Supplementary Materials

Data synthesis

If standard errors (to enable weighting the effect sizes using the inverse variance method) were not provided directly, they were estimated from reported confidence intervals (see Supplementary material for detailes):

$$\widehat{se}_{log} = \frac{log\{\hat{\theta}_U\} - log\{\hat{\theta}_L\}}{2 \times 1.96} \qquad \text{Eq.1}$$

where $\hat{\theta}_U$ and $\hat{\theta}_L$ denote the upper- and lower- bound estimates of the effect size metric (i.e. HR or OR). Where only the effect size and *P* value were reported, the corresponding standard score ($z$) was derived from the standard normal distribution, which was then used to estimate the standard error using:

$$\widehat{se}_{log} = \frac{log\{\hat{\theta}\}}{z} \qquad \text{Eq.2}$$

where $\theta$ denotes either the HR or the OR.

Table S1. Characteristics of eligible studies

| Author (Year of publication) | Type of study | Region | Cancer type | Treatment modality | N patients / N smokers | Outcome | Median F-up, in months | Inclusion in meta-analysis |
|---|---|---|---|---|---|---|---|---|
| Agarwal (2009) | Retrospective | Asia | Head & Neck cancer | Radiotherapy | 627 / 505 | LRR, DFS | 11 | Yes |
| Ajili (2013) | Retrospective | Africa | Bladder cancer | BCG immunotherapy | 112 / 81 | DFS | 30 | No |
| Alessi (2021) | Retrospective | N America | Lung cancer | Immunotherapy (pembrolizumab) | 221 / 212 | PFS | 26.9 | Yes |
| Al-Mamgani (2013) | Retrospective | Europe | Head & Neck cancer | Radiotherapy | 906/700 | LRR | 90 | Yes |
| Barnett (2011) | Retrospective | Europe | Breast cancer | Radiotherapy | 1014 / NR | Toxicity (skin toxicity) | NR | Yes |
| Boeri (2019) | Retrospective | N America | Bladder cancer | Chemotherapy (cisplatin-based) | 201/56 | pCR, LRR | 24.6 | No |
| Cavallo (2021) | Retrospective | Europe | Head & neck cancer | Radiotherapy | 132 / 24 | Toxicity (salivary gland sysfunction) | NR | Yes |
| Cho (2019) | Retrospective | Asia | Lung cancer | Immunotherapy | 178/111 | ORR, PFS | NR | Yes |
| Choi (2014) | Retrospective | Asia | Lung cancer | TKIs-EGFR (gefitinib-erlotinib) | 130/30 | PFS | NR | Yes |
| Cortellini (2020) | Retrospective | Europe | Lung cancer | Immunotherapy | 1026 / 348 | ORR, PFS | 14.6 | Yes |
| Cozzarini (2016) | Prospective | Europe | Prostate cancer | Radiotherapy | 125 / 22 | Toxicity (lymphopenia) | NR | Yes |
| de Graan (2012) | Retrospective | Europe | Various cancer types | Chemotherapy (taxane) | 276 / 62 | Toxicity (neutropenia) | NR | Yes |
| de Jongh (2003) | Retrospective | Europe | Various cancer types | Chemotherapy (cisplatin) | 400 / NR | Toxicity (renal, neuro-toxicity, ototoxicity) | NR | Yes |
| De Langhe (2014) | Retrospective | Europe | Breast cancer | Radiotherapy | 374 / 51 | Toxicity | NR | Yes |
| Dolan (2017) | Retrospective | N America | Germ cell tumours | Chemotherapy (cisplatin) | 680 / 51 | Toxicity (neurotoxicity) | NR | Yes |
| Engvall (2021) | Retrospective | Europe | Breast cancer | Chemotherapy (taxanes) | 397 / 64 | Toxicity (neurotoxicity) | NR | Yes |
| Fang (2018) | Retrospective | N America | Oesophageal cancer | CRT | 313 / 66 | pCR | NR | No |

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|---|---|---|---|---|---|---|---|---|
| Fodor (2022) | Retrospective | Europe | Breast cancer | Radiotherapy | 1325 / 263 | Toxicity (skin) | 72.4 | Yes |
| Fortin (2008) | Retrospective | N America | Head & Neck cancer | Radiotherapy | 1871 / 951 | LRR | 38 | Yes |
| Fujimoto (2018) | Retrospective | Asia | Lung cancer | Immunotherapy (nivolumab) | 613 / 482 | PFS | NR | Yes |
| Fukuokaya (2021) | Retrospective | Asia | Bladder cancer | Immunotherapy (pembrolizumab) | 59 / 19 | PFS | 8.2 | Yes |
| Fung (2021) | Retrospective | N America | Head & neck cancer | CRT | 334 / 169 | DFS | NR | Yes |
| Furrer (2017) | Retrospective | N America | Breast cancer | Trastuzumab | 131 / 17 | DFS | 88.8 | No |
| Fyles (2002) | Prospective | N America | Cervical cancer | Radiotherapy | 100 / 34 | LRR, DFS | 36 | Yes |
| Gainor (2020) | Retrospective | N America | Lung cancer | Immunotherapy (any checkpoint inhibitor) | 273/237 | PFS | 14.9 | Yes |
| Gillison (2012) | Randomized | N America | Head & Neck cancer | Radiotherapy, CRT | 256 / 23 | DFS | 111.6 | Yes |
| Goldvaser (2017) | Retrospective | Asia | Breast cancer | Hormonal therapy, chemotherapy | 617 / 101 | DFS | 61.9 | No |
| Guo (2014) | Retrospective | Asia | Head & Neck cancer | CRT | 400 / 193 | DFS | 80.2 | Yes |
| Hoff (2012) | Prospective | Europe | Head & Neck cancer | Radiotherapy | 232 / 162 | LRR, DFS | NR | Yes |
| Huang (2014) | Retrospective | Asia | Oesophageal cancer | CRT | 282 / 254 | pCR | NR | No |
| Igawa (2016) | Retrospective | Asia | Lung cancer | Chemotherapy (pemetrexed) | 116 / 78 | PFS | 12.9 (mean) | Yes |
| Isohashi (2012) | Retrospective | Asia | Cervical cancer | CRT | 97 / 23 | Toxicity (gastrointesti-nal) | 43 | No |
| Itaya (2007) | Retrospective | Asia | Lung cancer | Chemotherapy (carboplatin paclitaxel) | 98 / 68 | PFS | 24.8 | Yes |
| Ito (2021) | Retrospective | Asia | Lung cancer | Immunotherapy (PD-1 or PD-L1 inhibitors) | 676 / 574 | PFS | 34.3 | Yes |
| Jain (2015) | Retrospective | Asia | Lung cancer | TKIs EGFR (gefitinib, erlotinib) | 211 / 13 | PFS | NR | Yes |
| Kanai (2009) | Retrospective | Asia | Pancreatic cancer | Chemotherapy (Gemcitabine) | 103 / 51 | Toxicity (neutropenia) | NR | Yes |
| Keizman (2013) | Retrospective | Asia, N | Renal cell carcinoma | TKIs (sunitinib) | 278 / 59 | PFS | 55 | No |

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|---|---|---|---|---|---|---|---|---|
| | | America | | | | | | |
| Kelemen (2015) | Retrospective | N America | Ovarian cancer | Chemotherapy (mostly platina-based) | 432 / 86 | PFS | 41.3 | Yes |
| Kim (2013) | Retrospective | N America | Bladder cancer | Chemotherapy (cisplatin-based) | 139 / 41 | pCR, LRR | 46 | No |
| Kim (2014) | Retrospective | Asia | Lung cancer | TKIs EGFR (gefitinib, erlotinib) | 222 / 77 | PFS | 33.6 | Yes |
| Kim (2018) | Retrospective | Asia | Lung cancer | TKIs EGFR (gefitinib, erlotinib, afatinib, osimertinib) | 142 / 51 | PFS | 19.8 | Yes |
| Kim (2014) | Retrospective | Asia | Lung cancer | TKIs EGFR (gefitinib, erlotinib) | 222 / 77 | PFS | NR | No |
| Lan (2021) | Retrospective | Asia | Esophageal cancer | CRT | 321 / 218 | Toxicity (pneumonitis) | 21.5 | Yes |
| Levy (2014) | Retrospective | Europe | Head & Neck cancer | CRT (Cisplatin or cetuximab) | 194 / 73 | LRR, DFS | 29 | Yes |
| Lilla (2007) | Retrospective | Europe | Breast cancer | Radiotherapy | 268 / 29 | Toxicity (skin toxicity) | 51 | Yes |
| Lim (2014) | Retrospective | Asia | Lung cancer | TKIs EGFR (gefitinib, erlotinib) | 242 / 88 | PFS | NR | Yes |
| Liskamp (2016) | Retrospective | Europe | Head & neck cancer | CRT | 142 / 65 | LRR | 33 | Yes |
| Liu (2021) | Retrospective | Australia | Head & neck cancer | CRT | 250 / 129 | DFS | 61 | Yes |
| Li (2021) | Retrospective | Asia | Head & neck cancer | Radiotherapy | 77 / 28 | LRR | 30.3 | Yes |
| Lu (2013) | Retrospective | Asia | Lung cancer | Chemotherapy (pemetrexed) | 119 / 68 | ORR | NR | No |
| Luo (2022) | Retrospective | Asia | Lung cancer | Radiotherapy | 111 / 79 | LRR | NR | Yes |
| Mai (2007) | Retrospective | Europe | Anal cancer | RCT | 68 / 34 | LRR | 22 | Yes |
| Markoczy (2018) | Prospective | Europe | Lung cancer | TKIs EGFR (erlotinib) | 62 / 20 | PFS | 13.4 | Yes |
| Miao (2022) | Retrospective | Asia | Lung cancer | Immunotherapy (PD-1 or PD-L1 inhibitors) | 351 / 227 | PFS | NR | Yes |
| Mileshkin (2014) | Prospective | Australia | Endometrial cancer | CRT | 346 / 98 | DFS | NR | Yes |
| Miller (2019) | Retrospective | N America | Lung cancer | SBRT | 203 / 55 | DFS | 21.9 | Yes |

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|---|---|---|---|---|---|---|---|---|
| Nakagawa (2012) | Prospective | Asia | Lung cancer | TKIs EGFR (erlotinib) | 3439 / 1777 | Toxicity (lung toxicity) | NR | No |
| Ng (2019) | Retrospective | Asia, N America | Lung cancer | Immunotherapy (PD1 or PDL1 in-hibitors) | 189 / 97 | PFS | 7.1 | Yes |
| Nilsson (2022) | Retrospective | Europe | Anal cancer | CRT | 114 / 33 | Toxicity (gastrointestinal | 40 | Yes |
| Nishinarita (2018) | Retrospective | Asia | Lung cancer | TKIs EGFR (gefitinib, erlotinib) | 248 / 90 | PFS | 23.4 | Yes |
| O´Malley (2013) | Retrospective | N America | Various cancer types | Chemotherapy (Gemcitabine) | 137 / 12 | Toxicity (neutropenia) | NR | Yes |
| Ouyang (2013) | Retrospective | Asia | Head & Neck cancer | Radiotherapy | 1849 / 734 | DFS | 73.5 | No |
| Pan (2014) | Retrospective | Asia | Lung cancer | TKIs EGFR (erlotinib, gefitinib) | 48 / 11 | PFS | NR | Yes |
| Pantarotto (2007) | Retrospective | N America | Prostate cancer | Radiotherapy | 416 / 70 | LRR, biochemical DFS | 70.2 | Yes |
| Park (2022) | Retrospective | Asia | Lung cancer | TKIs EGFR (osirmetinib) | 61 / 22 | PFS | 36 | Yes |
| Park (2021) | Retrospective | Asia | Head & neck cancer | Radiotherapy | 103 / NR | Toxicity (dysgeusia) | NR | Yes |
| Park (2018) | Retrospective | Asia | Lung cancer | CRT | 472 / 131 | DFS | 66.5 | No |
| Park (2016) | Retrospective | Asia | Lung cancer | Chemotherapy (pemetrexed) | 227 / 68 | PFS | NR | Yes |
| Pasquier (2021) | Prospective | Europe | Breast cancer | Radiotherapy | 288 / 79 | Toxicity (skin) | 25.2 | Yes |
| Persson (2016) | Prospective | Europe | Breast cancer | Radiotherapy, endocrine treatment | 1065 / 206 | DFS | 61 | Yes |
| Pickles (2004) | Retrospective | N America | Prostate cancer | Radiotherapy | 417 / 88 | Biochemical DFS | 59 | No |
| Pignol (2014) | Prospective | N America, Europe | Breast cancer | Radiotherapy | 257 / 25 | Toxicity (skin toxicity) | NR | Yes |
| Sfakianos (2010) | Retrospective | N America | Bladder cancer | BCG | 623 / 483 | ORR, LRR, DFS | 80.9 | No |
| Sharp (2013) | Randomized | Europe | Breast cancer | Radiotherapy | 384 / 32 | Toxicity (skin toxicity) | NR | Yes |

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|---|---|---|---|---|---|---|---|---|
| Sha (2021) | Retrospective | Asia | Lung cancer | Radiotherapy | 126 / 55 | Toxicity (pneumonitis) | NR | Yes |
| Simino (2020) | Prospective | S America | Various cancer types | Chemotherapy (various) | 269 / 39 | Toxicity (nausea) | NR | Yes |
| Solanki (2013) | Prospective | N America | Prostate cancer | Radiotherapy | 633 / 124 | biochemical DFS, toxicity (urogenital) | 57 | Yes |
| Spigel (2022) | RCT | Global | Lung cancer | Immunotherapy (durvalumab) | 713 /649 | PFS | 34.2 | Yes |
| Stankovic (2016) | Prospective | Europe | Prostate cancer | Radiotherapy | 94 / 13 | Toxicity (urogenital) | 27 | No |
| Steinberger (2015) | Retrospective | N America | Prostate cancer | Radiotherapy | 2095 / 164 | biochemical DFS, toxicity (urogenital) | 95 | Yes |
| Sunaga (2021) | Retrospective | Asia | Head & neck cancer | Radiotherapy | 94 / 78 | Toxicity (mucositis) | NR | Yes |
| Sun (2021) | Retrospective | Asia | Head & neck cancer | Radiotherapy | 8649 / 2493 | DFS | NR | Yes |
| Tenti (2022) | Retrospective | Europe | Prostate cancer | Radiotherapy | 76 / 9 | DFS | 42.3 | Yes |
| Tho (2005) | Retrospective | Europe | Breast cancer | Radiotherapy | 92 / NR | Toxicity | NR | Yes |
| Trendowski (2021) | Retrospective | N America | Various | Chemotherapy | 1045 / NR | Toxicity (neurotoxicity) | NR | Yes |
| Tsao (2006) | Retrospective | N America | Lung cancer | Chemotherapy (various) | 873 / 355 | PFS | 40.7 | Yes |
| Vatca (2014) | Retrospective | N America | Head & Neck cancer | CRT | 72 / 30 | Toxicity (mucositis) | 26.4 | No |
| Vilhonen (2019) | Retrospective | Europe | Lung cancer | Chemotherapy (various) | 80 / 52 | PFS | NR | Yes |
| Waggoner (2006) | Prospective | N America | Cervical cancer | CRT | 316 / 133 | DFS | NR | Yes |
| Wang (2021) | Retrospective | N America | Lung cancer | Immunotherapy (any checkpoint inhibitor) | 269 / 1674 | PFS | NR | Yes |

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|---|---|---|---|---|---|---|---|---|
| Wang (2021) | Retrospective | Asia | Lung cancer | TKIs EGFR | | | | |
| (icotinib) | 2136 / 202 | PFS | NR | Yes | | | | |
| Won (2011) | Retrospective | Asia | Lung cancer | TKIs EGFR (gefitinib, erlotinib) | 87 / 19 | PFS | NR | Yes |
| Xie (2013) | Retrospective | Asia | Head & Neck cancer | Radiotherapy | 75 / 37 | DFS | 25 | No |
| Ying (2014) | Retrospective | Asia | Lung cancer | TKIs EGFR (gefitinib) | 273 / 112 | ORR, PFS | 18.5 | Yes |
| Zeng (2013) | Retrospective | Asia | Lung cancer | TKIs EGFR (gefitinib, erlotininb) | 159 / 47 | PFS | NR | Yes |
| Zhang (2022) | Retrospective | N America | Testicular cancer | Cisplatin | NR | Toxicity (neurotoxicity, tinnitus) | NR | Yes |

Abbreviations: NR, not reported; BCG, Bacillus Calmette Guerin; TKIs, tyrosine kinase inhibitors; EGFR, Epidermal Growth Factor Receptor; CRT, chemoradiotherapy; LRR, locoregional recurrence rate; DFS, disease-free survival; pCR, pathological complete response; PFS, progression-free survival; ORR, objective response rate; NR, not reported.

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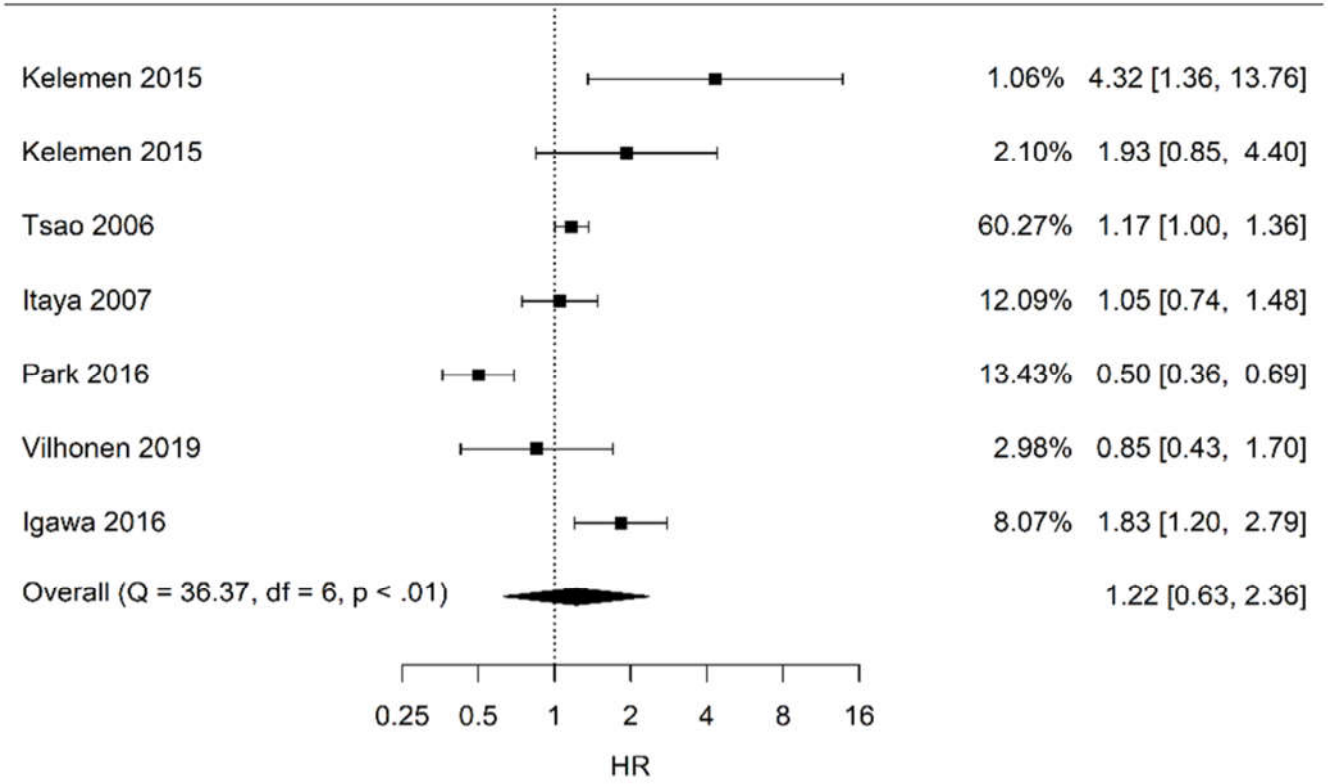



Figure S1 Forest plots on pooled Hazard Ratios (HR) on smoking during chemotherapy and efficacy in terms of progression-free survival (PFS)

HR > 1 indicates worse PFS for smokers during chemotherapy treatment while HR <1 indicates better PFS. Comparison group is non-smoker (former or never)

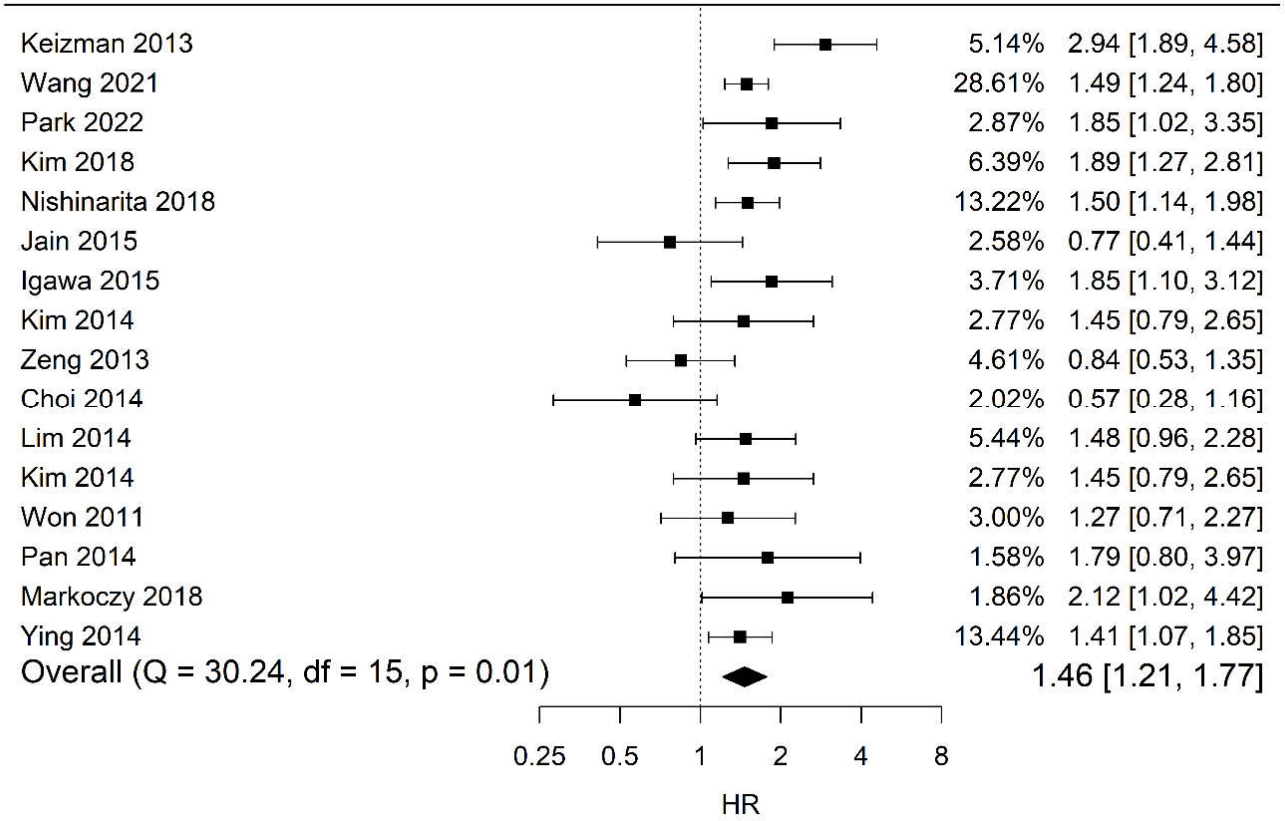



Figure S2 Forest plots on pooled Hazard Ratios (HR) on smoking during treatment with EGFR-tyrosine kinase inhibitors (EGFR-TKIs) and efficacy in terms of progression-free survival (PFS)

HR > 1 indicates worse PFS for smokers during EGFR-TKIs treatment while HR <1 indicates better PFS. Comparison group is non-smoker (former or never)

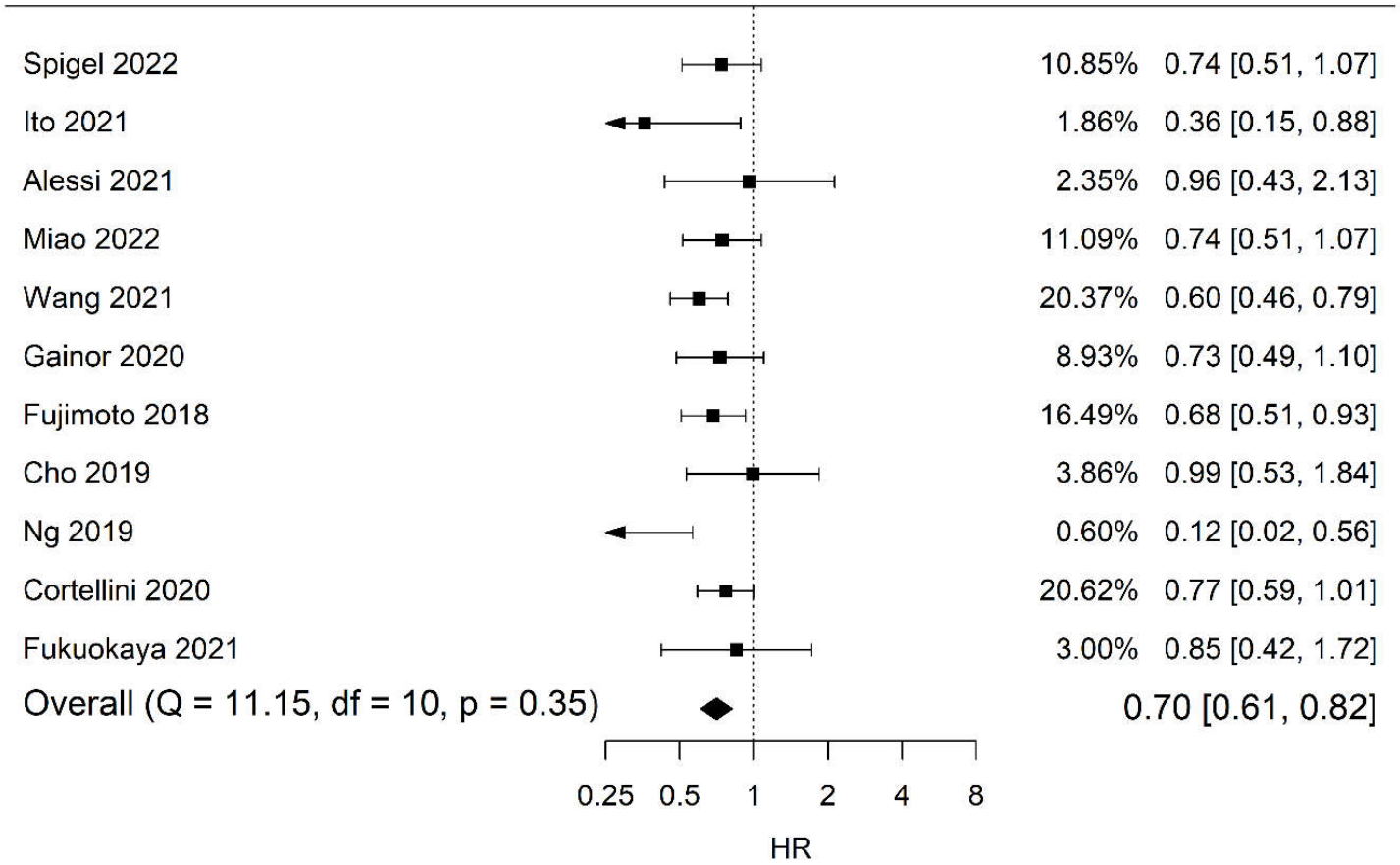



Figure S3 Forest plots on pooled Hazard Ratios (HR) on smoking during treatment with immunotherapy (checkpoint inhibitors) and efficacy in terms of progression-free survival (PFS)

HR > 1 indicates worse PFS for smokers during immunotherapy while HR <1 indicates better PFS. Comparison group is non-smoker (former or never)

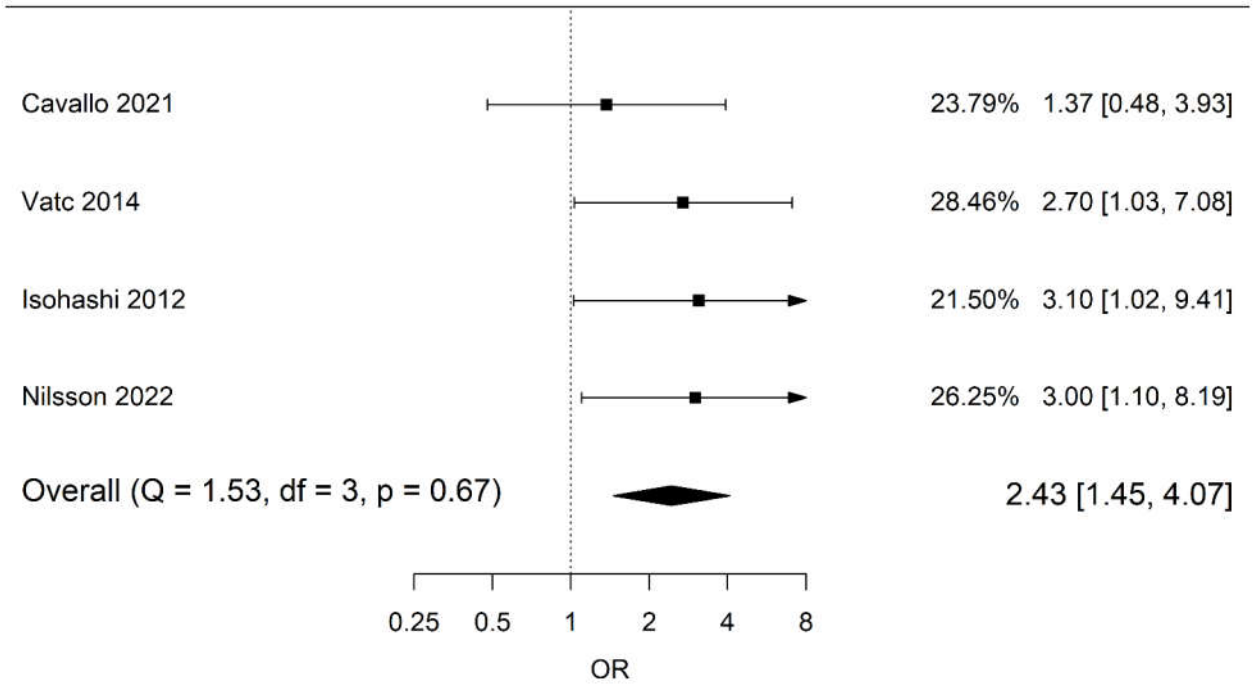



Figure S4. Forest plots on pooled Odds Ratios (OR) on smoking during radiochemotherapy and toxicity.

OR > 1 indicates higher risk for toxicity during treatment whereas OR < 1 indicates lower risk. Comparison group is non-smokers (former or never).

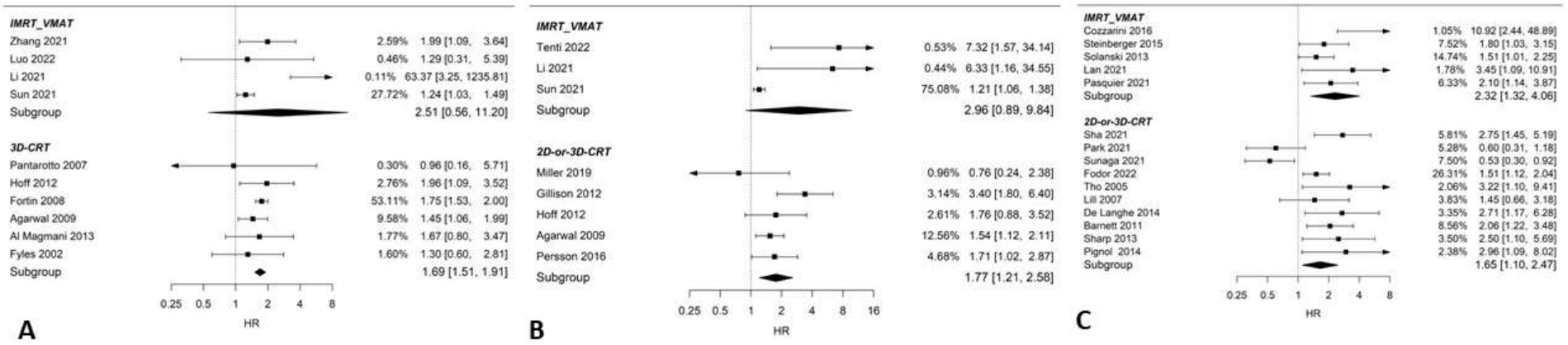



Figure S5. Subgroup analyses based on radiation technique (2D/3D conformal radiation therapy (CRT) vs. intensity modulated radiotherapy (IMRT)/Volumetric Modulated Arc Therapy (VMAT)) for the efficacy (A: locoregional recurrence; B: disease-free survival; Hazard Ratios) and radiation-induced toxicity (C; Odds Ratios) for smokers vs. non-smokers.

Pooled values > 1 indicates worse LRR or DFS or higher risk for radiation-induced toxicity for smokers during immunotherapy while pooled values <1 indicates better LRR or DFS or lower risk for toxicity. Comparison group is non-smokers (former or never).

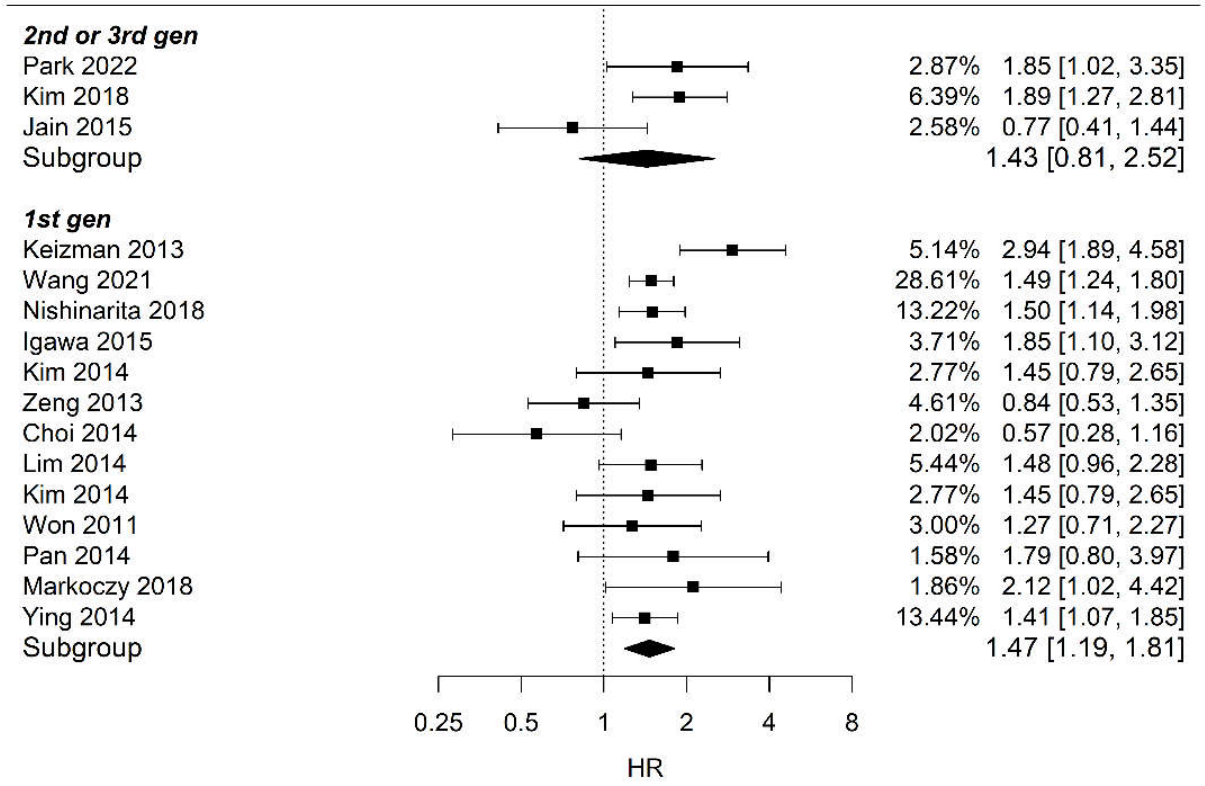



Figure S6 Subgroup analysis based on the generation (1st vs. 2nd or 3rd) of EGFR-tyrosine kinase inhibitors (EGFR-TKIs) and efficacy in terms of progression-free survival (PFS)

HR > 1 indicates worse PFS for smokers during EGFR-TKIs treatment while HR <1 indicates better PFS. Comparison group is non-smoker (former or never)

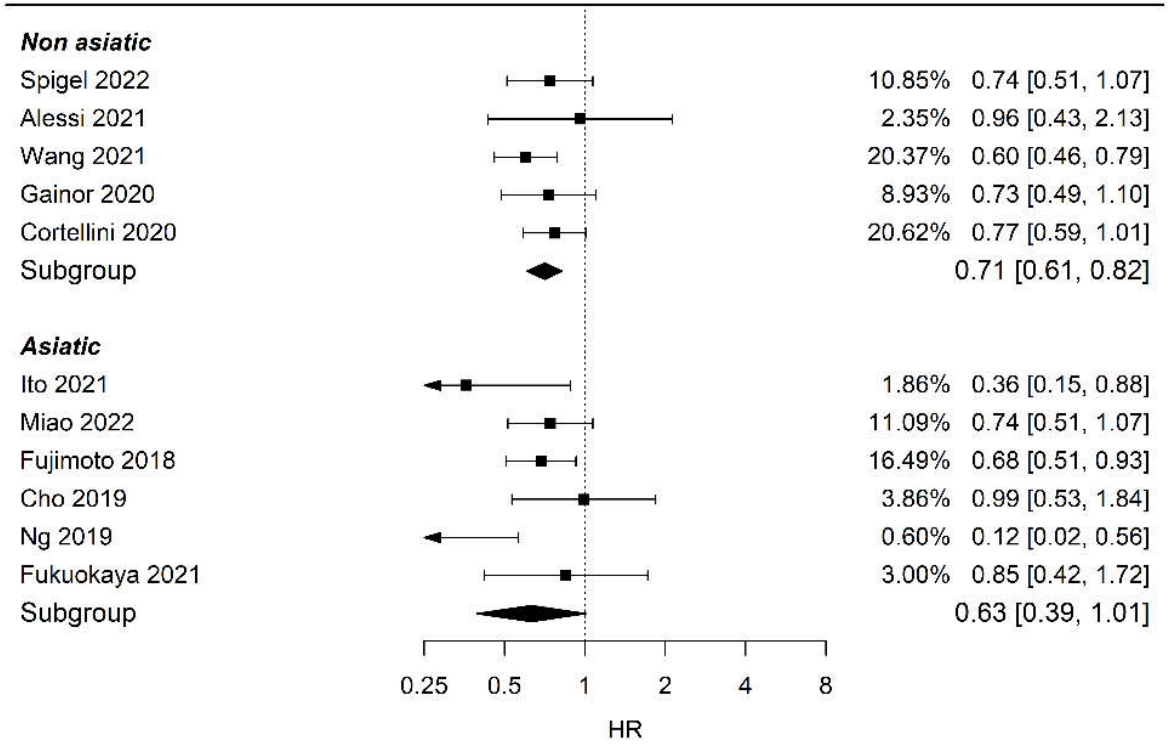



Figure S7 Subgroup analysis based on the race (asiatic vs. non-asiatic population) on smoking during treatment with immunotherapy (checkpoint inhibitors) and efficacy in terms of progression-free survival (PFS)

HR > 1 indicates worse PFS for smokers during immunotherapy while HR <1 indicates better PFS. Comparison group is non-smoker (former or never)

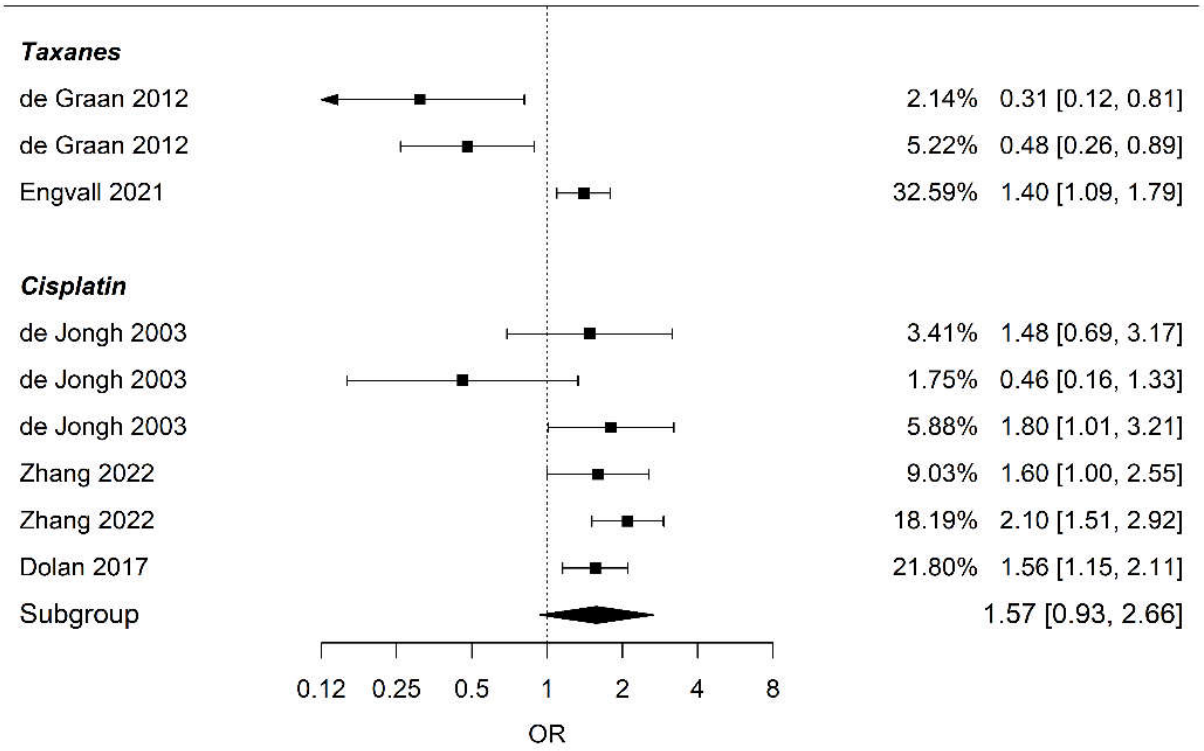



Figure S8 Subgroup analysis based on type of chemotherapeutic agent (taxanes vs. cisplatin) on smoking during chemotherapy and toxicity.

OR > 1 indicates higher risk for toxicity during treatment whereas OR < 1 indicates lower risk. Comparison group is non-smokers (former or never).

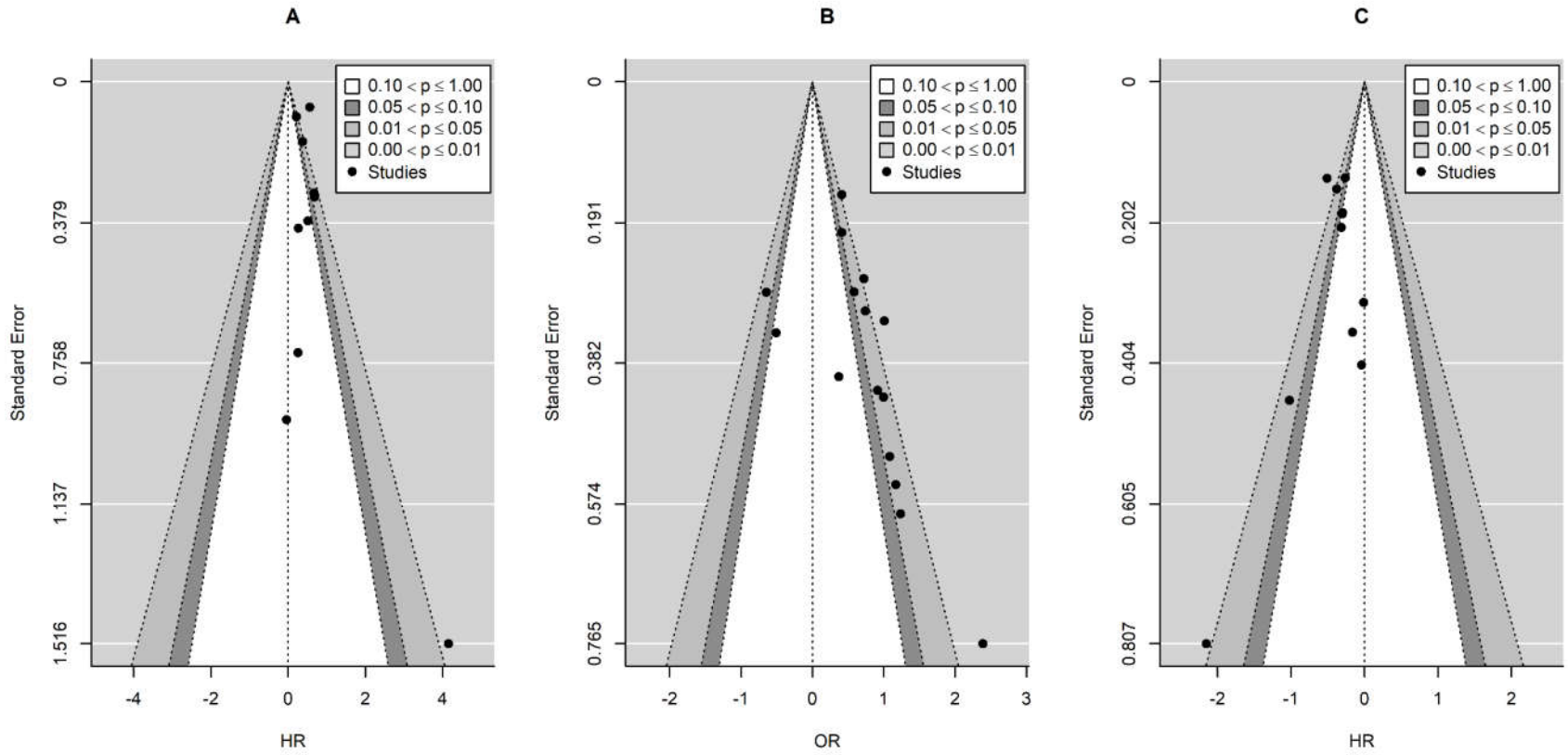



Figure S9 Contour enhanced funnel plots for three meta-analytic models. (A). Locoregional recurrence in patients treated with radiotherapy; (B) Radiation-induced toxicity; (C) progression-free survival in patients treated with immunotherapy. (B) may be suggestive of publication bias with potentially missing studies in areas of non-significance. Corresponding Egger's regression tests for funnel plot asymmetry (A): z = 1.13, p = 0.26; (B) z = 2.56, p = 0.01; (C) z = -1.02, p = 0.31 respectively.