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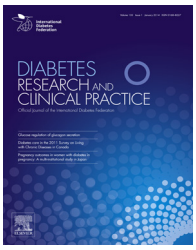

Genetic variants for type 2 diabetes and new-onset cancer in Chinese with type 2 diabetes

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ABSTRACT

Background: Diabetes is associated with an increased risk of cancer. This study aimed to evaluate associations between recently reported type 2 diabetes (T2D) susceptibility genetic variants and cancer risk in a prospective cohort of Chinese patients with T2D.

Methods: Seven single nucleotide polymorphisms (SNP) in *IGF2BP2*, *CDKAL1*, *SLC30A8*, *CDKN2A/B*, *HHEX* and *TCF7L2*, all identified from genome-wide association studies of T2D, were genotyped in 5900 T2D patients [age mean ± SD = 57 ± 13 years, % males = 46] without any known cancer at baseline. Associations between new-onset of cancer and SNPs were tested by Cox proportional hazard models with adjustment of conventional risk factors.

Results: During the mean follow-up period of 8.5 ± 3.3 years, 429 patients (7.3%) developed cancer. Of the T2D-related SNPs, the G-alleles of *HHEX* rs7923837 (hazard ratio [HR] (95% C.I.) = 1.34 (1.08–1.65); $P = 6.7 \times 10^{-3}$ under dominant model) and *TCF7L2* rs290481 (HR (95% C.I.) = 1.16 (1.01–1.33); $P = 0.040$ under additive model) were positively associated with cancer risk, while the G-allele of *CDKAL1* rs7756992 was inversely associated (HR (95% C.I.) = 0.80 (0.65–1.00); $P = 0.048$ under recessive model). The risk alleles of these significant SNPs exhibited combined effect on increasing cancer risk (per-allele HR (95% C.I.) = 1.25 (1.12–1.39); $P = 4.8 \times 10^{-5}$). The adjusted cancer risk was 2.41 (95% C.I. 1.23–4.69) for patients with four risk alleles comparing to patients without risk allele.

Conclusions: T2D-related variants *HHEX* rs7923837, *TCF7L2* rs290481 and *CDKAL1* rs7756992 increased cancer risk in patients with diabetes.

Impact: Our findings provide novel insights into the pathogenesis of cancer in diabetes.

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1. Introduction

Type 2 diabetes (T2D) is a heterogeneous disease characterized by insulin resistance and pancreatic β-cell dysfunction [1]. In different populations, the risk of cancer is increased by approximately 30% in subjects with diabetes or hyperglycaemia compared with the general population [2–4]. Epidemiological studies have showed that diabetic patients are at significantly higher risk for many forms of cancer including pancreas, liver, breast, colorectal, urinary tract, and female reproductive organs [3,5,6]. Mortality due to cancer is also moderately increased by 25% among patients with T2D compared with persons without diabetes [6]. Despite accumulating evidence of a close link between diabetes and cancer, the underlying cause of this association is incompletely understood.

Recently, more than 60 single nucleotide polymorphisms (SNPs) identified through genome-wide association studies (GWAS) have been confirmed to be associated with T2D [7,8]. Additionally, several SNPs were reported to be associated with T2D-related traits, such as fasting plasma glucose and insulin, insulin secretion and sensitivity as estimated by HOMA-IR and HOMA-B indices [9,10]. Most T2D genes have been found to be implicated in beta-cell dysfunction and are believed to increase risk of diabetes through reducing pancreatic insulin secretion [7,10,11]. An emerging phenomenon is the heterogeneity of genetic regions associated with type 2 diabetes, several of which are also found to be associated with other disorders such as ischemic heart disease. For example, a genetic region on chromosome 9p21, near *CDKN2A/B*, in addition to being associated with type 2 diabetes, also appear to harbor variants associated with ischemic heart disease [12], and may contribute to the association between T2D and coronary heart disease [13]. On the other hand, a genetic variant within *TCF2* is associated with increased risk of prostate cancer, and reduced risk of diabetes, in line with the observation that patients with type 2 diabetes have a reduced risk of prostatic cancer [14]. More recently, *TCF7L2*, a gene region most consistently demonstrated to be associated with type 2 diabetes, has been found to be associated with increased risk of colorectal cancer [15]. Overall, type 2 diabetes loci are enriched for genes involved in cell cycle regulation [7]. In this study, we hypothesized that T2D susceptibility genetic variants may act to increase the risk of cancer, which may partly explain the association between T2D and cancer. To test this hypothesis, we examined the associations of seven single nucleotide polymorphisms (SNP) in six T2D genes (*IGF2BP2*, *CDKAL1*, *SLC30A8*, *CDKN2A/B*, *HHEX* and *TCF7L2*) identified from the first wave of GWAS and studied their individual and joint effects on the risk of cancer in a large 8-year prospective cohort of Chinese with T2D.

2. Materials and methods

2.1. Subjects

The study design, ascertainment, inclusion criteria and clinical measurements of the study subjects have been described previously [4]. Briefly, the Hong Kong Diabetes Registry (HKDR) was established at the Prince of Wales Hospital since 1995. Our cohort consisted of 6013 unrelated T2D patients from HKDR enrolled between 1995 and 2005. All subjects were of southern Han Chinese ancestry residing in Hong Kong. We excluded patients in the following analysis if they had a known history of any kind of cancer or who were receiving cancer treatment at enrollment ($N = 113$). The clinical and biochemical characteristics of the study subjects are summarized in Table 1. This study was approved by the Clinical Research Ethics Committee of the Chinese University of Hong Kong. Written informed consent was obtained from each participating subject.

2.2. Clinical measurements and endpoint

All study subjects were examined in the morning after an overnight fast. Anthropometric parameters including body weight and height, waist circumference and blood pressure were measured and fasting blood samples were collected. Glomerular filtration rate (eGFR) was estimated using the abbreviated formula developed by the Modification of Diet in Renal Disease (MDRD) further adjusted for the Chinese ethnicity: $eGFR = 186 \times [S_{CR} \times 0.011]^{-1.154} \times [age]^{-0.203} \times [0.742$ if female$] \times [1.233$ if Chinese$]$ where S_{CR} is serum creatinine expressed as μmol/l and 1.233 is the adjusting coefficient for Chinese population [16]. Use of medications, including oral blood glucose-lowering agents and insulin, were recorded for all study patients. Anti-hypertensive medications included all classes that are indicated for hypertension, other than ACE inhibitors and ARBs. Lipid-lowering medications included statins and fibrates.

All clinical endpoints including hospital admissions and mortality were censored on 31st January, 2009 according to the databases from the Hospital Authority Central Computer System, which records admissions to all public hospitals. Using codes from the *International Classification of Diseases* – Ninth Revision (ICD-9), cancer endpoint was defined as having first incidence of any kind of cancer during follow-up (regardless of whether it was fatal or nonfatal: (1) malignant neoplasm of lip, oral cavity and pharynx: codes 140–149; (2) malignant neoplasm of digestive organs and peritoneum: codes 150–159; (3) malignant neoplasm of respiratory and intrathoracic organs: codes 160–165; (4) malignant neoplasm of bone, connective tissue, skin, and breast: codes 170–176; (5) malignant neoplasm of genitourinary organs: codes179–189; (6) malignant neoplasm of other and unspecified sites: codes 190–199; (7) malignant neoplasm of lymphatic and hematopoietic tissue: codes 200–208). Follow-up time was calculated from the enrollment date to the date of the first cancer event or death or censoring date, whichever came first.

2.3. Genotyping

We selected seven SNPs from six loci (*IGF2BP2* rs4402960, *CDKAL1* rs7756992, *SLC30A8* rs13266634, *CDKN2A/B* rs10811661, *HHEX* rs7923837, *TCF7L2* rs7903146 and rs290481) with genome-wide significant and well-replicated associations with T2D and/or T2D related traits in both Caucasian and Asian populations [8,17]. Genotyping of genomic DNA from all