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IL-10(-1082A/G)基因多态性和乳腺癌的相关性:Meta 分析 *

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摘要 目的:系统评价 IL-10(interleukin-10)-1082A/G 基因位点多态性和乳腺癌的相关性。**方法:**PUBMED 和 EMBASE 文献数据库收集关于 IL-10 rs1800896(-1082A/G)基因多态性和乳腺癌危险性的相关文献资料,提取原始数据。采用 STATA 软件 11.0 进行统计分析,以 OR 值和 95 %CI 作为 IL-10 基因多态性和乳腺癌发病风险的相关性检测指标,并根据对照来源进行分层分析。Q 检验和 I2 统计检测研究的异质性,并进行敏感性分析,Begg's 漏斗图和 Egger's 检验评价发表偏倚。**结果:**12 篇病例对照研究文献纳入本研究,包含 5038 例乳腺癌病例,5437 例对照。GG 和 AA 等位基因相比,OR 值为 1.134,95 %可信区间为 1.004-1.280,P<0.05。GG 和 AA+AG 相比,OR 值为 1.131,95 %可信区间为 1.018-1.257,P<0.05,提示存在相关性。在分层分析中,合并以社区来源人群为对照的研究,OR 值为 1.144,95 %可信区间为 1.028-1.273,P<0.05。**结论:**IL-10 的 -1082A/G 的 GG 等位基因和 A 等位基因相比,可能增加乳腺癌的发生风险。

关键词:IL-10;乳腺癌;基因多态性;meta 分析

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Correlation of Interleukin-10 -1082A/G Gene Polymorphism with Breast Cancer: a Meta Analysis*

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ABSTRACT Objective: To investigate the correlation of IL-10 -1082A/G polymorphisms with the risk of breast cancer. **Methods:** PubMed and EMBASE were searched for eligible studies. The odds ratio (OR) with 95 % confidence interval (CI) was summarized to a-s sess the relationship between -1082A/G polymorphisms and the risk of breast cancer. Heterogeneity was assessed by the Q-test and I2 statistics. Sensitivity analysis was conducted by removing one study at one time to evaluate the quality and consistency of the results. Publication bias was assessed by the modified Begg's funnel plot and Egger's test. All statistical analyses were done by Stata version 11.0. **Results:** Twelve articles were included in this study which contain 5,038 breast cancer cases and 5,437 control. GG compare with the AA genotype, the OR was 1.134, 95 % CI was 1.004-1.280, P<0.05. The OR for GG compare with AA+AG was 1.131, 95 % CI was 1.018-1.257, P<0.05. Further analysis were stratified by source of control, in the population-based case-control studies, the OR was 1.144, 95 %CI was 1.028-1.273, P<0.05. **Conclusions:** IL-10 -1082A/G GG genotypes might be associated with the increased risk of breast cancer in comparison to the carrier A genotype.

Key words: IL-10; Breast cancer; Polymorphisms; Meta-analysis

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前言

白介素 10(interleukin-10,IL-10)属于抗炎细胞因子,由 T 辅助 2 类细胞分泌,具有调节机体免疫和炎症反应的作用[1],在不同的肿瘤微环境中起着相反的调控作用[2]。细胞因子的基因多态性(single-nucleotide polymorphisms,SNPs)可以影响其编码蛋白的表达和活性,影响肿瘤的生长[3,4]。IL-10 有 5 个外显子,启动子区域包含至少 40 个基因多态性位点,这些多态性位点可能影响基因转录[5,6]。IL-10 启动子区域的基因多态性位点 rs1800896(-1082A/G)具有基因连锁不平衡性,和 IL-10 的表达有关[4,7]。有研究报道 -1082A/G 的纯合子 AA 基因型和 IL-10 低表达有关,并且和多种肿瘤有相关性[8-10]。但目前对 -1082A/G

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和乳腺癌发病风险的相关性并没有一致的结论。因此,本研究采用 meta 分析对 IL-10 的 -1082A/G 基因多态性位点和乳腺癌发生风险的相关性进行研究。

1 材料和方法

1.1 文献检索策略

全面检索 PUBMED 和 EMBASE 文献数据库，以 "interleukin-10/IL-10","breast cancer/breast carcinoma","polymorphism/SNP" 为关键词,收集 2015 年 12 月之前公开发表的关于 IL-10 rs1800896(-1082A/G)基因多态性和乳腺癌危险性的相关文献资料。并进一步从参考文献中搜索更多的研究资料。如果在不同文献中报道了同一人群的研究结果,则本研究选用资料最完整的一项研究纳入。

1.2 纳入和排除标准

本研究按以下标准纳入文献资料:(1)2015 年 12 月之前公开发表的关于 IL-10 基因多态性和乳腺癌相关性的病例对照研究;(2)原始数据完整,提供了综合的比值比数据(OR 值)和 95 %可信区间(95 % confidence interval, 95 %CI);(3)对照研究资料的基因型频率分布满足 Hardy-Weinberg 平衡 (HWE)。剔除标准:(1)重复发表的研究资料;(2)摘要、综述、病例报道、评论类文献;(3)剔除信息太少无法获取足够数据的文献。

1.3 数据提取

两个研究者独立提取数据，要求所有项目最后达到一致。提取的数据包括:第一作者、发表时间、国家、病例数、对照数、对照来源、匹配标准。

1.4 统计学分析

采用 Chi-squared 检验检测对照组是否符合 HWE 定律。用 OR 值和 95 %CI 作为 IL-10 基因多态性和乳腺癌发病风险的相关性检测指标。共有四种 ORs 形式:(1)罕见纯合子:常见纯合子模型 GG:AA;(2)杂合子:常见纯合子模型 AG:AA;(3)共显性模型:AG+GG:AA;(4)隐性模型 GG:AA+AG。其中 A 为等位基因,G 为次要等位基因。

采用 Q 检验和 I2 统计检测研究的异质性。Q 检验 P 值 >0.05 表明研究中无异质性。如无异质性采用固定效应模型评价总体 OR 值,如存在异质性则采用随机效应模型。进一步根据对照来源进行分层分析。敏感性分析依次去除每项研究以评价各项研究对 meta 分析结果的一致性。Begg's 漏斗图和 Egger's 检验评价发表偏倚,P 值 <0.05 提示存在发表偏倚。

所有的统计分析均采用 STATA 软件 11.0 完成。

2 结果

2.1 文献纳入

共有 12 篇病例对照研究文献纳入本研究[11-22],共包含5038 例乳腺癌病例,5437 例对照。各研究特点及原始数据见表 1。其中 10 项研究为来源于社区健康人群的病例对照研究(population-based case-control, PCC),2 项来源于医院对照人群的病例对照研究(hospital-based case-control, HCC)。计算最小等位基因频率(minor allele frequency, MAF),除一项研究未提供完整数据之外[13],其余各研究均符合 HWE 平衡(P >0.05)。

表 1 纳入研究的文献基本资料

Table 1 Characteristics of all the studies

Author (year)	Country	Case /control	SNP						HWE	MAF	Source of control
			Case			Control					
			GG	AG	AA	GG	AG	AA			
Vinod(2015)	India	125/160	18	31	76	15	78	67	0.25	0.34	PCC
Pooja(2012)	India	200/200	68		132	55		145	N/A	N/A	PCC
Kong(2010)	Chian	315/322	1	29	285	2	35	285	0.42	0.06	PCC
Schonfeld (2010)	America	859/1083	200	417	219	230	530	322	0.66	0.46	PCC
Gonullu (2007)	Turkey	38/24	3	22	13	1	7	16	0.83	0.19	PCC
Pharoah (2007)	UK	2203/2280	344	1003	695	346	1096	743	0.08	0.41	PCC
Balasubramanian (2006)	UK	497/498	121	253	123	117	260	121	0.32	0.5	PCC
Onay (2006)	Canada	398/372	103	205	90	71	194	107	0.31	0.45	PCC
Scola (2006)	Italy	84/110	16	40	28	21	45	40	0.21	0.41	PCC
Guzowski (2005)	America	50/25	12	28	10	4	12	9	1	0.4	HCC
Smith(2004)	UK	144/263	39	58	32	57	120	46	0.24	0.52	PCC
Giordani (2003)	Italy	125/100	11	54	60	16	51	33	0.61	0.41	HCC

Note: HWE, Hardy-Weinberg Equilibrium; MAF, minor allele frequency; PCC, population-based case-control; HCC, hospital-based case-control.

2.2 Meta 分析结果

对各文献进行异质性检验，GG vs. AA 和 GG vs. AA+AG 无异质性，采用固定效应模型，AG vs. AA 和 AG+GG vs. AA 存在异质性，采用随机效应模型。由于 Pooja[13]的研究仅提供 AG+GG 数据，故共显性模型 AG+GG vs. AA 包含 12 项研究，其余三种模型包含 11 项研究。各合并 OR 值及 95%可信区间见表 2。其中，GG 和 AA 等位基因相比，OR 值为 1.134，95%可信区间为 1.004-1.280，P<0.05，进一步根据对照来源进行分层分析，在以社区来源人群为对照的研究中，OR 值为 1.152，95%可信区间为 1.018-1.303，P<0.05，见图 1。在隐形模型中，GG 和 AA+AG 相比，OR 值为 1.131，95%可信区间为 1.018-1.257，P<0.05，同样在分层分析中，合并以社区来源人群为对照的研究，OR 值为 1.144，95%可信区间为 1.028-1.273，P<0.05，见图2。

表 2 -1082A/G 合并 OR 值及 95 %可信区间

Table 2 Pooled ORs and 95 %CI for -1082A/G

GG vs. AA		AG vs. AA		AG+GG vs. AA		GG vs. AA+AG	
OR(95 %CI)	P	OR(95 %CI)	P	OR(95 %CI)	P	OR(95 %CI)	P
Total							
1.134(1.004-1.280)	0.043	0.945(0.763-1.172)	0.608	1.014(0.838-1.226)	0.889	1.131(1.018-1.257)	0.022
PCC							
1.152(1.018-1.303)	0.024	0.960(0.770-1.197)	0.718	1.040(0.864-1.251)	0.68	1.144(1.028-1.273)	0.013
HCC							
0.668(0.327-1.367)	0.27	1.005(0.290-3.483)	0.994	1.015(0.250-4.123)	0.984	0.737(0.380-1.427)	0.365

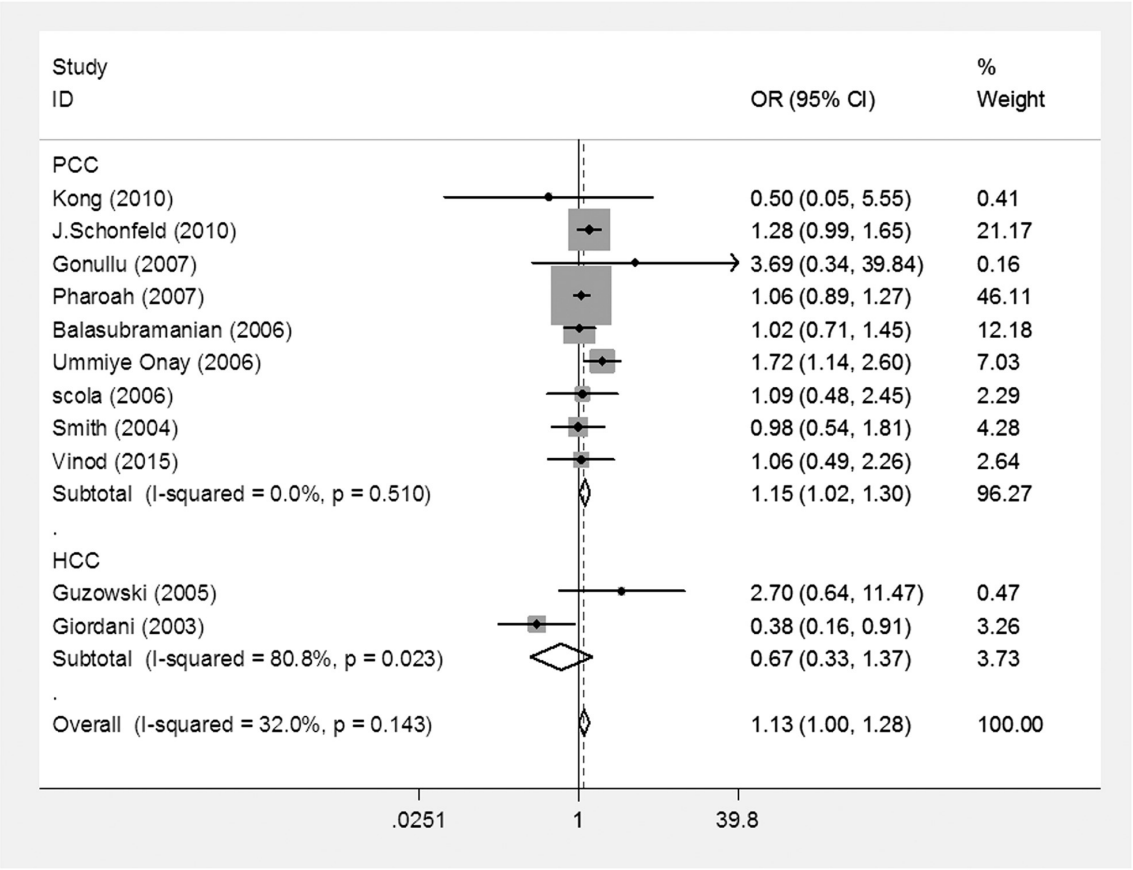

图 1 -1082A/G 基因多态性和乳腺癌相关风险森林图分层及汇总分析(GG vs. AA)

Fig.1 Forest plot of breast cancer risk associated with -1082A/G polymorphism(GG vs. AA)

2.3 敏感性分析和发表偏倚

我们将每项研究排除重新汇总 meta 分析，结果提示纳入文献质量稳定性良好，特异性无明显改变，见图 3。采用 Begg's 漏斗图（见图 4）和 Egger's 检验发表偏倚，95% CI 为 -1.43~1.403)，t=-0.03，P=0.978，提示无发表偏倚。

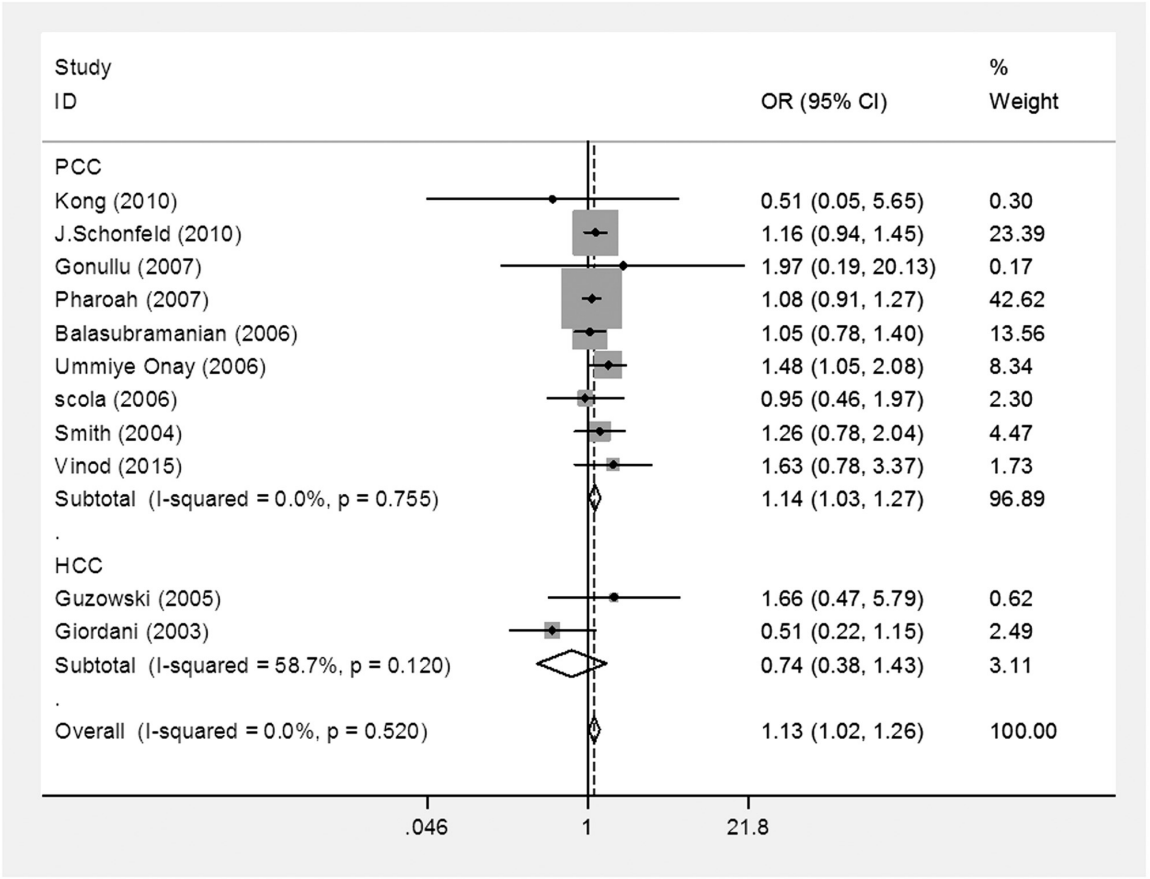

图 2 -1082A/G 基因多态性和乳腺癌相关风险森林图分层及汇总分析(GG vs. AA+AG)

Fig.2 Forest plot of breast cancer risk associated with -1082A/G polymorphism (GG vs. AA+AG)

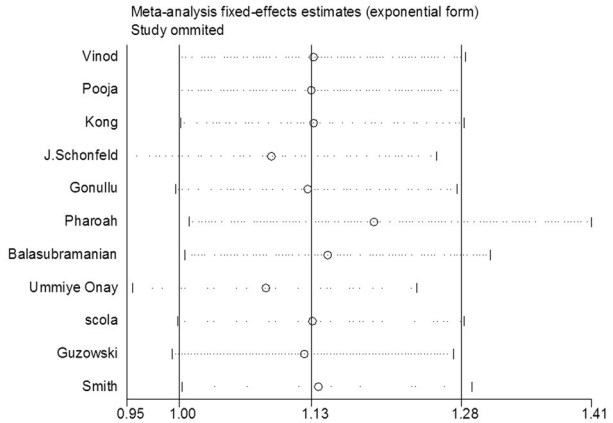

图 3 -1082A/G 基因多态性和乳腺癌相关风险敏感性分析(GG vs. AA)

Fig.3 Sensitivity analysis examining the association between -1082A/G and breast cancer (GG vs. AA)

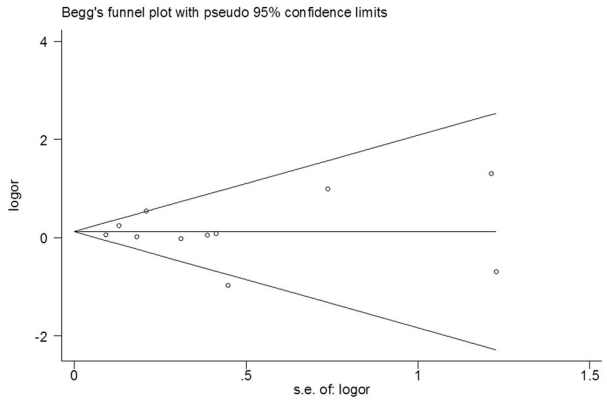

图 4 Begg's 漏斗图检验 -1082A/G 基因多态性和乳腺癌相关风险发表偏倚

Fig.4 Begg's plot for the assessment of publication bias for -1082A/G and breast cancer

表 3 Egger's 检验发表偏倚

Table 3 Egger's for the assessment of publication bias

Std Eff	Coef.	Std.Err.	t	P>|t|	95 %CI
Slope	0.1282926	0.1294358	0.99	0.348	-0.1645116 0.4210967
Bias	-0.0180358	0.6281528	-0.03	0.978	-1.439016 1.402945

3 讨论

既往已有研究者针对 IL-10 -1082A/G 基因多态性和乳腺癌的相关性进行 meta 分析,但由于纳入文献数量的限制,结果均提示无相关性[23,24]。随着研究数量的增多,本研究对 IL-10 的 -1082A/G 基因多态性位点和乳腺癌的相关性重新进行 meta 分析，此次共纳入 12 项研究，包含 5038 例乳腺癌病例,5437 例对照病例,meta 分析结果提示 GG 等位基因显著增加乳腺癌

风险。

IL-10 由 Th2 类细胞分泌，在不同的肿瘤微环境中起着相反的调控作用，一方面可以抑制免疫反应促进肿瘤生长，增强肿瘤细胞对细胞毒性 T 淋巴细胞的抵抗能力；另一方面可以通过抑制肿瘤血管生成达到抑制肿瘤的目的[25]。研究表明 IL-10 可以在体外促进乳腺癌细胞系 MCF-7 细胞增殖和迁移 [26]，乳腺癌基质细胞中 IL-10 的表达水平和总生存及无疾病进展生存有关，基质细胞高表达 IL-10 可以延长总生存期并降低远处转移风险[27]，而肿瘤细胞中 IL-10 低表达可以增加乳腺癌的不良预后风险[28]。同时，IL-10 还参与机体抗肿瘤免疫，Yekaterina 等研究发现在乳腺癌患者体内自然杀伤细胞表达 IL-10 增多，使得机体抗肿瘤免疫能力下降[29]。肿瘤相关巨噬细胞可以通过 IL-10/STAT3/bcl-2 通路增加乳腺癌对药物的抵抗[30]。

IL-10 的基因多态性和多种肿瘤有关[31-33]，机体内 IL-10 表达水平的改变 75 %是由于基因改变引起，因此 IL-10 基因位点改变可能可以调节 IL-10 表达，从而影响乳腺癌发病风险。尽管基因多态性位点的影响只是其中小部分，但是其作用也逐渐受到重视。研究显示 IL-10 的 -1082A/G 基因多态性位点可以影响基因转录和蛋白合成，从而影响 IL-10 的表达 [34]，并且 -1082G 基因多态性和乳腺癌低分化腺癌有关，ATA/GCA 单体型可以增加乳腺癌风险[35]。既往对乳腺癌患者 IL-10 基因多态性的研究中，病例组和对照组人群中 -1082A/G 基因多态性分布各有不同，部分研究显示 -1082A/G 和乳腺癌发病风险有关[11,12]。但 meta 分析均提示无相关性，本研究纳入更多研究之后，所得结果提示 GG 和 AA 等位基因相比，OR 值为 1.134，提示 G 等位基因可增加乳腺癌风险。本研究进一步根据对照组来源进行分层分析，在以社区人群为对照的研究中得出相同结论。我们采用 Begg's 漏斗图(见图 4)和 Egger's 检验发表偏倚，漏斗图型及统计结果均提示无发表偏倚存在。

但 meta 分析仍存在一定的限制性。首先，太少的样本量可能会影响研究结果。其次，由于没有足够的原始资料，对 IL-10 基因多态性和乳腺癌患者雌激素和孕激素受体状态的影响无法深入研究。此外，由于文献数量及样本量的限制，本文未对不同人种进行进一步分层分析。因此，对于 IL-10 的 -1082A/G 基因多态性和乳腺癌关系仍需更高质量及大样本的研究来得以证实。

本研究对 IL-10 的 -1082A/G 基因多态性和乳腺癌的发生风险进行了 meta 分析，提示 IL-10 的 -1082A/G 基因多态性 GG 等位基因显著增加乳腺癌的发生风险。

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