RESEARCH ARTICLE

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

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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

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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 caspases 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; Koornstra 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 cycteine-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.

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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 resolves 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.

Statistic 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 canner was accessed by calculating crude ORs (odds rations) 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 mode (Mantel et al., 1959) if there was not 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 (version9.0; Stata Corporation, College Station, TX).

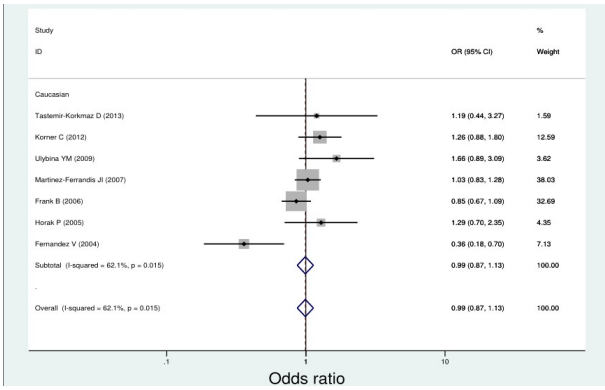

Figure 1. Forest Plot of ORs Cancer Risk Associated with the DR4 Polymorphism C626G (CC/CG Versus GG) by Source of Controls. The squares and horizontal lines correspond to the study-specific OR and 95%CI. The area of the squares reflects the study-specific weight. The diamond represents the pooled OR and 95%CI

Results

Eligible studies

We identified 2874 cases with different cancer types and 3220 controls described C626G genotypes (Table1), 1939 cases and 2536 controls described A683C genotypes (Table 1), and 1171 cases and 970 controls described A1322G genotypes (Table1). 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;

Table 1. The Distribution of DR4 Polymorphisms for Cases and Control in Caucasian

Author (Year)	Diseas	Case			Control			DR4	*P**
		GG	CG	CC	GG	CG	CC	polymorphisms	
Fernandez V (2004)	non-Hodgkin's lymphoma	41	23	46	16	49	26	C626G	0.39
Horak P (2005)	Ovarian cancer	28	51	13	36	50	14	C626G	0.611
Frank B (2005)	Breast cancer	157	242	120	312	566	122	C626G	3.49E-08
Frank B (2006)	Colorectal cancer	208	286	156	167	298	118	C626G	0.48
Martinez-Ferrandis JI (2007)	Breast cancer	257	440	202	214	352	166	C626G	0.36
Ulybina YM (2009)	Lung cancer	22	61	28	32	49	29	C626G	0.26
Mittal RD (2011)	Bladder cancer	86	97	17	97	113	15	C626G	0.02
Korner C (2012)	Hepatocelluar carcinoma	69	108	56	121	166	62	C626G	0.69
Tastemir-Korkmaz D (2013)	Lung cancer	14	34	12	8	12	10	C626G	0.28
Frank B (2005)	Breast cancer	331	156	24	678	362	52	A683C	0.68
Frank B (2006)	Colorectal cancer	399	216	29	384	181	18	A683C	0.55
Wolf S (2006)	Bladder cancer	117	54	8	110	27	0	A683C	0.20
Ulybina YM (2009)	Lung cancer	81	27	3	87	21	2	A683C	0.58
Mittal RD (2011)	Bladder cancer	73	105	22	91	113	21	A683C	0.09
Korner C (2012)	Hepatocelluar carcinoma	139	85	10	215	125	19	A683C	0.88
Tastemir-Korkmaz D (2013)	Lung cancer	41	19	0	21	7	2	A683C	0.23
Fernandez V (2004)	non-Hodgkin's lymphoma	80	32	2	75	15	1	A1322G	0.80
Horak P (2005)	Ovarian cancer	77	16	4	76	20	1	A1322G	0.80
Martinez-Ferrandis JI (2007)	Breast cancer	16	244	640	18	200	534	A1322G	0.89
Tastemir-Korkmaz D (2013)	Lung cancer	53	6	1	24	3	3	A1322G	0.0008

P*: P value for Hardy-Weinberg equilibrium in control group

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) P	Heterogeneity p value	Begg's test p value	Egger's test p value
C626G	Additive (C *vs* G)	Caucasian	1.042 (0.955-1.137) 0.586	0.355	0.652	0.932
	Dominant (C-carriers *vs* G/G)	Caucasian	0.991 (0.866-1.133) 0.015	0.892	0.881	0.921
	Recessive (C/C *vs* G-carriers)	Caucasian	1.136 (0.981-1.316) 0.191	0.088	0.652	0.858
A683C	Additive (A *vs* C)	Caucasian	1.140 (0.948-1.370) 0.028	0.164	0.453	0.288
	Dominant (A-carriers *vs* C/C)	Caucasian	1.156 (0.950-1.406) 0.080	0.148	0.293	0.145
	Recessive (A/A *vs* C-carriers)	Caucasian	1.125 (0.789-1.605) 0.284	0.515	0.881	0.897
A1322G	Additive (A *vs* G)	Caucasian	1.085 (0.913-1.289) 0.217	0.356	0.602	0.24
	Dominant (A-carriers *vs* G/G)	Caucasian	1.379 (0.934-2.035) 0.311	0.106	0.117	0
	Recessive (A/A *vs* G-carriers)	Caucasian	1.026 (0.831-1.268) 0.429	0.809	0.602	0.066

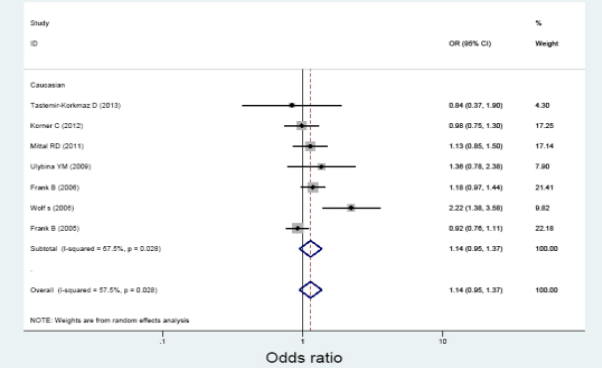

Figure 2. Forest Plot of ORs Cancer Risk Associated with the DR4 A683C Polymorphism (AA Versus CC) by Source of Controls. The squares and horizontal lines correspond to the study-specific OR and 95%CI. The area of the squares reflects the study-specific weight. The diamond represents the pooled OR and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

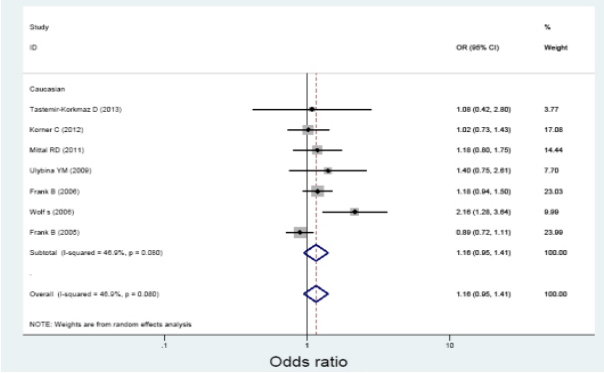

Figure 3. Forest Plot of ORs Cancer Risk Associated with the DR4 A683C Polymorphism (AA/AC Versus CC) by Source of Controls. The squares and horizontal lines correspond to the study-specific OR and 95%CI. The area of the squares reflects the study-specific weight. The diamond represents the pooled OR and 95%CI

dominant model: OR 0.991, 95%CI 0.866-1.133, p=0.015; recessive model: OR 1.136, 95%CI 0.981-1.316 p=0.191). Similarly, we also find the A683C polymorphism was associated with the cancer risk in Caucasian in additive and dominant genetic models (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; recessive model: OR 1.125, 95%CI 0.789-1.605 p=0.284). However, the A1322G polymorphism wasn't associated with the cancer risk in Caucasian in all genetic models (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).

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 often 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 mutationd 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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