EUROPEAN JOURNAL OF CANCER 45 (2009) 2598–2605

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TRAIL-R1 polymorphisms and cancer susceptibility: An evidence-based meta-analysis

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ARTICLE INFO

Article history:
Received 9 May 2009
Received in revised form 18 June 2009
Accepted 24 June 2009
Available online 28 July 2009

Keywords:
TRAIL-R1
Polymorphism
Cancer susceptibility
Meta-analysis

ABSTRACT

Published data on the association between tumour necrosis factor-related apoptosis-inducing ligand receptor 1 (TRAIL-R1 or DR4) polymorphisms rs20575 (C626G), rs2230229 (A1322G) and rs20576 (A683C) and cancer risk are inconclusive. To derive a more precise estimation of the relationship, a meta-analysis was performed. A total of nine studies, among which eight articles including 2941 cases and 3358 controls described C626G genotypes, three articles including 736 cases and 668 controls described A1322G genotypes and three studies totalling 1550 cases and 2257 controls described A683C genotypes were involved in this meta-analysis. Overall, all three polymorphisms were associated with cancer susceptibility. For C626G polymorphism, there was no association between C626G polymorphism and the risk of cancer in all genetic models when all the eligible studies were pooled into the meta-analysis. In the subgroup analysis by source of controls, statistically significantly reduced cancer risks were found among groups with population-based controls for CG versus CC (OR = 0.77, 95% CI:0.65–0.91, $P_{heterogeneity}$ = 0.007) and dominant model (OR = 0.84, 95% CI:0.72–0.99, $P_{heterogeneity}$ = 0.409). For A1322G polymorphism, we found it was associated with a significantly elevated cancer risk of all cancer types in different genetic models (homozygote comparison: OR = 2.80, 95% CI:1.16–6.76, $P_{heterogeneity}$ = 0.905; dominant model comparison: OR = 1.57, 95% CI:1.02–2.41, $P_{heterogeneity}$ = 0.167; and recessive model comparison: OR = 1.22, 95% CI:0.94–1.60, $P_{heterogeneity}$ = 0.535). Similar results were obtained from A683C polymorphism (homozygote comparison: OR = 3.21, 95% CI:1.26–8.20, $P_{heterogeneity}$ = 0.012; dominant model comparison: OR = 1.61, 95% CI: 1.09–2.36, $P_{heterogeneity}$ = 0.000; and recessive model comparison: OR = 2.79, 95% CI: 1.17–6.68, $P_{heterogeneity}$ = 0.025). In summary, this meta-analysis suggests that TRAIL-R1 C626G polymorphism is marginally associated with cancer susceptibility, and both TRAIL-R1 A1322G G allele and A683C C allele are associated with increased risk for cancer.

1. Introduction

Despite the significant advances in clinical research, surgical resection, radiotherapy and chemotherapy are still used as the primary method for cancer treatment. These conventional therapies, however, often induced systemic toxicity, are not entirely effective and eventually contribute to tumour resistance after repeated treatments. Thus, a therapy which is effective with little or no cytotoxicity is urgently needed. Tumour necrosis factor-related apoptosis-inducing ligand (TRAIL or Apo2 ligand) is the very one recently discovered. TRAIL is a type II transmembrane protein that was originally

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0959-8049/$ - see front matter
doi:10.1016/j.ejca.2009.06.023

identified and cloned based on the sequence homology of its extracellular domain with CD95L and tumour necrosis factor (TNF).[1,2] Like most other TNF family members, TRAIL forms homotrimers that bind to three receptor molecules.[3] However, unlike other TNF family members whose expression is tightly regulated and is often transiently expressed on activated cells, TRAIL mRNA is constitutively expressed in a wide range of tissues.[1] TRAIL induces apoptosis in a variety of transformed or tumour cells but not normal cells, making it an attractive agent for cancer therapy.[1,2] TRAIL induces apoptosis through interacting with its receptors. There are five TRAIL receptors, including TRAIL receptor 1 (TRAIL-R1 or death receptor 4, DR4), TRAIL receptor 2 (TRAIL-R2 or death receptor 5, DR5), Decoy receptors 1 (TRAIL-R3 or DcR1) and 2 (TRAIL-R4 or DcR2) and osteoprotegerin (OPG). Both DR4 and DR5 contain a conserved death domain (DD) motif and are proapoptotic receptors.[4] Unlike DR4 and DR5, DcR1 lacks an intracellular domain, while DcR2 has a truncated DD. Thus, these two receptors act as decoy receptors to antagonize TRAIL-induced apoptosis by competing for ligand binding.[4,5] When TRAIL binds to DR4 and/or DR5, the receptors become trimerised to form the death inducing signalling complex (DISC) and then recruit the adapter protein Fas-associated death domain protein (FADD) and caspase-8 or caspase-10, leading to activation of the executioner caspases including caspase-3 and in turn cleavage of the death substrates and causing cell death.

DR4, located on chromosome 8p21, was the first DR for TRAIL to be identified.[6] The DR4 type I membrane protein contains 486 amino acids, composed of two extracellular cysteine-rich pseudorepeats. The principal elements of the DR4 ligand-binding domain are encoded by exons 3 and 4.[7,8] As shown in the HapMap and dbSNP databases, the DR4 gene is highly polymorphic, but the most extensively studied polymorphism is the C to G substitution at position 626 rs20575 (C626G) in the ectodomain region of DR4. In addition, another two DR4 polymorphisms rs2230229 (A1322G) and rs20576 (A683C) are also extensively studied, but to a lesser extent than the C626G polymorphism. And these two polymorphisms are located in the death domain and the extracellular cysteine-rich domain of DR4, respectively. DR4 mutations have been described in different human cancers, such as lung, head and neck cancer, non-Hodgkin's lymphoma and breast cancer.[8–10]

Recently, many studies have investigated the role of the DR4 polymorphisms in the aetiology of cancers of various organs, including the bladder,[11,12] lymph tissue,[12,13] ovary,[14] colon,[15] stomach,[16,17] breast,[18,19] lung,[8] head and neck[8,12]and prostate.[12] However, the results of these studies remain inconclusive. In this report, we performed a meta-analysis to estimate the effect of these three polymorphisms on cancer risk.

2. Materials and methods

2.1. Publication search

PubMed and Embase were searched using the search terms: 'Death receptor 4', 'TRAIL-R1', 'polymorphism' and 'cancer' (last search was updated on 1 April 2009). All eligible studies were retrieved, and their bibliographies were checked for other relevant publications. Review articles and bibliographies of other relevant studies identified were hand-searched to find additional eligible studies. Only published studies with full text articles were included. When more than one of the same patient population was included in several publications, only the most recent or complete study was used in this meta-analysis.

2.2. Inclusion criteria

The inclusion criteria were: (a) evaluation of the TRAIL-R1 polymorphism and cancer risk, (b) case-control studies and (c) sufficient published data for estimating an odds ratio (OR) with 95% confidence interval (CI).

2.3. Data extraction

Information was carefully extracted from all eligible publications independently by two of the authors (Chen and Xu) according to the inclusion criteria listed above. Disagreement was resolved by discussion between the two authors. If these two authors could not reach a consensus, another author (Wu) was consulted to resolve the dispute and a final decision was made by the majority of the votes. The following data were collected from each study: first author's surname, publication date, country origin, ethnicity, cancer type, characteristics of controls, genotyping methods, total number of cases and controls, and numbers of cases and controls with TRAIL-R1 C626G, A1322G and A683C genotypes, respectively. For data that were not provided in tabular form or the main text, the required information were obtained by contacting the corresponding authors as possible as we can. Different ethnicity descents were categorised as European and Asian.

2.4. Statistical methods

Crude ORs with 95% CIs were used to assess the strength of association between the TRAIL-R1 C626G, A1322G and A683C polymorphisms and cancer risk. The statistical significance of the pooled OR was determined using the Z-test. We first estimated cancer risks associated with TRAIL-R1 C626G CG and GG genotypes, compared with the wild-type CC homozygote, and then evaluated the risks associated with (GG/CG) versus CC and GG versus (CG/CC), assuming the dominant and recessive effects of the variant G allele, respectively. Stratification analysis was also performed by cancer types, ethnicity, and source of controls. Gastric and colorectal cancers were defined as digestive tract cancers, and given the roles of oestrogen level in the aetiology of prostate, breast and ovarian cancers, they were defined as oestrogen-related cancers.[20] Colon, bladder, and head and neck cancers, were defined as smoking-related cancers, because tobacco smoking is an established risk factor for these cancers.[21–23]Then we examined whether the TRAIL-R1 C626G was associated with the risk of these cancers.

The pooled ORs for TRAIL A1322G genotypes AA, AG and A-allele carriers (AA + AG) against the GG genotype were calculated under a recessive model. Estimates for TRAIL-R1

A683C genotypes AA, AC and A-allele carriers (AA + AC) against the CC genotype were also calculated.

Heterogeneity assumption was checked by the chi-square-based Q-test.[24] A P-value >0.10 for the Q-test indicates a lack of heterogeneity among studies, so the pooled OR estimate of the each study was calculated by the fixed-effects model (the Mantel–Haenszel method).[25] Otherwise, the random-effects model (the DerSimonian and Laird method) was used.[26] An estimate of potential publication bias was carried out by the funnel plot, in which the standard error of log (OR) of each study was plotted against its log (OR). An asymmetric plot suggests a possible publication bias. Funnel plot asymmetry was assessed by the method of Egger's linear regression test, a linear regression approach to measure funnel plot asymmetry on the natural logarithm scale of the OR. The significance of the intercept was determined by the *t*-test suggested by Egger ($P < 0.05$ was considered representative of statistically significant publication bias).[27] Hardy–Weinberg equilibrium in the control group was tested by the chi-square test for goodness of fit, and a P-value of <0.05 was considered significant. All the statistical tests were performed with STATA version 10.0 (Stata Corporation, College Station, TX), using two-sided P-values.

3. Results

3.1. Study characteristics

There were 18 eligible studies as a result of the search and screening carried out on the basis of our eligibility criteria. During the extraction of data, nine articles were excluded, because they did not provide DR4 polymorphisms allele frequencies needed for OR calculation, leaving nine eligible studies that had assessed the association between TRAIL-R1 C626G, A1322G and A683C genotypes and cancer risk using human genomic DNA samples. The characteristics of selected studies are summarised in Table 1. Among the nine eligible studies, three only concerning C626G,[11,16,17] three concerning both C626G and A1322G,[13,14,19] two concerning both C626G and A683C,[15,18] and one only concerning A683C.[12] There were 2941 cases with different cancer types and 3358 controls described C626G genotypes, 736 cases and 668 controls described A1322G genotypes, and 1550 cases and 2257 controls described A683C genotypes. Wolf and colleagues[12] sorted the data in various cancers, respectively. Thus, they were considered separately for pooling subgroup analysis. There were seven studies of Europeans and two studies of Asians. Controls were mainly matched for sex and age, of which five were population-based and three were hospital-based. The distribution of genotypes in the controls of all studies was in agreement with Hardy–Weinberg equilibrium.

Table 1 – Main characteristics of all studies included in the meta-analysis.

Author, publication year	Country	Ethnicity	Cancer type	Sample size (case/control)	Source of controls	Genotyping method	Polymorphisms analysis	Result
Hazra 2003[11]	USA	European	Bladder cancer	253/215	Population	PCR-RFLP	C626G	S
Fernàndez 2004[13]	Spain	European	Non-Hodgkiń lymphomas	110/91	Population	PCR-RFLP	C626G A1322G	S
Frank 2005[18]	Germany	European	Breast cancer	519/1100	Population	TaqMan	C626G A683C	S
Horak 2005[14]	Austria	European	Ovarian cancer	92/100	Hospital	PCR-RFLP	C626G A1322G	NS
Kuraoka 2005[16]	Japan	Asian	Gastric cancer	274/344	Hospital	PCR-RFLP	C626G	NS
Frank 2006[15]	Germany	European	Colorectal cancer	659/607	Population	TaqMan	C626G A683C	S
Guo 2007[17]	China	Asian	Gastric cancer	135/169	Population	PCR-RFLP	C626G	NS
Martinez-Ferrandis 2007[19]	Spain	European	Breast cancer	899/732	Hospital	TaqMan	C626G A1322G	NS
Wolf 2006[12]	Germany	European	Mix cancer	395/582	Hospital	TaqMan	A683C	S

Mix cancer includes chronic lymphocytic leukaemia, mantle cell lymphoma, prostate cancer, head and neck squamous cell carcinoma and bladder cancer. S and NS indicate significant and not significant, respectively.

3.2. Meta-analysis results

The overall OR with its 95% CI did not show any association between the TRAIL-R1 C626G polymorphism and the risk for cancer (for GG versus CC: OR = 0.95; 95% CI = 0.82–1.11; $P_{heterogeneity} = 0.637$; for CG versus CC: OR = 0.88; 95% CI = 0.68–1.13; $P_{heterogeneity} = 0.006$; for dominant model:

Table 2 – Main results of pooled ORs and stratification analysis of the death receptor 4 (DR4) rs20575 (C626G) polymorphism on cancer risk in the meta-analysis.

	N	CG versus CC OR (95% CI) P_h	GG versus CC OR (95% CI) P_h	CG/GG versus CC OR (95% CI) P_h	GG versus CG/CC OR (95% CI) P_h
Total	8	0.88 (0.68,1.13)0.006	0.95 (0.82,1.11)0.637	0.91 (0.80,1.03)0.514	1.03 (0.82,1.31)0.004
Cancer types					
Digestive tract cancers	3	0.85 (0.67,1.08)0.123	0.96 (0.73,1.27)0.248	0.90 (0.72,1.12)0.348	1.14 (0.84,1.56)0.273
Oestrogen-related cancers	3	0.92 (0.77,1.10)0.343	0.95 (0.78,1.16)0.921	0.93 (0.79,1.10)0.565	1.01 (0.87,1.17)0.510
Others	2	0.71 (0.47,1.06)0.000	0.92 (0.59,1.45)0.139	0.80 (0.54,1.16)0.119	1.26 (0.28,5.72)0.000
Ethnicity					
European	6	0.80 (0.60,1.08)0.004	0.95 (0.81,1.11)0.796	0.88 (0.77,1.01)0.453	1.03 (0.80,1.34)0.002
Asian	2	1.21 (0.79,1.85)0.546	1.04 (0.59,1.82)0.107	1.14 (0.77,1.69)0.947	0.68 (0.13,3.54)0.107
Control source					
Hospital	3	1.07 (0.86,1.34)0.671	0.94 (0.73,1.22)0.353	1.02 (0.83,1.26)0.940	0.93 (0.76,1.13)0.299
Population	5	0.77 (0.65,0.91)0.007	0.96 (0.80,1.16)0.540	0.84 (0.72,0.99)0.409	1.10 (0.95,1.26)0.002

N indicates number of studies involved; P_h: *P*-value of Q-test for heterogeneity test.

OR = 0.91; 95% CI = 0.80–1.03; $P_{heterogeneity}$ = 0.514; for recessive model: OR = 1.03; 95% CI = 0.82–1.31; $P_{heterogeneity}$ = 0.004; Table 2). In the subgroup analysis by cancer types and ethnicity, we also did not find any association in all models (Fig. 1). However, In the subgroup analysis by source of controls, statistically significantly reduced cancer risks were found among groups with population-based controls for CG versus CC (OR = 0.77, 95% CI:0.65–0.91, $P_{heterogeneity}$ = 0.007) and dominant model (OR = 0.84, 95% CI:0.72–0.99, $P_{heterogeneity}$ = 0.409; Fig. 2). The data are shown in Table 2.

Overall, there was evidence of an association between the increased cancer risk and the variant genotypes TRAIL-R1 A1322G in different genetic models when all the eligible studies were pooled into the meta-analysis. Compared with the wild-type homozygote genotype, AA, the variant genotypes, AG and GG, were associated with marginally and statistically significant increased risk of all types of cancer, respectively (OR = 1.46, 95% CI: 0.94–2.28, $P_{heterogeneity}$ = 0.111 for AG; OR = 2.80, 95% CI: 1.16–6.76, $P_{heterogeneity}$ = 0.905 for GG; Table 3). In addition, significant main effects were also observed in both dominant and recessive models (dominant model: OR = 1.57, 95% CI: 1.02–2.41, $P_{heterogeneity}$ = 0.167; recessive model: OR = 1.22, 95% CI: 0.94–1.60, $P_{heterogeneity}$ = 0.535; Table 3). Notably, the G-variant genotypes (AG and GG) were associated with an increased cancer risk in a dose–response manner compared with the AA genotype (OR = 1.46, 95% CI: 0.94–2.28 for AG and OR = 2.80, 95% CI: 1.16–6.76 for GG; P_{trend} < 0.001).

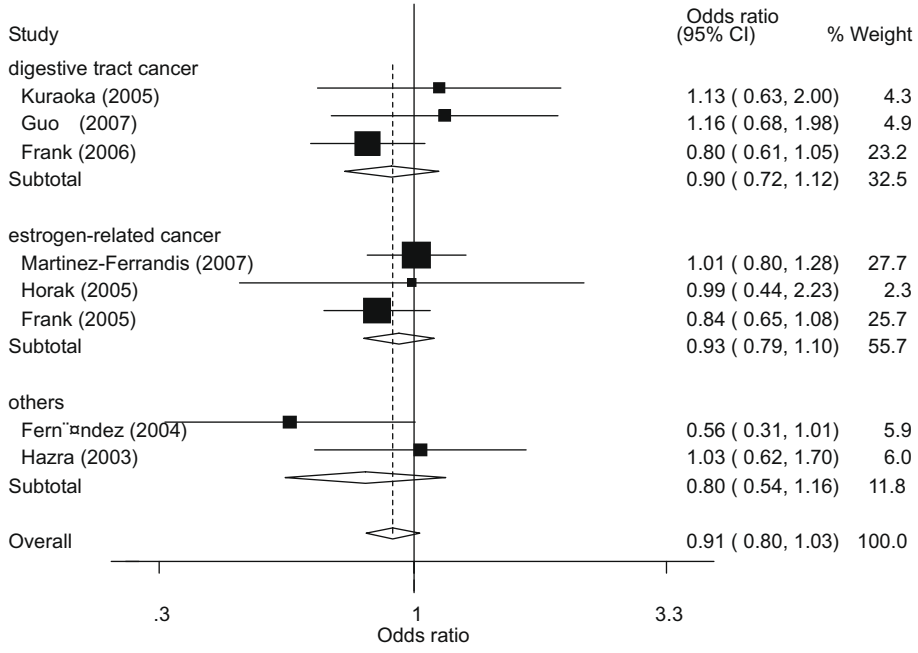

Fig. 1 – Forest plot of cancer risk associated with the death receptor 4 (DR4) C626G polymorphism (CG/GG versus CC) by cancer types. The squares and horizontal lines correspond to the study-specific OR and 95% CI. The area of the squares reflects the study-specific weight (inverse of the variance). The diamond represents the pooled OR and 95% CI.

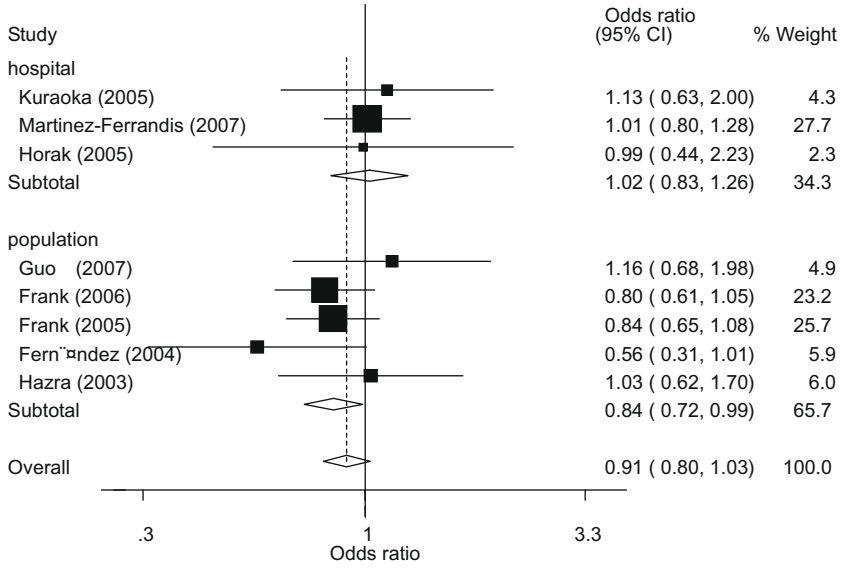

Fig. 2 – Forest plot of cancer risk associated with the DR4 C626G polymorphism (AC/CC versus AA) by source of controls. The squares and horizontal lines correspond to the study-specific OR and 95% CI. The area of the squares reflects the study-specific weight (inverse of the variance). The diamond represents the pooled OR and 95% CI.

Similarly, we also find an association between the increased cancer risk and the variant genotypes TRAIL-R1 A683C in different genetic models when all the eligible studies were pooled. When compared with the wild-type homozygote genotype, AA, the variant genotypes, AC and CC, were associated with marginally and statistically significant increased risk of all types of cancer, respectively (OR = 1.44, 95% CI: 0.99–2.08, $P_{heterogeneity} = 0.001$ for AC; OR = 3.21, 95% CI: 1.26–8.20, $P_{heterogeneity} = 0.012$ for CC; Table 3). In addition, significant main effects were also observed in both dominant and recessive models (dominant model: OR = 1.61, 95% CI: 1.09–2.36, $P_{heterogeneity} = 0.000$; recessive model: OR = 2.79, 95% CI: 1.17–6.68, $P_{heterogeneity} = 0.025$; Table 3). We also found that the G-variant genotypes (AC and CC) were associated with an increased cancer risk in a dose–response manner compared with the AA genotype (OR = 1.44, 95% CI: 0.99–2.08 for AC and OR = 3.21, 95% CI: 1.26–8.20 for CC; $P_{trend} < 0.001$). In the subgroup analysis by cancer types, significant elevated cancer risk was found in dominant model comparison (OR = 1.70, 95% CI:1.03–2.82, $P_{heterogeneity} = 0.037$; Fig. 3) among smoking-related cancers. As for haematological system cancers, increased cancer risks were found in homozygote comparison and recessive model comparison (Table 3).

3.3. *Sensitive analysis*

A single study involved in the meta-analysis was deleted each time to reflect the influence of the individual data-set to the pooled ORs, and the corresponding pooled ORs were not materially altered (data not shown).

3.4. *Bias diagnostics*

Begg's funnel plot and Egger's test were performed to assess the publication bias of the literature. The shapes of the funnel plots for the comparison of the 626G allele and the 626C allele seemed a little asymmetrical in all comparing models (figure not shown). Furthermore, Egger's test was used to provide statistical evidence for funnel plot a little asymmetry ($P = 0.034$). However, when we discarded the study that the number of cases or controls less than 100, the results did not suggest any evidence of publication bias ($P = 0.245$ for CG/GG versus CC). When we assess the publication bias of the literature about A1322G and A683C, both the funnel plots and Egger's test did not show any evidence of publication bias (figure not shown, Egger's test: $P = 0.170$ for A1322G; $P = 0.456$ for A683C).

4. Discussion

Apoptosis represents a physiological mechanism that eliminates damaged cells from an organism, thus controlling cell numbers and tissue size, and sustaining homeostasis. Suppression of apoptosis implicates deregulated cell proliferation and predisposition to cancer. The transmembrane death receptors of the TNF receptor superfamily mediate the activation of the central forces of regulated cell death – the caspases – triggering cell dissolution.[28,29] The proapoptotic DR4 has been characterised as the first DR to efficiently bind the TRAIL. Suppression of cell death signaling due to detrimental alterations in DR4 involves a deregulated cell proliferation and predisposes to cancer.[7,28–32]

It is well recognized that there is individual susceptibility to the same kind of cancer even with the same environmental exposure. Host factors, including polymorphisms of genes involved in carcinogenesis may have accounted for this difference. Therefore, genetic susceptibility to cancer has been a research focus in scientific community. Recently, genetic variants of the DR4 gene in the aetiology of several cancers have drawn increasing attention. However, the results are inconclusive. To better understanding of the association between the polymorphisms and cancer risk, a pooled analysis with

Table 3 – The results of four genetic models of the association between DR4 rs2230229 (A1322G), rs20576 (A683C) polymorphisms and cancer.

SNPs	Variable	Genotypes distribution of cases/controls			Heterozygote comparison OR (95% CI) P_h	Homozygote comparison OR (95% CI) P_h	Dominant model comparison OR (95% CI) P_h	Recessive model comparison OR (95% CI) P_h
A1322G		AA	AG	GG				
	Total	162/163	183/168	391/337	1.46 (0.94,2.28)0.111	2.80 (1.16,6.76) 0.905	1.57 (1.02,2.41)0.167	1.22 (0.94,1.60) 0.535
A683C		AA	AC	CC				
	Total	981/1529	497/658	72/70	1.44 (0.99,2.08)0.001	3.21 (1.26,8.20) 0.012	1.61 (1.09,2.36)0.000	2.79 (1.17,6.68) 0.025
	Cancer types							
	Oestrogen-related cancers	358/705	170/369	26/52	1.12 (0.54,2.33)0.137	1.06 (0.46,2.42)0.295	1.24 (0.51,2.99)0.081	1.02 (0.63,1.67)0.363
	Smoking-related cancers	541/604	283/235	39/18	1.50 (0.99,2.26)0.115	5.23 (0.71,38.36)0.075	1.70 (1.03,2.82)0.037	4.45 (0.68,28.90)0.096
	Hematological system cancers	82/220	44/54	7/0	1.29 (0.21,7.94)0.009	22.56 (2.77,183.74)0.812	1.87 (0.56,6.32)0.032	20.17 (2.48,163.67)0.654

SNPs: Single-nucleotide polymorphisms; P_h: P-value of Q-test for heterogeneity test.

a large sample, subgroup analysis performed, and heterogeneity explored is necessary.

In the present study, we only found an evidence of association between TRAIL-R1 rs20575 (C626G) polymorphism and cancer in the subgroup analysis by source of controls. Our results indicated that significantly reduced risks in DR4 CG and dominant model genotypes were found among studies using the population-based controls but not among studies with hospital-based controls. This reason may be that the hospital-based studies have some biases because such controls may just represent a sample of ill-defined reference population, and may not be representative of the general population very well, particularly when the genotypes under investigation were associated with the disease conditions that the hospital-based controls may have. Therefore, using a proper and representative population-based control subjects is very important to reduce biases in such genetic association studies. However, both TRAIL-R1 rs2230229 (A1322G) and rs20576 (A683C) polymorphisms were strongly associated with the risk of cancer.

As for TRAIL-R1 A1322G polymorphism, we found that individuals with GG genotype were associated with a higher cancer risk than participants with the CC genotype. Similar results were also obtained from analysing A683C polymorphism. Individuals with CC genotype were associated with a higher cancer risk than participants with the AA genotype. And we found that the increased cancer risk was much more significant among haematological system cancers. This may partially because different cancer types have different gene–environment interactions, or studies with small sample size may have insufficient statistical power to detect a slight effect or may have generated a fluctuated risk estimate.

Some limitations of this meta-analysis should be addressed. First, lack of the original data of the reviewed studies limited our further evaluation of potential interactions, because the interactions between gene–gene, gene–environment, and even different polymorphic loci of the same gene may modulate cancer risk. Second, misclassifications on disease status and genotypes may also influence the results, because cases in several studies were not confirmed by pathology or other gold standard methods, and the quality control of genotyping was also not well documented in some studies. Third, the numbers of published studies were not sufficiently large for a comprehensive analysis, particularly for any given cancer site. In spite of these, our meta-analysis also had some advantages. First, substantial number of cases and controls were pooled from different studies, which significantly increased statistical power of the analysis. Second, the quality of case–control studies included in the current meta-analysis was satisfactory based on our selection criteria. Third, we did not found significant publication bias indicating that the whole pooled result may be unbiased.

In summary, this meta-analysis identified an evidence of the association between the TRAIL-R1 rs2230229 (A1322G), rs20576 (A683C) polymorphisms and cancer risk, while little evidence indicated an association between TRAIL rs20575 (C626G) and risk of cancer. Our results also suggest that additional large studies are warranted to validate possible ethnic difference in the risk. Future studies should use standardised unbiased genotyping methods, homogeneous cancer

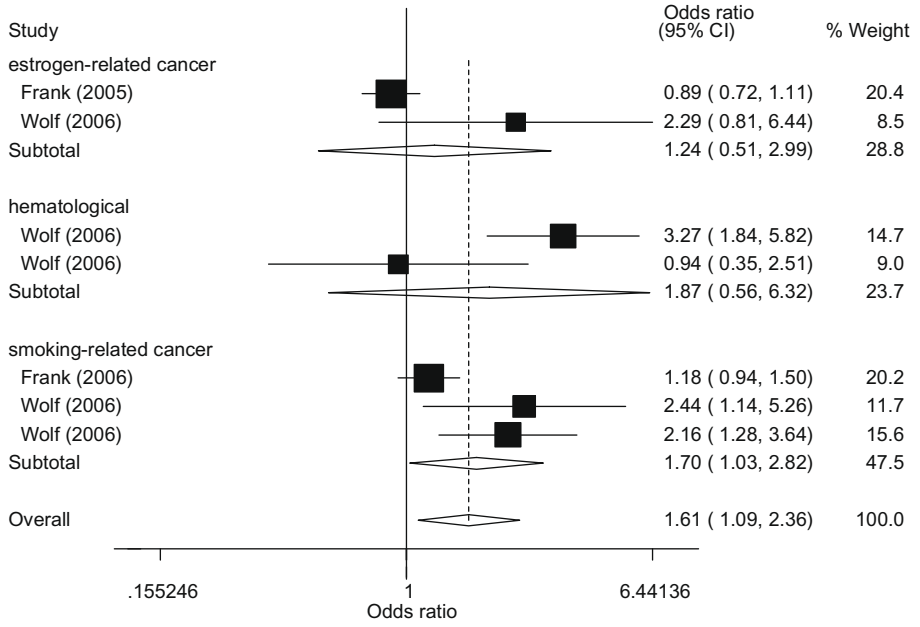

Fig. 3 – Forest plot of cancer risk associated with the DR4 A683C polymorphism (CG/GG versus CC) by cancer types. The squares and horizontal lines correspond to the study-specific OR and 95% CI. The area of the squares reflects the study-specific weight (inverse of the variance). The diamond represents the pooled OR and 95% CI.

patients, and well-matched controls with multi-ethnic groups. Moreover, gene–gene and gene–environment interactions should also be examined in the future analysis. These future studies should lead to better, comprehensive understanding of the association between the TRAIL-R1 polymorphisms and cancer risk.

Conflict of interest statement

None declared.

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