to polymorphisms of phase II enzymes, N-acetyl- transferases and sulfotransferases p.e., but with conflicting results [18].

Our hypothesis was that a variation in enzymatic activity resulting from a genetic polymorphism in the *UGT1A1* promoter, could influence the occurrence of polyps and/or modify their location or their characteristics. A relationship between the patient's genotype and their colorectal phenotype could identify groups of patients with different risks of polyps and therefore change our strategy for screening and monitoring.

Our study did not show any significant difference between patients homozygous for the *UGT1A1*28* allele and patients with the *UGT1A1*1* wild type allele, both in terms of the characteristics of cancer (pathology analysis, stage, molecular data) and polyps (type, number, location).

The median age at diagnosis, for patients treated for metastatic colorectal cancer in our hospital over a period of 4 years, was 65 years. This is five years younger than the median age at diagnosis of CRC in France, estimated at approximately 70 in 2013. This difference was probably because our study population consisted of patients with metastatic colorectal cancer, candidates for chemotherapy only. The male predominance (53.4%) was as expected in the French population (55%). The proportions of *UGT1A1*28* homozygous $(TA)_7/(TA)_7$ (7.9%), heterozygous $(TA)_7/(TA)_6$ (45.2%) and *UGT1A1*1* homozygous patients $(TA)_6/(TA)_6$ (49.6%) in our study population were similar to those of genotypes usually found in the general Caucasian population: between 8% and 20% for homozygous *28/*28, between 40% and 50% for heterozygous and between 30% and 50% for non-carriers of the variant *28 variant [9].

Bajro et al. showed that there was a higher frequency of UGT1A1*28 carriers than wild type UGT1A1*1 allele in colorectal cancer patients than in controls. After stratification on sex however, the UGT1A1*28 allele was a risk factor for CRC only in men [19]. Contrary to these results, the UGT1A1*28 allele was not more highly represented in our population of patients with colorectal cancer, indicating that its influence on the occurrence of cancer was not found in our study.

We were particularly interested in the UGT1A1 enzyme, because it is a phase II enzyme with multiple substrates, including procarcinogens (such as polycyclic aromatic hydrocarbons (PAHs)). Several studies have suggested that the genetic polymorphism of xenobiotic metabolizing enzymes, including phase II enzymes such as UGTs, could be a colorectal cancer risk factor [12,20]. Procarcinogens are xenobiotics whose metabolites acquire carcinogenicity, in particular by epoxide formation. The modification of phase II enzyme activity can be deleterious by decreasing the conjugation, and thus the elimination, of reactive metabolites. Polycyclic aromatic hydrocarbons or heterocyclic amines are examples of xenobiotics which could promote colorectal carcinogenesis. Thus, in the *Girard et al.* study, genetic polymorphisms of UGT1A1 and UGT1A9 were significantly associated with a risk of colorectal cancer, particularly when there was an exposure to dietary carcinogens (benzo(a)pyrene(BaP) in particular) [21]. We were also interested in UGT1A1 polymorphism because it is a predictive biomarker of irinotecan toxicity [22]. UGT1A1*28 patients are expected to experience more serious side effects induced by chemotherapy, and pre-therapeutic genotyping strategies exist to adapt irinotecan doses according to patient polymorphism [23].

The only significant difference found in our study concerned Aspirin use, which was more frequent in homozygous *28/*28 patients. There is good evidence that the regular use of aspirin or NSAIDs decreases the risk of colorectal cancer and adenomatous polyps [24]. Some studies have found significant results regarding the influence of NSAIDs and polymorphism of the genes encoding for Phase II enzymes genes, on the risk of colorectal cancer and adenomas [13]. Previous studies have, however, shown an interaction between the protective effects of aspirin or NSAIDs and the polymorphism of enzymes involved in their metabolism. Variant alleles of CYP2C9 and of several UGTs have been shown to modify the protective effects of aspirin against colon adenoma risk, albeit with contradictory results according to the studies and the type of neoplasia [13–15]. The influence of UGT1A1*28 polymorphism on the benefit of these treatments has not yet been evaluated. Our study was not, however, designed for this analysis and our observation does not contribute to this topic.

Aspirin is principally glucuronidated by UGT isoenzyme 1A6. It has been shown that the effect of chemoprevention by aspirin is variable according to the variants of UGT1A6 [25]. It is possible that the UGT1A1*28 variant could influence the metabolism of aspirin, decreasing its therapeutic efficacy. Such an effect, however, remains to be demonstrated. Another hypothesis would be that the risk of CRC is higher in the UGT1A1*28 group and that aspirin only decreases this higher baseline risk.

The main weakness of this study was the lack of controls, preventing us from assessing the exact influence of UGT1A1 polymorphism on the occurrence of adenoma and/or hyperplastic polyps, along with its potential role as a CRC risk factor.

Furthermore, the expression of xenobiotic metabolizing enzymes, in addition to being influenced by genetic polymorphism, may also be modified by environmental factors and by drugs. Thus, smoking, phenobarbital use (enzyme inducer) and diet (including cooked red meat consumption) are all potential confounding factors not taken into account [26].

The UGT1A family is large with highly polymorphic genes. Genotyping of several UGT families could help determine not only patients at higher risk of CRC, but also patients who could benefit from chemoprevention by aspirin.

5. Conclusion

Our study failed to demonstrate a link between genetic *UGT1A1* polymorphism and colorectal phenotype of patients with colorectal cancer, implying no need to change our colonoscopic monitoring strategy. Nevertheless, our study could suggest that chemoprevention with aspirin for CRC may not be advantageous in subgroups of patients with certain *UGT1A1* genetic polymorphisms. Further prospective studies, with a greater number of patients are needed to better define these subgroups.

Conflicts of interest
None declared.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments. The study was approved by the local ethics committee (N° 2018 059).

Informed consent

Informed consent was obtained from all individual participants included in the study.

Acknowledgment

Etienne DORVAL, Jean-Pierre BARBIEUX.

References

[1] Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer 2015;136:E359–86.
[2] Johnson CM, Wei C, Ensor JE, Smolenski DJ, Amos CI, Levin B, et al. Meta-analyses of colorectal cancer risk factors. Cancer Causes Control 2013;24:1207–22.
[3] Potter JD. Colorectal cancer: molecules and populations. J Natl Cancer Inst 1999;91:916–32.
[4] Ma Q. Xenobiotic-activated receptors: from transcription to drug metabolism to disease. Chem Res Toxicol 2008;21:1651–71.
[5] Zhang Q, Pi J, Woods CG, Andersen ME. Phase I to II cross-induction of xenobiotic metabolizing enzymes: a feedforward control mechanism for potential hormetic responses. Toxicol Appl Pharmacol 2009;237:345–56.
[6] Tukey RH, Strassburg CP. Human UDP-glucuronosyltransferases: metabolism, expression, and disease. Annu Rev Pharmacol Toxicol 2000;40:581–616.
[7] Ito N, Hasegawa R, Sano M, Tamano S, Esumi H, Takayama S, et al. A new colon and mammary carcinogen in cooked food, 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine (PhIP). Carcinogenesis 1991;12:1503–6.
[8] Shirai T, Sano M, Tamano S, Takahashi S, Hirose M, Futakuchi M, et al. The prostate: a target for carcinogenicity of 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine (PhIP) derived from cooked foods. Cancer Res 1997;57:195–8.
[9] Boyer JC, Etienne-Grimaldi MC, Thomas F, Quaranta S, Picard N, Loriot MA, et al. [Interest of UGT1A1 genotyping within digestive cancers treatment by irinotecan]. Bull Cancer 2014;101:533–53.
[10] Beutler E, Gelbart T, Demina A. Racial variability in the UDP-glucuronosyltransferase 1 (UGT1A1) promoter: a balanced polymorphism for regulation of bilirubin metabolism? Proc Natl Acad Sci U S A 1998;95:8170–4.
[11] Gallois C, Pernot S, Zaanan A, Taieb J. Colorectal cancer: why does side matter? Drugs 2018;78:789–98.
[12] van der Logt EM, Bergevoet SM, Roelofs HM, van Hooijdonk Z, te Morsche RH, Wobbes T, et al. Genetic polymorphisms in UDP-glucuronosyltransferases and glutathione S-transferases and colorectal cancer risk. Carcinogenesis 2004;25:2407–15.
[13] Chan AT, Hsu M, Zauber AG, Hawk ET, Bertagnolli MM. The influence of UGT1A6 variants and aspirin use in a randomized trial of celecoxib for prevention of colorectal adenoma. Cancer Prev Res (Phila) 2012;5:61–72.
[14] Bigler J, Whitton J, Lampe JW, Fosdick L, Bostick RM, Potter JD. CYP2C9 and UGT1A6 genotypes modulate the protective effect of aspirin on colon adenoma risk. Cancer Res 2001;61:3566–9.
[15] Scherer D, Koepl LM, Poole EM, Balavarca Y, Xiao L, Baron JA, et al. Genetic variation in UGT genes modify the associations of NSAIDs with risk of colorectal cancer: colon cancer family registry. Genes Chromosomes Cancer 2014;53:568–78.
[16] Sheth H, Northwood E, Ulrich CM, Scherer D, Elliott F, Barrett JH, et al. Interaction between polymorphisms in aspirin metabolic pathways, regular aspirin use and colorectal cancer risk: a case-control study in unselected white European populations. PLoS One 2018;13:e0192223.
[17] Boland CR, Thibodeau SN, Hamilton SR, Sidransky D, Eshleman JR, Burt RW, et al. A National Cancer Institute Workshop on Microsatellite Instability for cancer detection and familial predisposition: development of international criteria for the determination of microsatellite instability in colorectal cancer. Cancer Res 1998;58:5248–57.
[18] Goode EL, Potter JD, Bamlet WR, Rider DN, Bigler J. Inherited variation in carcinogen-metabolizing enzymes and risk of colorectal polyps. Carcinogenesis 2007;28:328–41.
[19] Bajro MH, Josifovski T, Panovski M, Jankulovski N, Nestorovska AK, Matevska N, et al. Promoter length polymorphism in UGT1A1 and the risk of sporadic colorectal cancer. Cancer Genet 2012;205:163–7.
[20] Strassburg CP, Vogel A, Kneip S, Tukey RH, Manns MP. Polymorphisms of the human UDP-glucuronosyltransferase (UGT) 1A7 gene in colorectal cancer. Gut 2002;50:851–6.
[21] Girard H, Butler LM, Villeneuve L, Millikan RC, Sinha R, Sandler RS, et al. UGT1A1 and UGT1A9 functional variants, meat intake, and colon cancer, among Caucasians and African-Americans. Mutat Res 2008;644:56–63.
[22] Gagne JF, Montminy V, Belanger P, Journault K, Gaucher G, Guillemette C. Common human UGT1A polymorphisms and the altered metabolism of irinotecan active metabolite 7-ethyl-10-hydroxycamptothecin (SN-38). Mol Pharmacol 2002;62:608–17.
[23] Fujii H, Yamada Y, Watanabe D, Matsuhashi N, Takahashi T, Yoshida K, et al. Dose adjustment of irinotecan based on UGT1A1 polymorphisms in patients with colorectal cancer. Cancer Chemother Pharmacol 2018.
[24] Wilkins T, McMechan D, Talukder A. Colorectal cancer screening and prevention. Am Fam Physician 2018;97:658–65.
[25] Chan AT, Tranah GJ, Giovannucci EL, Hunter DJ, Fuchs CS. Genetic variants in the UGT1A6 enzyme, aspirin use, and the risk of colorectal adenoma. J Natl Cancer Inst 2005;97:457–60.
[26] Ritter JK, Kessler FK, Thompson MT, Grove AD, Auyeung DJ, Fisher RA. Expression and inducibility of the human bilirubin UDP-glucuronosyltransferase UGT1A1 in liver and cultured primary hepatocytes: evidence for both genetic and environmental influences. Hepatology 1999;30:476–84.