Table S1. Characteristics of included studies for *MTHFR* 677 and 1298 loci distributions (82 papers).

| First Author | Year | Ethnicity  -Country | MTHFR 677 | | | | | | | | | | MTHFR 1298 | | | | | | | | | Quality Score |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Cases, n (%) | | | | Controls, source (s), n (%) | | | | | | Cases n (%) | | | Controls n (%) | | | | | |
| CC | | CT | TT | s | CC | CT | TT | HWE | | AA | AC | CC | AA | AC | CC | HWE | | |
| **Australia** |  |  |  |  |  |  |  |  |  |  | | |  |  |  |  |  |  |  | | |  |
| Beetstra | 2008 | Caucasian  -Australia | 9  (47.4) | | 6  (31.6) | 4  (21) | 1 | 29 (72.5) | 6  (15) | 5  (12.5) | | No | 4  (19) | 17  (81) | No data | 15  (36.6) | 26  (63.4) | 0  (0) | | No | | 17  (5, 6, 6) |
| **Europe** |  |  |  |  |  |  |  |  |  |  | |  |  |  |  |  |  |  | | |  |  |
| Weiner | 2010 | Caucasian  -Russia | 399  (47.7) | | 364  (43.5) | 74  (8.8) | 1 | 386  (49.6) | 326  (41.9) | 66  (8.5) | | Yes | 398  (47.9) | 353  (42.5) | 80  (9.6) | 379  (48.3) | 330  (42) | 76  (9.7) | | | Yes | 15  (7, 3, 5) |
| Ericson | 2009 | Caucasian  -Sweden | 255  (47.2) | | 235  (43.5) | 50  (9.3) | 1 | 531  (49.4) | 452  (42.1) | 91  (8.5) | | Yes | 242  (44.7) | 242  (44.7) | 57  (10.6) | 487  (45.4) | 480  (44.8) | 105  (9.8) | | | Yes | 22  (7, 9, 6) |
| Forsti | 2004 | Caucasian  -Finland, Poland | 134  (60.1) | | 81  (36.3) | 8  (3.6) | 1 | 181  (60.7) | 104  (34.9) | 13  (4.4) | | Yes | 94  (42.2) | 102  (45.7) | 27  (12.1) | 133  (44.6) | 127  (42.6) | 38  (12.8) | | | Yes | 9  (2, 3, 4) |
| Jakubowska | 2008 | Caucasian  -Poland | 154  (49.1) | | 126  (40.1) | 34  (10.8) | 1 | 134  (46.2) | 138  (47.6) | 18  (6.2) | | No | 151  (47.3) | 134  (42) | 34  (10.7) | 117  (40.3) | 144  (49.7) | 29  (10) | | | Yes | 21  (6, 9, 6) |
| Lissowska | 2007 | Caucasian  -Poland | 982  (49.7) | | 815  (41.3) | 177  (9) | 1 | 1132  (49.6) | 915  (40.1) | 235  (10.3) | | No # | 892  (44.9) | 874  (44) | 220  (11.1) | 1086  (47.7) | 941  (41.3) | 251  (11) | | | No # | 21  (8, 7, 6) |
| Ozen | 2013 | Caucasian  -Turkey | 28  (54.9) | | 18  (35.3) | 5  (9.8) | 1 | 76  (71.7) | 30  28.3 | 0  (0) | | Yes | 17  (33.3) | 29  (56.9) | 5  (9.8 | 71  (67) | 35  (33) | 0  (0) | | | No # | 22  (7, 9, 6) |
| Cam | 2009 | Caucasian  -Turkey | 48  (43.6) | | 49  (44.6) | 13  (11.8) | 1 | 47  (49.5) | 42  (44.2) | 6  (6.3) | | Yes | NA | | | | | | | | | 9  (3, 4, 2) |
| Hekim | 2007 | Caucasian  -Turkey | 22  (55) | | 16  (40) | 2  (5) | 1 | 38  (55.9) | 26  (38.2) | 4  (5.9) | | Yes | NA | | | | | | | | | 11  (6, 2, 3) |
| Deligezer | 2005 | Caucasian  -Turkey | 98  (51.8) | | 68  (36) | 23  (12.2) | 1 | 128  (57.4) | 83  (37.2) | 12  (5.4) | | Yes | NA | | | | | | | | | 14  (7, 2, 5) |
| Ergul | 2003 | Caucasian  -Turkey | 60  (50.8) | | 41  (34.8) | 17  (14.4) | 1 | 94  (48.7) | 87  (45.1) | 12  (6.2) | | Yes | 50  (42.4) | 48  (40.7) | 20  (16.9) | 90  (46.6) | 85  (44.1) | 18  (9.3) | | | Yes | 16  (7, 5, 4) |
| Kakkoura | 2015 | Caucasian  -Cyprus | 361  (33.9) | | 516  (48.4) | 188  (17.7) | 1 | 437  (37.8) | 526  (45.5) | 194  (16.7) | | Yes | 138  (12.9) | 465  (43.4) | 468  (43.7) | 150  (13.2) | 501  (44.1) | 486  (42.7) | | | Yes | 19  (6, 7, 6) |
| Papandreou | 2012 | Caucasian  -Greece | 105  (35) | | 150  (50) | 45  (15) | 1 | 99  (35) | 161  (56.9) | 23  (8.1) | | No # | 129  (43) | 135  (45) | 36  (12) | 136  (48) | 116  (41) | 31  (11) | | | Yes | 15  (6, 3, 6) |
| Kalemi | 2005 | Caucasian  -Greece | 19  (45.2) | | 16  (38.1) | 7  (16.7) | 1 | 23  (45.1) | 20  (39.2) | 8  (15.7) | | Yes | NA | | | | | | | | | 15  (7, 2, 6) |
| Langsenlehner | 2008 | Caucasian  -Austria | 40  (38.1) | | 48  (45.7) | 17  (16.2) | 1 | 51  (48.6) | 43  (40.9) | 11  (10.5) | | Yes | NA | | | | | | | | | 7  (5, 0, 2) |
| Grieu | 2004 | Caucasian  -Austria | 166  (49.7) | | 141  (42.2) | 27  (8.1) | 1 | 242  (43.9) | 259  (47) | 50  (9.1) | | Yes | NA | | | | | | | | | 17  (6, 7, 4) |
| Langsenlehner | 2003 | Caucasian  -Austria | 208  (42.1) | | 222  (44.9) | 64  (13) | 1 | 215  (43.4) | 215  (43.4) | 65  (13.2) | | Yes | NA | | | | | | | | | 17  (6, 6, 5) |
| Cerne | 2011 | Caucasian  -Slovenia | 222  (42.5) | | 238  (45.6) | 62  (11.9) | 1 | 108  (40.1) | 124  (46.1) | 37  (13.8) | | Yes | 258  (49.2) | 219  (41.8) | 47  (9) | 131  (48.7) | 117  (43.5) | 21  (7.8) | | | Yes | 24  (9, 9, 6) |
| Reljic | 2007 | Caucasian  -Croatia | 40  (43) | | 44  (47.3) | 9  (9.7) | 1 | 27  (41.5) | 34  (52.3) | 4  (6.2) | | Yes | NA | | | | | | | | | 20  (6, 9, 5) |
| Justenhoven | 2005 | Caucasian  -Germany | 249  (42.6) | | 274  (47) | 61  (10.4) | 1 | 261  (41.2) | 279  (44.1) | 93  (14.7) | | Yes | 273  (46.9) | 256  (44) | 53  (9.1) | 295  (46.5) | 266  (42) | 73  (11.5) | | | Yes | 17  (8, 3, 6) |
| Jakubowska | 2012 | Caucasian  -Great Britain | 2032  (42.5) | | 2166  (45.3) | 580  (12.2) | 2 | 1447  (43.2) | 1481  (44.2) | 422  (12.6) | | Yes | NA | | | | | | | | | 12  (5, 1, 6) |
| Campbell | 2002 | Caucasian  -UK | 140  (41.8) | | 162  (48.4) | 33  (9.8) | 1 | 118  (50.6) | 92  (39.5) | 23  (9.9) | | Yes | NA | | | | | | | | | 15  (7, 4, 4) |
| Sharp | 2002 | Caucasian  -UK | 30  (55.6) | | 19  (35.2) | 5  (9.2) | 1 | 25  (43.9) | 21  (36.8) | 11  (19.3) | | Yes | 27  (49.1) | 25  (45.5) | 3  (5.4) | 24  (40) | 25  (41.7) | 11  (18.3) | | | Yes | 19  (8, 6, 5) |
| Ferroni | 2009 | Caucasian  -Italy | 7  (38.9) | | 7  (38.9) | 4  (22.2) | 1 | 18  (38.3) | 25  (53.2) | 4  (8.5) | | Yes | 9  (50) | 8  (44.4) | 1  (5.6) | 31  (66) | 14  (29.8) | 2  (4.2) | | | Yes | 19  (7, 6, 6) |
| Macis | 2007 | Caucasian  -Italy | 14  (30.4) | | 20  (43.5) | 12  (26.1) | 1 | 28  (35) | 41  (51.2) | 11  (13.8) | | Yes | NA | | | | | | | | | 20  (7, 7, 6) |
| Henriquez-Hernandez | 2009 | Caucasian  -Spain | 52  (38.5) | | 65  (48.2) | 18  (13.3) | 1 | 107  (36.6) | 138  (47.3) | 47  (16.1) | | Yes | NA | | | | | | | | | 21  (8, 8, 5) |
| Guillem | 2007 | Caucasian  -Spain | 53  (37.3) | | 61  (43) | 28  (19.7) | 1 | 56  (38.9) | 67  (46.5) | 21  (14.6) | | Yes | 66  (46.5) | 60  (42.2) | 16  (11.3) | 69  (48.2) | 61  (42.7) | 13  (9.1) | | | Yes | 17  (6, 5, 6) |
| **North America** | | |  | |  |  |  |  |  |  | |  |  |  |  |  |  |  | | |  |  |
| Kotsopoulos | 2008 | Caucasian  -Canada | 383  (40.6) | | 421  (44.6) | 140  (14.8) | 1 | 252  (37.1) | 341  (50.1) | 87  (12.8) | | Yes # | 466  (49.5) | 390  (41.5) | 85  (9) | 398  (51) | 309  (39.6) | 73  (9.4) | | | Yes # | 22  (7, 9, 6) |
| Bentley | 2010 | Mixed  -US | 346  (36.8) | | 402  (42.8) | 191  (20.3) | 1 | 429  (35) | 592  (48.3) | 205  (16.7) | | Yes | NA | | | | | | | | | 14  (3, 5, 6) |
| Platek | 2009 | Mixed  -US | 429  (43.2) | | 446  (44.9) | 119  (11.9) | 1 | 788  (43.7) | 795  (44.1) | 219  (12.2) | | Yes | 443  (47.7) | 402  (43.3) | 83  (9) | 842  (47.3) | 758  (42.6) | 181  (10.1) | | | Yes | 25  (9, 10, 6) |
| Maruti | 2009 | Mixed  -US | 133  (41.8) | | 139  (43.7) | 46  (14.5) | 1 | 301  (46.5) | 284  (43.9) | 62  (9.6) | | Yes | NA | | | | | | | | | 22  (6, 10, 6) |
| Tao | 2009 | Mixed  -US | 969  (45.1) | | 915  (42.5) | 267  (12.4) | 1 | 813  (43.9) | 816  (44.1) | 223  (12) | | Yes | 927  (46.7) | 861  (43.4) | 198  (9.9) | 864  (47.2) | 779  (42.5) | 188  (10.3) | | | Yes | 22  (10, 6, 6) |
| Stevens | 2007 | Mixed  -US | 208  (42.1) | | 224  (45.3) | 62  (12.6) | 1 | 236  (47.8) | 193  (39) | 65  (13.2) | | No | 224  (45.3) | 228  (46.2) | 42  (8.5) | 252  (51.1) | 201  (40.8) | 40  (8.1) | | | Yes # | 21  (6, 9, 6) |
| Chen | 2005 | Mixed  -US | 398  (37.4) | | 476  (44.8) | 189  (17.8) | 1 | 440  (39.9) | 509  (46.1) | 155  (14) | | Yes # | 558  (52.5) | 417  (39.3) | 87  (8.2) | 536  (48.6) | 457  (41.4) | 110  (10) | | | Yes # | 24  (8, 10, 6) |
| Le Marchand | 2004 | Mixed  -US | 573  (48.2) | | 479  (40.3) | 137  (11.5) | 1 | 1211  (50.2) | 920  (38.1) | 283  (11.7) | | No | 741  (62.3) | 371  (31.2) | 77  (6.5) | 1493  (61.8) | 801  (33.2) | 120  (5) | | | Yes # | 24  (7, 11, 6) |
| Semenza | 2003 | Mixed  -US | 42  (40) | | 58  (55.2) | 5  (4.8) | 3 | 112  (45.3) | 111  (44.9) | 24  (9.8) | | Yes | NA | | | | | | | | | 20  (8, 6, 6) |
| Ramos-Silva | 2015 | Hispanic  -Mexico | 216  (43) | | 178  (36) | 103  (21) | 1 | 167  (49) | 140  (41) | 32  (10) | | Yes | NA | | | | | | | | | 16  (4, 6, 6) |
| **South America** | | |  | |  |  |  |  |  |  | |  |  |  |  |  |  |  | | |  |  |
| Barbosa | 2012 | Mixed  -Brazil | 65  (45.8) | | 66  (46.5) | 11  (7.7) | 1 | 74  (52.1) | 53  (37.3) | 15  (10.6) | | Yes | 55  (38.7) | 71  (50) | 16  (11.3) | 62  (43.7) | 72  (50.7) | 8  (5.6) | | | No # | 21  (5, 10, 6) |
| Carvalho | 2012 | Mixed  -Brazil | 76  (43.2) | | 83  (47.2) | 17  (9.6) | 1 | 87  (49.4) | 70  (39.8) | 19  (10.8) | | Yes | 68  (41.2) | 80  (48.5) | 17  (10.3) | 72  (43.6) | 84  (50.9) | 9  (5.5) | | | No # | 22  (9, 7, 6) |
| Batschauer | 2011 | Mixed  -Brazil | 27  (39.7) | | 34  (50) | 7  (10.3) | 1 | 42  (49.4) | 34  (40) | 9  (10.6) | | Yes | NA | | | | | | | | | 17  (8, 3, 6) |
| Ma | 2009 | Mixed  -Brazil | 225  (49.1) | | 188  (41.1) | 45  (9.8) | 1 | 222  (48.5) | 187  (40.8) | 49  (10.7) | | Yes | 269  (58.7) | 168  (36.7) | 21  (4.6) | 279  (60.9) | 157  (34.3) | 22  (4.8) | | | Yes | 24  (8, 10, 6) |
| Lopez-Cortes | 2015 | Mixed  -Ecuador | 25  (21.9) | | 75  (65.8) | 14  (12.3) | 1 | 69  (35.4) | 113  (57.9) | 13  (6.7) | | No | 110  (96.5) | 3  (2.6) | 1  (0.9) | 191  (98) | 3  (1.5) | 1  (0.5) | | | No | 21  (8, 7, 6) |
| **Asia** |  |  |  | |  |  |  |  |  |  | |  |  |  |  |  |  |  | | |  |  |
| Ma | 2009 | Asian  -Japan | 124  (32) | | 183  (47.1) | 81  (20.9) | 1 | 115  (29.7) | 188  (48.6) | 84  (21.7) | | Yes | 254  (65.5) | 119  (30.6) | 15  (3.9) | 256  (66.1) | 116  (30) | 15  (3.9) | | | Yes | 23  (8, 9, 6) |
| Suzuki | 2008 | Asia  -Japan | 150  (33) | | 220  (48.5) | 84  (18.5) | 1 | 338  (37.2) | 425  (46.8) | 146  (16) | | Yes | NA | | | | | | | | | 25  (10, 9, 6) |
| Lee | 2004 | Asia  -Korea | 58  (31.2) | | 96  (51.6) | 32  (17.2) | 1 | 50  (34) | 80  (54.4) | 17  (11.6) | | Yes | NA | | | | | | | | | 22  (8, 8, 6) |
| Huang | 2014 | Asia  -Taiwan | 596  (48.4) | | 533  (43.3) | 103  (8.3) | 1 | 538  (43.7) | 519  (42.1) | 175  (14.2) | | No | 796  (64.6) | 391  (31.7) | 45  (3.7) | 787  (63.9) | 386  (31.3) | 59  (4.8) | | | Yes # | 13  (4, 3, 6) |
| Cheng | 2008 | Asia  -Taiwan | 185  (53) | | 133  (38.1) | 31  (8.9) | 1 | 268  (50.6) | 221  (41.7) | 41  (7.7) | | Yes | 207  (59) | 125  (35.6) | 19  (5.4) | 310  (58) | 207  (38.8) | 17  (3.2) | | | No | 24  (9, 9, 6) |
| Yu | 2007 | Asia  -Taiwan | 56  (51.4) | | 44  (40.4) | 9  (8.2) | 1 | 225  (53.6) | 170  (40.5) | 25  (5.9) | | Yes | NA | | | | | | | | | 24  (8, 10, 6) |
| Chou | 2006 | Asia  -Taiwan | 73  (51.4) | | 51  (35.9) | 18  (12.7) | 1 | 132  (46.3) | 120  (42.1) | 33  (11.6) | | Yes | 104  (73.3) | 30  (21.1) | 8  (5.6) | 172  (60.4) | 95  (33.3) | 18  (6.3) | | | Yes | 24  (8, 11, 5) |
| Lin | 2004 | Asia  -Taiwan | 43  (48.9) | | 38  (43.2) | 7  (7.9) | 1 | 173  (50.6) | 145  (42.4) | 24  (7) | | Yes | NA | | | | | | | | | 24  (8, 10, 6) |
| Lin | 2015 | Asia  -China | 142  (61.4) | | 70  (30) | 20  (8.6) | 1 | 131  (55.3) | 82  (34.6) | 24  (10.1) | | No# | NA | | | | | | | | | 22  (5, 11, 6) |
| Lu | 2015 | Asia  -China | 170  (30.4) | | 288  (51.4) | 102  (18.2) | 1 | 226  (40.4) | 250  (44.6) | 84  (15) | | Yes | 369  (65.9) | 172  (30.7) | 19  (3.4) | 352  (62.9) | 185  (33) | 23  (4.1) | | | Yes | 23  (8, 9, 6) |
| He | 2014 | Asia  -China | 159  (51.3) | | 97  (31.3) | 54  (17.4) | 1 | 220  (57.7) | 117  (30.7) | 44  (11.6) | | No | 138  (44.5) | 132  (42.6) | 40  (12.9) | 173  (45.4) | 155  (40.7) | 53  (13.9) | | | Yes # | 18  (5, 8, 5) |
| Xi | 2014 | Asia  -China | 489  (59.8) | | 279  (34.1) | 50  (6.1) | 1 | 497  (58.6) | 298  (35.1) | 53  (6.3) | | Yes# | NA | | | | | | | | | 24  (7,11,6) |
| Jiang-Hua | 2014 | Asian  -China | 241  (45) | | 189  (35.4) | 105  (19.6) | 1 | 365  (54.3) | 226  (33.5) | 82  (12.2) | | No# | 258  (48.3) | 235  (43.9) | 42  (7.8) | 351  (52.2) | 280  (41.5) | 42  (6.3) | | | Yes | 21  (6, 9, 6) |
| Wang | 2014 | Asian  -China | 250  (57.5) | | 153  (35.2) | 32  (7.3) | 1 | 255  (58.6) | 150  (34.5) | 30  (6.9) | | Yes | 206  (47.4) | 176  (40.5) | 53  (12.1) | 214  (49.3) | 172  (39.5) | 49  (11.2) | | | Yes | 19  (7, 7, 5) |
| Weiwei | 2014 | Asian  -China | 156  (52.5) | | 97  (32.7) | 44  (14.8) | 1 | 185  (60.4) | 93  (30.4) | 28  (9.2) | | No# | 135  (45.6) | 129  (43.6) | 32  (10.8) | 151  (49.3) | 130  (42.5) | 25  (8.2) | | | Yes | 19  (4, 10, 5) |
| Liu | 2013 | Asian  -China | 250  (57.5) | | 153  (35.2) | 32  (7.3) | 1 | 255  (58.6) | 150  (34.5) | 30  (6.9) | | Yes | 206  (47.4) | 176  (40.4) | 53  (12.2) | 214  (49.2) | 172  (39.5) | 49  (11.3) | | | Yes | 21  (6, 10, 5) |
| Wu | 2012 | Asian  -China | 32  (42.7) | | 30  (40) | 13  (17.3) | 1 | 37  (49.3) | 32  (42.7) | 6  (8) | | Yes | 37  (49.3) | 32  (42.7) | 6  (8) | 42  (56) | 28  (37.3) | 5  (6.7) | | | Yes | 17  (6, 6, 5) |
| Hua | 2011 | Asian  -China | 65  (68.4) | | 21  (22.1) | 9  (9.5) | 1 | 52  (57.8) | 27  (30) | 11  (12.2) | | No | 50  (52.6) | 42  (44.2) | 3  (3.2) | 55  (61.1) | 32  (35.6) | 3  (3.3) | | | Yes | 13  (4, 5, 4) |
| Gao | 2009 | Asian  -China | 202  (32.4) | | 305  (48.9) | 117  (18.7) | 1 | 235  (37.7) | 301  (48.2) | 88  (14.1) | | Yes | 446  (71.5) | 169  (27.1) | 9  (1.4) | 425  (68.1) | 188  (30.1) | 11  (1.8) | | | Yes | 21  (9, 6, 6) |
| Li | 2009 | Asian  -China | 38  (58.5) | | 17  (26.1) | 10  (15.4) | 1 | 90  (62.9) | 50  (35) | 3  (2.1) | | Yes | NA | | | | | | | | | 18  (6, 6, 6) |
| Yuan | 2009 | Asian  -China | 16  (20) | | 35  (43.8) | 29  (36.2) | 1 | 32  (40) | 35  (43.8) | 13  (16.2) | | Yes | NA | | | | | | | | | 18  (5, 9, 4) |
| Jin | 2009 | Asian  -China | 92  (37.2) | | 115  (46.6) | 40  (16.2) | 1 | 49  (49) | 41  (41) | 10  (10) | | Yes | NA | | | | | | | | | 24  (9, 10, 5) |
| Kan | 2007 | Asian  -China | 74  (59.2) | | 29  (23.2) | 22  (17.6) | 1 | 65  (63.1) | 29  (28.2) | 9  (8.7) | | No | 70  (56) | 41  (32.8) | 14  (11.2) | 61  (60.4) | 32  (31.7) | 8  (7.9) | | | Yes | 8  (3, 2, 3) |
| Qi | 2004 | Asian  -China | 42  (19.4) | | 104  (47.9) | 71  (32.7 | 1 | 59  (27) | 105  (48.2) | 54  (24.8) | | Yes | 155  (71.4) | 58  (26.7) | 4  (1.9) | 144  (66) | 71  (32.6) | 3  (1.4) | | | Yes | 20  (6, 10, 4) |
| Shrubsole | 2004 | Asian  -China | 374  (33.6) | | 555  (49.9) | 183  (16.5) | 1 | 387  (33.4) | 577  (49.7) | 196  (16.9) | | Yes | 768  (68.5) | 311  (27.7) | 42  (3.8) | 824  (68.2) | 344  (28.5) | 40  (3.3) | | | Yes | 21  (6, 9, 6) |
| Inoue | 2008 | Asian  -Singapore | 239  (62.9) | | 120  (31.6) | 21  (5.5) | 1 | 393  (59.4) | 226  (34.1) | 43  (6.5) | | Yes | 225  (59.2) | 139  (36.6) | 16  (4.2) | 387  (58.5) | 234  (35.3) | 41  (6.2) | | | Yes | 19  (6, 7, 6) |
| Sangrajrang | 2010 | Asian  -Thailand | 410  (72.8) | | 144  (25.6) | 9  (1.6) | 1 | 366  (75.2) | 110  (22.6) | 11  (2.2) | | Yes | 302  (53.6) | 223  (39.6) | 38  (6.8) | 258  (53) | 206  (42.3) | 23  (4.7) | | | No | 23  (7, 10, 6) |
| Pooja | 2015 | Asian  -India | 437  (74.3) | | 134  (22.8) | 17  (2.9) | 1 | 386  (75.9) | 111  (21.9) | 11  (2.2) | | Yes | NA | | | | | | | | | 17  (8, 3, 6) |
| Prasad | 2011 | Asian  -India | 124  (95.4) | | 5  (3.8) | 1  (0.8) | 1 | 116  (92.8) | 8  (6.4) | 1  (0.8) | | Yes | NA | | | | | | | | | 12  (3, 5, 4) |
| Naushad | 2010 | Asian  -India | 185  (75.8) | | 56  (23) | 3  (1.2) | 1 | 205  (84) | 39  (16) | 0  (0) | | Yes | NA | | | | | | | | | 23  (7, 10, 6) |
| Mohammad | 2010 | Asian  -India | 168  (75.7) | | 53  (23.9) | 1  (0.4) | 1 | 198  (84.3) | 37  (15.7) | 0  (0) | | Yes | NA | | | | | | | | | 18  (6, 6, 6) |
| Mir | 2008 | Asian  -India | 29  (82.8) | | 6  (17.2) | 0  (0) | 1 | 19  (57.6) | 12  (36.4) | 2  (6) | | Yes | 15  (42.8) | 19  (54.3) | 1  (2.9) | 11  (33.3) | 22  (66.7) | 0  (0) | | | No | 15  (6, 5, 4) |
| Kalyankumar | 2006 | Asian  -India | 45  (51.1) | | 37  (42.1) | 6  (6.8) | 1 | 61  (64.2) | 31  (32.6) | 3  (3.2) | | Yes | 49  (55.7) | 33  (37.5) | 6  (6.8) | 65  (68.4) | 26  (27.4) | 4  (4.2) | | | Yes | 13  (7, 3, 3) |
| **Middle East Asia** | | |  | |  |  |  |  |  |  | |  |  |  |  |  |  |  | | |  |  |
| Akilzhanova | 2013 | Mid-Eastern -Kazakhstan | 181  (57.5) | | 109  (34.6) | 25  (7.9) | 1 | 287  (47.5) | 269  (44.5) | 48  (8) | | Yes | 138  (43.8) | 142  (45.1) | 35  (11.1) | 318  (52.6) | 242  (40.1) | 44  (7.3) | | | Yes | 21  (9, 7, 5) |
| Akram | 2012 | Mid-Eastern  -Pakistan | 65  (59.1) | | 25  (22.7) | 20  (18.2) | 1 | 55  (50) | 45  (40.9) | 10  (9.1) | | Yes | 35  (31.8) | 55  (50) | 20  (18.2) | 30  (27.3) | 75  (68.2) | 5  (4.5) | | | No | 12  (3, 6, 3) |
| Hosseini | 2011 | Mid-Eastern -Iran | 168  (57.1) | | 84  (28.6) | 42  (14.3) | 1 | 150  (50) | 90  (30) | 60  (20) | | No | 162  (55.1) | 96  (32.7) | 36  (12.2) | 105  (35) | 135  (45) | 60  (20) | | | Yes | 13  (5, 5, 3) |
| Lajin | 2012 | Mid-Eastern -Syria | 60  (50.4) | | 47  (39.5) | 12  (10.1) | 1 | 58  (46) | 58  (46) | 10  (8) | | Yes | 44  (37) | 52  (43.7) | 23  (19.3) | 65  (51.6) | 48  (38.1) | 13  (10.3) | | | Yes | 13  (6, 3, 4) |
| Awwad | 2015 | Mid-Eastern -Jordan | 66  (44) | | 69  (46) | 15  (10) | 1 | 79  (54.1) | 51  (34.9) | 16  (11) | | Yes | 68  (46.6) | 61  (41.8) | 17  (11.6) | 58  (43) | 64  (47.4) | 13  (9.6) | | | Yes | 18  (5, 8, 5) |
| Alshatwi | 2010 | Mid-Eastern  -Saudi Arabia | 336  (32.8) | | 516  (50.4) | 172  (16.8) | 1 | 351  (33.2) | 532  (50.3) | 174  (16.5) | | Yes | NA | | | | | | | | | 22  (8, 9, 5) |
| **Africa** | | |  | |  |  |  |  |  |  | |  |  | | | | | | | | |  |
| Diakite | 2012 | African  -Morocco | 39  (40.6) | | 51  (53.1) | 6  (6.3) | 1 | 69  (59) | 41  (35) | 7  (6) | | Yes | NA | | | | | | | | | 19  (7, 6, 6) |

HWE: Hardy Weinberg Equilibrium

#: HWE data updated (noted different from reports of original studies) based on available online calculator, retrieved at

http://www.tufts.edu/~mcourt01/Documents/Court%20lab%20-%20HW%20calculator.xls

Sources of controls: 1 = healthy adults, 2 = BRCA 1 or 2 carriers, 3 = clinic-based with breast diseases

Quality score ranges: 0 - 29 (external validity, 0 – 11; Internal Validity, 0 – 12; report quality, 0 - 6)

NA: Not available

UK: United Kingdom

US: United States of America

**Reference List of Studies included in the Meta-analysis**

19 Meta-analysis Papers

1. Xie SZ, Liu ZZ, Yu JH, Liu L, Wang W, Xie DL, Qin JB (2015). Association between the MTHFR C677T polymorphism and risk of cancer: Evidence from 446 case-control studies. *Tumour Biol,* 36(11):8953-72. doi: 10.1007/s13277-015-3648-z PMID: 26081619.
2. Pooja S, Carlus J, Sekhar D, Francis A, Gupta N, Konwar R, Kumar S, Kumar S, Thangaraj K, Rajender S. (2015). MTHFR 677C&gt;T polymorphism and the risk of breast cancer: Evidence from an original study and pooled data for 28031 cases and 31880 controls. *PLoS One,* 10(3):e0120654. doi: 10.1371/journal.pone.0120654. PMID: 25803740
3. Rai V. (2014). Methylenetetrahydrofolate Reductase A1298C Polymorphism and Breast Cancer Risk: A Meta-analysis of 33 Studies. *Ann Med Health Sci Res,* 4(6), 841-51. doi: 10.4103/2141-9248.144873. PMID: 25506474.
4. Rai V. (2014). The methylenetetrahydrofolate reductase C677T polymorphism and breast cancer risk in Asian populations. *Asian Pac J Cancer Prev*, 15(14), 5853-60. PMID: 25081713.
5. Zhong S, Chen Z, Yu X, Li W, Tang J, Zhao J. (2014). A meta-analysis of genotypes and haplotypes of methylenetetrahydrofolate reductase gene polymorphisms in breast cancer. *Mol Biol Rep*, 41(9), 5775-85. doi: 10.1007/s11033-014-3450-9. PMID: 24973876.
6. Li K, Li W, Dong X. (2014). Association of 677 C&gt; T (rs1801133) and 1298 A&gt; C (rs1801131) polymorphisms in the MTHFR gene and breast cancer susceptibility: A meta-analysis based on 57 individual studies. *PLoS One*, 9(6):e71290. doi: 10.1371/journal.pone.0071290. PMID: 24945727.
7. Liang H, Yan Y, Li T, Li R, Li M, Li S, Qin X. (2013). Methylenetetrahydrofolate reductase polymorphisms and breast cancer risk in Chinese population: A meta-analysis of 22 case-control studies. *Tumour Biol*. PMID: 24078451.
8. Jiao Z, Li D. (2013). Lack of association between MHTFR Glu429Ala polymorphism and breast cancer susceptibility: A systematic review and meta-analysis of 29 research studies. *Tumour Biol*, 34(2):1225-33. doi: 10.1007/s13277-013-0665-7. PMID: 23393023.
9. Babyshkina N, Malinovskaya E, Nazarenko M, Koval M, Gervas P, Potapova O, Slonimskaya E, Cherdyntseva N. (2013). The effect of folate-related SNPs on clinicopathological features, response to neoadjuvant treatment and survival in pre- and postmenopausal breast cancer patients. *Gene,* 518(2):397-404. doi: 10.1016/j.gene.2012.12.095. PMID: 23296054.
10. Yu L, Chen J. (2012). Association of MTHFR Ala222Val (rs1801133) polymorphism and breast cancer susceptibility: An update meta-analysis based on 51 research studies. *Diagn Pathol,* 7(7):171. doi: 10.1186/1746-1596-7-171. PMID: 23217001.
11. Vaĭner AS, Boiarskikh UA, Voronina EN, Selezneva IA, Sinkina TV, Lazarev AF, Petrova VD, Filipenko ML. (2010). [Polymorphic variants of folate metabolizing genes (C677T and A1298C MTHFR, C1420T SHMT1 and G1958A MTHFD) are not associated with the risk of breast cancer in West Siberian Region of Russia]. *Mol Biol (Mosk),* 44(5):816-23. Russian. PMID: 21090237.
12. Qiu LX, Zhang J, Li WH, Zhang QL, Yu H, Wang BY, Wang LP, Wang JL, Wang HJ, Liu XJ, Luo ZG, Wu XH. (2011). Lack of association between methylenetetrahydrofolate reductase gene A1298C polymorphism and breast cancer susceptibility. *Mol Biol Rep,* 38(4):2295-9. doi: 10.1007/s11033-010-0361-2. PMID: 21052845.
13. Zhang J, Qiu LX, Wang ZH, Wu XH, Liu XJ, Wang BY, Hu XC. (2010). MTHFR C677T polymorphism associated with breast cancer susceptibility: A meta-analysis involving 15,260 cases and 20,411 controls. *Breast Cancer Res Treat,* 123(2):549-55. doi: 10.1007/s10549-010-0783-5. PMID: 20143151.
14. Qi X, Ma X, Yang X, Fan L, Zhang Y, Zhang F, Chen L, Zhou Y, Jiang J. (2010). Methylenetetrahydrofolate reductase polymorphisms and breast cancer risk: A meta-analysis from 41 studies with 16,480 cases and 22,388 controls. *Breast Cancer Res Treat,* 123(2):499-506. doi: 10.1007/s10549-010-0773-7. PMID: 20135343.
15. Langsenlehner T, Renner W, Yazdani-Biuki B, Langsenlehner U. (2008). Methylenetetrahydrofolate reductase (MTHFR) and breast cancer risk: A nested-case-control study and a pooled meta-analysis. *Breast Cancer Res Treat,* 107(3):459-60. PMID: 17453338.
16. Lissowska J, Gaudet MM, Brinton LA, Chanock SJ, Peplonska B, Welch R, Zatonski W, Szeszenia-Dabrowska N, Park S, Sherman M, Garcia-Closas M. (2007). Genetic polymorphisms in the one-carbon metabolism pathway and breast cancer risk: A population-based case-control study and meta-analyses. *Int J Cancer,* 120(12):2696-703. PMID: 17311260.
17. Macis D, Maisonneuve P, Johansson H, Bonanni B, Botteri E, Iodice S, Santillo B, Penco S, Gucciardo G, D'Aiuto G, Rosselli Del Turco M, Amadori M, Costa A, Decensi A. (2007). Methylenetetrahydrofolate reductase (MTHFR) and breast cancer risk: a nested-case-control study and a pooled meta-analysis. *Breast Cancer Res Treat,* 106(2):263-71. PMID: 17260091.
18. Lewis SJ, Harbord RM, Harris R, Smith GD. (2006). Meta-analyses of observational and genetic association studies of folate intakes or levels and breast cancer risk. *J Natl Cancer Inst,* 98(22):1607-22. PMID: 17105984.
19. Zintzaras E. (2006). Methylenetetrahydrofolate reductase gene and susceptibility to breast cancer: A meta-analysis. *Clin Genet*, 69(4):327-36. PMID: 16630166.

4 Papers with Duplicate Use of Data on Gene Counts

1. Henríquez-Hernández LA, Pérez LF, Hernández AG, de León AC, Díaz-Chico B, Rosales AM. (2010). TYMS, MTHFR, p53 and MDR1 gene polymorphisms in breast cancer patients treated with adjuvant therapy. *Cancer Epidemiol,* 34(4):490-3. doi: 10.1016/j.canep.2010.03.004. PMID: 20371218.
2. Gao CM, Tang JH, Cao HX, Ding JH, Wu JZ, Wang J, Liu YT, Li SP, Su P, Matsuo K, Takezaki T, Tajima K. (2009). MTHFR polymorphisms, dietary folate intake and breast cancer risk in Chinese women. *J Hum Genet*, 54(7):414-8. doi: 10.1038/jhg.2009.57. PMID: 19557016.
3. Ericson UC, Ivarsson MI, Sonestedt E, Gullberg B, Carlson J, Olsson H, Wirfält E. (2009). Increased breast cancer risk at high plasma folate concentrations among women with the MTHFR 677T allele. *Am J Clin Nutr,* 90(5):1380-1389. doi: 10.3945/ajcn.2009.28064. PMID: 19759169.
4. Xu X, Gammon MD, Zhang H, Wetmur JG, Rao M, Teitelbaum SL, Britton JA, Neugut AI, Santella RM, Chen J. (2007). Polymorphisms of one-carbon-metabolizing genes and risk of breast cancer in a population-based study. *Carcinogenesis,* 28(7):1504-9. PMID: 17372271

82 Papers included in Meta-analysis

1. Awwad N, Yousef AM, Abuhaliema A, Abdalla I, Yousef M. (2015). [Relationship between Genetic Polymorphisms in MTHFR (C677T, A1298C and their Haplotypes) and the Incidence of Breast Cancer among Jordanian Females - Case-Control Study.](http://www.ncbi.nlm.nih.gov/pubmed/26163632) *Asian Pac J Cancer Prev,* 16(12):5007-11. PMID: 26163632.
2. Ramos-Silva A, Figuera LE, Soto-Quintana OM, Puebla-Pérez AM, Ramírez-Patiño R, Gutiérrez-Hurtado I, Carrillo-Moreno DI, Zúñiga-González GM, Dávalos-Rodríguez IP, Gallegos-Arreola MP. (2015). [Association of the C677T polymorphism in the methylenetetrahydrofolate reductase gene withbreast cancer in a Mexican population.](http://www.ncbi.nlm.nih.gov/pubmed/25966173) *Genet Mol Res.* 14(2):4015-26. doi: 10.4238/2015.April.27.16. PMID: 25966173.
3. Lin W, Cen YL, Lin Y, Su FX, Wu BH, Tang LY, Ren ZF. (2015). [Joint effects between urinary selenium and polymorphisms in methylation related genes on breast cancer risk.](http://www.ncbi.nlm.nih.gov/pubmed/25869796) *Neoplasma,* 62(3):491-9. doi: 10.4149/neo\_2015\_059. PMID: 25869796.
4. Pooja S, Carlus J, Sekhar D, Francis A, Gupta N, Konwar R, Kumar S, Kumar S, Thangaraj K, Rajender S. (2015). [MTHFR 677C&gt;T polymorphism and the risk of breast cancer: Evidence from an original study and pooled data for 28031 cases and 31880 controls.](http://www.ncbi.nlm.nih.gov/pubmed/25803740) *PLoS One,* 10(3):e0120654. doi: 10.1371/journal.pone.0120654. PMID: 25803740.
5. López-Cortés A, Echeverría C, Oña-Cisneros F, Sánchez ME, Herrera C, Cabrera-Andrade A, Rosales F, Ortiz M, Paz-Y-Miño C. (2015). [Breast cancer risk associated with gene expression and genotype polymorphisms of the folate- metabolizing MTHFR gene: A case-control study in a high altitude Ecuadorian mestizo population.](http://www.ncbi.nlm.nih.gov/pubmed/25801246) *Tumour Biol*, PMID: 25801246.
6. Kakkoura MG, Demetriou CA, Loizidou MA, Loucaides G, Neophytou I, Marcou Y, Hadjisavvas A, Kyriacou K. (2015). Single-nucleotide polymorphisms in one-carbon metabolism genes, Mediterranean diet and breast cancer risk: a case-control study in the Greek-Cypriot female population. *Genes Nutr*, 10(2):453. doi: 10.1007/s12263-015-0453-7. PMID:25604861.
7. Lu Q, Jiang K, Li Q, Ji YJ, Chen WL, Xue XH. (2015). Polymorphisms in the MTHFR gene are associated with breast cancer risk and prognosis in a Chinese population. *Tumour Biol*, PMID: 25566964.
8. He JM, Pu YD, Wu YJ, Qin R, Zhang QJ, Sun YS, Zheng WW, Chen LP. (2014). Association between dietary intake of folate and MTHFR and MTR genotype with risk of breast cancer. *Genet Mol Res*, 13(4):8925-31. doi: 10.4238/2014.October.31.7. PMID: 25366783.
9. Xi J, Su Y, Fadiel AB, Lin Y, Su FX, Jia WH, Tang LY, Ren ZF. (2014). Association of physical activity and polymorphisms in FGFR2 and DNA methylation related genes with breast cancer risk. *Cancer Epidemiol*, 38(6):708-14. doi: 10.1016/j.canep.2014.09.002. PMID: 25270516.
10. Jiang-Hua Q, De-Chuang J, Zhen-Duo L, Shu-de C, Zhenzhen L. (2014). Association of methylenetetrahydrofolate reductase and methionine synthase polymorphisms with breast cancer risk and interaction with folate, vitamin B6, and vitamin B 12 intakes. *Tumour Biol*, 35(12):11895-901. doi: 10.1007/s13277-014-2456-1. PMID: 25217320.
11. Wang ZG, Cui W, Yang LF, Zhu YQ, Wei WH. (2014). Association of dietary intake of folate and MTHFR genotype with breast cancer risk. *Genet Mol Res*, 13(3):5446-51. doi: 10.4238/2014.July.24.24. PMID: 25078601.
12. Huang CY, Chang WS, Shui HA, Hsieh YH, Loh CH, Wang HC, Ji HX, Hsiao CL, Hsu CM, Tsai CW, Bau DT. (2014). Evaluation of the contribution of methylenetetrahydrofolate reductase genotypes to Taiwan breast cancer. *Anticancer Res*, 34(8):4109-15. PMID: 25075036.
13. Weiwei Z, Liping C, Dequan L. Pak J. (2014). Association between dietary intake of folate, vitamin B6, B12 &amp; MTHFR, MTR Genotype and breast cancer risk. *Med Sci*, 30(1):106-10. doi: 10.12669/pjms.301.4189. PMID: 24639841.
14. Liu Y, Zhou LS, Xu XM, Deng LQ, Xiao QK. (2013). Association of Dietary Intake of Folate, Vitamin B6 and B12 and MTHFR Genotype with Breast Cancer Risk. *Asian Pac J Cancer Prev*,14(9):5189-92. PMID: 24175799.
15. Akilzhanova A, Nurkina Z, Momynaliev K, Ramanculov E, Zhumadilov Z, Rakhypbekov T, Hayashida N, Nakashima M, Takamura N. (2013). Genetic profile and determinants of homocysteine levels in Kazakhstan patients with breast cancer. *Anticancer Res,* 33(9):4049-59. PMID: 24023349.
16. Ozen F, Erdis E, Sik E, Silan F, Uludag A, Ozdemir O. (2013). Germ-line MTHFR C677T, FV H1299R and PAI-1 5G/4G Variations in Breast Carcinoma. *Asian Pac J Cancer Prev*, 14(5):2903-8. PMID: 23803051.
17. de Cássia Carvalho Barbosa R, da Costa DM, Cordeiro DE, Vieira AP, Rabenhorst SH. (2012). Interaction of MTHFR C677T and A1298C, and MTR A2756G gene polymorphisms in breast cancer risk in a population in Northeast Brazil. *Anticancer Res,* 32(11):4805-11. PMID: 23155246.
18. Diakite B, Tazzite A, Hamzi K, Jouhadi H, Nadifi S. (2012). Methylenetetrahydrofolate reductase C677T polymorphism and breast cancer risk in Moroccan women. *Afr Health Sci*, 12(2):204-9. doi: 10.4314/ahs.v12i2.20. PMID: 23056029.
19. Wu XY, Ni J, Xu WJ, Zhou T, Wang X. (2012). Interactions between MTHFR C677T-A1298C variants and folic acid deficiency affect breast cancer risk in a Chinese population. *Asian Pac J Cancer Prev,* 13(5):2199-206. PMID: 22901194.
20. Akram M, Malik FA, Kayani MA. (2012). Mutational analysis of the MTHFR gene in breast cancer patients of Pakistani population. *Asian Pac J Cancer Prev,* 13(4):1599-603. PMID: 22799374.
21. Jakubowska A, Rozkrut D, Antoniou A, Hamann U, Scott RJ, McGuffog L, et al. (2012). Association of PHB 1630 C&gt; T and MTHFR 677 C&gt; T polymorphisms with breast and ovarian cancer risk in BRCA1/2 mutation carriers: Results from a multicenter study.

*Br J Cancer,* 106(12):2016-24. doi: 10.1038/bjc.2012.160. PMID: 22669161.

1. Lajin B, Alhaj Sakur A, Ghabreau L, Alachkar A. (2012). Association of polymorphisms in one-carbon metabolizing genes with breast cancer risk in Syrian women. *Tumour Biol*, 33(4):1133-9. doi: 10.1007/s13277-012-0354-y. PMID: 22373582.
2. Hosseini M, Houshmand M, Ebrahimi A. (2011). MTHFR polymorphisms and breast cancer risk. *Arch Med Sci,* 7(1):134-7. doi: 10.5114/aoms.2011.20618. PMID: 22291746.
3. Carvalho Barbosa Rde C, Menezes DC, Freire TF, Sales DC, Alencar VH, Rabenhorst SH. (2012). Associations of polymorphisms of folate cycle enzymes and risk of breast cancer in a Brazilian population are age dependent. *Mol Biol Rep,* 39(4):4899-907. doi: 10.1007/s11033-011-1285-1. PMID: 22134752.
4. Prasad VV, Wilkhoo H. (2011). Association of the functional polymorphism C677T in the methylenetetrahydrofolate reductase gene with colorectal, thyroid, breast, ovarian, and cervical cancers. *Onkologie*, 34(8-9):422-6. doi: 10.1159/000331131. PMID: 21934341.
5. Papandreou CN, Doxani C, Zdoukopoulos N, Vlachostergios PJ, Hatzidaki E, Bakalos G, Ziogas DC, Koufakis T, Zintzaras E. (2012). Evidence of association between methylenetetrahydrofolate reductase gene and susceptibility to breast cancer: A candidate-gene association study in a South-eastern European population. *DNA Cell Biol*, 31(2):193-8. doi: 10.1089/dna.2011.1292. PMID: 21875371.
6. Batschauer AP, Cruz NG, Oliveira VC, Coelho FF, Santos IR, Alves MT, Fernandes AP, Carvalho MG, Gomes KB. (2011). HFE, MTHFR, and FGFR4 genes polymorphisms and breast cancer in Brazilian women. *Mol Cell Biochem*, 357(1-2):247-53. doi: 10.1007/s11010-011-0895-1. PMID: 21625954.
7. Ziva Cerne J, Stegel V, Gersak K, Novakovic S. (2011). Lack of association between methylenetetrahydrofolate reductase genetic polymorphisms and postmenopausal breast cancer risk. *Mol Med Rep*, 4(1):175-9. doi: 10.3892/mmr.2010.406. PMID: 21461582.
8. Naushad SM, Pavani A, Digumarti RR, Gottumukkala SR, Kutala VK. (2011). Epistatic interactions between loci of one-carbon metabolism modulate susceptibility to breast cancer. *Mol Biol Rep*, 38(8):4893-901. doi: 10.1007/s11033-010-0631-z. PMID: 21161404.
9. Mohammad NS, Yedluri R, Addepalli P, Gottumukkala SR, Digumarti RR, Kutala VK. (2011). Aberrations in one-carbon metabolism induce oxidative DNA damage in sporadic breast cancer. *Mol Cell Biochem*, 349(1-2):159-67. doi: 10.1007/s11010-010-0670-8. PMID: 21113649.
10. Hua Z, Wang Y, Ni J, Ge F, Zou T. (2011). Serum folate, vitamin b12 concentration and mthfr, ms gene polymorphism associated with risk of breast cancer research. *Mod Oncol*, 19:428–31.
11. Vaĭner AS, Boiarskikh UA, Voronina EN, Selezneva IA, Sinkina TV, Lazarev AF, Petrova VD, Filipenko ML. (2010). [Polymorphic variants of folate metabolizing genes (C677T and A1298C MTHFR, C1420T SHMT1 and G1958A MTHFD) are not associated with the risk of breast cancer in West Siberian Region of Russia]. *Mol Biol (Mosk),* 44(5):816-23. Russian. PMID: 21090237.
12. Alshatwi AA. (2010). Breast cancer risk, dietary intake, and methylenetetrahydrofolate reductase (MTHFR) single nucleotide polymorphisms. *Food Chem Toxicol*, 48(7):1881-5. doi: 10.1016/j.fct.2010.04.028. PMID: 20417243.
13. Sangrajrang S, Sato Y, Sakamoto H, Ohnami S, Khuhaprema T, Yoshida T. (2010). Genetic polymorphisms in folate and alcohol metabolism and breast cancer risk: A case-control study in Thai women. *Breast Cancer Res Treat*, 123(3):885-93. doi: 10.1007/s10549-010-0804-4. PMID: 20180013.
14. Maruti SS, Ulrich CM, Jupe ER, White E. (2009). MTHFR C677T and postmenopausal breast cancer risk by intakes of one-carbon metabolism nutrients: A nested case-control study. *Breast Cancer Res*, 11(6):R91. doi: 10.1186/bcr2462. PMID: 20030812.
15. Gao CM, Kazuo T, Tang JH, Cao HX, Ding JH, Wu JZ, Wang J, Liu YT, Li SP, Su P, Keitaro M, Toshiro T. Zhonghua Yu Fang Yi Xue Za Zhi. (2009). [MTHFR polymorphisms, dietary folate intake and risks to breast cancer]. *J Human Genetics,* 43(7):576-80. Chinese. PMID: 19954067.
16. Henríquez-Hernández LA, Murias-Rosales A, Hernández González A, Cabrera De León A, Díaz-Chico BN, Mori De Santiago M, Fernández Pérez L. (2009). Gene polymorphisms in TYMS, MTHFR, p53 and MDR1 as risk factors for breast cancer: A case-control study. *Oncol Rep,* 22(6):1425-33. PMID: 19885596.
17. Ferroni P, Palmirotta R, Martini F, Riondino S, Savonarola A, Spila A, Ciatti F, Sini V, Mariotti S, Del Monte G, Roselli M, Guadagni F. (2009). Determinants of homocysteine levels in colorectal and breast cancer patients. *Anticancer Res*. 29(10):4131-8. PMID: 19846961.
18. Ma E, Iwasaki M, Kobayashi M, Kasuga Y, Yokoyama S, Onuma H, Nishimura H, Kusama R, Tsugane S. (2009). Dietary intake of folate, vitamin B2, vitamin B6, vitamin B12, genetic polymorphism of related enzymes, and risk of breast cancer: a case-control study in Japan. *Nutr Cancer*, 61(4):447-56. doi: 10.1080/01635580802610123. PMID: 19838916.
19. Bentley AR, Raiszadeh F, Stover PJ, Hunter DJ, Hankinson SE, Cassano PA. (2010). No association between cSHMT genotypes and the risk of breast cancer in the Nurses' Health Study. *Eur J Clin Nutr*, 64(1):108-10. doi: 10.1038/ejcn.2009.104. PMID: 19707223.
20. Platek ME, Shields PG, Marian C, McCann SE, Bonner MR, Nie J, Ambrosone CB, Millen AE, Ochs-Balcom HM, Quick SK, Trevisan M, Russell M, Nochajski TH, Edge SB, Freudenheim JL. (2009). Alcohol consumption and genetic variation in methylenetetrahydrofolate reductase and 5-methyltetrahydrofolate-homocysteine methyltransferase in relation to breast cancer risk. *Cancer Epidemiol Biomarkers Prev*, 18(9):2453-9. doi: 10.1158/1055-9965.EPI-09-0159. PMID: 19706843.
21. Ma E, Iwasaki M, Junko I, Hamada GS, Nishimoto IN, Carvalho SM, Motola J Jr, Laginha FM, Tsugane S. (2009). Dietary intake of folate, vitamin B6, and vitamin B12, genetic polymorphism of related enzymes, and risk of breast cancer: A case-control study in Brazilian women. *BMC Cancer*, 9:122. doi: 10.1186/1471-2407-9-122. PMID: 19389261.
22. Ericson U, Sonestedt E, Ivarsson MI, Gullberg B, Carlson J, Olsson H, Wirfält E. (2009). Folate intake, methylenetetrahydrofolate reductase polymorphisms, and breast cancer risk in women from the Malmö Diet and Cancer cohort. *Cancer Epidemiol Biomarkers Prev*, 18(4):1101-10. doi: 10.1158/1055-9965.EPI-08-0401. PMID: 19336565.
23. Tao MH, Shields PG, Nie J, Marian C, Ambrosone CB, McCann SE, Platek M, Krishnan SS, Xie B, Edge SB, Winston J, Vito D, Trevisan M, Freudenheim JL. (2009). DNA promoter methylation in breast tumors: no association with genetic polymorphisms in MTHFR and MTR. *Cancer Epidemiol Biomarkers Prev*, 18(3):998-1002. doi: 10.1158/1055-9965.EPI-08-0916. PMID: 19240236.
24. Li WD, Chen SQ. (2009). Association of methylenetetrahydrofolate reductase C677T polymorphism and breast cancer risk. *J Prac Med*, 25:2031–2033.
25. Yuan H, Xu XY, Wang ZL. (2009). The relation between polymorphisms of methylenetetrahydrofolate reductase C677T and the risk of breast cancer. *J MuDanJiang Med Univ,* 30:2–4.
26. Jin ZZ, Lu Q, Ge DH, Zong M, Zhu QH. (2009). Effect of the methylenetetrahydrofolate reductase gene C677T polymorphism on C-erbB-2 methylation status and its association with cancer. *Mol Med Rep,* 2:283–289.
27. Beetstra S, Suthers G, Dhillon V, Salisbury C, Turner J, Altree M, McKinnon R, Fenech M. (2008). Methionine-dependence phenotype in the de novo pathway in BRCA1 and BRCA2 mutation carriers with and without breast cancer. *Cancer Epidemiol Biomarkers Prev,* 17(10):2565-71. doi: 10.1158/1055-9965.EPI-08-0140. PMID: 18842997.
28. Inoue M, Robien K, Wang R, Van Den Berg DJ, Koh WP, Yu MC. (2008). Green tea intake, MTHFR/TYMS genotype and breast cancer risk: The Singapore Chinese Health Study. *Carcinogenesis*, 29(10):1967-72. doi: 10.1093/carcin/bgn177. PMID: 18669903.
29. Cam R, Eroglu A, Egin Y, Akar N. (2009). Dihydrofolate reductase (DHRF) 19-bp intron-1 deletion and methylenetetrahydrofolate reductase (MTHFR) C677T polymorphisms in breast cancer. *Breast Cancer Res Treat*, 115(2):431-2. doi: 10.1007/s10549-008-0054-x. PMID: 18498051.
30. Kotsopoulos J, Zhang WW, Zhang S, McCready D, Trudeau M, Zhang P, Sun P, Narod SA. (2008). Polymorphisms in folate metabolizing enzymes and transport proteins and the risk of breast cancer. *Breast Cancer Res Treat*, 112(3):585-93. doi: 10.1007/s10549-008-9895-6. PMID: 18204969.
31. Suzuki T, Matsuo K, Hirose K, Hiraki A, Kawase T, Watanabe M, Yamashita T, Iwata H, Tajima K. (2008). One-carbon metabolism-related gene polymorphisms and risk of breast cancer. *Carcinogenesis*, 29(2):356-62. doi: 10.1093/carcin/bgm295. PMID: 18174236.
32. Mir MM, Dar JA, Dar NA, Dar MS, Salam I, Lone MM, Chowdary NA. (2008). Combined impact of polymorphism of folate metabolism genes; glutamate carboxypeptidase, methylene tetrahydrofolate reductase and methionine synthase reductase on breast cancer susceptibility in kashmiri women. *Int J Health Sci (Qassim),* 2(1):3-14. PMID: 21475466.
33. Cheng CW, Yu JC, Huang CS, Shieh JC, Fu YP, Wang HW, Wu PE, Shen CY. (2008). Polymorphism of cytosolic serine hydroxymethyltransferase, estrogen and breast cancer risk among Chinese women in Taiwan. *Breast Cancer Res Treat*, 111(1):145-55. PMID: 17896178.
34. Langsenlehner T, Renner W, Yazdani-Biuki B, Langsenlehner U. (2008). Methylenetetrahydrofolate reductase (MTHFR) and breast cancer risk: A nested-case-control study and a pooled meta-analysis. *Breast Cancer Res Treat*, 107(3):459-60. PMID: 17453338.
35. Yu CP, Wu MH, Chou YC, Yang T, You SL, Chen CJ, Sun CA. (2007). Breast cancer risk associated with multigenotypic polymorphisms in folate-metabolizing genes: A nested case-control study in Taiwan. *Anticancer Res*, 27(3B):1727-32. PMID: 17595805.
36. Reljic A, Simundic AM, Topic E, Nikolac N, Justinic D, Stefanovic M. (2007). The methylenetetrahydrofolate reductase (MTHFR) C677T polymorphism and cancer risk: The Croatian case-control study. *Clin Biochem*, 40(13-14):981-5. PMID: 17573062.
37. Stevens VL, McCullough ML, Pavluck AL, Talbot JT, Feigelson HS, Thun MJ, Calle EE. (2007). Association of polymorphisms in one-carbon metabolism genes and postmenopausal breast cancer incidence. *Cancer Epidemiol Biomarkers Prev*, 16(6):1140-7. PMID: 17548676.
38. Guillem VM, Collado M, Terol MJ, Calasanz MJ, Esteve J, Gonzalez M, Sanzo C, Nomdedeu J, Bolufer P, Lluch A, Tormo M. (2007). Role of MTHFR (677, 1298) haplotype in the risk of developing secondary leukemia after treatment of breast cancer and hematological malignancies. *Leukemia,* 21(7):1413-22. PMID: 17476281.
39. Lissowska J, Gaudet MM, Brinton LA, Chanock SJ, Peplonska B, Welch R, Zatonski W, Szeszenia-Dabrowska N, Park S, Sherman M, Garcia-Closas M. (2007). Genetic polymorphisms in the one-carbon metabolism pathway and breast cancer risk: A population-based case-control study and meta-analyses. *Int J Cancer*, 120(12):2696-703. PMID: 17311260.
40. Macis D, Maisonneuve P, Johansson H, Bonanni B, Botteri E, Iodice S, Santillo B, Penco S, Gucciardo G, D'Aiuto G, Rosselli Del Turco M, Amadori M, Costa A, Decensi A. (2007). Methylenetetrahydrofolate reductase (MTHFR) and breast cancer risk: A nested-case-control study and a pooled meta-analysis. *Breast Cancer Res Treat*, 106(2):263-71. PMID: 17260091.
41. Jakubowska A, Gronwald J, Menkiszak J, Górski B, Huzarski T, Byrski T, Edler L, Lubiński J, Scott RJ, Hamann U. (2007). Methylenetetrahydrofolate reductase polymorphisms modify BRCA1-associated breast and ovarian cancer risks. *Breast Cancer Res Treat,* 104(3):299-308. PMID: 17063264.
42. Hekim N, Ergen A, Yaylim I, Yilmaz H, Zeybek U, Oztürk O, Isbir T. (2007). No association between methylenetetrahydrofolate reductase C677T polymorphism and breast cancer. *Cell Biochem Funct*, 25(1):115-7. PMID: 16134079.
43. Kan XX, Zou TN, Wu XY, Wang X. (2007). Association between mTHFR genotype polymorphism and breast cancer susceptibility in human population from Yunnan. *Cancer Res Prev Treat,* 34:716–718.
44. Chou YC, Wu MH, Yu JC, Lee MS, Yang T, Shih HL, Wu TY, Sun CA. (2006). Genetic polymorphisms of the methylenetetrahydrofolate reductase gene, plasma folate levels and breast cancer susceptibility: a case-control study in Taiwan. *Carcinogenesis*, 27(11):2295-300. PMID: 16777985.
45. Kalyankumar Ch, Jamil K. (2006). Methylene tetrahydofolate reductase (MTHFR) C677T and A1298C polymorphisms and breast cancer in South Indian population. *Int J Cancer Res,* 2:143–151.
46. Justenhoven C, Hamann U, Pierl CB, Rabstein S, Pesch B, Harth V, Baisch C, Vollmert C, Illig T, Brüning T, Ko Y, Brauch H. (2005). One-carbon metabolism and breast cancer risk: no association of MTHFR, MTR, and TYMS polymorphisms in the GENICA study from Germany. *Cancer Epidemiol Biomarkers Prev*, 14(12):3015-8. PMID: 16365030.
47. Deligezer U, Akisik EE, Dalay N. (2005). Homozygosity at the C677T of the MTHFR gene is associated with increased breast cancer risk in the Turkish population. *In Vivo*, 19(5):889-93. PMID: 16097444.
48. Kalemi TG, Lambropoulos AF, Gueorguiev M, Chrisafi S, Papazisis KT, Kotsis A. (2005). The association of p53 mutations and p53 codon 72, Her 2 codon 655 and MTHFR C677T polymorphisms with breast cancer in Northern Greece. *Cancer Lett*, 10; 222(1):57-65. PMID: 15837541.
49. Chen J, Gammon MD, Chan W, Palomeque C, Wetmur JG, Kabat GC, Teitelbaum SL, Britton JA, Terry MB, Neugut AI, Santella RM. (2005). One-carbon metabolism, MTHFR polymorphisms, and risk of breast cancer. *Cancer Res*, 15; 65(4):1606-14. PMID: 15735051.
50. Lin WY, Chou YC, Wu MH, Huang HB, Jeng YL, Wu CC, Yu CP, Yu JC, You SL, Chu TY, Chen CJ, Sun CA. (2004). The MTHFR C677T polymorphism, estrogen exposure and breast cancer risk: a nested case-control study in Taiwan. *Anticancer Res,* 24(6):3863-8. PMID: 15736423.
51. Le Marchand L, Haiman CA, Wilkens LR, Kolonel LN, Henderson BE. (2004). MTHFR polymorphisms, diet, HRT, and breast cancer risk: The multiethnic cohort study. *Cancer Epidemiol Biomarkers Prev,* 13(12):2071-7. PMID: 15598763.
52. Grieu F, Powell B, Beilby J, Iacopetta B. (2004). Methylenetetrahydrofolate reductase and thymidylate synthase polymorphisms are not associated with breast cancer risk or phenotype. *Anticancer Res,* 24(5B):3215-9. PMID: 15510613.
53. Qi J, Miao XP, Tan W, Yu CY, Liang G, Lü WF, Lin DX. (2004). [Association between genetic polymorphisms in methylenetetrahydrofolate reductase and risk of breast cancer]. *Zhonghua Zhong Liu Za Zhi,* 26(5):287-9. Chinese. PMID: 15312365.
54. Lee SA, Kang D, Nishio H, Lee MJ, Kim DH, Han W, Yoo KY, Ahn SH, Choe KJ, Hirvonen A, Noh DY. (2004). Methylenetetrahydrofolate reductase polymorphism, diet, and breast cancer in Korean women. *Exp Mol Med*, 36(2):116-21. PMID: 15150439.
55. Försti A, Angelini S, Festa F, Sanyal S, Zhang Z, Grzybowska E, Pamula J, Pekala W, Zientek H, Hemminki K, Kumar R. (2004). Single nucleotide polymorphisms in breast cancer. *Oncol Rep*, 11(4):917-22. PMID: 15010895.
56. Shrubsole MJ, Gao YT, Cai Q, Shu XO, Dai Q, Hébert JR, Jin F, Zheng W. (2004). MTHFR polymorphisms, dietary folate intake, and breast cancer risk: Results from the Shanghai Breast Cancer Study. *Cancer Epidemiol Biomarkers Prev*, 13(2):190-6. PMID: 14973091.
57. Ergul E, Sazci A, Utkan Z, Canturk NZ. (2003). Polymorphisms in the MTHFR gene are associated with breast cancer. *Tumour Biol*, 24(6):286-90. PMID: 15004488.
58. Langsenlehner U, Krippl P, Renner W, Yazdani-Biuki B, Wolf G, Wascher TC, Paulweber B, Weitzer W, Samonigg H. (2003). The common 677C&gt; T gene polymorphism of methylenetetrahydrofolate reductase gene is not associated with breast cancer risk. *Breast Cancer Res Treat,* 81(2):169-72. PMID: 14572159.
59. Semenza JC, Delfino RJ, Ziogas A, Anton-Culver H. (2003). Breast cancer risk and methylenetetrahydrofolate reductase polymorphism. *Breast Cancer Res Treat*, 77(3):217-23. PMID: 12602921.
60. Campbell IG, Baxter SW, Eccles DM, Choong DY. (2002). Methylenetetrahydrofolate reductase polymorphism and susceptibility to breast cancer. *Breast Cancer Res*, 4(6):R14. PMID: 12473175.
61. Sharp L, Little J, Schofield AC, Pavlidou E, Cotton SC, Miedzybrodzka Z, Baird JO, Haites NE, Heys SD, Grubb DA. (2002). Folate and breast cancer: the role of polymorphisms in methylenetetrahydrofolate reductase (MTHFR). *Cancer Lett*, 181(1):65-71. PMID: 12430180.