Original Article · Originalarbeit

Breast Care

Breast Care 2011;6:126–129
DOI: 10.1159/000327515

Published online: April 29, 2011

Association between the TNF-α-238G>A and TGF-β1 L10P Polymorphisms and Breast Cancer Risk: A Meta-Analysis

Jun Guo[a]* Hua Meng[b]* Jianming Pei[a] Miaozhang Zhu[a]

[a]Department of Physiology, The School of Basic Medicine, The Fourth Military Medical University,
[b]Department of Geriatrics, First Affiliated Hospital to The Fourth Military Medical University, Xi'an, Shanxi, P.R. China

Keywords
TNF · TGF · Breast cancer · Polymorphism

Summary
Background: The tumor necrosis factors alpha and beta (TNF-α, TNF-β) can regulate a wide range of cellular responses and facilitate tumor growth and progression. However, the effects of the polymorphisms TNF-α-238G>A and transforming growth factor (TGF)-β1 L10P on breast cancer risk are still unclear or inconclusive. **Materials and Methods:** In order to provide a full estimation of the association with breast cancer, a meta-analysis of the most valid literature was performed by searching the databases PubMed, Web of Science, ScienceDirect, EBSCO, CNKI, and Google Scholar. **Results:** For TNF-α-238G>A, 3 studies including 35,578 cases and 38,095 controls were selected. For TGF-β1 L10P, 11 studies including 7,903 cases and 8,797 controls were selected. For TNF-α-238G>A, a significant association with breast cancer risk was found in the recessive model (odds ratio = 0.954, 95% confidence interval 0.912–0.998), but other models did not reach significance. For TGF-β1 L10P, no significant correlations were found. **Conclusions:** Our study indicates that TNF-α-238G>A may be associated with breast cancer incidence, although significance is weak. Its role as an indicator for cancer diagnosis should be studied more. Moreover, for TGF-β1 L10P, further comprehensive meta-analyses are necessary.

Schlüsselwörter
TNF · TGF · Mammakarzinom · Polymorphismus

Zusammenfassung
Hintergrund: Die Tumornekrosefaktoren alpha und beta (TNF-α, TNF-β) können eine Vielzahl von zellulären Vorgängen regulieren und unterstützen Tumorwachstum und -progression. Die Auswirkungen der Polymorphismen TNF-α-238G>A und TGF (transforming growth factor)-β1 L10P auf das Brustkrebsrisiko sind noch immer ungeklärt bzw. nicht eindeutig. **Material und Methoden:** Um die Assoziation dieser Polymorphismen mit dem Brustkrebsrisiko in vollem Umfang einschätzen zu können, wurde eine Metaanalyse der relevantesten Literatur durchgeführt. Zu diesem Zweck wurden die Databanken PubMed, Web of Science, ScienceDirect, EBSCO, CNKI und Google Scholar durchsucht. **Ergebnisse:** Für TNF-α-238G>A wurden 3 Studien mit insgesamt 35 578 Fällen und 38 095 Kontrollen selektiert. Für TGF-β1 L10P wurden 11 Studien mit insgesamt 7903 Fällen und 8797 Kontrollen selektiert. Unsere Ergebnisse zeigen ein signifikantes Brustkrebsrisiko in Verbindung mit TNF-α-238G>A im rezessiven Modell (Odds-Ratio = 0,954, 95%-Konfidenzintervall 0,912–0,998). In anderen Modellen wurde jedoch keine vergleichbare Signifikanz erreicht. Für TGF-β1 L10P konnte keine signifikante Korrelation gezeigt werden. **Schlussfolgerungen:** Unsere Studie gibt Hinweise auf einen Zusammenhang zwischen TNF-α-238G>A und der Inzidenz des Mammakarzinoms, obgleich nur eine schwache Signifikanz besteht. Die Rolle dieses Polymorphismus als ein Indikator in der Krebsdiagnose sollte eingehender untersucht werden. Für TGF-β1 L10P sollten ebenfalls weiterführende, umfassende Metaanalysen durchgeführt werden.

*These authors contributed equally to this work.

KARGER
Fax +49 761 4 52 07 14
Information@Karger.de
www.karger.com

1661-3791/11/0062-0126$38.00/0

Accessible online at:
www.karger.com/brc

Miaozhang Zhu, MD
Department of Physiology, The School of Basic Medicine
The Fourth Military Medical University
Xi'an, Shanxi 710032, P.R. China
Tel./Fax +86 2982545490
guojundoc@163.com or jguo2010@126.com

Introduction

Breast cancer is by far the most prevailing cancer in women. It was the second leading cause of cancer deaths in the US in 2008, following lung cancer. The mechanisms underlying breast cancer are still far from fully understood. Many susceptibility genes combined with environmental factors have been suggested to be important in the growth and development of cancer.

Studies investigating the relationship between common genetic variants and cancer risk are being reported with rapidly increasing frequency [1]. In this study, we tried to combine previous individual articles to obtain more precise estimates of breast cancer risk. An important genetic variant for inhibiting cancer development and growth is the tumor necrosis factor alpha (TNF-α) which is a member of the TNF/TNF cytokine receptor superfamily and involved in the maintenance and homeostasis of the immune system, inflammation, and host defense. Although TNF-α was originally regarded to cause hemorrhagic tumor necrosis at high concentrations in many types of cancers, low concentrations of TNF-α seem to increase tumor growth and progression. Studies examining the role of the TNF-α gene in breast cancer growth have shown that TNF-α can serve as a breast tumor promoter. TNF-α is a widely studied factor associated with tumor development and growth. Single nucleotide polymorphisms of TNF-α have attracted much attention regarding their potential use as detection indicators for certain cancers. So far, the polymorphism TNF-α-238G>A, rs361525 has not been investigated and its relationship with cancer risk has not been understood compared to another important polymorphism, TNF-α-308G/A. In a recent study by Fang et al. [2], the association between TNF-α-308G/A and breast tumor risk was confirmed through a meta-analysis. However, the accumulated literature for TNF-α-238G>A is not at all comprehensive based on our preliminary search of previous publications using the online scientific database PubMed. The present study provides the first detailed meta-analysis for TNF-α-308G/A and its association with breast cancer risk.

Transforming growth factor beta 1 (TGF-β1) is a potent inhibitor of proliferation of epithelial, endothelial and hematopoietic cells, and acts as a tumor suppressor [3]. However, TGF-β1 may facilitate tumor growth, as its overexpression can enhance tumor metastases [4]. The gene for TGF-β1 carries a common T/C variation of nucleotide 29, resulting in a leucine (L) to proline (P) polymorphism at codon 10 (TGFB1 L10P). Based on our literature search, no meta-analysis related to this position seems to have been carried out thus far.

In the present study, we review the literature on the 2 gene polymorphisms mentioned above in conjunction with breast cancer and offer a systematic meta-analysis of their association. The purpose of the study is to provide consistent evidence regarding the association of TGF-β1 L10P and TNF-α-238G>A with respect to breast cancer incidence.

Materials and Methods

Selection of Studies

The following databases or searching engines were used to search articles published online before January 2010: PubMed, Web of Science, ScienceDirect, EBSCO, CNKI, and Google Scholar. We used the terms 'TNF-alpha', 'TNF-α', '238', '308', 'TGF', 'TGF-β1', 'L10P', and 'breast' to identify the studies closely related to TNF-α, TGF-β1, and breast cancer risk. References were double checked by different authors to identify any missing studies in the database search. Review articles were hand-searched to find additional eligible references. Only published studies with available full text articles were included. When overlapping data of the same patient population were included in more than 1 publication, only the literature providing the full text was used in the analysis [2].

Table 1. Main characteristics of all studies for the TNF-α-238G>A polymorphism included in the meta-analysis

Author [ref.]	Year	Country	Ethnicity	Sample size (cases/controls), n	Cases, n			Controls, n		
					GG	GA	AA	GG	GA	AA
Gaudet et al. [9]	2007	US and Poland	Caucasian	5,269/4,982	4,723	527	19	4,547	421	14
Azmy et al. [10]	2004	UK	Caucasian	708/495	621	84	3	434	59	2
Gaudet et al. [6]	2009	European descendants	Caucasian	26,917/30,429	23,456	3,352	109	26,597	3,706	126
Gaudet et al. [6]	2009	Asian descendants	Asian	2,684/2,189	2,503	174	7	2,061	124	4

Table 2. Main characteristics of all studies for the TGF-β1 L10P polymorphism included in the meta-analysis

Author [ref.]	Year	Country	Ethnicity	Sample size (cases/controls), n	Cases, n			Controls, n		
					TT	TC	CC	TT	TC	CC
Lee et al. [11]	2005	Korea	Asian	498/501	135	228	135	148	235	118
Kamali-Sarvestani et al. [12]	2005	Iran	Asian	219/227	19	101	99	16	99	112
Feigelson et al. [13]	2006	US	Caucasian	485/481	182	233	70	181	221	79
Ziv et al. [14]	2001	US	Caucasian	19/121	9	10	0	47	65	9
Shin et al. [15]	2005	China	Asian	1,114/1,189	258	554	302	255	615	319
Le Marchand et al. [5]	2004	Japan	Asian	303/385	62	163	78	91	183	111
Le Marchand et al. [5]	2004	Europe, US, Australia	Caucasian	299/402	114	137	48	141	183	78
Jin et al. [16]	2004	Finland and Poland	Caucasian	638/439	270	282	86	189	196	54
Krippl et al. [3]	2003	Austria	Caucasian	495/499	196	219	80	182	229	88
Dunning et al. [1]	2003	Europe	Caucasian	2,648/2,902	470	1,639	539	1,169	1,354	379
Cox et al. [17]	2007	US	Caucasian	1,185/1,651	469	548	168	613	797	241

Statistical Analysis

We explored the association using an additive genetic model (for TNF-α: GG versus AA; for TGF-β1: TT versus CC), dominant model (for TNF-α: GG+GA versus AA; for TGF-β1: TT+TC versus CC), recessive model (for TNF-α: GG versus GA+AA; for TGF-β1: TT versus TC+CC), and allele contrast (for TNF-α: G allele versus A allele; for TGF-β1: T allele versus C allele). Odds ratios (ORs) and 95% confidence intervals (CIs) were used to assess the strength of the association between a single nucleotide polymorphism and breast cancer risk. The inverse variance weighting method was used for pooling. The heterogeneity of the data was quantified using Q statistic. Heterogeneity among studies was considered significant when p was < 0.1 (Q statistic). If there was significant heterogeneity among studies, the random effects model was used, otherwise, the fixed effects model was acceptable. Publication bias was represented by funnel plots and was further assessed using Egger's linear regression test ($p < 0.05$ was considered representative of statistically significant publication bias). When there was a significant publication with regard to gene polymorphisms and breast cancer risk, the Duval and Tweedie non-parametric 'trim and fill' method was applied to correct the publication bias. All statistical analyses were performed with the software Stata 10 (StataCorp LP, College Station, Texas, USA).

Results and Discussion

Literature Characteristics

In total, 11 studies, comprising 12 data sets with 7,903 cases and 8,797 controls, were included based on the selection criteria for analyzing the susceptibility risk of TGF-β1 L10P. The data from Le Marchand et al. [5] can be divided into 2 parts, one for the Caucasian population and another for the Asian population. For TNF-α-238G>A, 3 studies, comprising 4 data sets with 35,578 cases and 38,095 controls, were identified for analyzing its connection with breast cancer susceptibility. Similarly, the cohort data from Gaudet et al. [6] can be divided into 2 subsets based on ethnicity, which will be evaluated further (tables 1 and 2).

Association between TNF-α-238G>A and Breast Cancer Risk

Significantly different breast cancer risk was found for the recessive model (GG versus GA+AA) (fig. 1). After ethnic stratification (focusing on Caucasian), significant differences were no longer found, implying the importance of the Asian population (table 3). However, since only 1 record was available for the Asian population, a validated meta-analysis cannot be guaranteed. Therefore, further studies on the association between TNF-α-238G>A and breast cancer risk in Asian women are warranted. Our results suggested that the influence of the individual data sets on OR estimation was significant. The cohort data from Gaudet et al. [6] is the most influential (fig. 2). In addition, neither Begg's funnel plot nor Egger's test suggest any obvious evidences of publication bias ($p > 0.05$) (fig. 3).

Table 3. Results of the meta-analysis of TNF-α-238G>A and breast cancer risk

	OR	95% CI	Q	p
Total				
Additive model	0.972	0.768–1.228	0.88	0.83
Dominant model	0.976	0.772–1.23	0.818	0.845
Recessive model	0.954	0.912–0.998	6.147	0.105
Allele contrast	0.959	0.917–1.002	5.26	0.154
European				
Additive model	0.984	0.775–1.249	0.581	0.748
Dominant model	0.989	0.779–1.255	0.526	0.768
Recessive model	0.958	0.915–1.003	5.341	0.069
Allele contrast	0.962	0.920–1.007	4.509	0.105

OR = Odds ratio; 95% CI = 05% confidence interval; Q = Q statistics.

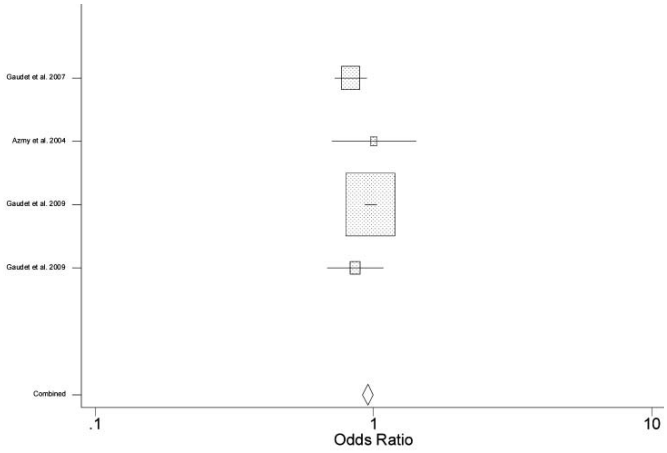

Fig 1. Forest plot for the association between breast cancer risk and TNF-α-238G>A based on the recessive model.

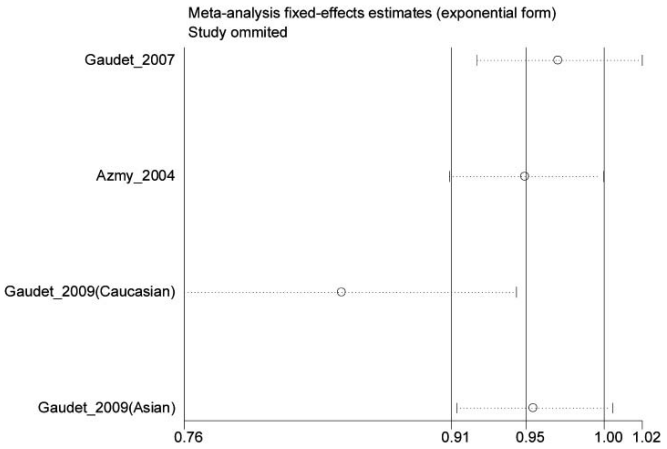

Fig. 2. Influence of individual literature on the overall meta-analysis for TNF-α-238G>A. As shown, the data for the Caucasian population by Gaudet et al. 2009 [6] was most dominant.

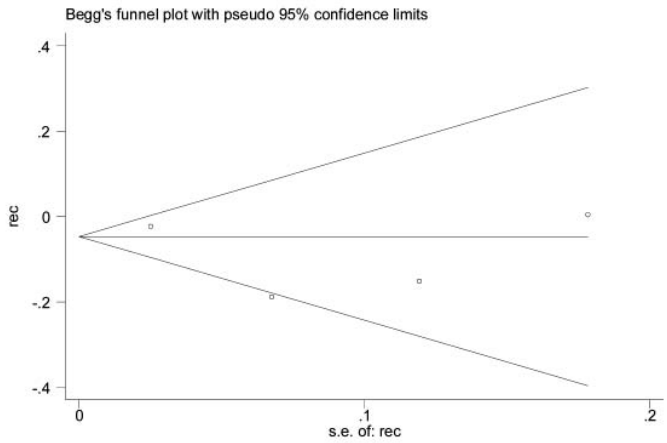

Fig. 3. Begg's funnel plot analysis to detect publication bias. Each point represents a separate study for the indicated association. The plot is for the recessive model of TNF-α-238G>A.

Association between TGF-β1 L10P and Breast Cancer Risk

We found no significant association between TGF-β1 L10P and breast cancer risk (table 4) with the random effects model. Although most genetic models present significant probabilities using the fixed effects model of meta-analysis, the results can still not be adopted rationally to reveal a relationship because the heterogeneity tests are significant (not shown). In the subsequent analysis based on ethnicity, no significant associations were found either.

Further Perspectives

There are still inconsistencies regarding TGF-β1 L10P and breast caner. Our work is congruent with the cohort study of Rebbeck et al. [7]. However, a recent meta-analysis by Qiu et al. [8] supports a positive association between TGF-β1 L10P and breast caner. This demonstrates that further evaluation of this gene polymorphism is necessary before a consensus can be reached.

A meta-analysis on TNF-α-238G>A has not been previously carried out. For the first time, our analysis confirmed that the TNF-α-238G>A is associated with breast cancer incidence, similar to TNF-α-308G/A [2]. However, because the literature on TNF-α-238G>A is still limited, the significance of the association is weak. Therefore, further studies on the application of TNF-α-238G>A as a clinical indicator are needed.

Overall, we attempted to reduce the lack of power exhibited by an individual study and combine different previous studies to perform a meta-analysis. We summarized the results of previous meta-analyses, and based on some new findings, we can provide a relative outline of the investigated gene polymorphisms and breast cancer risk. Our results should give new insights in breast cancer epidemiology.

Table 4. Results of the meta-analysis of TGF-β1 L10P and breast cancer risk

	OR	95% CI	Q	p
Total				
Additive model	0.930	0.623–1.390	167.85	0.0001
Dominant model	0.951	0.788–1.149	50.409	0.0001
Recessive model	0.948	0.664–1.352	252.762	0.0001
Allele contrast	0.968	0.842–1.114	66.316	0.0001
Asian				
Additive model	0.990	0.834–1.175	2.674	0.445
Dominant model	0.997	0.874–1.137	3.263	0.353
Recessive model	1.001	0.868–1.156	3.095	0.377
Allele contrast	1	0.908–1.102	1.024	0.795
European				
Additive model	0.897	0.501–1.607	144.087	0.0001
Dominant model	0.914	0.691–1.211	39.891	0.0001
Recessive model	0.930	0.569–1.519	226.847	0.0001
Allele contrast	0.952	0.782–1.162	56.18	0.0001

OR = Odds ratio; 95% CI = 05% confidence interval; Q = Q statistics.

Acknowledgements

This work was supported by the China Postdoctoral Science Foundation (20080440222).

Disclosure Statement

The authors declare no conflicts of interest.

References

1 Dunning AM, Healey CS, Pharoah PD, Teare MD, Ponder BAJ, Easton DF: A systematic review of genetic polymorphisms and breast caner risk. Cancer Epidem Biomak 1999;8:843–854.

2 Fang F, Yao L, Yu XJ, Yu L, Wu Q, Yu L: TNFα-308 G/A polymorphism is associated with breast cancer risk: a meta-analysis involving 10,184 cases and 12,911 controls. Breast Cancer Res Treat 2010;122:267–271.

3 Krippl P, Langsenlehner U, Renner W, et al.: The L10P polymorphism of the transforming growth factor-beta 1gene is not associated with breast cancer risk. Cancer Lett 2003;201:181–184.

4 Dumont N, Arteaga CL: Transforming growth factor-beta and breast cancer: tumor promoting effects of transforming growth factor-beta. Breast Cancer Res Treat 2000;2:125–132.

5 Le Marchand L, Haiman CA, van den Berg D, et al.: T29C polymorphism in the transforming growth factor beta1 gene and postmenopausal breast cancer risk: the Multiethnic Cohort Study. Cancer Epidemiol Biomarkers Prev 2004;13:412–415.

6 Gaudet MM, Milne RL, Cox A, et al.: Five polymorphisms and breast cancer risk: results from the Breast Cancer Association Consortium. Cancer Epidemiol Biomarkers Prev 2009;18:1610–1616.

7 Rebbeck TR, Antoniou AC, Llopis TC, et al.: No association of TGFB1 L10P genotypes and breast cancer risk in BRCA1 and BRCA2 mutation carriers: a multi-center cohort study. Breast Cancer Res Treat 2009;115:185–192.

8 Qiu LX, Yao L, Mao C, Chen B, Zhan P, et al.: TGFB1 L10P polymorphism is associated with breast cancer susceptibility: evidence from a meta-analysis involving 47,817 subjects. Breast Cancer Res Treat 2010;123:563–567.

9 Gaudet MM, Egan KM, Lissowska J, et al.: Genetic variation in tumor necrosis factor and lymphotoxin-alpha (TNF-LTA) and breast cancer risk. Hum Genet 2007;121:483–490.

10 Azmy IAF, Balasubramanian SP, Wilson AG, et al.: Role of tumour necrosis factor gene polymorphisms (-308 and -238) in breast cancer susceptibility and severity. Breast Cancer Res 2004;6:R395–R400.

11 Lee KM, Park SK, Hamajima N, et al.: Genetic polymorphisms of TGF-beta1 & TNF-beta and breast cancer risk. Breast Cancer Res Treat 2005;90:149–55.

12 Kamali-Sarvestani E, Merat A, Talei AR: Polymorphism in the genes of alpha and beta tumor necrosis factors (TNF-α and TNF-β) and gamma interferon (IFN-γ) among Iranian women with breast cancer. Cancer Lett 2005;223:113–9.

13 Feigelson HS, Patel AV, Diver WR, et al.: Transforming growth factor beta receptor type I and transforming growth factor beta1 polymorphisms are not associated with postmenopausal breast cancer. Cancer Epidemiol Biomarkers Prev 2006;15:1236–1237.

14 Ziv E, Cauley J, Morin PA, Saiz R, Browner WS: Association between the T29-->C polymorphism in the transforming growth factor beta1 gene and breast cancer among elderly white women: the Study of Osteoporotic Fractures. JAMA 2001;285:2859–2863.

15 Shin A, Shu XQ, Cai Q, et al.: Genetic polymorphisms of the transforming growth factor-β1 gene and breast cancer risk: a possible dual role at different cancer stages. Cancer Epidemiol Biomarkers Prev 2005;14:1567–1570.

16 Jin Q, Hemminki K, Grzybowska E, et al.: Polymorphisms and haplotype structures in genes for transforming growth factor beta1 and its receptors in familial and unselected breast cancers. Int J Cancer 2004;112:94–99.

17 Cox DG, Penney K, Guo Q, Hankinson SE, Hunter DJ: TGFB1 and TGFBR1 polymorphisms and breast cancer risk in the nurses' health study. BMC Cancer 2007;7:175.