Association of DR4 (TRAIL-R1) Polymorphisms with Cancer Risk in Caucasians: an Updated Meta-analysis

Wei Chen¹², Wen-Ru Tang¹, Ming Zhang², Kwenjen Chang²*, Yun-Lin Wei²*

Abstract

Death receptor 4 (TRAIL-R1 or DR4) polymorphisms have been associated with cancer risk, but findings have been inconsistent. To estimate the relationship in detail, a meta-analysis was here performed. A search of PubMed was conducted to investigate the association between DR4 C626G, A683C and A1322G polymorphisms and cancer risk, using odds ratios (ORs) with 95% confidence intervals. The results suggested that DR4 C626G and A683C polymorphisms were indeed associated with cancer risk (for C626G, dominant model, OR 0.991, 95% CI 0.866-1.133, p=0.015; for A683C, additive model, OR=1.140, 95% CI: 0.948-1.370, p=0.028; dominant model, OR=1.156, 95% CI: 0.950-1.406, p=0.080) in the Caucasian subgroup. However, the association was not significant between DR4 polymorphism A1322G with cancer risk in Caucasians (For A1322G, additive model: OR 1.085, 95% CI 0.931-1.289, p=0.217; dominant model: OR 1.379, 95% CI 0.934-2.035, p=0.311; recessive model: OR 1.026, 95% CI 0.831-1.268 p=0.429.). In summary, our finding suggests that DR4 polymorphism C626G and A683 rather than A1322G are associated with cancer risk in Caucasians.

Keywords: Death receptor 4 (DR4) - polymorphism - Caucasians - cancer risk

Introduction

Tumor necrosis factor-related apoptosis-inducing ligand (TRAIL), a new member of the TNF superfamily, is a transmembrane protein which can selectively kill cancer cells but not normal cells, making it an attractive agent for cancer therapy (Yagita et al., 2004). TRAIL induces apoptosis by binding to DR4 and DR5 and subsequent activation of the apoptotic cascade through caspase-8 and Fas-associating death domain (FADD), forming the death inducing death-inducing signaling complex (DISC), leading to activation of the executioner caspasases and causing cell death (MacFarlane et al., 1997; Pan et al., 1997; Sprick et al., 2000).

DR4 may play an important role during cell death signaling either as an endogenous factor in the regulation of tumor cells (Wajant et al., 2002). DR4 consists of two extracellular cysteine-rich, ligand-binding pseudorepeats (50s and 90s loops), one single transmembrane helix as well as the apoptosis-triggering cytoplasmic death domain (Hengartner et al., 2000; Evan et al., 2001; Koonrstra et al., 2003; Bouralexis et al., 2005). Some data indicate that normal variations within the sequence of apoptotic genes may lead to suboptimal apoptotic capacity and therefore increased cancer risk. DR4 polymorphisms have been described in different human cancer, such as breast, gastric, bladder, lung cancer and endometriosis (Kuraoka et al., 2005; Wolf et al., 2006; Ulybina et al., 2009; Kim et al., 2012). Polymorphism in the ectodomain of DR4 C626G (rs4871857), A683C (rs17088993) and A1322G (rs2230229) were found in a higher frequency in primary tumors of different origin as compared to matched controls (Fisher et al., 2001). The C626G in the ectodomain region of DR4, whereas A683C in extracellular cysteine-rich domain and A1322G in the death domain of DR4 (Chen et al., 2009).

A number of studies have been conducted to investigate the potential association between DR4 polymorphisms and cancer in human. However, the results have been controversial. Therefore, we conducted a meta-analysis to estimate the possible influence of three DR4 polymorphisms on the risk of cancer.

Materials and Methods

Publication search

PubMed was searched using the search terms “TRAIL-R1 or DR4, or death receptor 4”, “polymorphism” and “cancer” (last search update was on May 10, 2013). Case-control studies containing available genotype frequencies of C626G, A683C and A1322G were chosen. Additional studies were identified by a manual search of the references of original studies. Only the Caucasian ethnicity was included in our paper used in meta-analysis.

¹Faculty of Medicine, ²Faculty of Life Science and Technology, Kunming University of Science and Technology, Kunming, China
*For correspondence: homework18@126.com, kwenjenchang@yahoo.com
Data extraction

Information was carefully extracted from all investigators independently by two of the authors (Chen and Zhang) a consensus on inclusion criteria listed above. Disagreement was resolved by discussion between the two authors. Otherwise, other authors (Tang and Wei) were consulted to resolve. A final decision was made by the majority of the votes. The following data were sought for: first author’s surname, publication year, country origin, ethnicity (categorized as African, Asian or Caucasian), genotyping total number of cases and controls.

Statistical analysis

Information was carefully extracted from each study, the following date of DR4 polymorphisms were assessed for Hardy-Weinberg equilibrium. The strength of association between DR4 polymorphism and cancers was accessed by calculating crude ORs (odds ratios) with 95% CIs (confidence intervals). The pooled ORs were performed for additive genetic model, dominant model and recessive model, respectively. Heterogeneity assumption was checked by a chi-square based Q-test. A significant Q-statistic (p<0.05) indicated heterogeneity among studies. The pooled OR estimate of each study was calculated by the fixed-effects model (Mantel et al., 1959) if there was no significant heterogeneity. Otherwise, the random-effects model was used (DerSimonian et al., 1986).

The potential for publication bias was carried out by a Begg’s test (funnel plot method) and Egger’s linear regression test (p<0.05 considered representative of statistical significance) (Egger et al., 1997). All statistical analyses were performed with Stata version (version 9.0; Stata Corporation, College Station, TX).

Results

Eligible studies

We identified 2874 cases with different cancer types and 3220 controls described C626G genotypes (Table 1), 1939 cases and 2536 controls described A683C genotypes (Table 1), and 1171 cases and 970 controls described A1322G genotypes (Table 1). Considered separately for pooling subgroup analysis. The distribution of genotypes in the controls of all the studies was in agreement with Hardy-Weinberg equilibrium, except two studies (Frank et al., 2005; Mittal et al., 2011).

Meta analysis

The results of the association between the DR4 polymorphism C626G, A683C and A1322G and cancer and the heterogeneity test were shown in Table 2 and Figures (Figures 1-3). The overall results suggested that the evidence of an association between the cancer risk in Caucasian and C626G in dominant genetic models (additive model: OR 1.042, 95% CI 0.955-1.137, p=0.586;
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Table 2. ORs and 95% CI for Cancer and the DR4 Polymorphisms Under Different Genetic Models

| DR4 polymorphisms | Genetic model | Population | Pooled OR (95%CI) | Heterogeneity | Begg’s test | Egger’s test |
|-------------------|---------------|------------|-------------------|--------------|-------------|--------------|
| C626G             | Additive (C vs G) | Caucasian | 1.042 (0.955-1.137) | 0.355 | 0.652 | 0.952 |
|                   | Dominant (C-carriers vs G/G) | Caucasian | 0.991 (0.866-1.133) | 0.315 | 0.892 | 0.921 |
|                   | Recessive (C/C vs G/G) | Caucasian | 1.136 (0.981-1.316) | 0.191 | 0.088 | 0.858 |
| A683C             | Additive (A vs C) | Caucasian | 1.140 (0.948-1.370) | 0.028 | 0.164 | 0.453 |
|                   | Dominant (A-carriers vs B/C) | Caucasian | 1.156 (0.950-1.406) | 0.080 | 0.148 | 0.288 |
|                   | Recessive (A/A vs C/C) | Caucasian | 1.125 (0.789-1.605) | 0.284 | 0.515 | 0.897 |
| A1322G            | Additive (A vs G) | Caucasian | 1.085 (0.913-1.289) | 0.217 | 0.356 | 0.602 |
|                   | Dominant (A-carriers vs G/G) | Caucasian | 1.379 (0.934-2.035) | 0.311 | 0.106 | 0.117 |
|                   | Recessive (A/A vs G/G) | Caucasian | 1.026 (0.831-1.268) | 0.429 | 0.809 | 0.602 |

Figure 2. Forest Plot of ORs Cancer Risk Associated with the DR4 A683C Polymorphism (AA Versus CC) by Source of Controls. The squares and horizontal lines correspond to the study-specific OR and 95% CI. The area of the squares reflects the study-specific weight. The diamond represents the pooled OR and 95% CI.

Publication bias
Funnel plot, Egger’s test and the Begg’s test were done to estimate the publication bias of literatures. The results of the Egger’s test (p>0.05), and the Begg’s test (p>0.05) provided statistical evidence for funnel plot symmetry in the Caucasian subgroups in Table 2.

Discussion
It is biologically plausible that exposure to cancer is a result of the accumulation of genetic variation and a combination of environmental exposure. The genetic susceptibility to cancer may be attributed to the SNP of major genetic pathways. And genetic susceptibility to cancer has been a research focus on scientific community. Recently, DR4 gene variants in the etiology of cancers have drawn increasing attention. Some studies have attempted to discover a possible association between the DR4 polymorphism C626G, A683C and A1322G and the risk of different cancer in population. It is possible that point DR4 polymorphism might be found in cancer in Caucasian ethnicity.

The DR4 C626G polymorphism is the most extensively studied polymorphism in the literatures. But previous studies have produced inconsistent results. With bladder cancer, no differences in genotype or haplotype distribution for C626G polymorphism in DR4 gene were found between bladder cancer patients and controls in Spain (Martinez-Ferrandisa et al., 2007). In Ovarian cancer, alteration of the DR4 gene including C626G does not lead to clinically relevant ovarian cancer predisposition (Horaka et al., 2005). On the contrary, Hazra. (2003) showed an increased risk of C to G transition in 626 position of exon 4 of DR4 gene in bladder cancer. Frank B (Frank et al., 2006) reported that the heterozygous carriers of DR4 626C>G showed a significant association with a decreased colorectal cancer risk. At 2009, Chen B (Frank et al., 2009) indicated that the C626G polymorphism in DR4 gene is associated with cancer susceptibility by a meta-analysis. However, three studies have been published since 2009 increasing the number of cancer (Chen et al., 2009; Korner et al., 2012; Tastemir-Korkmaz et al., 2013). In our meta-analysis indicates DR4 C626G polymorphism is associated with cancer in Caucasian susceptibility.

Similarly, the other missense mutation is DR4 A683C polymorphism studied in the literatures. Tastemir-
Korkmaz D (Tastemir-Korkmaz et al., 2013) find A683C polymorphism the CC variant may be the protective variant in Turkish population with lung cancer. The same result also in an evidence-based meta-analysis by Chen B (Chen et al., 2009). In our studies, DR4 polymorphism A683C is associated with cancer, especially the AC and CC variants in Caucasian.

As for DR4 A1322G polymorphisms not associated with cancer in Caucasian susceptibility. Martinez-Ferrandis JI (Martinez-Ferrandisa et al., 2007) was found no association between A1322G polymorphism and breast cancer in Spanish women, the same result also in Turkish population with lung cancer (Tastemir-Korkmaz et al., 2013). Whereas the DR4 death domain A1322G polymorphism was significantly more frequent in Mantle Cell Lymphoma and chronic lymphocytic leukemia patients than in a sex and age-adjusted healthy population (Fernandez et al., 2004). Maybe using a proper and representative cancer-based and population-based control subjects is very important to reduce biases in genetic studies.

In conclusion, this meta-analysis suggests that the DR4 polymorphism C626G and A683C rather than A1322G are associated with the cancer risk in Caucasian. Future well designed large studies might be necessary to validate this association in different populations incorporated with environmental factors in the susceptibility of singleness cancer.

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References

Bouralexis S, Findlay DM, Evdokiou A (2005). Death to the bad guys: targeting cancer via Apo2L/TRAIL. Apoptosis, 10, 35-51.

Chen B, Liu S, Wang XL, et al (2009). TRAIL-R1 polymorphisms and cancer susceptibility: an evidence-based meta-analysis. Eur J Cancer, 45, 2598-605.

Desimonia R, Laird N (1986). Meta-analysis in clinical trials. Control Clin Trials, 7, 177-88.

Egger M, Davey Smith G, Schneider M, et al (1997). Bias in meta-analysis detected by a simple, graphical test. BMJ, 315, 629-34.

Evans GM, Voukden KH (2001). Proliferation, cell cycle, and apoptosis in cancer. Nature, 411, 342-8.

Fernandez V, Jares P, Bea S, et al (2004). Frequent polymorphic changes but not mutations of TRAIL receptors DR4 and DR5 in mantle cell lymphoma and other B-cell lymphoid neoplasms. Haematologica, 93, 1322-31.

Fisher MJ, Virmani AK, Wu L, et al (2001). Nucleotide substitution in the ectodomain of TRAIL receptor DR4 is associated with lung cancer and head and neck cancer. Clin Cancer Res, 7, 1688-97.

Frank B, Hemminki K, Shanmugam KS, et al (2005). Association of death receptor 4 haplotype 626C-683C with an increased breast cancer risk. Carcinogenesis, 26, 1975-7.

Frank B, Shanmugam KS, Beckmann L, et al (2006). Death receptor 4 variants and colorectal cancer risk. Cancer Epidemiol Biomarkers Prevent, 15, 2002-5.

Hazra A, Chamberlain RM, Grossman HB, et al (2003). Death receptor 4 and bladder cancer risk. Cancer Res, 63, 1157-9.

Hengartner MO (2000). The biochemistry of apoptosis. Nature, 407, 770-6.

Horaka P, Pilsa D, Roessler M, et al (2005). Common death receptor 4 (DR4) polymorphisms do not predispose to ovarian cancer. Gynecol Oncol, 97, 514-8.

Kim H, Ku SY, Suh CS, et al (2012). Association between endometriosis and polymorphisms in tumor necrosis factor-related apoptosis-inducing ligand (TRAIL), TRAIL receptor and osteoprotegerin genes and their serum levels. Arch Gynecol Obstet, 286, 147-53.

Koornstra JJ, Kleibeuker JH, Van Geelen CM, et al (2003). Expression of TRAIL (TNF-related apoptosis-inducing ligand) and its receptors in normal colonicmucosa, adenomas, and carcinomas. J Pathol, 200, 327-35.

Körner C, Riesner K, Krämer B, et al (2012). TRAIL receptor I (DR4) polymorphisms C626G and A683C are associated with an increased risk for hepatocellular carcinoma (HCC) in HCV-infected patients. BMC Cancer, 12, 85.

Kuraoka K, Matsumura S, Sanada Y, et al (2005). A single nucleotide polymorphism in the extracellular domain of TRAIL receptor DR4 at nucleotide 626 in gastric cancer patients in Japan. Oncol Rep, 14, 465-70.

MacFarlane M, Ahmad M, Srinivasula SM, et al (1997). Identification and molecular cloning of two novel receptors for the cytokotoxic ligand TRAIL. J Biol Chem, 272, 25417-20.

Mantel N, Haenszel W (1959). Statistical aspects of the analysis of data from retrospective studies of disease. J Natl Cancer Inst, 22, 719-48.

Martinez-Ferrandisa JI, Rodriguez-Lovecpez R, Milne RC, et al (2007). Polymorphisms in TRAIL receptor genes and risk of breast cancer in Spanish women. Cancer Biomark, 3, 89-93.

Mittal RD, Srivastava P, Mittal T, et al (2011). Association of death receptor 4, Caspase 3 and 5 gene polymorphism with increased risk to bladder cancer in North Indians. Eur J Surg Oncol, 37, 727-33.

Pan GH, Ni J, Wei YF, et al (1997). An antagonist decoy receptor and a death domain-containing receptor for TRAIL. Science, 277, 815-8.

Pan GH, ORourke K, Chinnaiyan AM, et al (1997). The receptor for the cytotoxic ligand TRAIL. Science, 276, 111-3.

Sprick MR, Weigand MA, Rieser E, et al (2000). FADD/MORT1 and caspase-8 are recruited to TRAIL receptors 1 and 2 and are essential for apoptosis mediated by TRAIL receptor 2. Immunity, 12, 599-609.

Tastemir-Korkmaz D, Demirhan O, Kuleci S, et al (2013). There is no significant association between death receptor 4 (DR4) gene polymorphisms and lung cancer in Turkish population. Pathol Oncol Res, 19, 779-84.

Ulybina YM, Kuligina ES, Mitsushkina NV, et al (2009). Coding polymorphisms in Casp5, Casp8 and DR4 genes may play a role in predisposition to lung cancer. Cancer Lett, 278, 183-91.

Wajant H, Pfizennairer K, Scheurich P (2002). TNF-related apoptosis inducing ligand (TRAIL) and its receptors in tumor surveillance and cancer therapy. Apoptosis, 7, 449-59.

Wolf S, Mertens D, Pecher A, et al (2006). Ala228 variant of tral receptor 1 affecting the ligand binding site is associated with chronic lymphocytic leukemia, mantle cell lymphoma, prostate cancer, head and neck squamous cell carcinoma and bladder cancer. Int J Cancer, 118, 1831-5.

Yagit A, Takeda K, Hayakawa Y, et al (2004). TRAIL and its receptors as targets for cancer therapy. Cancer Sci, 95, 777-83.