**Title: Aspirin use and common cancer risk: a meta-analysis of cohort studies and randomized controlled trials**

**Supplementary Box 1. Credibility assessment criteria for meta-analyses of cohort studies and randomized controlled trials.**

|  |  |
| --- | --- |
| **Evidence class**  | **Classification criteria**  |
| Convincing (class I) | Associations with *P*<10-6; more than 1,000 cases having the event of interest (or more than 20,000 participants for continuous outcomes); the largest component study reporting a nominal statistically significant result (*P*<0.05); a 95% prediction interval that excluded the null; no large heterogeneity (I2<50%); no evidence of small study effect (*P*>0.10); no excess significance bias (*P*>0.10). |
| Highly suggestive(class II) | Associations with *P*<10-6, more than 1,000 cases (or more than 20,000 participants for continuous outcomes) and the largest component study reporting a statistically significant result (*P*<0.05).  |
| Suggestive (class III) | Associations with *P*<10-3 and more than 1,000 cases (or more than 20,000 participants for continuous outcomes). |
| Weak (class IV) | Remaining statistically significant associations with *P*<0.05. |

**Supplementary Table 1. Search strategy.**

|  |  |
| --- | --- |
| **Search strategy** | **Databases: Ovid Medline(R), EMBASE****Last update:16 Oct 2020****Search limit: Humans**  |
| 1. Aspirin terms
 | (Aspirin OR Aspirins OR “Acetyl Salicylic Acid” OR ASA OR “Acetylsalicylic Acid” OR Acetylsalicylic OR acetylsalicylate OR “salicylic acid” OR salicylate OR “2-(Acetyloxy)benzoic Acid” OR “2-Acetoxybenzoic Acid” OR “o-Acetylsalicylic Acid” OR “o-Acetoxybenzoic Acid” OR Acylpyrin OR Aloxiprimum OR Colfarit OR Dispril OR Easprin OR Ecotrin OR Endosprin OR Magnecyl OR Micristin OR Polopirin OR Polopiryna OR Solprin OR Solupsan OR Zorprin OR Acetysal).mp |
| 1. Cancer terms
 | (cancer OR cancers OR neoplasm OR neoplasms).mp |
| 1. Combination
 | 1 AND 2 |

**Supplementary Table 2. Basic characteristics and main findings for each study.**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Author, Year** | **Outcome** | **Population** | **Aspirin use** | **Events** | **Participants** | **Metric** | **Effect size (95% CI)** |
| Paganini-Hill et al, 1989(1) | CRC | General | Regular use | 153 | 11767 | RR | 1.50 (1.10-2.20) |
| CRC | General | Daily use | 153 | 11767 | RR | 1.50 (1.10-2.20) |
| Giovannucci et al, 1994(2) | CRC | Men | Regular use | 251 | 48084 | RR | 0.68 (0.52-0.92) |
| Stürmer et al, 1998(3) | CRC | Men | Regular use | 341 | 22071 | RR | 1.03 (0.83-1.28) |
| Larsson et al, 2006(4) | CRC | General | Regular use | 705 | 74250 | RR | 0.87 (0.75-1.01) |
| CRC | General | Daily use | 487 | 74024 | RR | 0.77 (0.59-0.99) |
| CRC | General | ≥ 5 yrs | 444 | 73981 | RR | 0.75 (0.58-0.99) |
| Mahipal et al, 2006(5) | CRC | Women | Regular use | 239 | 7844 | HR | 0.79 (0.59-1.04) |
| CRC | Women | Daily use | 255 | 6345 | HR | 0.76 (0.58-1.00) |
| Jacobs et al, 2007(6) | CRC | General | Regular use | 672 | 51407 | RR | 0.85 (0.72-1.00) |
| CRC | General | Daily use | 672 | 51407 | RR | 0.85 (0.72-1.00) |
| CRC | General | ≥ 5 yrs | 480 | 36193 | RR | 0.68 (0.52-0.90) |
| Siemes et al, 2008(7) | CRC | General | Regular use | 124 | 7621 | HR | 0.51 (0.34-0.77) |
| Friis et al, 2009(8) | CRC | General | Regular use | 504 | 47774 | RR | 0.87 (0.64-1.18) |
| CRC | General | Daily use | 482 | 47752 | RR | 0.73 (0.49-1.10) |
| Ruder et al, 2011(9) | CRC | General | Regular use | 3880 | 301240 | HR | 0.91 (0.85-0.98) |
| CRC | General | Daily use | 2072 | 301240 | HR | 0.86 (0.79-0.94) |
| Hollestein et al, 2014(10) | CRC | General | Regular use | 972 | 109276 | HR | 1.02 (0.98-1.06) |
| CRC | General | Daily use | 972 | 109276 | HR | 1.02 (0.98-1.06) |
| CRC | General | ≥ 5 yrs | 96 | 14612 | HR | 1.32 (0.96-1.80) |
| Lin et al, 2015(11) | CRC | General | Regular use | 277 | 60828 | HR | 0.32 (0.20-0.50) |
| CRC | General | Daily use | 335 | 47382 | HR | 0.32 (0.20-0.50) |
| CRC | General | ≥ 5 yrs | 25 | 37929 | HR | 0.32 (0.20-0.50) |
| Cao et al, 2016(12) | CRC | General | Regular use | 2895 | 135965 | RR | 0.81 (0.75-0.88) |
| Park et al, 2017(13) | CRC | General | Regular use | 3100 | 183199 | HR | 0.88 (0.67-1.16) |
| CRC | General | ≥ 5 yrs | 2547 | 183199 | HR | 0.79 (0.61-1.02) |
| Kuo et al, 2018(14) | CRC | General | Regular use | 62691 | 125327 | OR | 0.94 (0.90-0.99) |
| CRC | General | Daily use | 52299 | 104497 | OR | 0.89 (0.83-0.97) |
| Tsoi et al, 2018(15) | CRC | General | Regular use | 18454 | 612509 | OR | 0.76 (0.74-0.79) |
| CRC mortality | General | Pre-diagnostic | 9026 | 612509 | OR | 0.51 (0.49-0.54) |
| Cea Soriano et al, 2019(16) | CRC | General | Regular use | 3033 | 13033 | RR | 0.66 (0.60-0.73) |
| Rodríguez-Miguel et al, 2019(17) | CRC | General | Regular use | 15491 | 75491 | OR | 1.00 (0.88-1.13) |
| Troelsen et al, 2020(18) | CRC | General | Regular use | 13509 | 1648762 | RR | 0.91 (0.82-1.00) |
| CRC | General | ≥ 5 yrs | 13509 | 1648762 | RR | 0.91 (0.82-1.00) |
| Ratnasinghe et al, 2004(19) | CRC mortality | General | Pre-diagnostic | 193 | 22834 | RR | 1.07 (0.71-1.60) |
| Chan et al, 2009(20) | CRC mortality | General | Post-diagnostic | 222 | 1279 | RR | 0.71 (0.53-0.95) |
| Coghill et al, 2010(21) | CRC mortality | General | Pre-diagnostic | 316 | 1549 | RR | 0.75 (0.56-1.00) |
| CRC mortality | General | Post-diagnostic | 334 | 1549 | RR | 0.77 (0.59-1.00) |
| McCowan et al, 2012(22) | CRC mortality | General | Pre-diagnostic | 1047 | 3016 | RR | 0.96 (0.84-1.11) |
| CRC mortality | General | Post-diagnostic | 951 | 2920 | RR | 0.58 (0.45-0.75) |
| Cardwell et al, 2014(23) | CRC mortality | General | Post-diagnostic | 1559 | 9089 | RR | 0.98 (0.82-1.19) |
| Goh et al, 2014(24) | CRC mortality | General | Post-diagnostic | 181 | 726 | RR | 0.71 (0.43-1.16) |
| Bains et al, 2016(25) | CRC mortality | General | Post-diagnostic | 6533 | 23162 | RR | 1.00 (0.87-1.14) |
| Gray et al, 2018(26) | CRC mortality | General | Pre-diagnostic | 3655 | 10408 | RR | 0.96 (0.88-1.05) |
| CRC mortality | General | Post-diagnostic | 1064 | 8391 | RR | 1.10 (0.94-1.29) |
| Ventura et al, 2018(27) | CRC mortality | General | Post-diagnostic | 308 | 101098 | RR | 0.71 (0.52-0.97) |
| Loomans-Kropp et al, 2019(28) | CRC mortality | General | Pre-diagnostic | 193 | 60844 | RR | 0.62 (0.46-0.85) |
| Thun et al, 1993(29) | Gastric cancer | General | Regular use | 169 | 635031 | RR | 0.60 (0.42-0.85) |
| Ratnasinghe et al, 2004(19) | Gastric cancer | General | Regular use | 48 | 22834 | RR | 0.82 (0.38-1.81) |
| Abnet et al, 2009(30) | Gastric cancer | General | Regular use | 360 | 311115 | HR | 0.57 (0.39-0.85) |
| Epplein et al, 2009(31) | Gastric cancer | General | Regular use | 430 | 169292 | HR | 0.73 (0.61-0.89) |
| Gastric cancer | General | ≥ 5 yrs | 309 | 169171 | HR | 0.68 (0.50-0.93) |
| Hollestein et al, 2014(10) | Gastric cancer | General | Regular use | 268 | 109276 | HR | 0.95 (0.88-1.01) |
| Gastric cancer | General | Daily use | 268 | 109276 | HR | 0.95 (0.88-1.01) |
| Gastric cancer | General | ≥ 5 yrs | 28 | 109276 | HR | 0.88 (0.51-1.51) |
| Cao et al, 2016(12) | Gastric cancer | General | Regular use | 451 | 135965 | HR | 0.85 (0.70-1.03) |
| Spence et al, 2018(32) | Gastric cancer | General | Regular use | 2391 | 4654 | HR | 0.96 (0.85-1.08) |
| Kim et al, 2018(33) | Gastric cancer | General | Regular use | 4520 | 375039 | HR | 0.63 (0.48-0.83) |
| Gastric cancer | General | Daily use | 4520 | 379559 | HR | 0.63 (0.48-0.83) |
| Tsoi et al, 2019(34) | Gastric cancer | General | Regular use | 5827 | 612509 | RR | 0.42 (0.38-0.46) |
| Gastric cancer | General | ≥ 5 yrs | 5827 | 612509 | RR | 0.42 (0.38-0.46) |
| Garcia Rodriguez et al, 2020(35) | Gastric cancer | General | Regular use | 469 | 3079 | OR | 0.46 (0.38-0.57) |
| Friedman et al, 1980(36) | Breast cancer | Women | Regular use | NA | NA | RR | 0.20 (0.05-0.80) |
| Breast cancer | Women | Daily use | NA | NA | RR | 0.20 (0.05-0.80) |
| Paganini-Hill et al, 1989(1) | Breast cancer | Women | Regular use | 181 | 7220 | RR | 0.96 (0.73-1.25) |
| Breast cancer | Women | Daily use | 181 | 7401 | RR | 0.96 (0.73-1.25) |
| Harris et al, 1999(37) | Breast cancer | Women | Regular use | 276 | 19776 | RR | 0.57 (0.40-0.81) |
| Breast cancer | Women | Daily use | 280 | 19719 | RR | 0.64 (0.45-0.90) |
| Ratnasinghe et al, 2004(19) | Breast cancer | Women | Regular use | 131 | 12834 | RR | 0.82 (0.49-1.36) |
| Marshall et al, 2005(38) | Breast cancer | Women | Regular use | 2391 | 114640 | RR | 1.02 (0.80-1.31) |
| Breast cancer | Women | Daily use | NA | NA | RR | 0.98 (0.86-1.13) |
| Breast cancer | Women | ≥ 5 yrs | NA | NA | RR | 1.07 (0.96-1.20) |
| Gallicchio et al, 2007(39) | Breast cancer | Women | Regular use | 253 | 15651 | RR | 0.93 (0.61-1.41) |
| Gill et al, 2007(40) | Breast cancer | Women | Regular use | 914 | 54592 | HR | 1.01 (0.79-1.30) |
| Breast cancer | Women | ≥ 5 yrs | 1005 | 59466 | HR | 1.05 (0.88-1.25) |
| Jacobs et al, 2007(6) | Breast cancer | Women | Regular use | 835 | 50735 | RR | 1.02 (0.88-1.19) |
| Breast cancer | Women | Daily use | 835 | 25661 | RR | 1.02 (0.88-1.19) |
| Breast cancer | Women | ≥ 5 yrs | 626 | 18338 | RR | 0.83 (0.63-1.10) |
| Friis et al, 2008(41) | Breast cancer | Women | Regular use | 287 | 24439 | RR | 1.23 (0.89-1.72) |
| Breast cancer | Women | Daily use | 493 | 24439 | RR | 1.22 (0.80-1.70) |
| Gierach et al, 2008(42) | Breast cancer | Women | Regular use | 1752 | 124372 | RR | 0.97 (0.88-1.07) |
| Breast cancer | Women | Daily use | 774 | 126124 | RR | 0.93 (0.85-1.01) |
| Ready et al, 2008(43) | Breast cancer | Women | Regular use | 479 | 37676 | HR | 0.99 (0.80-1.23) |
| Breast cancer | Women | ≥ 5 yrs | 411 | 31756 | HR | 0.90 (0.64-1.27) |
| Siemes et al, 2008(7) | Breast cancer | Women | Regular use | 89 | 4560 | HR | 1.05 (0.65-1.71) |
| Eliassen et al, 2009(44) | Breast cancer | Women | Regular use | 1002 | 111290 | RR | 1.07 (0.89-1.29) |
| Breast cancer | Women | ≥ 5 yrs | 895 | 111290 | RR | 1.26 (0.88-1.80) |
| Bardia et al, 2011(45) | Breast cancer | Women | Regular use | 1581 | 14504 | RR | 0.80 (0.71-0.90) |
| Breast cancer | Women | Daily use | 778 | 14504 | RR | 0.71 (0.60-0.83) |
| Bosco et al, 2011(46) | Breast cancer | Women | Regular use | 1275 | 50226 | RR | 0.90 (0.75-1.07) |
| Breast cancer | Women | ≥ 5 yrs | 1170 | 50226 | RR | 0.78 (0.58-1.05) |
| Brasky et al, 2014(47) | Breast cancer | Women | Regular use | 3626 | 93272 | HR | 1.11 (1.00-1.24) |
| Breast cancer | Women | ≥ 5 yrs | 3213 | 83985 | HR | 1.05 (0.89-1.23) |
| Hollestein et al, 2014(10) | Breast cancer | Women | Regular use | 585 | 55597 | HR | 1.02 (0.97-1.08) |
| Breast cancer | Women | Daily use | 585 | 55597 | HR | 1.02 (0.97-1.08) |
| Breast cancer | Women | ≥ 5 yrs | 37 | 55597 | HR | 1.18 (0.76-1.82) |
| Kim et al, 2015(48) | Breast cancer | Women | Regular use | 1554 | 50883 | HR | 0.87 (0.68-1.13) |
| Breast cancer | Women | Daily use | 1964 | 50883 | HR | 1.07 (0.95-1.21) |
| Breast cancer | Women | ≥ 5 yrs | 1771 | 50883 | HR | 0.88 (0.65-1.20) |
| Cao et al, 2016(12) | Breast cancer | Women | Regular use | 607 | 135965 | RR | 0.98 (0.93-1.02) |
| Clarke et al, 2017(49) | Breast cancer | Women | Regular use | 852 | 113479 | HR | 0.84 (0.72-0.98) |
| Yang et al, 2017(50) | Breast cancer | Women | Regular use | 849 | 148739 | HR | 0.81 (0.70-0.92) |
| Bens et al, 2018(51) | Breast cancer | Women | Regular use | 1407 | 62261 | HR | 0.88 (0.72-1.08) |
| Breast cancer | Women | Daily use | 1357 | 62261 | HR | 0.97 (0.77-1.23) |
| Breast cancer | Women | ≥ 5 yrs | 1313 | 55871 | HR | 0.87 (0.63-1.21) |
| Ajrouche et al, 2019(52) | Breast cancer | Women | Regular use | 2103 | 61087 | SHR | 0.82 (0.54-1.26) |
| Breast cancer | Women | ≥ 5 yrs | 2103 | 61087 | SHR | 0.82 (0.54-1.26) |
| Kehm et al, 2019(53) | Breast cancer | Women | Regular use | 2341 | 8233 | HR | 0.63 (0.57-0.71) |
| Tsoi et al, 2019(34) | Breast cancer | Women | Regular use | 4478 | 612509 | RR | 1.14 (1.04-1.25) |
| Breast cancer | Women | ≥ 5 yrs | 4478 | 612509 | RR | 1.14 (1.04-1.25) |
| Bertrand et al, 2020(54) | Breast cancer | Women | Regular use | 1594 | 53126 | HR | 0.92 (0.81-1.04) |
| Breast cancer | Women | ≥ 5 yrs | 1421 | 53126 | HR | 0.91 (0.78-1.06) |
| Blair et al, 2007(55) | Breast cancer mortality | Women | Post-diagnostic | 48 | 592 | HR | 0.53 (0.30-0.93) |
| Wernli et al, 2011(56) | Breast cancer mortality | Women | Post-diagnostic | 148 | 3058 | HR | 0.64 (0.27-1.37) |
| Barron et al, 2012(57) | Breast cancer mortality | Women | Pre-diagnostic | 361 | 5304 | HR | 0.80 (0.62-1.04) |
| Breast cancer mortality | Women | Post-diagnostic | 361 | 5304 | HR | 0.99 (0.68-1.45) |
| Fraser et al, 2014(58) | Breast cancer mortality | Women | Post-diagnostic | 815 | 4627 | HR | 0.42 (0.31-0.55) |
| Holmes et al, 2014(59) | Breast cancer mortality | Women | Post-diagnostic | 165 | 5630 | HR | 0.96 (0.80-1.16) |
| Murray et al, 2014(60) | Breast cancer mortality | Women | Post-diagnostic | 1435 | 7132 | HR | 0.98 (0.81-1.20) |
| Bradley et al, 2016(61) | Breast cancer mortality | Women | Pre-diagnostic | 153 | 2925 | HR | 0.95 (0.68-1.31) |
| Menamin et al, 2017(62) | Breast cancer mortality | Women | Pre-diagnostic | 1215 | 15140 | HR | 0.95 (0.81-1.11) |
| Breast cancer mortality | Women | Post-diagnostic | 1190 | 15140 | HR | 0.92 (0.75-1.14) |
| Frisk et al, 2018(63) | Breast cancer mortality | Women | Pre-diagnostic | 1075 | 21140 | HR | 0.93 (0.77-1.12) |
| Breast cancer mortality | Women | Post-diagnostic | 1075 | 21201 | HR | 0.99 (0.79-1.23) |
| Wang et al, 2018(64) | Breast cancer mortality | Women | Pre-diagnostic | 226 | 1216 | HR | 0.87 (0.59-1.29) |
| Paganini-Hill et al, 1989(1) | Prostate cancer | Men | Regular use | 131 | 4366 | RR | 0.95 (0.65-1.33) |
| Prostate cancer | Men | Daily use | 131 | 4366 | RR | 0.95 (0.65-1.33) |
| Habel et al, 2002(65) | Prostate cancer | Men | Regular use | 2574 | 90100 | RR | 0.76 (0.60-0.98) |
| Prostate cancer | Men | Daily use | 2574 | 90100 | RR | 0.76 (0.60-0.98) |
| Ratnasinghe et al, 2004(19) | Prostate cancer | Men | Regular use | 121 | 9869 | RR | 1.11 (0.60-2.05) |
| Platz et al, 2005(66) | Prostate cancer | Men | Regular use | 141 | 1031 | RR | 0.76 (0.54-1.07) |
| Jacobs et al, 2007(6) | Prostate cancer | Men | Regular use | 1986 | 52721 | RR | 1.02 (0.93-1.12) |
| Prostate cancer | Men | Daily use | 1986 | 52721 | RR | 1.02 (0.93-1.12) |
| Prostate cancer | Men | ≥ 5 yrs | 1301 | 33313 | RR | 0.81 (0.70-0.94) |
| Siemes et al, 2008(7) | Prostate cancer | Men | Regular use | 150 | 4654 | HR | 1.04 (0.73-1.47) |
| Brasky et al, 2010(67) | Prostate cancer | Men | Regular use | 1547 | 34132 | HR | 0.98 (0.87-1.09) |
| Prostate cancer | Men | ≥ 5 yrs | 1295 | 34132 | HR | 0.96 (0.83-1.11) |
| Shebl et al, 2012(68) | Prostate cancer | Men | Regular use | 2725 | 22583 | RR | 0.92 (0.85-0.99) |
| Prostate cancer | Men | Daily use | 2725 | 22583 | RR | 0.92 (0.85-0.99) |
| Hollestein et al, 2014(10) | Prostate cancer | Men | Regular use | 882 | 53679 | HR | 1.02 (0.98-1.06) |
| Prostate cancer | Men | Daily use | 882 | 53679 | HR | 1.02 (0.98-1.06) |
| Prostate cancer | Men | ≥ 5 yrs | 93 | 53679 | HR | 1.25 (0.90-1.73) |
| Nordström et al, 2015(69) | Prostate cancer | Men | Regular use | 8430 | 185667 | OR | 1.12 (1.00-1.25) |
| Lapi et al, 2016(70) | Prostate cancer | Men | Regular use | 187 | 13453 | HR | 0.64 (0.48-0.86) |
| Prostate cancer | Men | ≥ 5 yrs | 108 | 13453 | HR | 0.42 (0.21-0.91) |
| Skriver et al, 2016(71) | Prostate cancer | Men | Regular use | 34522 | 206742 | OR | 0.94 (0.91-0.97) |
| Downer et al, 2017(72) | Prostate cancer | Men | Regular use | 378 | 22071 | HR | 0.66 (0.50-0.85) |
| Prostate cancer | Men | ≥ 5 yrs | 340 | 22071 | HR | 0.66 (0.50-0.86) |
| Ma et al, 2018(73) | Prostate cancer | Men | Regular use | 14870 | 643368 | SIR | 0.87 (0.85-0.88) |
| Prostate cancer | Men | ≥ 5 yrs | 6200 | 643368 | SIR | 0.31 (0.30-0.32) |
| Ajrouche et al, 2019(52) | Prostate cancer | Men | Regular use | 2421 | 49938 | SHR | 0.79 (0.71-0.88) |
| Prostate cancer | Men | ≥ 5 yrs | 2421 | 49938 | SHR | 0.79 (0.71-0.88) |
| Downer et al, 2019(74) | Prostate cancer | Men | Regular use | 542 | 49409 | HR | 0.80 (0.66-0.96) |
| Prostate cancer | Men | ≥ 5 yrs | 59 | 13918 | HR | 0.42 (0.23-0.79) |
| Prostate cancer mortality | Men | Post-diagnostic | 804 | 49384 | HR | 0.82 (0.71-0.95) |
| Hurwitz et al, 2019(75) | Prostate cancer | Men | Regular use | 817 | 6594 | HR | 1.05 (0.91-1.22) |
| Prostate cancer | Men | Daily use | 463 | 4527 | HR | 1.12 (0.90-1.39) |
| Prostate cancer mortality | Men | Post-diagnostic | 90 | 6594 | HR | 0.59 (0.36-0.96) |
| Tsoi et al, 2019(34) | Prostate cancer | Men | Regular use | 6771 | 612509 | RR | 0.95 (0.88-1.03) |
| Prostate cancer | Men | ≥ 5 yrs | 6771 | 612509 | RR | 0.95 (0.88-1.03) |
| Prause et al, 2020(76) | Prostate cancer | Men | Regular use | 392 | 4314 | HR | 0.84 (0.62-1.16) |
| Prostate cancer | Men | ≥ 5 yrs | 392 | 4314 | HR | 0.84 (0.62-1.16) |
| Skriver et al, 2020(77) | Prostate cancer | Men | Regular use | 1898 | 26339 | HR | 1.02 (0.90-1.15) |
| Prostate cancer | Men | Daily use | 1594 | 26339 | HR | 1.06 (0.90-1.25) |
| Prostate cancer | Men | ≥ 5 yrs | 1448 | 26339 | HR | 1.02 (0.78-1.33) |
| Choe et al, 2012(78) | Prostate cancer mortality | Men | Post-diagnostic | 334 | 7369 | HR | 0.43 (0.21-0.87) |
| Caon et al, 2014(79) | Prostate cancer mortality | Men | Pre-diagnostic | 1098 | 4419 | HR | 0.91 (0.65-1.28) |
| Flahavan et al, 2014(80) | Prostate cancer mortality | Men | Pre-diagnostic | 276 | 2936 | HR | 0.88 (0.67-1.15) |
| Grytli et al, 2014(81) | Prostate cancer mortality | Men | Post-diagnostic | 1010 | 3561 | HR | 0.94 (0.78-1.14) |
| Jacobs et al, 2014(82) | Prostate cancer mortality | Men | Post-diagnostic | 246 | 7419 | HR | 0.98 (0.74-1.29) |
| Assayag et al, 2015(83) | Prostate cancer mortality | Men | Post-diagnostic | 1793 | 2594 | HR | 1.46 (1.29-1.65) |
| Zhou et al, 2018(84) | Prostate cancer mortality | Men | Post-diagnostic | 244 | 26890 | HR | 0.81 (0.58-1.14) |
| Prostate cancer mortality | Men | Pre-diagnostic | 283 | 26890 | HR | 0.98 (0.83-1.17) |
| Paganini-Hill et al, 1989(1) | Lung cancer | General | Regular use | 95 | 11767 | RR | 1.25 (0.71-2.20) |
| Lung cancer | General | Daily use | 95 | 11767 | RR | 1.25 (0.71-2.20) |
| Ratnasinghe et al, 2004(19) | Lung cancer | General | Regular use | 410 | 22834 | RR | 0.81 (0.62-1.07) |
| Hayes et al, 2006(85) | Lung cancer | Women | Regular use | 236 | 16644 | HR | 1.10 (0.84-1.43) |
| Lung cancer | Women | Daily use | 219 | 13347 | HR | 1.21 (0.92-1.59) |
| Jacobs et al, 2007(6) | Lung cancer | General | Regular use | 656 | 51391 | RR | 1.07 (0.91-1.25) |
| Lung cancer | General | Daily use | 656 | 51391 | RR | 1.07 (0.91-1.25) |
| Lung cancer | General | ≥ 5 yrs | 439 | 32451 | RR | 0.98 (0.76-1.25) |
| Siemes et al, 2008(7) | Lung cancer | General | Regular use | 84 | 4649 | HR | 0.90 (0.56-1.45) |
| Slatore et al, 2009(86) | Lung cancer | General | Regular use | 569 | 66248 | HR | 0.90 (0.71-1.15) |
| Hollestein et al, 2014(10) | Lung cancer | General | Regular use | 915 | 109276 | HR | 1.06 (1.01-1.10) |
| Lung cancer | General | Daily use | 915 | 109276 | HR | 1.06 (1.01-1.10) |
| Lung cancer | General | ≥ 5 yrs | 75 | 109276 | HR | 1.17 (0.83-1.64) |
| Baik et al, 2015(87) | Lung cancer | Women | Regular use | 1158 | 143841 | HR | 0.97 (0.84-1.13) |
| Lung cancer | Women | ≥ 5 yrs | 1013 | 143841 | HR | 0.95 (0.81-1.12) |
| Cao et al, 2016(12) | Lung cancer | General | Regular use | 2430 | 135965 | RR | 1.05 (0.97-1.14) |
| Tsoi et al, 2019(34) | Lung cancer | General | Regular use | 24908 | 612509 | RR | 0.65 (0.62-0.68) |
| Lung cancer | General | ≥ 5 yrs | 24908 | 612509 | RR | 0.65 (0.62-0.68) |
| Kang et al, 2020(88) | Lung cancer | General | Regular use | 5990 | 732199 | HR | 0.99 (0.92-1.06) |
| Lung cancer | General | Daily use | NA | NA | HR | 0.95 (0.86-1.06) |

Abbreviations: CRC, colorectal cancer; yrs, years; NA, not available.

**Supplementary Table 3. Basic characteristics and main findings for each RCT.**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Author, Year** | **Trial design** | **Outcome** | **Exposure** | **Treatment duration** | **Follow-up period** | **Events** | **Sample size** | **Estimates (95% CI)** |
| Peto et al, 1988(89) | Primary + Secondary | CRC | Daily | 6 yrs | 0-12 yrs | 45 | 5139 | 0.82 (0.45-1.50) |
| Primary + Secondary | CRC | Daily | 6 yrs | 10-19 yrs | 88 | 5139 | 0.66 (0.43-1.00) |
| Stürmer et al, 1998(3) | Primary + Secondary | CRC | Daily | 5 yrs | 0-12 yrs | 341 | 22071 | 1.03 (0.83-1.27) |
| Rothwell et al, 2010(90) | Primary + Secondary | CRC | Daily  | ≥2.5 yrs | ≥20 yrs | 185 | 7383 | 0.69 (0.51, 0.93) |
| Primary + Secondary | CRC | Daily | ≥5 yrs | ≥20 yrs | 316 | 14033 | 0.68 (0.54, 0.87) |
| Cook et al, 2013(91) | Primary + Secondary | CRC | Daily | 10.1 yrs | 0-12 yrs | 294 | 39876 | 0.96 (0.76-1.21) |
| Primary + Secondary | CRC | Daily | 10.1 yrs | 10-19 yrs | 157 | 39876 | 0.59 (0.42-0.81) |
| Peto et al, 1988(89) | Primary  | CRC mortality | Daily | 6 yrs | 0-20 yrs | 99 | 5139 | 0.74 (0.49-1.09) |
| Rothwell et al, 2010(90) | Primary + Secondary | CRC mortality | Daily  | ≥2.5 yrs | ≥20 yrs | 119 | 7383 | 0.54 (0.36, 0.80) |
| Primary + Secondary | CRC mortality | Daily | ≥5 yrs | ≥20 yrs | 193 | 14033 | 0.57 (0.42, 0.78) |
| Flossmann et al, 2007(92) | Primary | Gastric cancer | Daily | ≥5 yrs | ≥20 yrs | 46 | 6076 | 1.01 (0.54, 1.86) |
| Rothwell et al, 2011(93) | Primary + Secondary | Gastric cancer mortality | Daily | 0-5 yrs | Any | <36 | 23535 | 1.85 (0.81, 4.23) |
| Primary + Secondary | Gastric cancer mortality | Daily | ≥5 yrs | Any | <36 | 23535 | 3.09 (0.64, 14.91) |
| Primary + Secondary | Gastric cancer mortality | Daily | ≥5 yrs | 0-10 yrs | <71 | 10502 | 1.36 (0.64, 2.90) |
| Primary + Secondary | Gastric cancer mortality | Daily | ≥5 yrs | 10-20 yrs | <71 | 10502 | 0.42 (0.23, 0.79) |
| Primary + Secondary | Gastric cancer mortality | Daily | ≥5 yrs | 0-20 yrs | 71 | 10502 | 0.69 (0.43, 1.10) |
| Flossmann et al, 2007(92) | Primary | Breast cancer | Daily | ≥5 yrs | ≥20 yrs | 12 | 6076 | 0.90 (0.26, 3.07) |
| Primary | Prostate cancer | Daily | ≥5 yrs | ≥20 yrs | 313 | 6076 | 0.87 (0.69, 1.10) |
| Rothwell et al, 2011(93) | Primary + Secondary | Prostate cancer mortality | Daily | 0-5 yrs | Any | <37 | 23535 | 0.70 (0.29, 1.73) |
| Primary + Secondary | Prostate cancer mortality | Daily | ≥5 yrs | Any | <37 | 23535 | 0.52 (0.20, 1.34) |
| Primary + Secondary | Prostate cancer mortality | Daily | ≥5 yrs | 0-10 yrs | <210 | 10502 | 0.83 (0.47, 1.46) |
| Primary + Secondary | Prostate cancer mortality | Daily | ≥5 yrs | 10-20 yrs | <210 | 10502 | 0.80 (0.58, 1.09) |
| Primary + Secondary | Prostate cancer mortality | Daily | ≥5 yrs | 0-20 yrs | 210 | 10502 | 0.81 (0.61, 1.06) |
| Peto et al, 1988(89) | Primary | Lung cancer | Daily | 6 yrs | Any | 28 | 5199 | 0.64 (0.29-1.41) |
| Lee et al, 1995(94) | Primary | Lung cancer | Any | NA | Any | 128 | 22071 | 0.88 (0.62-1.25) |
| Flossmann et al, 2007(92) | Primary | Lung cancer | Daily | ≥5 yrs | ≥20 yrs | 169 | 6076 | 0.96 (0.70, 1.32) |
| Cook et al, 2013(91) | Primary | Lung cancer | Daily | 10.1 yrs | Any | 431 | 39876 | 1.04 (0.86-1.26) |
| Rothwell et al, 2011(93) | Primary + Secondary | Lung cancer mortality | Daily | 0-5 yrs | Any | <198 | 23535 | 0.92 (0.65, 1.30) |
| Primary + Secondary | Lung cancer mortality | Daily | ≥5 yrs | Any | <198 | 23535 | 0.68 (0.42, 1.10) |
| Primary + Secondary | Lung cancer mortality | Daily | ≥5 yrs | 0-10 yrs | <326 | 10502 | 0.68 (0.50, 0.92) |
| Primary + Secondary | Lung cancer mortality | Daily | ≥5 yrs | 10-20 yrs | <326 | 10502 | 0.75 (0.55, 1.02) |
| Primary + Secondary | Lung cancer mortality | Daily | ≥5 yrs | 0-20 yrs | 326 | 10502 | 0.71 (0.58, 0.89) |

Abbreviations: CRC, colorectal cancer; yrs, years; NA, not available.

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