

Table S1. Summary of findings.

Question: LMP1 gene variants in Nasopharyngeal carcinoma

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LMP1 variants		Relative (95% CI)	Absolute (95% CI)		
Xhol loss in NPC vs. other tu biopsy												
10	observational studies	not serious ^{ab}	not serious	not serious	not serious	all plausible residual confounding would reduce the demonstrated effect	319/384 (83.1%)	102/190 (53.7%)	OR 6.19 (3.55 to 10.78)	341 more per 1,000 (from 268 more to 389 more)	⊕⊕⊕○ MODERATE	CRITICAL
Xhol loss NPC vs. healthy respondents biopsy												
4	observational studies	serious ^{ab}	not serious	not serious	serious ^c	strong association all plausible residual confounding would reduce the demonstrated effect	116/122 (95.1%)	45/73 (61.6%)	OR 14.17 (4.99 to 40.20)	341 more per 1,000 (from 273 more to 368 more)	⊕⊕○○ LOW	CRITICAL
Xhol loss NPC biopsy vs. healthy TWs												
4	observational studies	serious ^{ab}	not serious	not serious	serious ^c	very strong association all plausible residual confounding would suggest spurious effect, while no effect was observed	147/154 (95.5%)	49/65 (75.4%)	OR 24.60 (4.42 to 136.94)	233 more per 1,000 (from 177 more to 244 more)	⊕⊕⊕○ MODERATE	CRITICAL
Xhol loss NPC vs. other EBV-associated non-NPC tumors biopsy in endemic regions												
7	observational studies	serious ^{ab}	not serious	not serious	not serious	all plausible residual confounding would reduce the demonstrated effect	215/244 (88.1%)	96/124 (77.4%)	OR 2.10 (0.94 to 4.68)	104 more per 1,000 (from 11 fewer to 167 more)	⊕⊕○○ LOW	CRITICAL
Xhol loss NPC vs. other EBV-associated non-NPC tumors biopsy in non-endemic regions												
3	observational studies	very serious ^{ab,c}	not serious	not serious	serious ^c	very strong association all plausible residual confounding would reduce the demonstrated effect	9/25 (36.0%)	1/50 (2.0%)	OR 11.84 (2.32 to 60.45)	175 more per 1,000 (from 25 more to 532 more)	⊕⊕○○ LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LMP1 variants		Relative (95% CI)	Absolute (95% CI)		

30-bp deletion NPC vs. healthy respondents biopsy

4	observational studies	not serious	not serious	not serious	not serious	all plausible residual confounding would reduce the demonstrated effect	98/128 (76.6%)	36/57 (63.2%)	OR 3.53 (1.48 to 8.43)	227 more per 1,000 (from 86 more to 304 more)	⊕⊕⊕○ MODERATE	IMPORTANT
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30-bp deletion NPC biopsy vs. healthy respondents TWs

6	observational studies	not serious	not serious	not serious	not serious	all plausible residual confounding would reduce the demonstrated effect	248/273 (90.8%)	119/171 (69.6%)	OR 3.77 (2.21 to 6.44)	200 more per 1,000 (from 139 more to 241 more)	⊕⊕⊕○ MODERATE	IMPORTANT
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30-bp deletion NPC biopsy vs. other EBV-associated non-NPC tumors biopsy

20	observational studies	not serious	serious	serious ^d	not serious	all plausible residual confounding would reduce the demonstrated effect	393/533 (73.7%)	246/441 (55.8%)	OR 1.79 (0.79 to 4.04)	135 more per 1,000 (from 59 fewer to 278 more)	⊕○○○ VERY LOW	IMPORTANT
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30-bp deletion NPC vs. healthy respondents TWs

3	observational studies	not serious	not serious	not serious	not serious	all plausible residual confounding would reduce the demonstrated effect	79/153 (51.6%)	55/96 (57.3%)	OR 1.25 (0.71 to 2.21)	54 more per 1,000 (from 85 fewer to 175 more)	⊕⊕⊕○ MODERATE	IMPORTANT
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30-bp deletion NPC blood vs Healthy blood

5	observational studies	not serious	serious ^a	serious ^d	not serious	all plausible residual confounding would reduce the demonstrated effect	52/201 (25.9%)	34/179 (19.0%)	OR 0.82 (0.18 to 3.83)	29 fewer per 1,000 (from 149 fewer to 283 more)	⊕○○○ VERY LOW	IMPORTANT
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30-bp deletion NPC vs. other EBV-associated non-NPC tumors biopsy in endemic regions

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LMP1 variants		Relative (95% CI)	Absolute (95% CI)		
7	observational studies	not serious	not serious	not serious	not serious	all plausible residual confounding would reduce the demonstrated effect	197/223 (88.3%)	110/142 (77.5%)	OR 1.59 (0.83 to 3.06)	71 more per 1,000 (from 34 fewer to 139 more)	 MODERATE	IMPORTANT

30-bp deletion NPC vs. healthy respondents biopsy in endemic regions

5	observational studies	not serious	serious ^a	not serious	serious ^c	strong association all plausible residual confounding would reduce the demonstrated effect	135/171 (78.9%)	45/80 (56.3%)	OR 6.91 (1.18 to 40.35)	336 more per 1,000 (from 40 more to 419 more)	 LOW	IMPORTANT
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30-bp deletion NPC biopsy vs. healthy respondents TWs in endemic regions

6	observational studies	not serious	serious ^c	not serious	not serious	all plausible residual confounding would reduce the demonstrated effect	222/247 (89.9%)	114/155 (73.5%)	OR 2.80 (1.62 to 4.84)	151 more per 1,000 (from 83 more to 195 more)	 LOW	IMPORTANT
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30-bp deletion NPC vs. other EBV-associated non-NPC tumors biopsy in non-endemic regions

7	observational studies	not serious	not serious	serious ^d	not serious	all plausible residual confounding would reduce the demonstrated effect	20/84 (23.8%)	32/80 (40.0%)	OR 0.67 (0.33 to 1.36)	91 fewer per 1,000 (from 220 fewer to 76 more)	 LOW	IMPORTANT
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69-bp deletion NPC vs. other EBV-associated non-NPC tumors biopsy

4	observational studies	not serious	not serious	not serious	not serious	all plausible residual confounding would reduce the demonstrated effect	18/123 (14.6%)	5/62 (8.1%)	OR 1.70 (0.63 to 4.61)	49 more per 1,000 (from 28 fewer to 207 more)	 MODERATE	IMPORTANT
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69-bp deletion NPC biopsy vs. healthy respondents periheral blood

4	observational studies	not serious	serious ^a	not serious	not serious	all plausible residual confounding would reduce the demonstrated effect	17/168 (10.1%)	5/106 (4.7%)	OR 2.22 (0.26 to 18.60)	52 more per 1,000 (from 34 fewer to 432 more)	 LOW	IMPORTANT
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Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LMP1 variants		Relative (95% CI)	Absolute (95% CI)		

B95-8 NPC vs. healthy respondents biopsy

3	observational studies	serious ^a	serious ^a	serious ^d	not serious	all plausible residual confounding would reduce the demonstrated effect	12/62 (19.4%)	5/29 (17.2%)	OR 1.27 (0.44 to 3.67)	37 more per 1,000 (from 88 fewer to 261 more)	⊕○○○ VERY LOW	NOT IMPORTANT
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B95.8-A NPC vs. healthy respondents TWs

3	observational studies	serious ^a	serious ^a	serious ^d	not serious	all plausible residual confounding would reduce the demonstrated effect	10/83 (12.0%)	14/29 (48.3%)	OR 0.16 (0.00 to 5.90)	353 fewer per 1,000 (from -- to 364 more)	⊕○○○ VERY LOW	IMPORTANT
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B95.8/A NPC vs. healthy respondents peripheral blood

3	observational studies	not serious	not serious	not serious	not serious	all plausible residual confounding would suggest spurious effect, while no effect was observed	10/65 (15.4%)	46/66 (69.7%)	OR 0.06 (0.02 to 0.17)	576 fewer per 1,000 (from 653 fewer to 416 fewer)	⊕⊕⊕○ MODERATE	IMPORTANT
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China 1 NPC vs. other EBV-associated non-NPC tumors biopsy

4	observational studies	not serious	not serious	not serious	not serious	all plausible residual confounding would suggest spurious effect, while no effect was observed	12/76 (15.8%)	13/36 (36.1%)	OR 0.33 (0.13 to 0.85)	204 fewer per 1,000 (from 293 fewer to 37 fewer)	⊕⊕⊕○ MODERATE	IMPORTANT
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China 1 NPC vs. other EBV-associated non-NPC tumors peripheral blood

3	observational studies	not serious	serious ^a	not serious	not serious	all plausible residual confounding would suggest spurious effect, while no effect was observed	20/61 (32.8%)	24/39 (61.5%)	OR 0.10 (0.00 to 2.34)	477 fewer per 1,000 (from -- to 174 more)	⊕⊕○○ LOW	NOT IMPORTANT
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China 1 NPC vs. other EBV-associated non-NPC tumors TWs

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LMP1 variants		Relative (95% CI)	Absolute (95% CI)		
3	observational studies	not serious	serious ^a	serious ^d	serious ^c	all plausible residual confounding would suggest spurious effect, while no effect was observed	37/87 (42.5%)	36/77 (46.8%)	OR 0.25 (0.01 to 7.88)	288 fewer per 1,000 (from 459 fewer to 406 more)	 VERY LOW	NOT IMPORTANT

Med NPC vs. other EBV-associated non-NPC tumours biopsy

4	observational studies	not serious	not serious	not serious	not serious	all plausible residual confounding would suggest spurious effect, while no effect was observed	29/76 (38.2%)	13/36 (36.1%)	OR 1.14 (0.50 to 2.63)	31 more per 1,000 (from 141 fewer to 237 more)	 MODERATE	IMPORTANT
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Med NPC vs. other EBV-associated non-NPC tumors peripheral blood

3	observational studies	not serious	serious ^a	serious ^d	not serious	all plausible residual confounding would suggest spurious effect, while no effect was observed	18/61 (29.5%)	6/39 (15.4%)	OR 2.26 (0.21 to 24.18)	137 more per 1,000 (from 117 fewer to 661 more)	 VERY LOW	NOT IMPORTANT
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Med NPC vs. other EBV-associated non-NPC tumors TWs

3	observational studies	not serious	not serious	not serious	not serious	all plausible residual confounding would suggest spurious effect, while no effect was observed	21/87 (24.1%)	7/77 (9.1%)	OR 1.95 (0.67 to 5.69)	72 more per 1,000 (from 28 fewer to 272 more)	 MODERATE	IMPORTANT
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North Carolina NPC vs. other EBV-associated non-NPC tumors biopsy

3	observational studies	not serious	not serious	not serious	not serious	all plausible residual confounding would reduce the demonstrated effect	2/59 (3.4%)	6/35 (17.1%)	OR 0.20 (0.04 to 0.90)	132 fewer per 1,000 (from 163 fewer to 14 fewer)	 MODERATE	IMPORTANT
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CI: Confidence interval; OR: Odds ratio; TW: throat washings

Explanations

- a. There was no confounding control in the study design, neither in the analysis.
- b. There was a selection bias due to inappropriately classified respondents (by regions, not by outcome).
- c. 95%CI of the odds ratio is wide, as thresholds for grading were considered trivial from 1 to 2.5, small from 2.5 to 5, moderate from 5 to 10, and large 10 and more
- d. There were results in both directions i.e. some studies reported higher, other lower prevalence of LMP1 gene variant in NPCs
- e. There was a great heterogeneity between studies assessed by I2 statistics in Review Manager