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UGT2B17 Deletion Polymorphism is a Risk Factor for Upper Aero digestive-Tract Cancer in Japanese: A Case-Control Study

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Abstract

Background: The UDP-glucuronosyltransferase 2 family polypeptide B17 (UGT2B17) detoxifies carcinogens found in tobacco smoke and ethanol in alcoholic drinks. Tobacco carcinogens and ethanol synergistically raise the risk for upper aero digestive tract (UADT) cancer (head and neck squamous carcinoma, and esophageal cancer). Deletion polymorphism of the UGT2B17 gene (UGT2B17-deletion) is a much more common copy number variant among Japanese than other populations. Thus, we conducted a nested and age/gender-matched case-control (1:1) study to determine if UGT2B17-deletion associates with cancer risk, including UADT-cancer in Japanese.

Methods: Polymerase chain reaction was used to determine UGT2B17-deletion using DNA samples derived from peripheral blood or tumor tissue. Cases were cancer patients and controls were non-cancer patients. Non-conditional and conditional logistic regression analyses were performed. To overcome the issue of multiple-testing, Bonferroni correction was applied to set $p < 0.003$ as statistically significant.

Results: A total of 3,092 patients were enrolled. UGT2B17-deletion was detected in 74% of the 1,887 non-cancer patients and 77% of the 1,205 cancer patients. UGT2B17-deletion was a significant risk factor for UADT-cancer development: odds ratio, 2.07; 95% confidence interval, 1.34 to 3.20, p=0.001. In contrast, UGT2B17-deletion was not a risk for any other type of cancers represented in our study population.

Conclusions: These results suggest that UGT2B17-deletion may associate to increase the risk of UADT-cancer in Japanese.

Keywords: UGT2B17; Cancer; Tumor; Susceptibility; Smoking; Alcohol

Abbreviations:

25OHD: 25-hydroxyvitamin D; 95%CI: 95% Confidence Intervals; HNSCC: Head and Neck Squamous Cell Carcinoma: OR: Odds Ratios; PCR: Polymerase Chain Reaction; SNPs: Single-Nucleotide Polymorphisms; UADT: Upper Aerodigestive Tract; UGT2B17: UDP-Glucuronosyltransferase 2 Family Polypeptide B17.

Introduction

UDP-glucuronosyltransferase (UGT) belongs to family of enzymes glucuronidate carcinogens, C19 steroids, and xenobiotics [1-3]. UGT2B17 is a member of the UGT family, and deletion polymorphism of the UGT2B17 gene (UGT2B17-deletion) is a much more common copy number variant (CNV) among Japanese than other populations [4-7]. UGT2B17 metabolize androgen hormones. The UGT2B17-deletion may therefore decrease androgen elimination and thus may associate with the development of prostate cancer, since the growth of these cancerous cells is facilitated by androgens [8]. However, it remains controversial whether UGT2B17-deletion is a genuine risk factor for prostate cancer [9] or not [10]. UGT2B17-deletion is associated with decreased glucuronidation of tobacco-specific carcinogens [11] and may be associated with increased risk of lung adenocarcinoma in women [12], although the latter was not confirmed in a recent study [13]. In addition, UGT2B17 was shown to be responsible for 32% of all ethanol glucuronidation [14]. Tobacco and alcohol are major risk factors for upper aerodigestive tract (UADT) cancer, which includes head and neck cancer, and esophageal cancer [15], because these mucosal membranes are exposed directly to

tobacco smoke and alcoholic drink. Multiple alcohol dehydrogenase gene polymorphisms were reported to associate with UADT cancer in the Japanese population [16]. However, the effects of UGT2B17-deletion have not been studied, despite UGT2B17-deletion being highly prevalent in Japanese. Therefore, we aimed to examine the association between UGT2B17-deletion and UADT cancer as well as other types of cancers by conducting age- and gender-matched and nested case-control studies.

Methods

Study design

As a posthoc analyses, we retrospectively used DNA samples of nine prospective cohort studies conducted separately and designed for other objectives: 1) cardiosurgery (n=287), recruited in 2010 at the intensive care unit of Jichi Medical University Saitama Medical Center to study associations between circulating 25-hydroxyvitamin D (25OHD) levels, single-nucleotide polymorphisms (SNPs) of vitamin D receptor and predicted operative mortality of patients with cardiovascular disease [17]; 2) dialysis (n=1,042), ongoing project started from 2011; 3) diabetes mellitus (n=422), recruited between 2011 and 2012 at outpatient clinics of Jikei University school of medicine and Shin-Kashiwa clinic to study associations between 25OHDs, SNPs of vitamin D receptor and renal function of patients with diabetes [18]; 4) neurological diseases (n=355) , ongoing project started from 2012 at division of neurology, Katsushika Medical Center, Jikei University School of Medicine; 5) ovarian cancer (n=242) ongoing project at department of Obstetrics and Gynecology, Jikei University Hospital; 6) lung cancer (n=138), ongoing project started from 2009 at department of surgery, Jikei University Hospital; 7) head and neck squamous cell carcinoma (HNSCC) (n=225), recruited between 2006 and 2012 at department of otorhinolaryngology, Jikei University Hospital [19]; 8) esophagogastrointestinal tract cancer (n=268), ongoing study started from 2010 at Department of Surgery, International University of Health and Welfare; and 9) thyroid cancer (n=113), ongoing study started from 2001 at division of head and neck, Cancer Institute Hospital, Japanese Foundation for Cancer Research. Each of the nine study protocols was reviewed and approved by the Ethics Committee for Biomedical Research of the Institutional Review Board at the Jikei University School of Medicine, the Jichi Medical University School of Medicine, the International University of Health and Welfare, and the Cancer Institute Hospital of Japanese Foundation for Cancer Research. A total of 3,092 patients provided written informed consent to participate in these studies. The entire process of study design, analysis of UGT2B17-deletions, and data analysis was performed in the Division of Molecular Epidemiology, Jikei University School of Medicine. Clinical information was obtained from clinical and surgical charts. Cancer was pathologically diagnosed in detail using tumor tissue specimens.

Both case and control were nested in the study cohorts by matching age and gender. Specifically, the case cohorts comprised patients with any kind of cancer, or specific for each kind of cancer. For each case, one control of the same age and gender was randomly selected from patients without cancer from the mixture of study cohorts.

Samples

With each patient's consent, peripheral blood samples or tumor tissue were collected during a visit to an outpatient clinic and during an operational procedure, respectively. QIAamp DNA Micro Kits 50 (Qiagen, Tokyo, Japan) were used to purify extracted DNA, and NanoVue Plus (General Electric Healthcare Japan, Tokyo, Japan) was used to measure DNA concentration in each sample. The samples were then frozen at -80°C until use.

Polymerase chain reaction to differentiate CNVs of the UGT2B17 gene

There is a high level of sequence identity between the UGT2B17 and UGT2B15 genes. Therefore, gene-specific polymerase chain reaction (PCR) primers were used to distinguish UGT2B17 from UGT2B15, and to distinguish among zero, one and two copies of the UGT2B17 gene. Marker D (Forward primer 5'-TCACAAGTCAATCTCCCATCC-3', Reverse primer 5'-CTGCAGAATATGTCAATAATTGGC-3') is positive for one copy and two copies (100 bp), and Marker J (Forward primer 5'-TGCACAGAGTTAAGAAATGGAGAGATGTG-3', Reverse primer 5'-GATCATCCTATATCCTGACAGAATT-3') is positive for only one copy (900 bp) [20,21]. PCR reactions were carried out in 25-µl mixtures containing 1 µg of genomic DNA, 2.5 µL of 10xLA PCR buffer II, 2 µL of dNTP (400 µM), 0.25 µL of LA Taq (Takara Bio Inc., Shiga, Japan), 18.25 µL of nuclease-free water, and 0.5 µL of each of the two primers (100 pmol/µL). Each reaction mixture was incubated at 94°C for 3 min and then subjected to 30 cycles of 94°C for 20s, 60°C for 30s, and 72°C for 90s. Each reaction was then incubated at 16°C until analysis.

Statistical analysis

The chi-square test was used to evaluate significant differences in the frequency of UGT2B17-deletion polymorphism. Study populations were composed of cases and controls and we used conditional logistic regression to calculate odds ratios (OR) and 95% confidence intervals (95%CI) as estimates of the cancer risk. Each $p<0.05$ was considered statistically significant. Moreover, the Bonferroni correction was used to correct for multiple testing. Logistic regression was performed 12 times for all kinds of cancer, namely, UADT-cancer (head and neck cancer, and esophageal cancer) and 13 other kinds of cancers. The difference was considered significant when the p-value was less than 0.004 that was obtained as p 0.05 divided by 12 time-analyses. All statistical analyses were performed using STATA 13.1 (STATA Corp., College Station, TX).

Results

Characteristics of cohorts

The characteristics of the patients in the cohorts are shown in Table 1. Mean age was 64 years and males comprised 58% of the study population. The frequency of the UGT2B17-deletion was 75% in total, and ranged from 70% to 80% in different cohorts, which was not significantly different among the cohorts (p=0.088).

Cohort of patients with	Total, n (%)	Age, mean (SD)	Male, n (%)	Cancer, n (%)	UGT2B17 gene deletion polymorphism, n (%)

Cardiosurgery	287 (9)	67 (11)	75 (32)	0 (0)	201 (70)
Dialysis	1,042 (34)	63 (12)	731 (70)	166 (16)	792 (76)
Diabetes mellitus	422 (14)	62 (12)	289 (68)	45 (11)	309 (73)
Neurological diseases	355 (11)	70 (13)	170 (48)	8 (2)	273 (77)
Ovarian cancer	242 (8)	54 (11)	0 (0)	242 (100)	178 (74)
Lung cancer	138 (4)	67 (9)	103 (76)	138 (100)	99 (72)
Head and neck squamous cell carcinoma	225 (7)	63 (11)	182 (81)	225 (100)	181 (80)
Esophagogastrointestinal tract cancer	268 (9)	66 (11)	173 (65)	268 (100)	214 (80)
Thyroid cancer	113 (4)	60 (15)	36 (32)	113 (100)	85 (75)
Total	3,092 (100)	64 (12)	1,759 (58)	1,205 (40)	2,332 (75)

Table 1: Patient characteristics.

Cancers in these cohorts

In the mixture of nine cohorts, 1,887 patients did not have cancer and 1,205 did have cancer (Table 2). The frequency of UGT2B17-deletion was 74% in non-cancer patients and 77% in cancer patients, which was not significantly different (p=0.15). Next, patients with various cancers were categorized by type of cancer (Table 3). The frequency of UGT2B17-deletion ranged from 67% to 87% depending on cancer type.

	Number of patients	Age (years) mean (SD)	Gender male (%)	UGT2B17 gene deletion polymorphism, n (%)
Patients without cancer	1,887	64 (13)	1,117 (59)	1,402 (74)
Patients with cancer	1,205	63 (12)	642 (53)	930 (77)
Total	3,092	64 (12)	1,759 (57)	2,332 (75)

Table 2: Deletion polymorphism of the UGT2B17 gene in non-cancer and cancer patients.

	Number of patients	Age (years) mean (SD)	Gender Male (%)	UGT2B17 gene deletion polymorphism, n (%)
Renal cell cancer	31	61 (10)	24 (77)	27 (87)
Esophageal cancer	29	70 (9)	26 (90)	25 (86)
Colorectal cancer	170	67 (10)	104 (62)	140 (82)
Head and neck squamous cell carcinoma	226	63 (11)	183 (81)	181 (80)
Breast cancer	18	65 (10)	0 (0)	14 (78)
Gastric cancer	151	67 (11)	107 (71)	115 (76)
Thyroid cancer	119	60 (15)	38 (32)	90 (76)
Ovarian cancer	243	54 (11)	0 (0)	179 (74)
Lung cancer	146	68 (9)	110 (77)	107 (73)
Hematologic malignancy	11	69 (10)	8 (73)	8 (73)
Other cancers	39	67 (11)	20 (51)	29 (74)
Prostate cancer	16	72 (8)	16 (100)	11 (69)

Hepatocellular carcinoma	6	72 (12)	6 (100)	4 (67)

Table 3: Deletion polymorphism of the UGT2B17 gene in patients with 13 types of cancer.

All cancers

A nested case-control study was performed for all cancer patients and all non-cancer patients. For each of 996 cases, age and gender were completely matched with controls randomly selected from the non-cancer patients (Table 4). Analysis by conditional logistic regression showed a similar trend: OR, 1.24; 95%CI, 1.02 to 1.51, p=0.035. However, these p-values were considered not significant on the basis of multiple testing theory.

	UGT2B17 copy number variants		**Total**
Number of copies	0 copy	1 or 2 copies	
Case with cancer	776	220	996
Control without cancer	731	265	996
Total	1,507	485	1,992

Table 4: Nested and age/gender-matched case-control study of all of cancers.

UADT-cancers

The UGT2B17 gene is associated with gene-protection due to its glucuronidation of carcinogens in tobacco smoke and of ethanol. Therefore, we focused on UADT cancers: head and squamous cell carcinoma, and esophageal cancer. For each case in the UADT-cancer cohort, one age- and gender-matched patient was selected from the non-cancer cohort as a control (Table 5). The analysis by conditional logistic regression showed a significant result: OR, 2.07; 95%CI, 1.34 to 3.20, p=0.001. This p-value was significantly smaller than the pre-defined cutoff point of p=0.004 and thus was considered as significant.

	UGT2B17 copy number variants		**Total**
	0 copy	**1 or 2 copies**	
Case with UADT cancer	206	49	255
Control without cancer	174	81	255
	380	130	510

Table 5: Nested and age/gender-matched case-control study of UADT cancer.

Other cancers

An age/gender-matched case-control study was applied to each kind of cancer in a manner similar to UADT-cancer: renal cell cancer, colorectal cancer, breast cancer, gastric cancer, thyroid cancer, ovarian cancer, lung cancer, hematologic malignancy, prostate cancer, and hepatic cell cancer. In colorectal cancer, UGT2B17-deletion was more frequent in cases than in controls: OR, 1.85; 95% CI, 1.07 to 3.22, p=0.020. Analysis by conditional logistic regression showed a similar trend: OR, 1.90; 95% CI, 1.11 to 3.27, p=0.020. These p-values were larger than the pre-defined cutoff point and thus the associations were considered as not significant. Furthermore, there were no significant differences between the other types of cancers and UGT2B17.

Discussion

This study found that UGT2B17-deletion was a significant risk only for the development of UADT-cancer, which is the first report to our knowledge. Head and neck squamous cell carcinomas (HNSCC) arise from mucosa lining the paranasal sinuses, nasal cavities, oral cavity, nasopharynx, oropharynx, hypopharynx and larynx. These anatomical sites can be directly exposed to extremely high levels of carcinogens via tobacco and alcohol use. Indeed, at least 75% of HNSCC from the oral cavity, pharynx and larynx are attributed to smoking and/or alcohol use [22]. In addition, tobacco and alcohol use synergistically raise the risk of HNSCC [23]. Moreover, a synergistic effect between smoking tobacco and consuming alcohol has been reported for esophageal cancer [24]. UGT2B17 at least partially glucuronides carcinogens in tobacco smoke and ethanol in alcoholic drinks; consequently, UGT2B17-deletion can result in decreased elimination of carcinogens and ethanol, which explains the main result of this study that UGT2B17-deletion may be a risk for UADT-cancer.

On the other hand, UGT2B17-deletion was not a significant factor for cancer itself in this study. Recent meta-analysis also showed that UGT2B17-deletion was not associated with cancer susceptibility [25], consistent with our results. However, this meta-analysis included only four kinds of cancer: prostate cancer, lung cancer, colorectal cancer, and breast cancer, whereas our study included many types of cancers.

With the exception of UADT-cancer, the other type of cancer had no significant association with UGT2B17-deletion in this study. A

previous study showed significant association in women with lung adenocarcinoma [12], but another recent study could not detect significant association in lung cancer [13]. On the other hand, UGT2B17-deletion was reported to associate with a decreased colorectal cancer risk in a Caucasian population [26], which is opposite direction to our and previous reports, and has not been supported by other reports. Currently, therefore, there is no clear evidence showing association between UGT2B17-deletion and cancer risk.

There are several limitations to this study. First, controls were not healthy adults but patients with diabetes, cardiac disease, and neurological diseases. However, UGT2B17-deletion was observed in 74% of healthy adults [5], which is equal to the frequency of 74% observed in patients without cancer in this study. Second, ovarian, head and neck, colorectal, gastric, lung, and thyroid cancers were dominant in our sample population, but the distribution did not reflect the real frequency of each cancer in the Japanese population. Third, the number of patients with each cancer type was too small to allow the detection of statistically significant differences, although a total number of 1,402 cancer patients were included in this study. Fourth, the results obtained in our study may only be applicable to the Japanese population, in which UGT2B17-deletion is much more prevalent than in other populations.

Conclusion

Deletion polymorphism of the UGT2B17 gene may associate with UADT-cancer risk in the Japanese population.

Author's Contributions

MU, KY, HK, and AO designed the study. AN, TH, YS, HO, TA, MS, MN, YT, KT, KW, HK, and AO contributed to collecting the tissue samples and clinical data. NA and AM have carried out molecular studies. AM and MU performed analysis and interpretation of data. MU participated in drafting the manuscript. All authors have read and approved the final manuscript.

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References

1. Vienneau DS, DeBoni U, Wells PG (1995) Potential genoprotective role for UDP-glucuronosyltransferases in chemical carcinogenesis: initiation of micronuclei by benzo(a)pyrene and benzo(e)pyrene in UDP-glucuronosyltransferase-deficient cultured rat skin fibroblasts. Cancer Res 55: 1045-1051.
2. Beaulieu M, Lévesque E, Hum DW, Bélanger A (1996) Isolation and characterization of a novel cDNA encoding a human UDP-glucuronosyltransferase active on C19 steroids. J Biol Chem 271: 22855-22862.
3. Turgeon D, Carrier JS, Chouinard S, Bélanger A (2003) Glucuronidation activity of the UGT2B17 enzyme toward xenobiotics. Drug Metab Dispos 31: 670-676.
4. Wilson W 3rd, Pardo-Manuel de Villena F, Lyn-Cook BD, Chatterjee PK, Bell TA, et al. (2004) Characterization of a common deletion polymorphism of the UGT2B17 gene linked to UGT2B15. Genomics 84: 707-714.
5. Okano M, Ueda T, Nishitani Y, Kano H, Ikekita A, et al. (2013) UDP-glucuronosyltransferase 2B17 genotyping in Japanese athletes and evaluation of the current sports drug testing for detecting testosterone misuse. Drug Test Anal 5: 166-181.
6. Xue Y, Sun D, Daly A, Yang F, Zhou X, et al. (2008) Adaptive evolution of UGT2B17 copy-number variation. Am J Hum Genet 83: 337-346.
7. Angstadt AY, Berg A, Zhu J, Miller P, Hartman TJ, et al. (2013) The effect of copy number variation in the phase II detoxification genes UGT2B17 and UGT2B28 on colorectal cancer risk. Cancer 119: 2477-2485.
8. Gauthier-Landry L, Blanger A, Barbier O (2015) Multiple roles for udp-glucuronosyltransferase (UGT)2B15 and UGT2B17 enzymes in androgen metabolism and prostate cancer evolution. J Steroid Biochem Mol Biol 145: 187-192.
9. Kpoghomou MA, Soatiana JE, Kalembo FW, Bishwajit G, Sheng W (2013) UGT2B17 Polymorphism and Risk of Prostate Cancer: A Meta-Analysis. ISRN Oncol 2013: 465916.
10. Olsson M, Lindström S, Häggkvist B, Adami HO, Bälter K, et al. (2008) The UGT2B17 gene deletion is not associated with prostate cancer risk. Prostate 68: 571-575.
11. Chen G, Giambrone NE Jr, Dluzen DF, Muscat JE, Berg A, et al. (2010) Glucuronidation genotypes and nicotine metabolic phenotypes: importance of functional UGT2B10 and UGT2B17 polymorphisms. Cancer Res 70: 7543-7552.
12. Gallagher CJ, Muscat JE, Hicks AN, Zheng Y, Dyer AM, et al. (2007) The UDP-glucuronosyltransferase 2B17 gene deletion polymorphism: sex-specific association with urinary 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol glucuronidation phenotype and risk for lung cancer. Cancer Epidemiol Biomarkers Prev 16: 823-828.
13. Gruber M, Le T, Filipits M, Gsur A, Mannhalter C, et al. (2013) UDP-glucuronosyltransferase 2B17 genotype and the risk of lung cancer among Austrian Caucasians. Cancer Epidemiol 37: 625-628.
14. Al Saabi A, Allorge D, Sauvage FL, Tournel G, Gaulier JM, et al. (2013) Involvement of UDP-glucuronosyltransferases UGT1A9 and UGT2B7 in ethanol glucuronidation, and interactions with common drugs of abuse. Drug Metab Dispos 41: 568-574.
15. Anantharaman D, Marron M, Lagiou P, Samoli E, Ahrens W, et al. (2011) Population attributable risk of tobacco and alcohol for upper aerodigestive tract cancer. Oral Oncol 47: 725-731.
16. Oze I, Matsuo K, Suzuki T, Kawase T, Watanabe M, et al. (2009) Impact of multiple alcohol dehydrogenase gene polymorphisms on risk of upper aerodigestive tract cancers in a Japanese population. Cancer Epidemiol Biomarkers Prev 18: 3097-3102.
17. Yang TL, Chen XD, Guo Y, Lei SF, Wang JT, et al. (2008) Genome-wide copy-number-variation study identified a susceptibility gene, UGT2B17, for osteoporosis. Am J Hum Genet 83: 663-674.
18. Tsutsumi Y, Sanui M, Shimojima A, Ishioka H, Urashima M (2012) A cross-sectional study of the association between circulating 25-hydroxyvitamin D levels and predicted operative mortality of patients with cardiovascular disease. J Nutr Sci Vitaminol 58: 327-332.
19. Yokoyama K, Nakashima A, Urashima M, Suga H, Mimura T, et al. (2012) Interactions between serum vitamin D levels and vitamin D receptor gene FokI polymorphisms for renal function in patients with type 2 diabetes. PLoS One 7: e51171.
20. Urashima M, Hama T, Suda T, Suzuki Y, Ikegami M, et al. (2013) Distinct effects of alcohol consumption and smoking on genetic alterations in head and neck carcinoma. PLoS One 8: e80828.
21. Chew S, Mullin BH, Lewis JR, Spector TD, Prince RL, et al. (2011) Homozygous deletion of the UGT2B17 gene is not associated with osteoporosis risk in elderly Caucasian women. Osteoporos Int 22: 1981-1986.

22. Hashibe M, Brennan P, Benhamou S, Castellsague X, Chen C, et al. (2007) Alcohol drinking in never users of tobacco, cigarette smoking in never drinkers, and the risk of head and neck cancer: pooled analysis in the International Head and Neck Cancer Epidemiology Consortium. J Natl Cancer Inst 99: 777-789.

23. Hashibe M, Brennan P, Chuang SC, Boccia S, Castellsague X, et al. (2009) Interaction between tobacco and alcohol use and the risk of head and neck cancer: pooled analysis in the International Head and Neck Cancer Epidemiology Consortium. Cancer Epidemiol Biomarkers Prev 18: 541-550.

24. Yaegashi Y, Onoda T, Morioka S, Hashimoto T, Takeshita T, et al. (2014) Joint effects of smoking and alcohol drinking on esophageal cancer mortality in Japanese men: findings from the Japan collaborative cohort study. Asian Pac J Cancer Prev 15: 1023-1029.

25. Deng X, Cheng Y, Yang X, Li S, Zhao R, et al. (2014) Meta-analysis reveals a lack of association between UGT2B17 deletion polymorphism and tumor susceptibility. PLoS One 9: e96812.

26. Angstadt AY, Berg A, Zhu J, Miller P, Hartman TJ, et al. (2013) The effect of copy number variation in the phase II detoxification genes UGT2B17 and UGT2B28 on colorectal cancer risk. Cancer 119: 2477-2485.