Original Article Glutathione S-transferase M₁ polymorphism and bladder cancer risk: a meta-analysis involving 50 studies

Zhi-Ping Qi¹, Er-Jiang Zhao², Bo Li¹, Rui-Xia Bai¹

¹The Medical Group of Zhengzhou First People's Hospital, Zhengzhou 450004, Henan, China; ²Affiliated Tumor Hospital of Zhengzhou University, Henan Tumor Hospital, Zhengzhou 450008, Henan, China

Received September 27, 2016; Accepted January 20, 2017; Epub March 1, 2017; Published March 15, 2017

Abstract: Glutathione S-transferase M_1 (GST M_1) is an important family of phase II isoenzymes involved in inactivation of procarcinogens, which are factors that contribute to cancer genesis and progression. Null status of GST M_1 is associated with decreased enzyme activity, and it has been widely studied as risk factor in bladder cancer (BC) susceptibility. However, the GST M_1 null variant and BC form unclear association. We carried out meta-analysis to clarify the influence of GST M_1 deficiency on BC. We estimated the pooled odds ratio (OR) with its 95% confidence interval (Cl) to assess the association of the two conditions. Fifty studies with a total of 12,527 cases and 16,275 controls were included into the meta-analysis, which was not confined to a specific population. Overall, our meta-analysis supports the hypothesis that the GST M_1 null variant is a determinant of BC susceptibility (OR=1.41 [1.30, 1.52], P<0.00001). The same patterns were observed in Caucasians (OR=1.38 [1.23, 1.55], P<0.00001), Africans (OR=1.68 [1.04, 2.71], P=0.03) and Asians (OR=1.48 [1.35, 1.61], P<0.00001). Furthermore, positive associations were also observed in both hospital-based (OR=1.48 [1.35, 1.61], P<0.00001) and population-based (OR=1.26 [1.10, 1.43], P=0.0006) studies. When data were stratified based on smoking status, we noted that smoking modified the association between GST M_1 deficiency and BC risk (OR=1.41 [1.20, 1.65], P<0.0001) in smokers. However, no association was observed in non-smoking populations. In conclusion, this meta-analysis suggests that GST M_1 null variant is a risk factor of BC.

Keywords: Glutathione S-transferase M₁, polymorphism, bladder cancer, meta-analysis

Introduction

Bladder cancer (BC) is one of the most common cancers of the urinary tract and ranks fourth in the incidence of all common epidemic cancers. The disease also has increasing incidence and death rate. The United States estimates suggested that approximately 74,000 new BC cases were diagnosed, and 16,000 patients died in 2015 [1]. Although the etiology of BC remains largely unknown, a complex combination of genetic and environmental factors is currently accepted to contribute to BC development.

Glutathione S-transferases (GSTs) are members of a multigene family of isoenzymes; These enzymes currently include seven classes [2]. Among such compounds, polymorphisms of GSTM₄ (GSTM₄), which is expressed in many tissues, are among the most important and extensively studied in humans. GSTM, deletion was identified to cause formation of null alleles. Individuals with homozygous deletion of the GSTM, locus may have abolished enzyme activities and decreased ability to detoxify several xenobiotics. On the other hand, GSTM, null genotype exhibited weaker defence mechanisms against oxidative stress- and free radical-mediated cellular damage [3]. These types of cellular damage can produce chromosomal damage [4]. Therefore, individuals with GSTM, null genotypes may be at increased risks of developing cancer, especially lung, breast, gastric and BC [5-8]. However, various studies reported inconsistent results regarding the correlation between GSTM, genotype and individual susceptibility to BC [9, 10]. To clarify the effect of GSTM,



Figure 1. Flow chart of included studies in the current meta-analysis.

status on BC risk, we conducted an updated meta-analysis of published studies.

Materials and methods

Publication search

PubMed, Embase and Springer were separately searched (dated up to 4/20/2016) by two authors using combinations of the following keywords: "glutathione S-transferase M_1 " or "GST M_1 ", "bladder" or "urothelial", and "cancer" or "carcinoma", without any language restriction. A manual search was also conducted on reference lists of reviews and retrieved articles. Abstracts or unpublished studies were excluded. Additional articles were identified through a manual search of references cited in relevant articles.

Eligibility criteria

The studies included in this meta-analysis met the following criteria: (1) Case-control study of human BC; (2) Pathologically confirmed diagnosis of BC; (3) Sufficient data of sample size, odds ratio (OR) and 95% confidence interval (Cl); (4) Most recent or contain complete data when identifying multiple studies with identical sample group or overlapping data.

Data extraction

Data were carefully and independently extracted from all eligible publications based on the inclusion criteria, and disagreement was

resolved through discussion among the current authors. From each of the eligible study, the following data were extracted independently: First author, years of publication, sources of controls, ethnicity of studied population, number of genotyped cases and controls. Different ethnicities were categorised as Caucasian, Asian, African and mixed individuals. In terms of control sources, studies were also categorised as either population-based or hospital-based.

Statistical analysis

Statistical analysis was carried out using Review Manager 5.1. The OR corresponding to 95% CI was used to assess strength of association between GSTM₁ null polymorphism and BC risk. A Chi-square-based Q-statistic test and an I² test were performed to assess heterogeneity between studies (I²<25%, no heterogeneity; I²=25%-50%, moderate heterogeneity; I²>50%, large or extreme heterogeneity). Significance levels for heterogeneity were defined as P<0.01 and I²>50%. Publication bias of the meta-analysis was evaluated using funnel plot and Egger's weighted regression method.

Results

Study characteristics

We obtained 50 relevant articles examining GSTM, polymorphism and BC risk based on our eligibility criteria [11-60] (Figure 1). Table 1 lists the identified studies and their major characteristics. The data for this analysis included 12,527 cases and 16,275 controls for GSTM, polymorphism. The studies were published between 1995 and 2014. These researches were conducted in various populations of different ethnicities: 30 involved Caucasians, 12 involved Asians and four involved Africans. We also stratified all studies based on the source of controls: 32 were hospital-based, and the other 18 were population-based. Although not universal, smoking histories were ascertained from cases and controls in 18 studies.

| | | | | | - | | 2 | | |
|--------------------------|------|-------------|-----------|----------|------|-----|----------|-----|--|
| Author | Year | Country | Ethnicity | Design - | Case | | Control | | |
| Reszka [11] | 2014 | Poland | Caucasian | PB | 149 | 95 | 165 | 200 | |
| Wang MI [12] | 2014 | China | Asian | HB | 699 | 351 | 834 | 570 | |
| Cevlan GG [13] | 2015 | Ireland | Caucasian | HB | 22 | 43 | 31 | 39 | |
| Matic [14] | 2013 | Serbia | Caucasian | HB | 111 | 90 | 61 | 61 | |
| Berber [15] | 2013 | Turkey | Caucasian | PB | 54 | 60 | 51 | 63 | |
| Kang [16] | 2013 | South Korea | Asian | HB | 65 | 45 | 103 | 117 | |
| Savic-Radoievic [17] | 2013 | Serbia | Caucasian | HB | 45 | 35 | 32 | 28 | |
| Ovsiannikov [18] | 2012 | Germany | Caucasian | HB | 102 | 94 | 122 | 113 | |
| Lesseur [19] | 2012 | USA | Caucasian | PB | 378 | 275 | 508 | 420 | |
| Safarineiad [20] | 2013 | Iran | Caucasian | HB | 50 | 116 | 93 | 239 | |
| Öztürk [21] | 2011 | Turkey | Caucasian | PB | 98 | 78 | 51 | 46 | |
| Goerlitz [22] | 2011 | Egypt | African | PB | 344 | 274 | 564 | 578 | |
| Henríguez-Hernández [23] | 2012 | Spain | Caucasian | HB | 23 | 67 | 17 | 64 | |
| Salinas-Sánchez [24] | 2010 | Spain | Caucasian | HB | 109 | 92 | 78 | 115 | |
| Altavli [25] | 2009 | Turkev | Caucasian | HB | 58 | 77 | 65 | 63 | |
| Grando [26] | 2009 | Brazil | mixed | PB | 40 | 60 | 33 | 67 | |
| Rouissi [27] | 2009 | Tunisia | African | PB | 63 | 62 | 56 | 69 | |
| Song [28] | 2009 | China | Asian | HB | 131 | 77 | 108 | 104 | |
| Zupa [29] | 2009 | Italy | Caucasian | PB | 13 | 10 | 68 | 53 | |
| Covolo [30] | 2008 | Italy | Caucasian | HB | 128 | 69 | 111 | 100 | |
| Golka [31] | 2008 | Germany | Caucasian | HB | 184 | 109 | 88 | 88 | |
| Shao [32] | 2008 | China | Asian | HB | 85 | 117 | 81 | 191 | |
| Moore [33] | 2007 | Spain | Caucasian | HB | 683 | 394 | 524 | 498 | |
| Cengiz [34] | 2007 | Turkev | Caucasian | HB | 34 | 17 | 22 | 31 | |
| Murta-Nascimento [35] | 2007 | Spain | Caucasian | HB | 428 | 251 | 367 | 368 | |
| Zhao [36] | 2007 | USA | Caucasian | HB | 324 | 298 | 317 | 316 | |
| McGrath [37] | 2006 | USA | Mixed | HB | 109 | 82 | 483 | 439 | |
| García-Closas [38] | 2005 | Spain | Caucasian | HB | 716 | 422 | 571 | 561 | |
| Karagas [39] | 2005 | USA | mixed | PB | 210 | 144 | 309 | 233 | |
| Kellen [40] | 2005 | UK | Caucasian | PB | 312 | 267 | 597 | 466 | |
| Kim [41] | 2005 | Korea | Asian | HB | 92 | 61 | 73 | 80 | |
| Sobti [42] | 2005 | India | Asian | PB | 37 | 63 | 24 | 52 | |
| Srivastava [43] | 2005 | India | Asian | PB | 43 | 63 | 140 | 230 | |
| Hung [44] | 2004 | Italy | Caucasian | HB | 132 | 69 | 112 | 102 | |
| Moore [45] | 2004 | Argentina | mixed | PB | 54 | 52 | 49 | 60 | |
| Srivastava [46] | 2004 | India | Asian | HB | 42 | 64 | 54 | 128 | |
| Schroeder [47] | 2003 | USA | Caucasian | HB | 137 | 93 | 101 | 112 | |
| Jeong [48] | 2003 | Korean | Asian | HB | 75 | 51 | 99 | 105 | |
| Giannakopoulos [49] | 2002 | Greece | Caucasian | HB | 56 | 33 | 56 | 91 | |
| Lee [50] | 2002 | Korean | Asian | HB | 149 | 83 | 86 | 79 | |
| Ma [51] | 2002 | China | Asian | PB | 20 | 12 | 99 | 83 | |
| Aktas [52] | 2001 | Turkey | Caucasian | HB | 56 | 47 | 70 | 132 | |
| Törüner [53] | 2001 | Turkey | Caucasian | HB | 75 | 46 | 55 | 66 | |
| Schnakenberg [54] | 2000 | Germany | Caucasian | HB | 93 | 64 | 129 | 94 | |
| Steinhoff [55] | 2000 | Germany | Caucasian | HB | 80 | 55 | 57 | 70 | |
| Salagovic [56] | 1999 | Slovak | Caucasian | PB | 40 | 36 | 123 | 125 | |
| Abdel-Rahman [57] | 1998 | Egypt | African | PB | 26 | 11 | 15 | 19 | |
| Anwar [58] | 1996 | Egypt | African | PB | 19 | 3 | 10 | 11 | |
| Brockmöller [59] | 1996 | Germany | Caucasian | HB | 218 | 156 | 192 | 181 | |
| Katoh [60] | 1995 | Japan | Asian | PB | 51 | 32 | 43 | 58 | |

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

Abbreviations: PB, population-based study; HB, hospital-based study.

Glutathione S-transferase $\rm M_1$ polymorphism and bladder cancer risk

| Study or Subgroup Events Total Weight M-H. Random, 95%; Cl. M-H. Random, 95%; Cl. Akta 2001 66 103 70 202 1.7% 0.73 [0.45, 1.19] Akta 2001 66 103 70 220 1.7% 0.73 [0.45, 1.19] Arwar 1996 19 2.2 10 2.1 0.3% 6.97 [1.57, 3.07] Berder 2013 5.4 114 15% 1.11 [0.66, 1.87] | | case | case Control | | Odds Ratio | | Odds Ratio | | |
|--|--|-------------|--------------|------------|------------|--------|--------------------|--------------------------------------|--|
| Abdel-Rahman 1998 26 37 15 34 0.6% 2.99 [1:13, 7.66] Atlas 2001 56 103 70 202 17% 2.25 [1:33, 3.56] Allay! 2009 58 135 65 128 1.7% 0.75 [0.45, 1.19] Berber 2013 54 114 51 114 1.5% 0.75 [0.45, 1.19] Cengiz 2007 34 51 122 53 0.8% 2.26 [1.27, 6.26] Coviol 2008 128 197 111 2.1% 1.37 [1.41, 1.97] Garcia-Closes 2005 7.16 1138 2.3% 1.37 [1.41, 1.97] Gorbiz 2001 124 618 142 3.7% 1.29 [1.60, 1.57] Gorbiz 2005 7.16 138 1.26 [1.60, 1.57] Gorbiz 2008 184 618 142 3.7% 1.29 [1.61, 1.57] | Study or Subgroup | Events | Total | Events | Total | Weight | M-H, Random, 95% C | M-H, Random, 95% Cl | |
| Aktag 2001 66 103 70 202 1.7% 0.25 [1.83, 3.65] | Abdel-Rahman 1998 | 26 | 37 | 15 | 34 | 0.6% | 2.99 [1.13, 7.96] | | |
| Altayi 2009 58 135 65 128 1.7% 0.73 [0.45, 1.19] Berber 2013 54 114 51 114 15.7, 30.87 Berbor 2013 54 114 51 122 23% 122 [0.99, 1.76] Cengiz 2007 34 51 122 53 0.8% 228 [127, 6.26] Covido 2008 128 197 111 211 1.4% 167 [114, 1.37] Giana Acoosa 2005 716 1138 39% 167 [141, 1.37] * Gonitiz 2011 344 618 541 142 37% 129 [106, 1.57] * Gonitiz 2011 344 618 56 117 1.4% 129 [106, 1.57] * Gonitiz 2011 344 618 56 1107 * Gonitiz 2011 * 167 [141, 1.27] Grando 2000 40 100 31 100 13% 135 [157, 2.67] * Hum 2004 124 18% 168 [106, 2.60] * * * Jeong 2003 75 126 99 | Aktas 2001 | 56 | 103 | 70 | 202 | 1.7% | 2.25 [1.38, 3.65] | | |
| Anwar 1996 19 22 10 22 10 3% 6.97 [1.57, 30.87] Berder 2013 54 114 114 15% 1.11 [0.66, 1.87] Brockmöller 1996 218 374 122 53 0.8% 22 [2.76, 2.6] Caryla 2007 34 51 12 53 0.8% 22 [2.76, 2.6] Caryla 2007 13 14 51 114 112 17 124 167 [141, 1.47] Garcia-Closas 2005 716 1138 571 112 2.4% 156 [160, 4.75] | Altayli 2009 | 58 | 135 | 65 | 128 | 1.7% | 0.73 [0.45, 1.19] | | |
| Berber 2013 54 114 51 114 15% 111 [0.66, 1.87] Terchnöler 1966 218 374 112 22 63 0.8% 2.82 [1.27, 6.26] Cengiz 2007 34 51 22 53 0.8% 2.82 [1.27, 6.26] Cengiz 2007 34 51 22 53 0.8% 2.82 [1.27, 6.26] Covolo 2006 128 197 111 211 2.1% 167 [1.12, 2.49] Garnia-Cosas 2005 716 1138 571 1132 3.9% 167 [1.14, 1.97] Cocola 2008 146 233 88 176 2.2% 169 [1.16, 2.47] Crando 2009 40 100 33 100 1.3% 1.28 [1.65, 2.47] Functional 2009 40 100 33 100 1.3% 1.28 [0.63, 2.41] Hung 2004 132 201 112 2.14 2.1% 174 [1.7, 2.59] Hung 2004 132 201 112 2.14 2.1% 174 [1.7, 2.59] Karagas 2005 51 83 43 101 1.3% 1.56 [1.00, 2.44] Karagas 2005 121 354 309 542 3.0% 1.10 [0.84, 1.44] Karagas 2005 121 354 309 542 3.0% 1.10 [0.84, 1.44] Karagas 2005 121 354 309 542 3.0% 1.10 [0.84, 1.44] Karagas 2005 121 354 309 542 3.0% 1.10 [0.84, 1.44] Karagas 2005 121 378 653 508 928 3.6% 1.14 [0.98, 1.34] Karagas 2005 122 378 653 508 928 3.6% 1.14 [0.98, 1.34] Karagas 2005 124 378 653 508 928 3.6% 1.14 [0.98, 1.34] Karagas 2005 124 378 653 508 928 3.6% 1.14 [0.98, 1.34] Karagas 2005 124 378 653 508 928 3.6% 1.14 [0.98, 1.34] Karagas 2012 378 653 508 928 3.6% 1.14 [0.98, 1.34] Mai 2002 20 32 99 182 2.7% 1.21 [0.88, 1.65] Mai 2013 111 201 61 122 1.8% 1.26 [1.10, 2.46] Mai 2013 111 201 61 122 1.8% 1.26 [1.10, 2.46] Mai 2013 111 201 61 122 1.8% 1.26 [1.10, 2.46] Mai 2013 111 201 61 122 1.8% 1.26 [1.36, 1.46] Mai 2013 111 201 61 122 1.8% 1.26 [1.36, 1.46] Mai 2013 111 201 61 122 1.8% 1.26 [1.36, 1.46] Mai 2013 111 201 61 122 1.8% 1.26 [1.36, 1.46] Mai 2013 111 201 61 122 1.8% 1.26 [1.36, 1.46] Mai 2013 111 201 61 122 1.8% 1.26 [1.36, 1.47] Mai 2014 54 106 49 109 1.4% 1.27 [1.74, 2.17] Mai 2015 121 2.23% 1.66 [1.36, 1.46] Mai 2013 111 201 02 13 2.2% 1.65 [1.36, 1.47] Mai 2014 54 106 49 109 1.4% 1.27 [1.74, 2.17] Mai 2014 144 2.44 [1.46 3.66 [1.36, 1.46] Mai 2013 15 16 [1.37, 2.20] Mai 2014 144 2.44 [1.56 [1.57, 2.20] Mai 2013 15 16 [1.57, 2.20] Mai 2014 144 2.44 [1.56 [1.66, 1.77] Mai 2015 13 12 2.2% 1.66 [1.77, 1.66 [1.77, 2.4] | Anwar 1996 | 19 | 22 | 10 | 21 | 0.3% | 6.97 [1.57, 30.87] | | |
| Brockmöller 1996 216 374 192 373 2.9% 1.32 [0.99, 1.76] Ceylan GG 2015 22 65 31 70 10% 0.64 [0.32, 1.29] Garcia-Closas 2005 128 197 111 211 21% 167 [1.41, 1.97] Giannakopoulos 2002 56 89 56 147 1.4% 2.76 [1.60, 4.75] Gorditz 2011 344 618 664 1142 3.7% 1.29 [1.06, 1.57] Grando 2008 184 233 88 176 2.2% 1.69 [1.62, 247] Gording 2012 134 611 654 1142 2.1% 1.74 [1.17, 2.59] Terrando 2009 112 214 2.1% 1.74 [1.17, 2.59] Henriquez-Hernández 2012 23 90 17 81 0.9% 1.29 [0.63, 2.64] Henriquez-Hernández 2012 23 90 17 81 0.9% 1.29 [0.63, 2.64] Henriquez-Hernández 2012 354 309 542 3.0% 1.10 [0.84, 1.44] Hang 2004 100 354 309 542 3.0% 1.10 [0.84, 1.44] Karaga 2005 210 354 309 542 3.0% 1.10 [0.84, 1.44] Karaga 2005 210 354 309 542 3.0% 1.10 [0.84, 1.44] Karaga 2005 312 579 597 1063 3.6% 0.91 [0.74, 1.12] Henriquez-Hernández 2012 378 663 508 928 3.6% 1.14 [0.03, 2.64] Henriquez-Hernández 2012 378 663 508 928 3.6% 1.14 [0.03, 1.39] Kellen 2005 312 579 597 1063 3.6% 0.91 [0.74, 1.12] Henriquez-Hernández 2012 378 663 508 928 3.6% 1.14 [0.04, 1.56] Hezeu 2012 149 232 86 165 2.1% 1.65 [1.10, 2.48] Herniquez-Hernández 2012 378 663 508 928 3.6% 1.14 [0.03, 1.39] Haz 2002 129 91 162 2.18% 1.28 [1.07, 2.47] Haz 2002 149 232 86 165 2.1% 1.65 [1.0, 2.48] Haz 2002 149 123 2.86 1.52 [1.10, 2.48] Haz 2002 149 123 2.86 1.55 [1.10, 2.48] Haz 2003 157 129 2.23 2.7% 1.21 [0.88, 1.65] Haz 2004 54 106 49 109 1.4% 1.22 [0.74, 2.17] Haz 2007 128 2.47 2.47 [1.74] Haz 2008 185 2.02 [1.10, 2.27% 1.21 [0.88, 1.65] Haz 2008 185 2.02 [1.10, 2.28% 1.165 [1.30, 2.29] Haz 2009 131 2.00 [1.22 2.2% 1.65 [1.30, 2.20] Haz 2009 131 2.00 [1.22 2.2% 1.65 [1.30, 2.20] Haz 2009 131 2.00 [1.22 2.2% 1.65 [1.10, 2.20] Haz 2009 133 2.00 [1.22 2.2% 1.65 [1.10, 2.20] Haz 2009 133 2.00 [1.22 2.2% 1.65 [1.10, 2.20] Haz 2009 133 2.01 [2.22 | Berber 2013 | 54 | 114 | 51 | 114 | 1.5% | 1.11 [0.66, 1.87] | | |
| Cengiz 2007 34 51 22 65 31 70 10% 0.64 1032. 129 Covolo 2006 128 197 111 211 2.1% 167 11.2.49 Covolo 2008 128 197 111 211 2.1% 167 11.12.49 Covolo 2008 128 197 111 211 2.1% 167 11.12.49 Cianakopoulos 2002 56 89 56 147 14% 2.76 [16.0.4.75] Covolo 2008 144 23 88 176 2.39% 1.69 [1.16.2.47] Cianakopoulos 2002 168 56 147 14% 2.76 [16.0.4.75] Covolo 2008 144 23 88 176 2.2% 1.29 [1.06, 1.57] Crando 2009 40 100 33 100 1.3% 1.39 [0.76.2.41] Hung 2004 132 201 112 214 2.1% 1.74 [1.7.2.59] Charage 2005 121 354 309 542 30% 1.10 [0.84, 1.44] Karages 2005 210 354 309 542 30% 1.10 [0.84, 1.44] Karages 2005 121 354 309 542 30% 1.10 [0.84, 1.44] Karages 2005 121 354 309 542 30% 1.10 [0.84, 1.44] Karages 2005 122 579 71 1063 3.6% 0.91 [0.74, 1.12] Kim 2005 92 153 73 153 1.8% 1.65 [1.05.2.60] Maic 2013 111 201 61 122 1.8% 1.56 [1.05.2.64] Maic 2013 111 201 61 122 1.8% 1.56 [1.05.2.64] Maic 2013 111 201 61 122 1.8% 1.26 [1.0.2.44] Maic 2012 378 653 508 928 3.6% 1.14 [0.93, 1.39] Maic 2013 111 201 61 122 1.8% 1.26 [1.0.2.44] Maic 2013 111 201 61 122 1.8% 1.26 [1.0.2.44] Maic 2013 111 201 61 122 1.8% 1.26 [1.0.2.48] Maic 2013 111 201 61 122 2.3% 2.2% 1.01 [0.68] 1.47 [Murta-Nascimento 2007 428 679 357 735 3.5% 1.66 [1.38, 1.66] More 2007 683 1077 735 3.5% 1.00 [1.37, 2.64] Maic 2013 15 0 160 93 332 C.7% 1.21 [0.88, 1.65] Maic 2010 75 121 223 2.8% 1.66 [1.38, 1.96] Maic 2013 15 0 160 93 332 C.7% 1.21 [0.86, 1.86] Maic 2010 109 201 77 128 128 2.2% 1.66 [1.36, 1.96] Maic 2010 75 121 224 1.5% 1.10 [0.61, 1.22] Maic 2005 37 100 24 76 1.1% 1.27 [0.68, 2.39] Maic 2010 75 121 2.2% 1.6% 1.10 [0.61, 2.2] Maic 2006 85 202 317 633 3.4% 1.08 [0 | Brockmöller 1996 | 218 | 374 | 192 | 373 | 2.9% | 1.32 [0.99, 1.76] | - | |
| Ceylan GG 2015 22 65 31 70 10% 0.64 [0.3; 1.29] Garcia-Closas 2005 716 1138 571 112 21% 167 [141, 1.97] Giannakopoulos 2002 56 89 56 147 14% 2.76 [16.0, 4.75] Golda 2008 164 233 88 176 2.2% 1.69 [1.16, 2.47] Golda 2008 164 233 88 176 2.2% 1.69 [1.16, 2.47] Forndo 2009 140 100 33 100 1.3% 1.35 [0.76, 2.41] Henriquez-Hemindez 2012 23 90 17 81 0.9% 1.29 [0.3, 2.64] Henriquez-Hemindez 2012 23 90 17 81 0.9% 1.29 [0.3, 2.64] Kargags 2005 210 354 309 642 3.0% 1.10 [0.84, 1.44] Kardp 195 51 83 43 101 1.3% 2.156 [1.0, 2.44] Kardpags 2005 210 354 309 642 3.0% 1.10 [0.84, 1.44] Katch 1995 51 83 43 101 1.3% 2.15 [1.19, 3.89] Kellen 2005 312 579 597 1063 3.6% 0.91 [0.74, 1.12] Lesseur 2012 378 663 508 928 6.6% 1.14 [0.92, 1.39] Kellen 2005 312 579 597 1063 3.6% 0.91 [0.74, 1.12] Kardpags 2005 210 354 309 642 3.0% 1.10 [0.84, 1.44] Kardp 195 51 83 43 101 1.3% 2.15 [1.19, 3.89] Kellen 2005 312 579 597 1063 3.6% 0.91 [0.74, 1.12] Kardpags 2005 210 32 99 182 0.8% 1.40 [0.85, 3.03] Kellen 2005 312 579 597 1063 3.6% 0.91 [0.74, 1.2] Kardpags 2005 312 579 597 1063 3.6% 1.14 [0.93, 1.39] Kellen 2005 312 579 597 1063 3.6% 1.14 [0.93, 1.39] Kellen 2005 312 579 597 1063 3.6% 1.14 [0.93, 1.39] Kellen 2005 312 579 597 1063 3.6% 1.14 [0.93, 1.39] Kellen 2005 312 579 597 1063 3.6% 1.14 [0.93, 1.39] Kellen 2005 312 579 597 1063 3.6% 1.14 [0.94, 1.39] Kellen 2005 312 579 597 1063 3.6% 1.14 [0.94, 1.49] Kellen 2005 312 579 597 1063 3.6% 1.14 [0.94, 1.39] Kellen 2006 312 579 597 1063 3.6% 1.14 [0.94, 1.39] Kellen 2007 149 232 86 165 2.1% 1.66 [1.10, 2.48] Kellen 2002 149 232 86 165 2.1% 1.25 [1.10, 2.48] Kellen 2003 312 2.0% 1.14 [0.94, 1.39] Kellen 2004 54 106 49 109 1.4% 1.27 [0.74, 2.17] Kellen 2013 2006 154 102 2.38% 1.65 [1.38, 1.96] Kellen 2003 157 129 2.23 2.0% 1.11 [0.74, 1.67] Kellen 2004 54 106 49 109 1.4% 1.27 [0.74, 2.17] Kellen 2013 50 166 93 332 2.0% 1.13 [0.66, 1.38] Kellen 2008 85 202 41 2.27 2.2% 1.63 [1.12, 2.30] Kellen 2009 131 200 109 210 78 193 2.1% 1.76 [1.17, 2.00] Kellen 2003 137 50 106 212 2.2% 1.66 [1.31, 2.19] Kelle | Cengiz 2007 | 34 | 51 | 22 | 53 | 0.8% | 2.82 [1.27, 6.26] | | |
| Covido 2008 128 197 111 211 2.1% 167 [1.12, 2.49] Garcia-Closes 2005 7.6 1138 571 1132 3.9% 167 [1.41, 1.97] Giannakopoulos 2002 56 89 56 147 1.4% 2.76 [1.60, 4.75] Giannakopoulos 2002 56 89 56 147 1.4% 2.76 [1.60, 4.75] Goardiz 2011 344 618 564 1142 3.7% 1.29 [1.06, 1.57] Grand 2009 40 100 33 100 1.3% 1.36 [0.76, 2.41] Funriquez-Hernández 2012 3.90 17 81 0.9% 1.29 [0.63, 2.64] Funriquez-Hernández 2012 3.90 17 81 0.9% 1.56 [1.00, 2.44] Kanga 2003 75 126 99 204 1.8% 1.66 [1.10, 2.44] Kanga 2005 2.10 352 4.00 4.18% 1.66 [1.03, 2.61] Kanga 2005 5.1 83 430 101 1.3% 2.15 [1.10, 2.44] Kanga 2005 3.12 579 597 1063 3.6% 0.91 [0.74, 1.12] Lesseur 2012 3.78 6.53 508 922 3.6% 1.66 [1.10, 2.48] Kalen 2005 3.12 579 597 1063 3.6% 0.91 [0.74, 1.12] Lesseur 2012 3.78 6.53 508 922 3.6% 1.46 [0.50, 2.60] Matic 2013 111 201 61 122 1.8% 1.66 [1.10, 2.48] Macoo 2007 6.83 1077 524 1022 3.8% 1.66 [1.05, 2.60] Matic 2013 111 201 61 122 1.8% 1.23 [0.79, 1.94] McGranth 2006 109 191 483 922 2.7% 1.21 [0.88, 1.65] Matic 2013 111 201 61 122 1.8% 1.23 [0.79, 1.94] McGranth 2006 109 191 483 922 2.7% 1.21 [0.88, 1.65] Matic 2013 101 2.12 1.8% 1.22 [0.7, 2.64] Matic 2013 101 2.12 1.8% 1.22 [0.7, 2.64] Matic 2013 101 2.20 166 122 1.8% 1.25 [0.7, 2.64] Matic 2013 107 524 1022 3.8% 1.66 [1.37, 2.64] Matic 2013 101 2.12 1.65 1.25 (0.6) Matic 2013 50 166 93 3.32 0.0% 1.11 [0.74, 1.67] Matic 2013 50 166 93 3.32 0.0% 1.11 [0.74, 1.67] Matic 2013 50 166 93 3.32 0.0% 1.11 [0.74, 1.67] Matic 2013 50 166 93 3.32 0.0% 1.11 [0.74, 1.67] Matic 2013 50 166 93 3.32 0.0% 1.11 [0.74, 1.67] Matic 2013 50 166 93 3.32 0.0% 1.11 [0.74, 1.67] Matic 2013 50 166 93 3.32 0.0% 1.11 [0.74, 1.67] Matic 2013 50 166 93 3.32 0.0% 1.11 [0.74, 1.67] Matic 2013 50 166 93 3.32 0.0% 1.11 [0.74, 1.67] Matic 2013 50 166 93 3.32 0.0% 1.11 [0.74, 1.67] Matic 2013 50 166 93 3.32 0.0% 1.11 [0.74, 1.67] Matic 2013 50 166 93 3.32 0.0% 1.11 [0.74, 1.67] Matic 2013 50 166 93 3.32 0.0% 1.11 [0.74, 1.67] Matic 2013 50 166 93 3.32 0.0% 1.11 [0.74, 1.67] Matic 2013 50 166 93 3.32 0.0% 1.11 [0. | Ceylan GG 2015 | 22 | 65 | 31 | 70 | 1.0% | 0.64 [0.32, 1.29] | | |
| Garcia-Closas 2005 716 1138 571 1132 3.9% 167 [14.1, 197] | Covolo 2008 | 128 | 197 | 111 | 211 | 2.1% | 1.67 [1.12, 2.49] | | |
| Giannakopoulos 2002 56 99 56 147 1.4% 2.76 [16.0.4.75] Gorditz 2011 344 618 564 1142 3.7% 1.28 [1.06.157] Golka 2008 40 100 33 100 1.3% 1.38 [0.76, 2.41] Hung 2004 132 201 112 214 2.1% 1.7.4 [1.17, 2.59] Hung 2004 132 201 112 214 2.1% 1.7.4 [1.17, 2.59] Kang 2013 65 110 103 220 1.8% 1.66 [1.03, 2.61] Kang 2013 65 110 103 220 1.8% 1.66 [1.03, 2.61] Kang 2005 210 354 309 542 3.0% 1.10 [0.84, 1.44] Kang 32005 210 354 309 542 3.0% 1.10 [0.84, 1.44] Kang 32005 21 33 73 153 1.8% 1.65 [1.10, 2.48] Kang 2002 149 232 86 165 2.1% 1.65 [1.10, 2.48] Kim 2005 92 153 73 153 1.8% 1.65 [1.10, 2.48] Kim 2005 92 153 73 153 1.8% 1.65 [1.10, 2.48] Kim 2005 12 579 597 1065 3.6% 0.91 [0.74, 1.12] Lee 2002 149 232 86 165 2.1% 1.65 [1.10, 2.48] Kim 2005 12 778 653 508 923 3.6% 1.144 [0.65, 3.03] Ma 2002 20 32 99 182 0.8% 1.40 [0.65, 3.03] Ma 2002 109 191 483 922 2.7% 1.21 [0.88, 1.65] Matic 2013 111 201 61 122 1.8% 1.23 [0.79, 1.94] McGrath 2006 109 191 483 922 2.7% 1.21 [0.88, 1.65] Moore 2004 54 106 49 109 1.4% 1.22 [0.74, 2.17] Worta-Nascimento 2007 633 1077 524 1022 3.8% 1.66 [1.38, 1.96] Wurta-Nascimento 2007 63 11077 524 1022 3.8% 1.25 [0.76, 2.06] Salagovic 1999 40 76 123 2.48 [1.57] Salagovic 1999 40 76 123 2.48 [1.57] Salagovic 2013 111 201 78 193 2.1% 1.77 [1.13, 2.11] Worta-Nascimento 2007 63 157 129 2.23 2.0% 1.01 [0.69, 1.47] Reszka 2014 149 244 165 365 2.6% 190 [1.37, 2.64] Salagovic 1999 40 76 123 2.48 [1.57] Salagovic 1999 40 76 123 2.48 [1.57] Salagovic 1999 40 76 123 2.48 [1.56] [1.10, 7.4, 1.67] Salagovic 2013 50 166 93 332 2.0% 1.11 [0.74, 1.67] Salagovic 2013 50 126 56 125 1.6% 1.56 [0.10, 2.48] Salagovic 2013 50 126 57 127 1.6% 1.72 [1.09, 2.82] Shore 2003 137 230 10 213 22% 1.64 [1.11, 2.42] Shore 2003 137 230 10 213 2.2% 1.64 [1.11, 2.42] Shore 2003 137 230 10 213 2.2% 1.64 [1.11, 2.42] Shore 2003 137 230 10 214 56 122 2.2% 1.64 [1.11, 2.42] Shore 2003 137 230 10 214 76 1.1% 1.30 [0.67, 1.50] Shore 2007 324 622 117 63 3.14 [1.90, 2.92] Shore 2009 13 2.38 68 217 0.6% 1.00 | García-Closas 2005 | 716 | 1138 | 571 | 1132 | 3.9% | 1.67 [1.41, 1.97] | - | |
| Georitiz 2011 344 618 564 1142 3.7% 12.9 [1.06, 1.57] T Goka 2009 40 100 33 100 1.3% 1.35 [0.76, 2.41] T Henriquez-Hernández 2012 23 90 17 81 0.9% 1.29 [0.63, 2.64] T Jeong 2003 75 126 99 204 1.8% 1.56 [1.00, 2.44] T Jeong 2003 75 126 99 204 1.8% 1.64 [1.03, 2.61] T Kang 2013 65 110 103 2.20 1.8% 1.64 [1.03, 2.61] T Kabah 1995 51 83 43 101 1.3% 2.15 [1.19, 3.89] T Kiab 1995 51 83 43 101 1.3% 1.65 [1.10, 2.44] T Kaboh 1995 91 163 3.6% 0.91 [0.74, 1.12] T T Kabo 2002 20 32 99 182 0.8% 1.40 [0.85, 3.03] T | Giannakopoulos 2002 | 56 | 89 | 56 | 147 | 1.4% | 2.76 [1.60, 4.75] | | |
| Goka 2008 184 293 88 176 2.2% 1.69 [1.16, 2.47] Grando 2009 40 100 33 100 1.3% 1.29 [0.63, 2.64] Hung 2004 132 201 112 214 2.1% 1.74 [1.17, 2.59] Jeong 2003 75 126 99 204 1.8% 1.64 [1.03, 2.64] Kang 2013 65 110 103 220 1.8% 1.64 [1.03, 2.64] Kangas 2005 210 354 309 524 3.0% 1.01 [0.84, 1.44] Kangas 2005 312 579 597 1063 3.6% 0.91 [0.74, 1.12] Kalen 2005 312 579 575 573 1033 1.86 [1.10, 2.48] Lesseur 2012 138 434 101 133 2.21 [51, 19, 3.8] Maic 2013 111 201 61 1.22 [1.8% 1.65 [1.10, 2.48] Mocre 2004 54 106 49 109 1.4% 1.23 [0.79, 1.94] <t< td=""><td>Goerlitz 2011</td><td>344</td><td>618</td><td>564</td><td>1142</td><td>3.7%</td><td>1.29 [1.06, 1.57]</td><td>-</td></t<> | Goerlitz 2011 | 344 | 618 | 564 | 1142 | 3.7% | 1.29 [1.06, 1.57] | - | |
| Grando 2009 40 100 33 100 1.3% 1.25 [0.63, 2.64] Henriquez-Hernández 2012 23 90 17 81 0.9% 1.29 [0.63, 2.64] Jeong 2003 75 126 99 204 1.8% 1.56 [1.00, 2.44] Kang 2013 65 110 103 220 1.8% 1.64 [10.3, 2.61] Kang 2013 65 110 103 220 1.8% 1.64 [10.3, 2.61] Kang 2013 65 158 3.43 101 1.3% 2.16 [1.9] 3.89] Kalen 2005 312 579 597 1063 3.6% 0.91 [0.74, 1.12] Kim 2005 92 153 73 153 1.8% 1.65 [1.01, 0.48] Lees 2002 149 223 86 165 2.1% 1.40 [0.65, 3.03] Matic 2013 111 201 61 122 1.8% 1.23 [0.79, 1.94] McGrath 2006 109 194 3.9% 1.55 [1.04, 2.17] | Golka 2008 | 184 | 293 | 88 | 176 | 2.2% | 1.69 [1.16, 2.47] | - | |
| Hemriquez-Henråndez 2012 23 90 17 81 0.9% 1.29 [0.63.2.64] Hung 2004 132 201 112 214 2.1% 1.74 [1.17, 2.59] Kang 2013 65 110 103 220 1.8% 1.64 [1.03.2.61] Kang 2015 51 83 43 101 1.3% 2.15 [1.19.3.89] Kang 2005 312 579 557 1063 3.6% 0.91 [0.74, 1.12] Kim 2005 322 153 73 153 1.8% 1.65 [1.00, 2.44] Kang 202 149 222 86 165 2.1% 1.65 [1.10, 2.48] Lee seur 2012 378 653 508 298 3.6% 1.14 [0.93, 1.39] Ma 2002 20 32 99 142 0.8% 1.140 [0.65, 3.03] Ma 2002 20 32 99 142 0.8% 1.140 [0.65, 3.03] Ma 2002 20 32 99 142 0.8% 1.140 [0.65, 3.03] Ma 2002 20 32 99 142 0.8% 1.140 [0.65, 3.03] Ma 2002 20 32 99 142 0.8% 1.140 [0.65, 3.03] Ma 2002 20 32 99 142 0.8% 1.140 [0.65, 3.03] Ma 2002 20 32 99 142 0.8% 1.140 [0.65, 3.03] Ma 2002 20 32 99 142 0.8% 1.140 [0.65, 3.03] Ma 2002 20 32 99 142 0.8% 1.140 [0.65, 3.03] Ma 2002 20 32 99 142 0.8% 1.140 [0.65, 3.03] Ma 2002 20 51 90 91 44 122 1.8% 1.23 [0.74, 2.17] More 2007 683 1077 524 1022 3.8% 1.65 [1.38, 1.96] Murta-Nascimento 2007 428 679 367 735 3.5% 1.71 [1.38, 2.11] Murta-Nascimento 2007 428 679 367 735 6.26% 1.130 [1.37, 2.64] Murta-Nascimento 2007 428 679 337 225 22% 1.01 [0.66, 1.47] Texpus 8204 4 149 244 155 365 2.6% 1.130 [1.37, 2.64] Salagovic 1999 40 76 123 248 1.5% 1.13 [0.68, 1.89] Salagovic 1999 40 76 123 248 1.5% 1.13 [0.76, 2.06] Salana-Sanchez 2010 109 201 78 183 2.1% 1.75 [1.17, 2.60] Salana-Sanchez 2013 45 80 32 60 1.0% 1.13 [0.57, 2.20] Sonakaboteg 2000 83 157 712 2.2% 1.06 [0.70, 1.60] Schnaked 199 200 73 13 20 101 213 2.2% 1.68 [1.17, 2.57] Sobi 2005 37 100 24 76 1.1% 1.27 [0.68, 2.39] To 3.209 131 2.08 108 212 2.2% 1.76 [1.17, 2.57] To 3.34% 1.08 [0.67, 1.35] To 3.34% 1.08 [0.67, 1.35] To 3.34% 1.08 [0.67, 1.35] To 3.35% 1.11 [0.74, 1.57] To 3.35% 1.11 [0.74, 1.57] To 3.35% 1.11 [0.74, 1.57] To 3.35% 1.11 [0.74, 1.57] To 3.34% 1.08 [0.67, 1.35] To 3.34% 1.08 [0.67, 1.35] To 3.34% 1.0 | Grando 2009 | 40 | 100 | 33 | 100 | 1.3% | 1.35 [0.76, 2.41] | | |
| Hung 2004 132 201 112 214 2.1% 1.74 [1,17, 2.50] Jeong 2003 75 126 99 204 1.8% 1.56 [1,00, 2.44] Kang 2013 65 110 103 220 1.8% 1.56 [1,00, 2.44] Kang 2013 65 10 103 200 1.8% 1.56 [1,00, 2.44] Kacho 1995 51 83 43 101 1.3% 2.15 [1,10, 3.89] Kelen 2005 312 579 597 1063 3.6% 0.91 (0.74, 112) 1.40 Lee 2002 149 223 86 165 2.1% 1.85 (1.05, 2.60) 1.40 Leeseur 2012 378 653 508 928 3.6% 1.14 (0.93, 1.39) 1.40 MacGrath 2006 109 194 203 2.2% 1.21 (0.86, 1.65] 1.40 Mocra 2007 633 1077 524 1022 3.8% 1.65 (1.33, 1.96] 1.40 Varta-Nascimento 2007 633 1077 524 1022 3.8% | Henriquez-Hernández 2012 | 23 | 90 | 17 | 81 | 0.9% | 1.29 [0.63, 2.64] | - - | |
| Jeeng 2003 75 126 99 204 1.8% 1.56 [100.2.4] Kang 2013 65 110 103 220 1.8% 1.64 [1.03, 2.61] Kang 2005 210 354 309 542 3.0% 1.10 [0.84, 1.44] Katoh 1995 51 83 43 101 1.3% 2.15 [1.19, 3.89] Kim 2005 312 579 557 1063 3.6% 0.91 [0.74, 1.12] Kim 2005 92 153 73 153 1.8% 1.65 [1.05, 2.60] Lee 2002 149 232 86 165 2.1% 1.65 [1.10, 2.48] Leesseur 2012 378 653 508 928 3.6% 1.144 [0.39, 1.39] Ma 2002 20 32 99 182 0.8% 1.140 [0.65, 3.03] Matic 2013 111 201 61 122 1.8% 1.23 [0.79, 1.94] McGrath 2006 109 191 483 922 2.7% 1.21 [0.88, 1.65] Moore 2007 683 1077 524 1022 3.8% 1.66 [1.38, 1.96] Muta-Nascimento 2007 428 679 367 735 3.5% 1.71 [1.38, 1.96] Muta-Nascimento 2007 428 679 367 735 3.5% 1.171 [1.38, 1.96] Muta-Nascimento 2007 428 679 367 256 125 1.6% 1.25 [0.76, 2.06] Muta-Nascimento 2007 428 679 367 254 1.5% 1.130 [0.68, 1.47] Paszka 2014 149 244 165 365 2.6% 1.90 [1.37, 2.64] Rousis 2009 63 125 56 125 1.6% 1.25 [0.76, 2.06] Salinas-Sánchez 2010 109 201 78 193 2.1% 1.75 [1.17, 2.60] Salinas-Sánchez 2010 109 201 78 193 2.1% 1.75 [1.17, 2.60] Salinas-Sánchez 2010 109 201 78 193 2.1% 1.75 [1.17, 2.60] Salinas-Sánchez 2010 109 201 78 193 2.1% 1.75 [1.17, 2.60] Salinas-Sánchez 2010 109 201 78 193 2.1% 1.55 [1.72, 2.0] Schneader 2003 137 100 24 76 1.1% 1.13 [0.67, 2.20] Schneader 2003 137 100 24 77 1.1% 1.57 [1.17, 2.61] Salinas-Sánchez 2010 193 201 78 193 2.1% 1.75 [1.17, 2.61] Schneader 2010 135 57 127 1.6% 1.79 [1.08, 2.38] Shao 2008 85 202 81 272 2.2% 1.61 [1.11, 2.42] Trivinastwa 2004 42 106 54 182 1.6% 1.56 [0.94, 2.57] Total (95% CI) 12527 16275 100.0% 1.41 [1.30, 1.52] Total (95% CI) 12527 16275 100.0% 1.41 [1.30, 1.52] Tota | Hung 2004 | 132 | 201 | 112 | 214 | 2.1% | 1.74 [1.17, 2.59] | - | |
| Kang 2013 65 110 103 220 1.8% 1.64 [1.03, 2.61] Kang as 2005 2.10 354 309 542 3.0% 1.10 [0.84, 1.44] Kabn 1995 51 83 43 101 1.3% 2.15 [1.19, 3.89] Kellen 2005 312 579 597 1063 3.6% 0.91 [0.74, 1.12] Lee 2002 149 232 86 165 2.1% 1.65 [1.10, 2.48] Leeseur 2012 378 653 508 928 3.6% 1.44 [0.93, 3.9] Maiz 2013 111 201 61 122 1.8% 1.65 [1.10, 2.48] McGrath 2006 109 191 483 922 2.7% 1.21 [0.84, 1.65] Moore 2004 54 106 49 109 1.4% 1.27 [0.74, 2.17] More 2007 683 107 524 1022 3.5% 1.71 [1.38, 2.11] Ovisianikov 2012 102 196 122 235 2.6% 1.09 [1.37, 2.64] Salagovic 1999 40 61 < | Jeong 2003 | 75 | 126 | 99 | 204 | 1.8% | 1.56 [1.00, 2.44] | | |
| Karagas 2005 210 354 309 542 3.0% 1.10 0.84, 1.44 Katoh 1995 51 83 43 101 1.3% 2.15 [1.10, 3.89] Katoh 1995 51 83 43 101 1.3% 0.16 [1.07, 4.12] Kim 2005 92 153 73 153 1.8% 1.65 [1.0, 2.48] Lee 2002 149 232 86 165 2.1% 1.65 [1.0, 2.48] Lesseur 2012 378 653 508 928 3.6% 1.14 [0.93, 1.39] | Kang 2013 | 65 | 110 | 103 | 220 | 1.8% | 1.64 [1.03, 2.61] | | |
| Kabh 1995 51 83 43 101 1.3% 2.15[1.19,3.89] Kellen 2005 312 579 597 1063 3.6% 0.91 [0.74, 1.12] Lee 2002 149 232 86 165 2.1% 1.65 [1.05, 2.60] Lee 2002 149 232 86 165 2.1% 1.65 [1.05, 2.60] Lesseur 2012 378 653 508 928 3.6% 1.14 [0.93, 1.39] Maic 2013 111 201 61 122 1.8% 1.23 [0.79, 1.94] McGrath 2006 109 191 483 922 2.7% 1.21 [0.88, 1.65] Mutta-Nascimento 2007 683 1077 524 1022 3.8% 1.65 [1.38, 1.96] Ovaiannikov 2012 102 196 122 235 2.2% 1.01 [0.69, 1.47] Reszka 2014 149 244 165 365 1.56 [1.78, 2.06] | Karagas 2005 | 210 | 354 | 309 | 542 | 3.0% | 1.10 [0.84, 1.44] | + | |
| Kellen 2005 312 579 597 1063 3.6% 0.91 [0.74, 1.12] Kim 2005 92 153 73 153 1.8% 1.65 [1.0, 2.48] Lees 2002 149 232 86 165 2.1% 1.65 [1.0, 2.48] Lees 2002 20 32 99 182 0.8% 1.14 [0.93, 1.39] Ma 2002 20 32 99 182 0.8% 1.40 [0.65, 3.03] Matic 2013 111 201 61 122 1.8% 1.23 [0.79, 1.94] Moore 2004 54 106 49 109 1.4% 1.27 [0.74, 2.17] Moore 2007 683 1077 524 1022 3.8% 1.65 [1.38, 1.96] T Vosiannikov 2012 102 196 122 225 1.01 [0.69, 1.47] T Salaranejad 2013 50 166 93 332 2.0% 1.11 [0.74, 1.67] T Salaranejad 2013 45 80 32 60 < | Katoh 1995 | 51 | 83 | 43 | 101 | 1.3% | 2.15 [1.19, 3.89] | | |
| Kim 2006 92 153 73 153 1.8% 1.65 [1.05, 2.60] Lee 2002 149 232 86 165 2.1% 1.65 [1.02, 2.48] Leesseur 2012 378 653 508 928 3.6% 1.14 [10, 3, 1.39] Ma 2002 20 32 99 182 0.8% 1.40 [0.65, 3.03] Matic 2013 111 201 61 122 1.8% 1.23 [0.79, 1.94] McGrath 2006 109 191 483 922 2.7% 1.21 [0.88, 1.65] Moore 2004 54 106 49 109 1.4% 1.27 [0.74, 2.17] Moore 2007 683 1077 524 1022 3.8% 1.65 [1.38, 1.96] T Mutra-Nascimento 2007 428 679 367 735 3.5% 1.71 [1.38, 2.11] T Ovaiannikov 2012 102 196 122 235 2.6% 1.90 1.47 Rouissi 2009 63 125 56 125 <td>Kellen 2005</td> <td>312</td> <td>579</td> <td>597</td> <td>1063</td> <td>3.6%</td> <td>0.91 [0.74, 1.12]</td> <td>+</td> | Kellen 2005 | 312 | 579 | 597 | 1063 | 3.6% | 0.91 [0.74, 1.12] | + | |
| Lee 2002 149 232 86 165 2.1% 1.65 [1.10, 2.48] Lesseur 2012 378 653 508 928 3.6% 1.44 [0.85, 3.03] Matic 2013 111 201 61 122 1.8% 1.23 [0.79, 1.94] McGrath 2006 109 191 483 922 2.7% 1.21 [0.84, 1.65] Moore 2007 683 1077 524 1022 3.8% 1.65 [1.38, 1.96] Mutra-Nascimento 2007 428 679 367 735 3.5% 1.77 [1.38, 2.11] Ovsiannikov 2012 102 196 122 235 2.2% 1.01 [0.69, 1.47] Reszka 2014 149 244 165 365 2.6% 1.90 [1.37, 2.64] Rouissi 2009 63 125 56 125 1.6% 1.25 [0.76, 2.06] Satarinejad 2013 50 166 93 332 2.0% 1.11 [0.74, 1.67] Satarinejad 2013 50 166 93 322 0.0% 1.11 [0.74, 1.67] Sataroheve 2000 93 157 129 223 2.0% 1.06 [0.70, 1.60] Schroeder 2003 137 230 101 213 2.2% 1.63 [1.12, 2.38] Song 2009 131 208 108 212 2.2% 1.63 [1.12, 2.38] Song 2009 131 208 108 212 2.2% 1.64 [1.11, 2.42] Srivastava 2004 42 106 54 182 1.6% 1.27 [0.72, 1.74] Steinhoff 2000 80 135 57 127 1.6% 1.79 [1.09, 2.92] Srivastava 2004 42 106 54 182 1.6% 1.56 [0.94, 2.57] Srivastava 2004 42 2 317 633 3.4% 1.08 [0.87, 1.35] Srivastava 2004 42 2 317 633 3.4% 1.08 [0.87, 1.35] Total (95% CI) 7 1257 16275 100.0% 1.41 [1.30, 1.52] Total events 7262 8097 Heterogeneity, Tau" = 0.03; Chi" = 99.92, df = 49 (P < 0.0001); P = 51% Total (95% CI) 7 1250 df = 49 (P < 0.0001); P = 51% Total events 7262 8.63 (P < 0.00001) | Kim 2005 | 92 | 153 | 73 | 153 | 1.8% | 1.65 [1.05, 2.60] | | |
| Lesseur 2012 378 653 508 928 3.6% 1.14 [0.93, 1.39] Ma 2002 20 32 99 182 0.8% 1.40 [0.65, 3.03] Matic 2013 111 201 61 122 1.8% 1.23 [0.79, 1.94] McGrath 2006 109 191 483 922 2.7% 1.21 [0.88, 1.65] Moore 2004 54 106 49 109 1.4% 1.27 [0.74, 2.17] Moore 2007 683 1077 524 1022 3.8% 1.65 [1.38, 1.96] Wutta-Nascrimento 2007 428 679 357 735 3.5% 1.71 [1.38, 2.11] Visiannikov 2012 102 196 122 235 2.2% 1.01 [0.69, 1.47] Reszka 2014 149 244 165 365 2.6% 1.90 [1.37, 2.64] Reszka 2014 149 244 165 365 2.6% 1.90 [1.37, 2.64] Safarinejad 2013 50 166 93 332 2.0% 1.11 [0.74, 1.67] Salagovic 1999 40 76 123 248 1.5% 1.13 [0.68, 1.89] Salinas-Sánchez 2010 109 201 78 193 2.1% 1.75 [1.17, 2.60] Savic-Radojevic 2013 45 80 32 60 1.0% 1.13 [0.67, 2.20] Schnakenberg 2000 93 157 129 223 2.0% 1.06 [0.70, 1.60] Schroeder 2003 137 230 101 213 2.2% 1.63 [1.12, 2.38] Shab 2008 85 202 81 272 2.2% 1.71 [1.17, 2.51] Sobi 2005 37 100 24 76 1.1% 1.27 [0.48, 2.39] Schrakenberg 2000 90 131 208 108 0212 2.2% 1.64 [1.11, 2.42] Srivastava 2004 42 106 54 182 1.6% 1.56 [0.94, 2.57] Srivastava 2004 42 106 54 182 1.6% 1.56 [0.94, 2.57] Srivastava 2004 42 106 54 182 1.6% 1.56 [0.94, 2.57] Srivastava 2004 42 106 54 182 1.6% 1.56 [0.94, 2.57] Srivastava 2004 42 106 54 182 1.6% 1.56 [0.94, 2.57] Srivastava 2004 42 106 54 182 1.6% 1.56 [0.94, 2.57] Srivastava 2004 42 106 54 182 1.6% 1.56 [0.94, 2.57] Srivastava 2004 42 106 54 182 1.6% 1.18 [1.17, 3.27] Vang ML 2014 699 1050 834 1404 3.9% 1.38 [1.17, 1.51] Total (95% Cl) 12527 16275 100.0% 1.41 [1.30, 1.52] Total events 7262 8097 Heterogeneity: Tau" = 0.03; Chi ² = 99.92, df = 49 (P < 0.0001); P = 51% Test or overall effect: 2 = 8.63 (P < 0.0001) | Lee 2002 | 149 | 232 | 86 | 165 | 2.1% | 1.65 [1.10, 2.48] | | |
| $ \begin{array}{c ccccccccccccccccccccccccccccccccccc$ | Lesseur 2012 | 378 | 653 | 508 | 928 | 3.6% | 1.14 [0.93, 1.39] | + | |
| $\begin{array}{cccccccccccccccccccccccccccccccccccc$ | Ma 2002 | 20 | 32 | 99 | 182 | 0.8% | 1 40 [0 65, 3 03] | | |
| $ \begin{array}{c c c c c c c c c c c c c c c c c c c $ | Matic 2013 | 111 | 201 | 61 | 122 | 1.8% | 1.23 [0.79, 1.94] | | |
| $ \begin{array}{c c c c c c c c c c c c c c c c c c c $ | McGrath 2006 | 109 | 191 | 483 | 922 | 2.7% | 1 21 [0 88 1 65] | | |
| $ \begin{array}{c ccccccccccccccccccccccccccccccccccc$ | Moore 2004 | 54 | 106 | 49 | 109 | 1.4% | 1.27 [0.74, 2.17] | | |
| Murta-Nascimento 2007 428 679 367 735 3.5% 1.71 [1.38, 2.11] Ovsiannikov 2012 102 196 122 235 2.2% 1.01 [0.69, 1.47] Reszka 2014 149 244 165 365 2.6% 1.25 [0.76, 2.06] Rouissi 2009 63 125 56 125 1.6% 1.25 [0.76, 2.06] Safarinejad 2013 50 166 93 332 2.0% 1.11 [0.77, 2.60] Salagovic 1999 40 76 123 248 1.5% 1.13 [0.68, 1.89] Salasovic 2010 109 201 78 193 2.1% 1.75 [1.17, 2.60] Savic-Radojevic 2013 45 80 32 60 1.0% 1.13 [0.67, 2.20] 1.05 Schnakenberg 2000 93 157 129 223 2.0% 1.06 [0.07, 1.60] 1.77 Schoeder 2003 137 230 101 213 2.2% 1.64 [1.17, 2.51] 1.55 Sobi 2005 <t< td=""><td>Moore 2007</td><td>683</td><td>1077</td><td>524</td><td>1022</td><td>3.8%</td><td>1 65 [1 38 1 96]</td><td>+</td></t<> | Moore 2007 | 683 | 1077 | 524 | 1022 | 3.8% | 1 65 [1 38 1 96] | + | |
| $ \begin{array}{c c c c c c c c c c c c c c c c c c c $ | Murta-Nascimento 2007 | 428 | 679 | 367 | 735 | 3.5% | 1 71 [1 38, 2 11] | - | |
| Orbital Micro CollTotal | Ovsiannikov 2012 | 102 | 196 | 122 | 235 | 2.2% | 1 01 [0 69 1 47] | + | |
| Roulssi 200963125561251.6%1.251.751.751.251.751.251.751.251.751.251.751.251.751.251.751.251.751.251.751.111.751.111.751.111.751.111.751.111.751.111.751.111.751.111.751.131.651.751.111.75 <th< td=""><td>Reszka 2014</td><td>149</td><td>244</td><td>165</td><td>365</td><td>2.6%</td><td>1 90 [1 37 2 64]</td><td>-</td></th<> | Reszka 2014 | 149 | 244 | 165 | 365 | 2.6% | 1 90 [1 37 2 64] | - | |
| Notice 2003100100100100100100100Safarinejad 201350166933322.0%1.11 $[0.74, 1.67]$ Salagovic 199940761232481.5%1.13 $[0.68, 1.89]$ Salinas-Sánchez 2010109201781932.1%1.75 $[1.17, 2.60]$ Savic-Radojevic 2013458032601.0%1.13 $[0.67, 1.60]$ Schnakenberg 2000931571292232.0%1.06 $[0.70, 1.60]$ Schroeder 20031372301012132.2%1.63 $[1.12, 2.38]$ Shao 200885202812722.2%1.71 $[1.17, 2.51]$ Sobi 2005371002476 1.1% 1.27 $[0.68, 2.39]$ Song 20091312081082122.2%1.64 $[1.11, 2.42]$ Srivastava 200442106541821.6%1.56 $[0.94, 2.57]$ Srivastava 2005431061403701.9%1.12 $[0.72, 1.74]$ Steinhoff 200080135571271.6%1.79 $[1.09, 2.92]$ Törüner 200175121551211.5%1.96 $[1.17, 3.27]$ Wang ML 2014699105083414043.9%1.36 $[1.15, 1.61]$ Zupa 2009132368121 0.6% 1.01 $[0.41, 2.49]$ Özt | Rouissi 2009 | 63 | 125 | 56 | 125 | 1.6% | 1 25 [0 76 2 06] | | |
| Salagovic 199940761232481.5%1.13[0.68, 1.89]Salinas-Sánchez 2010109201781932.1%1.75[1.17, 2.60]Savic-Radojevic 2013458032601.0%1.13[0.57, 2.20]Schnakenberg 2000931571292232.0%1.06[0.70, 1.60]Schroeder 20031372301012132.2%1.63[1.12, 2.38]Shao 200885202812722.2%1.71[1.17, 2.51]Sobi 20053710024761.1%1.27[0.68, 2.39]Song 20091312081082122.2%1.64[1.11, 2.42]Srivastava 200442106541821.6%1.56[0.94, 2.57]Srivastava 2005431061403701.9%1.12[0.72, 1.74]Steinhoff 200080135571271.6%1.79[1.09, 2.92]Törüner 200175121551211.5%1.96[1.17, 3.27]Wang ML 2014699105083414043.9%1.36[1.15, 1.61]Zhao 20073246223176333.4%1.08[0.87, 1.35]Zupa 20091323681210.6%1.01[0.41, 2.49]Öztürk 20119817651971.6%1.13[0.69, 1.86]Total (95% Cl)12527 <td< td=""><td>Safarineiad 2013</td><td>50</td><td>166</td><td>93</td><td>332</td><td>2.0%</td><td>1 11 [0 74 1 67]</td><td>+</td></td<> | Safarineiad 2013 | 50 | 166 | 93 | 332 | 2.0% | 1 11 [0 74 1 67] | + | |
| Salinas-Sánchez 2010109201781932.1%1.75[1.7, 2.60]Salinas-Sánchez 2010109201781932.1%1.75[1.7, 2.60]Savic-Radojevic 2013458032601.0%1.13[0.57, 2.20]Schnakenberg 2000931571292232.0%1.06[0.70, 1.60]Schroeder 20031372301012132.2%1.63[1.12, 2.38]Shao 200885202812722.2%1.71[1.17, 2.51]Sobti 20053710024761.1%1.27[0.68, 2.39]Song 20091312081082122.2%1.64[1.11, 2.42]Srivastava 200442106541821.6%1.56[0.94, 2.57]Srivastava 2005431061403701.9%1.12[0.72, 1.74]Steinhoff 200080135571271.6%1.79[1.09, 2.92]Törüner 200175121551211.5%1.96[1.17, 3.27]Wang ML 2014699105083414043.9%1.36[1.13[0.69, 1.35]Zupa 20091323681210.6%1.01[0.41, 2.49]Öztürk 20119817651971.6%1.13[0.69, 1.86]Total (95% CI)1252716275100.0%1.41[1.30, 1.52]100Total events | Salagovic 1999 | 40 | 76 | 123 | 248 | 1.5% | 1 13 [0 68 1 89] | | |
| Savic-Radojevic 2013 45 80 32 60 1.0% 1.13 [1.67, 2.20] Schnakenberg 2000 93 157 129 223 2.0% 1.06 [0.57, 2.20] Schnakenberg 2003 137 230 101 213 2.2% 1.63 [1.17, 2.51] Sobti 2005 37 100 24 76 1.1% 1.27 [0.68, 2.39] Song 2009 131 208 108 212 2.2% 1.64 [1.11, 2.42] Srivastava 2004 42 106 54 182 1.6% 1.79 [1.09, 2.92] Törüner 2001 75 121 55 121 1.5% 1.96 [1.7, 3.27] Wang ML 2014 699 1050 834 1404 3.9% 1.36 [1.13, 0.69, 1.86] Zupa 2009 13 23 68 121 0.6% 1.01 [0.41, 2.49] 1.01 Öztürk 2011 98 176 51 97 1.6% 1.01 [0.41, 2.49] 1.01 1.01 1.01 1.01 1.01 1. | Salinas-Sánchez 2010 | 109 | 201 | 78 | 193 | 2.1% | 1 75 [1 17 2 60] | | |
| Schnakenberg 2000 93 157 129 223 2.0% 1.06 [0.70, 1.60] Schnakenberg 2003 137 230 101 213 2.2% 1.66 [1.12, 2.38] Shao 2008 85 202 81 272 2.2% 1.71 [1.17, 2.51] Sobti 2005 37 100 24 76 1.1% 1.27 [0.68, 2.39] Song 2009 131 208 108 212 2.2% 1.64 [1.11, 2.42] Srivastava 2004 42 106 54 182 1.6% 1.56 [0.72, 1.74] Steinhoff 2000 80 135 57 127 1.6% 1.79 [1.09, 2.92] Törüner 2001 75 121 55 121 1.5% 1.96 [1.17, 3.27] Wang ML 2014 699 1050 834 1404 3.9% 1.36 [1.15, 1.61] Total (95% Cl) 12527 16275 100.0% 1.41 [1.30, 1.52] Iotal events 7262 8097 Heterogeneity: Tau ² = 0.03; Chi ² = 99.92, df = 49 (P < 0.0001); H ² = 51% | Savic-Radojevic 2013 | 45 | 80 | 32 | 60 | 1.0% | 1 13 [0 57 2 20] | _ _ _ | |
| Schroeder 2003 137 230 101 213 2.2% 1.63 [1.12, 2.38] Shao 2008 85 202 81 272 2.2% 1.71 [1.17, 2.51] Sobti 2005 37 100 24 76 1.1% 1.27 [0.68, 2.39] Song 2009 131 208 108 212 2.2% 1.64 [1.11, 2.42] Srivastava 2004 42 106 54 182 1.6% 1.56 [0.94, 2.57] Srivastava 2005 43 106 140 370 1.9% 1.12 [0.72, 1.74] Steinhoff 2000 80 135 57 127 1.6% 1.79 [1.09, 2.92] Törüner 2001 75 121 1.5% 1.96 [1.17, 3.27] | Schnakenberg 2000 | 93 | 157 | 129 | 223 | 2.0% | 1.06 [0.70, 1.60] | + | |
| Shao 2003 101 213 213 212% 1.05 [1.12, 2.50] Shao 2008 85 202 81 272 2.2% 1.71 [1.17, 2.51] Sobit 2005 37 100 24 76 1.1% 1.27 [0.68, 2.39] Song 2009 131 208 108 212 2.2% 1.64 [1.11, 2.42] Srivastava 2004 42 106 54 182 1.6% 1.56 [0.94, 2.57] Srivastava 2005 43 106 140 370 1.9% 1.12 [0.72, 1.74] Steinhoff 2000 80 135 57 127 1.6% 1.79 [1.09, 2.92] Törüner 2001 75 121 55 121 1.5% 1.96 [1.17, 3.27] Wang ML 2014 699 1050 834 1404 3.9% 1.36 [1.15, 1.61] Zhao 2007 324 622 317 633 3.4% 1.08 [0.87, 1.35] Zupa 2009 13 23 68 121 0.6% 1.01 [0.41, 2.49] Öztürk 2011 98 176 51 97 1.6% <td< td=""><td>Schroeder 2003</td><td>137</td><td>230</td><td>101</td><td>213</td><td>2.0%</td><td>1 63 [1 12 2 38]</td><td></td></td<> | Schroeder 2003 | 137 | 230 | 101 | 213 | 2.0% | 1 63 [1 12 2 38] | | |
| Sobi 2000303202012122.2.%1.11 [1.11, 2.51]Sobi 20053710024761.1%1.27 [0.68, 2.39]Song 20091312081082122.2%1.64 [1.11, 2.42]Srivastava 200442106541821.6%1.56 [0.94, 2.57]Srivastava 2005431061403701.9%1.12 [0.72, 1.74]Steinhoff 200080135571271.6%1.79 [1.09, 2.92]Törüner 200175121551211.5%1.96 [1.17, 3.27]Wang ML 2014699105083414043.9%1.36 [1.15, 1.61]Zhao 20073246223176333.4%1.08 [0.87, 1.35]Zupa 20091323681210.6%1.01 [0.41, 2.49]Öztürk 20119817651971.6%1.13 [0.69, 1.86]Total (95% CI)1252716275100.0%1.41 [1.30, 1.52]Total events726280971.41 [1.30, 1.52]1.41 [1.30, 1.52]Heterogeneity: Tau² = 0.03; Chi² = 99.92, df = 49 (P < 0.0001); l² = 51% | Shao 2008 | 85 | 202 | 81 | 272 | 2.2% | 1 71 [1 17 2 51] | - | |
| Song 2009 131 208 108 212 2.2% 1.64 [1.11, 2.42] Srivastava 2004 42 106 54 182 1.6% 1.56 [0.94, 2.57] Srivastava 2005 43 106 140 370 1.9% 1.12 [0.72, 1.74] Steinhoff 2000 80 135 57 127 1.6% 1.79 [1.09, 2.92] Törüner 2001 75 121 55 121 1.5% 1.96 [1.17, 3.27] Wang ML 2014 699 1050 834 1404 3.9% 1.36 [1.15, 1.61] Zhao 2007 324 622 317 633 3.4% 1.08 [0.87, 1.35] Zupa 2009 13 23 68 121 0.6% 1.01 [0.41, 2.49] Öztürk 2011 98 176 51 97 1.6% 1.41 [1.30, 1.52] I.41 I.41 Total (95% CI) 12527 16275 100.0% 1.41 I.41 I.40 I.41 I.40 I.41 I.40 I.41 I.40 | Sobti 2005 | 37 | 100 | 24 | 76 | 1 1% | 1 27 [0 68 2 39] | | |
| Solvastava 2004 42 106 54 182 1.6% 1.56 [0.94, 2.57] Srivastava 2005 43 106 140 370 1.9% 1.12 [0.72, 1.74] Steinhoff 2000 80 135 57 127 1.6% 1.79 [1.09, 2.92] Törüner 2001 75 121 55 121 1.5% 1.96 [1.17, 3.27] Wang ML 2014 699 1050 834 1404 3.9% 1.36 [1.15, 1.61] Zhao 2007 324 622 317 633 3.4% 1.08 [0.87, 1.35] Zupa 2009 13 23 68 121 0.6% 1.01 [0.41, 2.49] Öztürk 2011 98 176 51 97 1.6% 1.13 [0.69, 1.86] Total (95% Cl) 12527 16275 100.0% 1.41 [1.30, 1.52] 1.01 1.01 1.00 Total events 7262 8097 1.41 [1.30, 1.52] 1.01 0.01 0.1 1 10 100 Fayours experimental | Song 2009 | 131 | 208 | 108 | 212 | 2.2% | 1.64 [1.11.2.42] | | |
| Srivastava 2004 42 100 04 102 1.00 | Srivestava 2004 | 42 | 106 | 54 | 182 | 1.6% | 1 56 [0 94 2 57] | | |
| Steinhoff 2000 80 135 57 127 1.6% 1.79 [1.09, 2.92] Törüner 2001 75 121 55 121 1.5% 1.96 [1.17, 3.27] Wang ML 2014 699 1050 834 1404 3.9% 1.36 [1.15, 1.61] Zhao 2007 324 622 317 633 3.4% 1.08 [0.87, 1.35] Zupa 2009 13 23 68 121 0.6% 1.01 [0.41, 2.49] Öztürk 2011 98 176 51 97 1.6% 1.13 [0.69, 1.86] Total (95% Cl) 12527 16275 100.0% 1.41 [1.30, 1.52] + Heterogeneity: Tau ² = 0.03; Chi ² = 99.92, df = 49 (P < 0.0001); l ² = 51% - - - Test for overall effect: Z = 8.63 (P < 0.00001) | Srivastava 2004 | 42 | 106 | 140 | 370 | 1.0% | 1 12 [0 72 1 74] | | |
| Oten intol 2000 00 130 01 121 1.13 $[1.15, [1.50, 2.52]]$ Törüner 2001 75 121 55 121 1.5% 1.96 $[1.17, 3.27]$ Wang ML 2014 699 1050 834 1404 3.9% 1.36 $[1.15, 1.61]$ Zhao 2007 324 622 317 633 3.4% 1.08 $[0.87, 1.35]$ Zupa 2009 13 23 68 121 0.6% 1.01 $[0.41, 2.49]$ Öztürk 2011 98 176 51 97 1.6% 1.13 $[0.69, 1.86]$ Total (95% Cl) 12527 16275 100.0% 1.41 $[1.30, 1.52]$ Image: the stand | Steinboff 2000 | 80 | 135 | 57 | 127 | 1.6% | 1 70 [1 00 2 02] | | |
| Wang ML 2014 699 1050 834 1404 3.9% 1.36 [1.17, 3.27] Zhao 2007 324 622 317 633 3.4% 1.08 [0.87, 1.35] Zupa 2009 13 23 68 121 0.6% 1.01 [0.41, 2.49] Öztürk 2011 98 176 51 97 1.6% 1.13 [0.69, 1.86] Total (95% Cl) 12527 16275 100.0% 1.41 [1.30, 1.52] 4 Total events 7262 8097 1.41 [1.30, 1.52] 1.41 [1.30, 1.52] 1.41 [1.30, 1.52] Total events 7262 8097 1.41 [1.30, 1.52] 1.41 [1.30, 1.52] 1.41 [1.30, 1.52] Test for overall effect: Z = 8.63 (P < 0.00001) | Törüper 2001 | 75 | 121 | 55 | 121 | 1.5% | 1.06 [1.17, 3.27] | | |
| Total (95% Cl) 12527 16275 100.0% 1.41 1.30 1.52 Total (95% Cl) 12527 16275 100.0% 1.41 1.30 1.52 Total events 7262 8097 1.41 1.41 1.30 1.52 Test for overall effect: Z = 8.63 (P < 0.00001) | Wang ML 2014 | 600 | 1050 | 834 | 1404 | 3 0% | 1 36 [1 15 1 61] | - | |
| 2 Into 2007 524 622 517 635 5476 1.00 [0.57 , 1.50] Zupa 2009 13 23 68 121 0.6% 1.01 [0.41 , 2.49] Öztürk 2011 98 176 51 97 1.6% 1.13 [0.69 , 1.86] Total (95% Cl) 12527 16275 100.0% 1.41 [1.30 , 1.52] Total events 7262 8097 Heterogeneity: Tau ² = 0.03 ; Chi ² = 99.92 , df = 49 (P < 0.0001); l ² = 51% 0.01 0.1 1 100 Test for overall effect: Z = 8.63 (P < 0.00001) Favours experimental Favours control | Zhao 2007 | 324 | 622 | 317 | 633 | 3.3% | 1.08 [0.87, 1.35] | + | |
| Zupa 2009 13 23 00 121 0.5% $1.01[0.41, 2.49]$ Öztürk 2011 98 176 51 97 1.6% $1.13[0.69, 1.86]$ Total (95% Cl) 12527 16275 100.0% $1.41[1.30, 1.52]$ Total events 7262 8097 Heterogeneity: Tau ² = 0.03; Chi ² = 99.92, df = 49 (P < 0.0001); l ² = 51% 0.01 0.1 1 10 100 Test for overall effect: Z = 8.63 (P < 0.00001) | Zupa 2009 | 13 | 23 | 68 | 121 | 0.6% | 1.00 [0.07, 1.00] | | |
| Total (95% Cl) 12527 16275 100.0% 1.41 [1.30, 1.52] Total events 7262 8097 Heterogeneity: Tau ² = 0.03; Chi ² = 99.92, df = 49 (P < 0.0001); I ² = 51% 0.01 0.1 1 10 100 Test for overall effect: Z = 8.63 (P < 0.00001) | Öztürk 2011 | 13 | 176 | 51 | 07 | 1.6% | 1 13 [0.60 1 96] | | |
| Total (95% CI) 12527 16275 100.0% 1.41 [1.30, 1.52] Total events 7262 8097 Heterogeneity: Tau ² = 0.03; Chi ² = 99.92, df = 49 (P < 0.0001); I ² = 51% 0.01 0.1 1 10 100 Test for overall effect: Z = 8.63 (P < 0.00001) | OZIUR ZUTT | 90 | 170 | 51 | 51 | 1.0 % | 1.15 [0.09, 1.00] | | |
| Total events 7262 8097 Heterogeneity: Tau ² = 0.03; Chi ² = 99.92, df = 49 (P < 0.0001); I ² = 51% 0.01 0.1 1 100 Test for overall effect: Z = 8.63 (P < 0.00001) | Total (95% CI) | | 12527 | | 16275 | 100.0% | 1.41 [1.30, 1.52] | • | |
| Heterogeneity: Tau ² = 0.03; Chi ² = 99.92, df = 49 (P < 0.0001); I ² = 51% I < | Total events | 7262 | | 8097 | | | | | |
| Test for overall effect: Z = 8.63 (P < 0.00001) Favours experimental Favours control | Heterogeneity: Tau ² = 0.03; Cł | ni² = 99.92 | 2, df = 49 |) (P < 0.0 | 001); l² | = 51% | | | |
| | Test for overall effect: Z = 8.63 | 8 (P < 0.00 | 0001) | | | | 1 | Favours experimental Favours control | |

Figure 2. Forest plot for association between GSTM₁ polymorphism and BC risk. Abbreviations: CI, confidence interval; M-H, Mantel-Haenszel.

Meta-analysis results

Extreme heterogeneity was observed among the 50 eligible studies ($l^2=51\%$, P<0.0001). Overall data showed that individuals who carried the GSTM₁ null genotype had significantly increased BC risks compared with those who carried the GSTM₁ genotype (OR=1.41 [1.30, 1.52], P<0.00001) (**Figure 2**). In the subgroup analyses, the same significant associations were observed among Caucasians (OR=1.38 [1.23, 1.55], P<0.00001), Africans (OR=1.68 [1.04, 2.71], P=0.03) and Asians (OR=1.46 [1.33, 1.61], P<0.00001) (**Table 2**).

| cancernsk | | | | | | |
|-------------------|----|-------------------|-------------|--------|-----------------|--|
| Subgroup | Ν | OR (95% CI) | Р | l² (%) | Ph ^a | |
| Total | 50 | 1.41 [1.30, 1.52] | <0.00001 | 51 | <0.0001 | |
| Ethnicity | | | | | | |
| Caucasian | 24 | 1.38 [1.23, 1.55] | <0.00001 65 | | <0.00001 | |
| Asian | 18 | 1.46 [1.33, 1.61] | <0.00001 25 | | =0.16 | |
| African | 4 | 1.68 [1.04, 2.71] | =0.03 | 60 | =0.06 | |
| Source of control | | | | | | |
| PB | 18 | 1.26 [1.10, 1.43] | =0.0006 | 41 | =0.04 | |
| HB | 32 | 1.48 [1.35, 1.61] | <0.00001 | 44 | =0.004 | |
| Smoking status | | | | | | |
| Smoking | 18 | 1.41 [1.20, 1.65] | <0.0001 | 42 | =0.03 | |
| No-smoking | 18 | 1.17 [0.94, 1.46] | =0.15 | 37 | =0.06 | |
| Sex | | | | | | |
| Male | 6 | 1.37 [1.11, 1.69] | =0.003 0 | | =0.72 | |
| Female | 5 | 1.89 [1.19, 3.00] | =0.007 | 4 | =0.39 | |
| | | | | | | |

Table 2. Summary of ORs for $\ensuremath{\mathsf{GSTM}}_1$ polymorphism and bladder cancer risk

Notes: ^a*P*-value for heterogeneity. Abbreviations: OR, odds ratio; PB, populationbased study; HB, hospital-based study.



Figure 3. Funnel plot analysis for detecting publication bias. OR values for the main effects of GSTM_1 are shown.

In the stratified analyses based on source of controls, the GSTM_1 null genotype showed a significant association with increased BC susceptibility in hospital-based (OR=1.48 [1.35, 1.61], P<0.00001) and population-based studies (OR=1.26 [1.10, 1.43], P=0.0006).

We noted that smoking modified the association between GSTM_1 polymorphism and BC risk (OR=1.41 [1.20, 1.65], P<0.0001) in smokers. When we stratified the population based on gender, we observed a significant association

between $GSTM_1$ polymorphism and BC risk in males (OR=1.37 [1.11, 1.69], P= 0.0003) and females (OR= 1.89 [1.19, 3.00], P=0.007).

Publication bias

Funnel plot and Egger's test were conducted to estimate publication bias of the metaanalysis. **Figure 3** shows the absence of publication bias in the funnel plots. Results of Egger's test provide statistical evidence for the funnel plot symmetry (t=1.46, P= 0.151).

Discussion

At present, the underlying mechanisms of BC remain unknown. Researchers recognize that BC development is caused by complex interactions of both genetic and environmental factors. Environmental factors, such as procarcinogens, are mainly metabolised by various metabolising enzymes in the human body. Different degrees of BC risk are possibly associated with interindividual variations in genetic and cellular mechanisms of detoxification of carcinogenic chemicals, such as sequence variations in genes coding for the GST family.

GSTs are a family of phase II enzymes, which are primarily

involved in detoxification of primary metabolites through conjugation with glutathione to produce readily excreted hydrophilic products. Until recently, a number of studies focused on GSTs, especially GSTM₁, and BC risk.

In 1993, Bell et al. firstly reported the association between GSTM_1 deficiency and increased BC risk. Following the first report, similar studies were conducted in different countries by other researchers [61]. However, most of these studies were based on relatively small samples, and some studies reported conflicting results. A small sample often has insufficient influence, which may lead to inaccurate conclusions. Therefore, combining data from various studies reduces the random error [62]. The meta-analysis enabled us to apply the same criteria to all study datasets and to obtain more accurate estimates of results.

In 2011, Jiang conducted a meta-analysis of data from previous studies and suggested that $GSTM_1$ null status is associated with increased BC risk [63]. Afterward, many new case-control studies investigated the association between $GSTM_1$ null genotype and BC risk in the past five years. Thus, an updated meta-analysis is needed.

Our meta-analysis of 12,527 BC cases and 16,275 controls from 50 case-control studies provides evidence that the GSTM, null genotype is associated with increased BC risk. Compared with previous research, the metaanalysis by Jiang 2011 yielded significant association between the GSTM, polymorphism and BC risk in worldwide populations (OR=1.409 [1.267-1.568], P<0.001); The observation was similar to our study results (OR=1.41 [1.30, 1.52], P<0.00001). Our research revealed the possible association of GSTM, with increased BC risk in Africans through analysis of four studies. However, the previous meta-analysis did not show this result. In the stratified analysis based on source of controls, the previous metaanalysis showed that patients with BC had no association with GSTM, in population-based studies (OR=1.088 [0.970-1.221], P=0.151); This result was different from that of our study. Furthermore, our meta-analysis also indicates that GSTM, is possibly associated with increased BC risk in smoking people but not in non-smoking individuals. When considering the gender, we observed a significant association between GSTM, polymorphism and BC risk in both males and females. All these outcomes were not included in the previous metaanalysis.

Our study was more stringent and comprehensive compared with previous meta-analyses. Firstly, more up-to-date studies (50 studies) were selected to provide statistically significant results. Secondly, we observed lower heterogeneity ($l^2=51\%$ vs. 72.6%), although our metaanalysis embodied more studies. Thirdly, stratified analyses were performed in detail to investigate the association between GSTM_1 null genotype and BC risk with various control designs. We suggest that the determination of the role of the GSTM_1 null genotype on BC susceptibility is mainly influenced by study designs based on different control individuals in this meta-analysis.

Despite the clear strengths of our study, it does have some limitations. Firstly, only published studies were included. Therefore, publication bias possibly occurred. Secondly, extreme heterogeneity was noted in the studies analysed in the meta-analysis. Such degree of heterogeneity might be caused by study designs, source of controls and differences in genetic backgrounds. Thirdly, overall outcomes were based on individual unadjusted ORs. Thus, a more precise evaluation requires adjustment for other potentially suspected factors.

Conclusion

Our meta-analysis suggests that the $GSTM_1$ null genotype is associated with enhanced BC risk. Specifically, increased BC risk was observed among Caucasians, Asians and Africans with the $GSTM_1$ null genotype. A significant gene-environment interaction was observed to influence the association between the $GSTM_1$ null genotype and BC risk. In addition, our results showed the strong association between BC risk and $GSTM_1$ null genotype in both males and females and in the smoking group. We suggest that well-designed, highquality epidemiological studies with larger populations can be conducted to further support our findings.

Acknowledgements

We thank all participating investigators in this study.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Zhi-Ping Qi, The Medical Group of Zhengzhou First People's Hospital, 56 Dongda Street, Zhengzhou 450004, Henan Province, China. E-mail: dagene@126.com

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