Supplementary

Appendix 1

1. The search strategy of PubMed.

#37 Search #36 AND #23
#36 Search #32 NOT #35
#35 Search #33 NOT #34
#34 Search humans[MeSH Terms]
#33 Search animals[MeSH Terms]
#32 Search #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31
#31 Search drug therapy[MeSH Subheading]
#30 Search trial[Title/Abstract]
#29 Search groups[Title/Abstract]
#28 Search randomly[Title/Abstract]
#27 Search placebo[Title/Abstract]
#26 Search randomized[Title/Abstract]
#25 Search controlled clinical trial[Publication Type]
#24 Search randomized controlled trial[Publication Type]
#23 Search #21 AND #22
#22 Search #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20
#21 Search #1 OR #2 OR #3 OR #4 OR #5
#20 Search avelumab[Title/Abstract]
#19 Search durvalumab[Title/Abstract]
#18 Search atezolizumab[Title/Abstract]
#17 Search tremelimumab[Title/Abstract]
#16 Search ipilimumab[Title/Abstract]
#15 Search pembrolizumab[Title/Abstract]
#14 Search nivolumab[Title/Abstract]
#13 Search B7-H1 Antigen[Title/Abstract]
#12 Search anti-programmed cell death ligand 1[Title/Abstract]
#11 Search anti-programmed cell death 1[Title/Abstract]
#10 Search CTLA-4[Title/Abstract]
#9 Search PD-L1[Title/Abstract]
#8 Search PD-1[Title/Abstract]
#7 Search ICIs[Title/Abstract]
#6 Search immune checkpoint inhibitor*[Title/Abstract]
#5 Search NSCLC[Title/Abstract]
#4 Search non small cell lung carcinoma[Title/Abstract]
#3 Search non-small cell lung cancer*[Title/Abstract]
#2 Search non small cell lung cancer*[Title/Abstract]
#1 Search carcinoma, non small cell lung[MeSH Terms]

2. The search strategy of Embase.

#31. #22 AND #30
#30. #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29
#29. 'controlled trial':ti,ab,kw
#28. 'groups':ti,ab,kw
#27. 'control':ti,ab,kw
#26. 'randoml*':ti,ab,kw
#25. 'randomly':ti,ab,kw
#24. 'randomized':ti,ab,kw
#23. 'randomized controlled trial':ti,ab,kw
#22. #4 AND #21

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#21. #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20
#20. 'nivolumab':ti,ab,kw
#19. 'pembrolizumab':ti,ab,kw
#18. 'ipilimumab':ti,ab,kw
#17. 'tremelimumab':ti,ab,kw
#16. 'ticilimumab':ti,ab,kw
#15. 'atezolizumab':ti,ab,kw
#14. 'durvalumab':ti,ab,kw
#13. 'avelumab':ti,ab,kw
#12. 'anti-cytotoxic t lymphocyte associated antigen 4':ti,ab,kw
#11. 'ctla-4':ti,ab,kw#10. 'anti-programmed cell death ligand 1':ti,ab,kw
#9. 'anti-programmed cell death 1':ti,ab,kw
#8. 'pd-l1':ti,ab,kw
#7. 'pd-1':ti,ab,kw
#6. 'immune checkpoint inhibitor*':ti,ab,kw
#5. 'ici':ti,ab,kw
#4. #1 OR #2 OR #3
#3. 'non small cell lung carcinoma':ti,ab,kw
#2. 'nsclc':ti,ab,kw
#1. 'non small cell lung cancer':ti,ab,kw

3. The search strategy of Cochrane library.

#1 MeSH descriptor: [Carcinoma, Non-Small-Cell Lung] explode all trees
#2 (non small cell lung cancer):ti,ab,kw
#3 ("non small cell lung carcinoma"):ti,ab,kw
#4 (nonsmall cell lung cnacer):ti,ab,kw
#5 (NSCLC):ti,ab,kw
#6 {OR #1-#5}
#7 (immune checkpoint inhibitor*):ti,ab,kw
#8 (ICI):ti,ab,kw
#9 (PD-1):ti,ab,kw
#10 (PD-L1):ti,ab,kw
#11 (anti-programmed cell death 1):ti,ab,kw
#12 (anti-programmed cell death ligand 1):ti,ab,kw
#13 (CTLA-4):ti,ab,kw
#14 (cytotoxic T lymphocyte antigen 4):ti,ab,kw
#15 {OR #7-#14}
#16 (avelumab):ti,ab,kw
#17 (durvalumab):ti,ab,kw
#18 (atezolizumab):ti,ab,kw
#19 (tremelimumab):ti,ab,kw
#20 (ipilimumab):ti,ab,kw
#21 (pembrolizumab):ti,ab,kw
#22 (nivolumab):ti,ab,kw
#23 {OR #15-#22}
#24 {AND #6, #23}
#25 (random*):ti,ab,kw
#26 (control):ti,ab,kw
#27 (trial):ti,ab,kw
#28 (placebo):ti,ab,kw
#29 (groups):ti,ab,kw
#30 {OR #25-#29}
#31 {AND #24, #30}

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Table S1 The risk of bias of included studies according to the 'risk of bias' assessment tool of Cochrane Handbook for Systematic Review of Interventions

Study ID	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data addressed	Selective reporting
CheckMate 017	Low risk. Quote: "We randomly assigned... in a 1:1 ratio..."	Unclear risk. Quote: "The trial was open label...". But insufficient information to permit judge of high or low risk.	Unclear risk. Quote: "The trial was open label...". But insufficient information to permit judge of high or low risk.	Unclear risk. Quote: "The trial was open label...". But insufficient information to permit judge of high or low risk.	Low risk. Only 12 (4%) didn't receive treatment with a study drug after randomization. All participants finished follow-up.	Low risk. The conformity between protocol and reported outcomes.
CheckMate 026	Low risk. Quote: "We randomly assigned, in a 1:1 ratio..."	Unclear risk. Quote: "The trial was open label...". But insufficient information to permit judge of high or low risk.	Unclear risk. Quote: "The trial was open label...". But insufficient information to permit judge of high or low risk.	Unclear risk. Quote: "The trial was open label...". But insufficient information to permit judge of high or low risk.	Low risk. Only 11 (2%) didn't receive treatment with a study drug after randomization. All participants finished follow-up.	Low risk. The conformity between protocol and reported outcomes.
CheckMate 057	Low risk. Quote: "Patients were randomized to... in a 1:1 ratio..."	Unclear risk. Quote: "The trial was open label...". But insufficient information to permit judge of high or low risk.	Unclear risk. Quote: "The trial was open label...". But insufficient information to permit judge of high or low risk.	Unclear risk. Quote: "The trial was open label...". But insufficient information to permit judge of high or low risk.	Low risk. No missing outcome data.	Low risk. The conformity between protocol and reported outcomes.
CheckMate 078	Low risk. Quote: "Patients were randomly assigned 2:1 to..."	Unclear risk. Quote: "The trial was open label...". But insufficient information to permit judge of high or low risk.	Unclear risk. Quote: "The trial was open label...". But insufficient information to permit judge of high or low risk.	Unclear risk. Quote: "The trial was open label...". But insufficient information to permit judge of high or low risk.	Low risk. Only 1 patients in the experimental group and 10 patients in the control group didn't receive treatment after randomization. All participants finished follow-up.	Low risk. The conformity between protocol and reported outcomes.
CheckMate 227	Low risk. Quote: "randomly assigned (in a 1:1:1 ratio)..."	Unclear risk. Quote: "The trial was open label...". But insufficient information to permit judge of high or low risk.	Unclear risk. Quote: "The trial was open label...". But insufficient information to permit judge of high or low risk.	Unclear risk. Quote: "The trial was open label...". But insufficient information to permit judge of high or low risk.	Low risk. No missing outcome data.	Low risk. The conformity between protocol and reported outcomes.
Govindan R 2017	Low risk. Quote: "Patients...were randomly assigned (1:1) to..."	Low risk. Quote: "In this double-blind trial..."	Low risk. Quote: "In this double-blind trial..."	Low risk. Quote: "In this double-blind trial..."	Low risk. No missing outcome data.	Low risk. The conformity between protocol and reported outcomes.
IMpower130	Low risk. Quote: "Patients were randomly assigned with permuted block randomisation (block size of six)...."	Unclear risk. Quote: "The trial was open label...". But insufficient information to permit judge of high or low risk.	Unclear risk. Quote: "The trial was open label...". But insufficient information to permit judge of high or low risk.	Unclear risk. Quote: "The trial was open label...". But insufficient information to permit judge of high or low risk.	Low risk. One patient died before randomization, this patient was excluded from the intention-to-treat population.	Low risk. The conformity between protocol and reported outcomes.
JAVELIN Lung 200	Low risk. Quote: "Patients were ...were Randomly assigned (1:1) via an interactive voice-response system"	Unclear risk. Quote: "The trial was open label...". But insufficient information to permit judge of high or low risk.	Unclear risk. Quote: "...neither investigators nor patients were masked to assigned study treatments." But insufficient information to permit judge of high or low risk.	Unclear risk. Quote: "...neither investigators nor patients were masked to assigned study treatments." But insufficient information to permit judge of high or low risk.	Low risk. No missing outcome data.	Low risk. The conformity between protocol and reported outcomes.
KEYNOTE-024	Low risk. Quote: "Eligible patients were randomly assigned (1:1)..."	Unclear risk. Quote: "The trial was open label...". But insufficient information to permit judge of high or low risk.	Unclear risk. Quote: "The trial was open label...". But insufficient information to permit judge of high or low risk.	Unclear risk. Quote: "The trial was open label...". But insufficient information to permit judge of high or low risk.	Low risk. No missing outcome data.	Low risk. The conformity between protocol and reported outcomes.
KEYNOTE-189	Low risk. Quote: "we randomly assigned (in a 2:1 ratio)..."	Low risk. Quote: "In this double-blind trial..."	Low risk. Quote: "In this double-blind trial..."	Low risk. Quote: "In this double-blind trial..."	Low risk. Only 5 patients in the experimental group and 4 patients in the control group didn't receive treatment with a study drug after randomization. All participants finished follow-up.	Low risk. The conformity between protocol and reported outcomes.
OAK Study	Low risk. Quote: "Permuted block-randomisation (block size of eight) via an interactive voice or web response system (bracket) was used to assign patients in a 1:1 ratio to..."	Unclear risk. Quote: "The trial was open label...". But insufficient information to permit judge of high or low risk.	Unclear risk. Quote: "The trial was open label...". But insufficient information to permit judge of high or low risk.	Unclear risk. Quote: "The trial was open label...". But insufficient information to permit judge of high or low risk.	Low risk. No missing outcome data.	Low risk. The conformity between protocol and reported outcomes.
PACIFIC	Low risk. Quote: "We randomly assigned patients, in a 2:1 ratio..."	Low risk. Quote: "In this double-blind trial..."	Low risk. Quote: "In this double-blind trial..."	Low risk. Quote: "In this double-blind trial..."	Low risk. No missing outcome data.	Low risk. The conformity between protocol and reported outcomes.

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Table S2 Subgroup analysis of smoking status specific pooled hazard ratio (OS and PFS)

Subgroups	OS_Never smokers			OS_Current/former smokers			PFS_Never smokers			PFS_Current/former smokers		
	No. of trials	Pooled HR	Inter-group heterogeneity	No. of trials	Pooled HR	Inter-group heterogeneity	No. of trials	Pooled HR	Inter-group heterogeneity	No. of trials	Pooled HR	Inter-group heterogeneity
Lines												
> 1st line	6	0.75 (0.50, 1.12)	I^2=0.0%; P=0.32	7	0.82 (0.70, 0.96)	I^2=59.1%; P=0.12	3	0.78 (0.44, 1.38)	I^2=0.0%; P=0.53	4	0.70 (0.55, 0.89)	I^2=0.0%; P=0.79
1st line	5	0.98 (0.69, 1.40)		5	0.71 (0.63, 0.79)		5	1.25 (0.32, 4.81)		6	0.74 (0.50, 1.11)	
Drugs												
Nivolumab	3	0.83 (0.61, 1.12)	I^2=66.3%; P=0.02	4	0.70 (0.60, 0.81)	I^2=58.5%; P=0.03	3	0.98 (0.79, 1.22)	I^2=72.5%; P=0.03	5	0.82 (0.73, 0.92)	I^2=85.6%; P=0.001
Atezolizumab	2	0.83 (0.56, 1.22)		2	0.79 (0.70, 0.89)		1	0.63 (0.35, 1.12)		1	0.64 (0.53, 0.77)	
Pembrolizumab	2	0.32 (0.10, 0.98)		2	0.57 (0.47, 0.71)		1	0.43 (0.23, 0.81)		1	0.53 (0.43, 0.66)	
Avelumab	1	1.69 (0.97, 2.95)		1	0.83 (0.66, 1.04)							
Ipilimumab	1	1.19 (0.71, 1.99)		1	0.88 (0.74, 1.05)							
Durvalumab	1	0.44 (0.21, 0.90)		1	0.70 (0.56, 0.88)							
Histological subtypes												
NSCLC	6	0.81 (0.60, 1.08)	I^2=20.3%; P=0.29	6	0.73 (0.66, 0.81)	I^2=9.2%; P=0.33	4	1.30 (0.38, 4.38)	I^2=0.0%; P=0.44	5	0.83 (0.57, 1.21)	I^2=0%; P=0.13
Non-squamous	4	0.53 (0.22, 1.30)		4	0.65 (0.53, 0.79)		4	0.74 (0.36, 1.53)		4	0.66 (0.51, 0.84)	
Squamous	1	1.19 (0.71, 1.99)		2	0.73 (0.50, 1.09)					1	0.63 (0.48, 0.83)	

OS, overall survival; PFS, progressive-free survival.

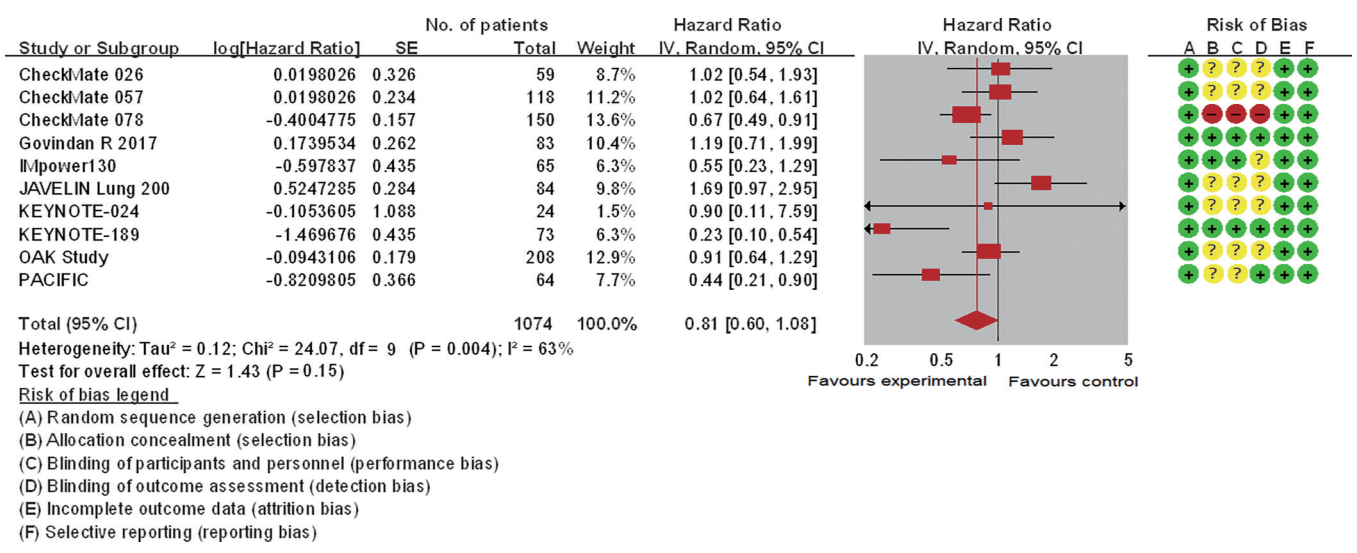

Figure S1 The forest plot involved 11 eligible studies and 1,074 participants in terms of overall survival (OS) of non-smokers. The risk of bias mainly originated from allocation concealment, blinding of participants and personnel and blinding of outcome assessment. And severe heterogeneity was identified across these studies. The pooled hazard ratio based on random effect model showed a tendency of improvement of OS in the experimental group versus control group without statistical significance (P=0.15).

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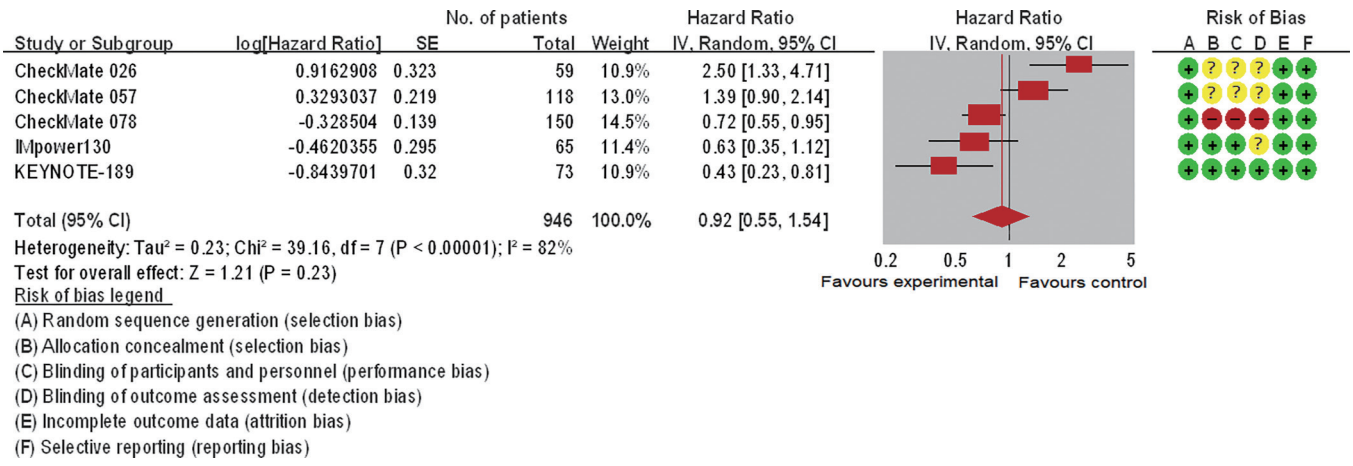

Figure S2 The forest plot involved 7 eligible studies (8 trials) and 946 participants in terms of progressive-free survival (PFS) of non-smokers. The risk of bias mainly originated from allocation concealment, blinding of participants and personnel and blinding of outcome assessment. And extreme heterogeneity was identified across these studies. The pooled hazard ratio based on random effect model showed a tendency of improvement of PFS in the experimental group versus control group without statistical significance (P=0.23).

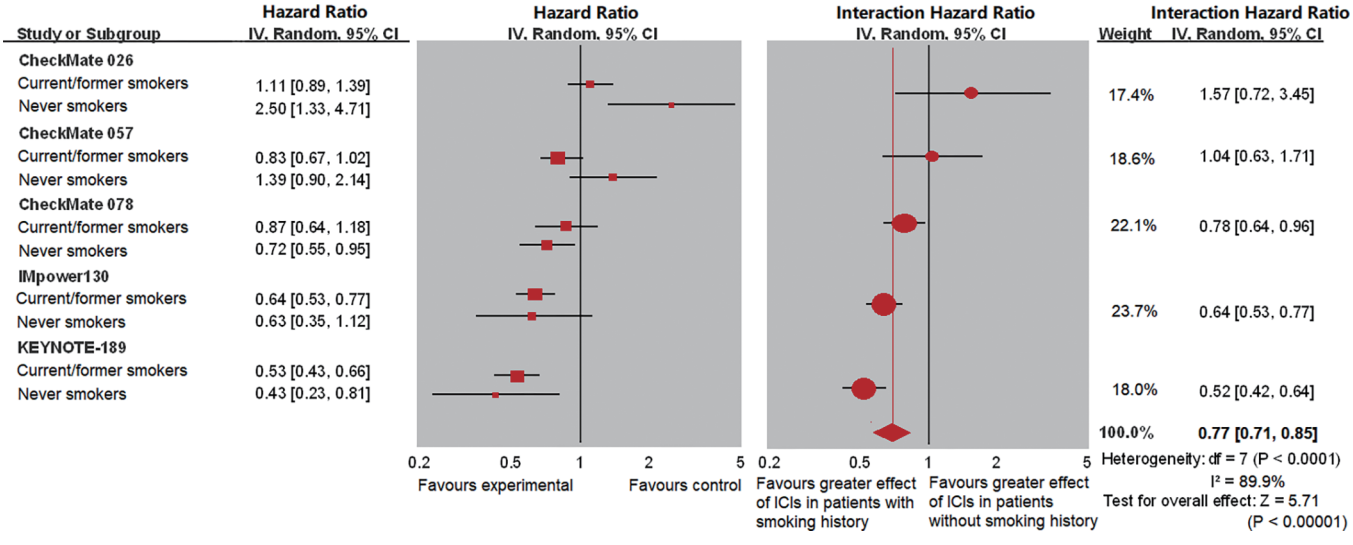

Figure S3 The interaction hazard ratio of progressive-free survival (PFS) involved 8 studies by smoking history (current/former versus never smokers). The left panel shows the effect of HR (95% CI) for each subgroup within each trial. The right panel shows the interaction between HR (95% CI) and smoking history, along with a meta-analysis of the interaction estimates. And severe heterogeneity was discovered across these studies (I^2=89.9%, P<0.00001). It showed that there was a significant difference in the efficacy of immune checkpoint inhibitors in terms of PFS between never and current/former smokers, when compared with controls for each smoking status.

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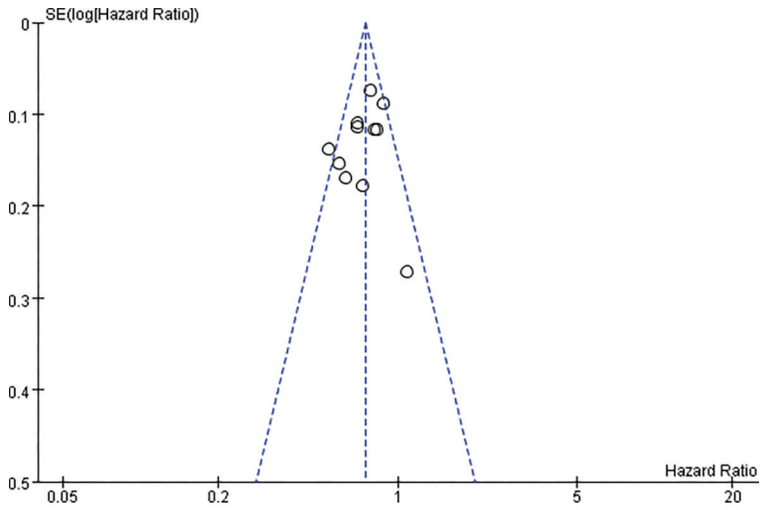

Figure S4 The funnel plot was generated across studies reporting overall survival data of current/former smokers. There has no obvious publication bias across included studies according to the plot.

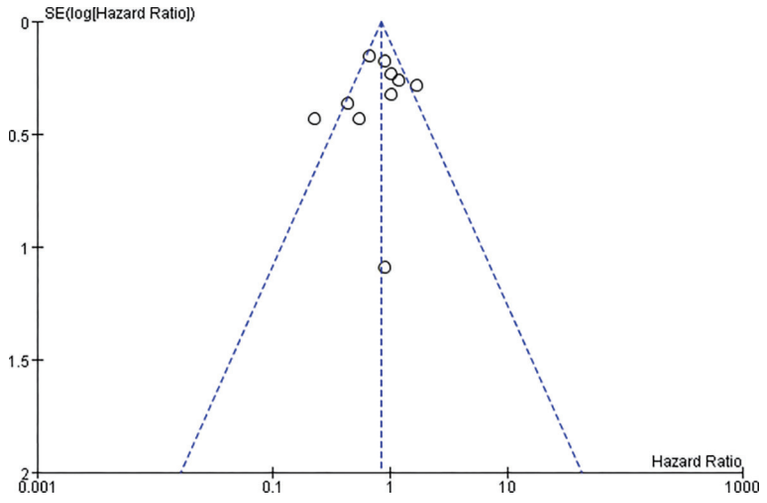

Figure S5 The funnel plot was generated across studies reporting overall survival data of non-smokers. There has a slight publication bias across included studies according to the plot.

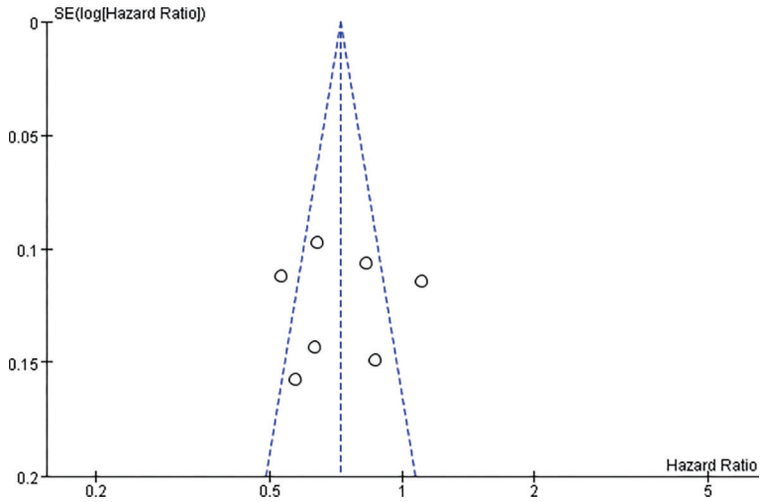

Figure S6 The funnel plot was generated across studies reporting progressive-free survival data of current/former smokers. There has a slight publication bias across included studies according to the plot.

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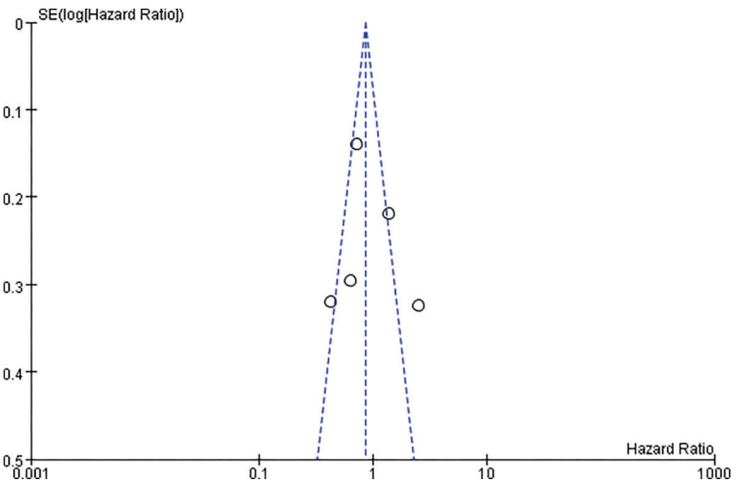

Figure S7 The funnel plot was generated across studies reporting progressive-free survival data of non-smokers. There has a slight publication bias across included studies according to the plot.

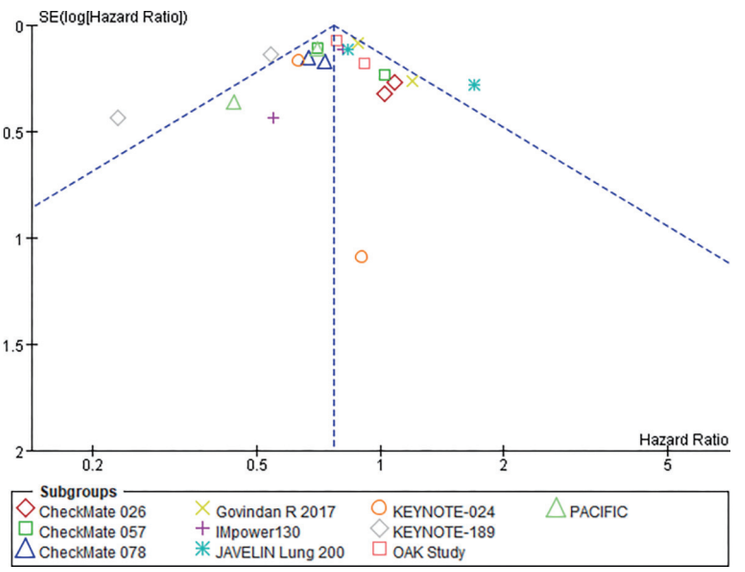

Figure S8 The funnel plot was generated across studies reporting overall survival data comparing current/former with never smokers. There has a slight publication bias across included studies according to the plot.

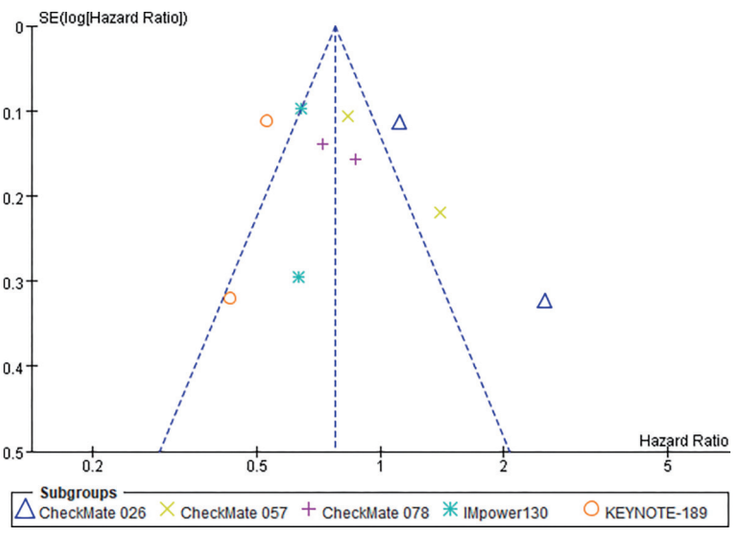

Figure S9 The funnel plot was generated across studies reporting progressive-free survival data comparing current/former with never smokers. There has a median publication bias across included studies according to the plot.

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