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

8UDVKLPD 1DNDVKLPD +DPD 6X]XNL 2KGDL UD $NLED 6X]XNL 1DR\D 07VXPL 8DIXQH $VRGD <RNR\DPD:DGD .
.RMLPD +QG 2NDPRWR $

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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 io.

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.

	1XPEHU RI SDWLHQWV	$JH 6'	*HQGHU PDOH	8*7 % JHQH GHOHWLRQ SRO\PRU
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:

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

UGT2B17 gene is associated with gene-protection due to itsglucuronidation of carcinogens in tobacco smoke and of ethanol.Therefore, we focused

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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