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EPIDEMIOLOGY

TNFα −308 G/A polymorphism is associated with breast cancer risk: a meta-analysis involving 10,184 cases and 12,911 controls

Fang Fang · Lei Yao · Xiao Jia Yu · Lu Yu · Qi Wu · Long Yu

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Abstract Tumor necrosis factor α (TNFα) is a pleiotropic cytokine which can regulate a wide variety of cellular responses. Low concentrations of TNFα seem to increase tumor growth and progression. The −308 G/A polymorphism in TNFα has been implicated in breast cancer risk but the published data remain inconclusive. In order to derive a more precise estimation of the relationship, a meta-analysis was performed by searching PubMed, Web of Science, ScienceDirect, EBSCO, CNKI, and Chinese Biomedicine Database. 11 studies including 10,184 cases and 12,911 controls were collected for TNFα −308 G/A polymorphism. Crude ORs with 95% CIs were used to assess the strength of association between the TNFα −308 G/A polymorphism and breast cancer risk. The pooled ORs were performed for codominant model (GG versus AA; GA versus AA), dominant model (GG + GA versus AA), recessive model (GG versus GA + AA), and G allele versus A allele, respectively. Overall, significantly elevated breast cancer risk was found for recessive model (OR = 1.10, 95% CI = 1.04–1.17) and for G allele versus A allele (OR = 1.08, 95% CI = 1.02–1.14). In the subgroup analysis by ethnicity, significantly increased risks were also found among Caucasians for recessive model and for G allele versus A allele (for recessive model: OR = 1.10, 95% CI = 1.04–1.17; for G allele versus A allele: OR = 1.09, 95% CI = 1.03–1.14). However, no significant associations were found among Asians for all genetic models. In conclusion, this meta-analysis suggests that the TNFα −308 G allele is a risk factor for developing breast cancer, especially for Caucasians.

Keywords TNFα · Polymorphism · Breast cancer · Susceptibility · Meta-analysis

F. Fang · L. Yao · X. J. Yu · L. Yu · Q. Wu · L. Yu
State Key Laboratory of Genetic Engineering, Institute of Genetics, School of Life Sciences, Fudan University, Shanghai, China

L. Yu (✉)
Institutes of Biomedical Sciences, Fudan University, Shanghai, China
e-mail: Longyu@fudan.edu.cn

Introduction

Breast cancer is by far the most frequent cancer of women [1]. It is expected to be the second leading cause of USA cancer deaths in 2008, preceded only by lung cancer [2]. The mechanism of breast carcinogenesis is still not fully understood. Low-penetrance susceptibility genes combining with environmental factors have been suggested to be important in the development of cancer [3]. To date, many reports have been published on common low-penetrant genes associated with an increased breast cancer risk [4]. An important one is tumor necrosis factor α (TNFα), a member of the TNF/TNFR cytokine superfamily which is involved in maintenance and homeostasis of the immune system, inflammation, and host defence [5]. Although TNFα was originally characterized to cause hemorrhagic tumor necrosis at high concentrations in many types of cancer, low concentrations of TNFα seem to increase tumor growth and progression [6]. Studies examining the role of the TNFα gene in breast cancer growth have revealed evidence for TNFα as a breast tumor promoter [7]. An important polymorphism (rs1800629, −308 G/A), located 308 bp upstream from the TNF start site within the promoter region of TNFα contains a G-to-A substitution and has been considered to influence the TNFα transcriptional activity [8, 9]. The association between TNFα levels and

breast cancer risk has been observed in previous study [10]. Therefore, it is conceivable that the TNFα −308 G/A polymorphism may have relationship with the breast cancer risk. To date, a number of studies have investigated the role of TNFα −308 G/A polymorphism in breast cancer risk [11–25]. However, the results of those studies remain inconclusive, potentially due to the possible small effect of the polymorphism on breast cancer risk or the relatively small sample size in each of published studies. Hence, a meta-analysis of 11 eligible studies involving 10,184 cases and 12,911 controls was performed to help us derive a more precise estimation of the relationship between TNFα −308 G/A polymorphism and breast cancer risk.

Methods

Publication search

We searched the articles using the search terms "tumor necrosis factor α", "TNFα", "polymorphism", and "breast" in PubMed, Web of Science, ScienceDirect, EBSCO, CNKI, and Chinese Biomedicine Database without a language limitation, and the last search was updated on December 7, 2009. All searched studies' bibliographies were checked for other relevant publications. Review articles were hand-searched to find additional eligible studies. Only published studies with full text articles were included. When overlapping data of the same patient population were included in more than one publication, only the most recent or complete study was used in this meta-analysis.

Inclusion criteria

The following inclusion criteria were used for the literature selection: (a) articles about TNFα −308 G/A polymorphism and breast cancer risk, (b) case–control studies, and (c) sufficient published data for estimating an odds ratio (OR) with 95% confidence interval (CI).

Data extraction

Two investigators (Fang and Yao) extracted information from all eligible publications independently according to the inclusion criteria listed above. Disagreement was resolved by discussion between the two investigators. The following characteristics were collected from each study: first author's surname, publication date, country of origin, ethnicity, source of control groups, total number of cases and controls, and numbers of cases and controls with the GG, GA, and AA genotypes, respectively. For those studies of different ethnic groups, data were extracted separately for each of the ethnic groups, categorized as Asian, Caucasian, and unknown ethnicity. We did not define any minimum number of patients to include a study in our meta-analysis.

Statistical methods

Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated to assess the strength of the association between TNFα −308 G/A polymorphism and breast cancer risk. We explored the association for codominant model (GG versus AA; GA versus AA), dominant model (GG + GA versus AA), recessive model (GG versus GA + AA) and G allele versus A allele, respectively. In order to evaluate the ethnicity-specific effect, subgroup analyses were performed by ethnicities as well. A χ^2-based Q-test was performed to check the heterogeneity [26]. If the Q-test revealed a P value of more than 0.10, it indicates a lack of heterogeneity among the studies and the pooled ORs were calculated according to the fixed effects model (the Mantel–Haenszel method) [27]. Otherwise, the random effects model (the DerSimonian–Laird method) [28] was used. The one-way sensitivity analyses were performed to assess the stability of the meta-analysis' results. An estimate of potential publication bias was also carried out using the funnel plot and the Egger's linear regression test. An asymmetric funnel plot suggests a possible publication bias, and a P less than 0.05 in the Egger's test was considered representative of statistically significant publication bias [29]. All statistical analyses listed above were performed with the software Stata version 10.0 (Stata Corporation, College Station, TX).

Results

Study characteristics

In total, 11 studies with 10,184 cases and 12,911 controls met the inclusion criteria and were used in the pooled analyses [11–21]. Table 1 lists the studies identified and their main characteristics. Of the 11 studies, sample sizes ranged from 190 to 10,145. There were 9 studies of Caucasians, 1 study of Asians, and 1 study of unknown ethnicity. Among the 11 studies, 9 articles used controls derived from healthy populations and 2 articles used hospital-based controls. Genotypes' distributions in the controls of 10 studies were in agreement with Hardy–Weinberg equilibrium.

Main results

The main results of this meta-analysis were listed in Table 2. Overall, when all the eligible studies were pooled

Table 1 Main characterics of all studies included in the meta-analysis

Author	Year	Country	Ethnicity	Source of controls	Sample size (case/control)	Cases			Controls			HWE (controls)
						GG	GA	AA	GG	GA	AA	
Mestiri [11]	2001	Tunisia	Unknown	Population	243/174	167	53	23	117	53	4	0.48
Giordani [12]	2003	Italy	Caucasian	Hospital	125/100	104	19	2	84	15	1	0.72
Azmy [13]	2004	UK	Caucasian	Population	705/498	475	208	22	313	167	18	0.46
Smith [14]	2004	UK	Caucasian	Population	123/214	98	21	4	146	56	12	0.04
Kamali-Sarvestani [15]	2005	Iran	Asian	Population	223/235	192	31	0	203	32	0	0.26
Scola [16]	2006	Italy	Caucasian	Population	84/106	71	12	1	79	26	1	0.47
Gallicchio [17]	2007	USA	Caucasian	Population	59/907	44	14	1	593	273	41	0.19
Gaudet [18]	2007	USA and Poland	Caucasian	Population	5,159/4,986	3681	1346	132	3490	1369	127	0.61
Sirotkovic-Skerlev [19]	2007	Croatia	Caucasian	Hospital	158/76	136	22	0	68	8	0	0.63
Ostashkin [20]	2008	Russia	Caucasian	Population	167/139	126	39	2	108	28	3	0.47
MARIE-GENICA [21]	2009	Germany	Caucasian	Population	3,138/5,476	2238	822	78	3795	1527	154	0.98

HWE Hardy–Weinberg equilibrium

Table 2 Results of meta-analysis for TNFα −308G/A polymorphism and breast cancer risk

Study groups	n[a]	Cases/controls	GG vs. AA		GA vs. AA		Dominant model		Recessive model		G allele vs. A allele	
			OR (95% CI)	P[b]	OR (95% CI)	P[b]	OR (95% CI)	P[b]	OR (95% CI)	P[b]	OR (95% CI)	P[b]
Total	11	10,184/12,911	1.06 (0.90, 1.26)	0.241	0.95 (0.80, 1.13)	0.200	1.03 (0.87, 1.22)	0.222	1.10 (1.04, 1.17)[c]	0.445	1.08 (1.02, 1.14)[c]	0.279
Caucasian	9	9,718/12,502	1.12 (0.94, 1.33)	0.865	1.01 (0.85, 1.21)	0.965	1.09 (0.92, 1.29)	0.911	1.10 (1.04, 1.17)[c]	0.283	1.09 (1.03, 1.14)[c]	0.278
Asian	1	223/235	–[d]	–	–[d]	–	–[d]	–	0.98 (0.57, 1.66)	–	0.98 (0.59, 1.63)	–

[a] Number of comparisons

[b] P value of Q-test for heterogeneity test, only fixed effects model was used in this meta-analysis because the P values for heterogeneity test were all higher than 0.1

[c] Statistically significant results

[d] The ORs of Asians in the subgroup analysis for GG versus AA, GA versus AA and dominant model can not be calculated because there is not any sample detected with the genotype AA in either case or control of the Asian's study [15]

into the meta-analysis, significantly increased breast cancer risk was found for recessive model (OR = 1.10, 95% CI = 1.04–1.17) (Fig. 1) and for G allele versus A allele (OR = 1.08, 95% CI = 1.02–1.14). In the stratified analysis by ethnicity, significantly increased risks were also found among Caucasians for recessive model and for G allele versus A allele (for recessive model: OR = 1.10, 95% CI = 1.04–1.17; for G allele versus A allele: OR = 1.09, 95% CI = 1.03–1.14) (Table 2); however, no significantly increased risk was found among Asians for all genetic models (Table 2).

Sensitivity analyses and publication bias

Our results suggested the influences of the individual data set to the pooled ORs were not significant. In addition, neither Begg's funnel plot nor Egger's test suggest any obvious evidence of publication bias (data not presented).

Discussion

It has been suggested that single nucleotide polymorphisms (SNPs) are the most common sources of human genetic variation, and they may contribute to an individual's susceptibility to cancer [30]. So far, growing number of studies have investigated the role of TNFα −308 G/A in the development of breast cancer, but the results are inconclusive. Hence we performed this meta-analysis of 11 studies, involving 10,184 cases and 12,911 controls, to estimate the association specifically. Our results indicated that the TNFα −308 G allele is a risk factor for developing breast cancer. This result may be biologically plausible.

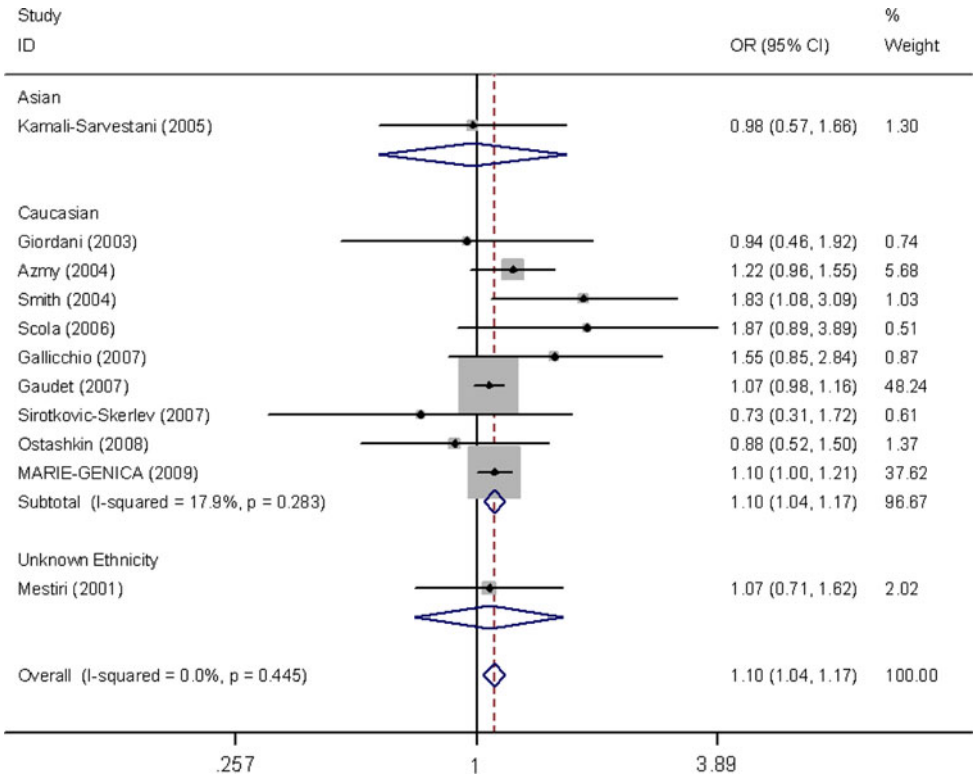

Fig. 1 Forest plot for the association between breast cancer risk and TNFα −308G/A polymorphism for recessive model

Some studies have reported that the TNFα −308 G/A polymorphism can alter TNFα's expression levels [8, 9]. Since TNFα is known to have both pro- and anti-carcinogenic properties [10] and chronically produced TNFα can play the role of a tumor promoter [18], the −308 G/A polymorphism of TNFα may act as an indirect breast cancer risk factor through changing the expression level of TNFα. In the subgroup analysis, significant association was found in Caucasians but not in Asians for recessive model and G allele versus A allele, suggesting a possible role of ethnic differences in genetic backgrounds and the environment they lived in.

The results of our meta-analysis strongly support the conclusion that the TNFα −308 G allele is a risk factor for developing breast cancer according to the large sample size and the significant associations for the recessive model and for G allele versus A allele in total and in Caucasians. However, there still may be some limitations in this meta-analysis. First, the controls included in our analysis were not uniformly defined. Although most of the controls were selected mainly from healthy populations, some were hospital-based. Therefore, these studies may have included the control groups who have different risks of developing breast cancer so that non-differential misclassification bias was possible. Second, in the subgroup analyses, there is only one study of Asians and the sample of Asians was relatively small, not having enough statistical power to explore the real association. Third, our data lack the information of age, sex, environmental factors, and lifestyle, so that our results were based on unadjusted estimates and a more precise analysis should be conducted in the future.

In conclusion, our meta-analysis with a large sample size strongly suggests that the TNFα −308 G allele is a risk factor for developing breast cancer, especially for Caucasians. However, further prospective researches with more convincing experimental proofs are necessary and expected. Such researches may eventually lead to our better, comprehensive understanding of the association mechanism between the TNFα −308 G/A polymorphism and breast cancer risk.

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