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Incidence and risk of severe infections associated with anti-epidermal growth factor receptor monoclonal antibodies in cancer patients: a systematic review and meta-analysis

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Abstract

Background: Anti-epidermal growth factor receptor (EGFR)-monoclonal antibodies (MoAbs) have been widely used in a variety of malignancies. Severe infections (≥grade 3) are potentially life-threatening adverse events with these drugs. However, the contribution of anti-EGFR MoAbs to infections is still unknown. We performed this meta-analysis to determine the overall incidence and risk of severe infections in cancer patients treated with these drugs.

Methods: The databases of PubMed and abstracts presented at oncology conferences and published in the proceedings were searched for relevant studies from January 2000 to May 2014. Summary incidences, relative risks (RRs) and 95% confidence intervals (CIs) were calculated by using either random effects or fixed effect models according to the heterogeneity of included studies.

Results: A total of 14,066 patients from 26 randomized controlled trials (RCTs) were included. The use of anti-EGFR-MoAbs significantly increased the risk of developing severe infections (RR 1.34, 95%CI: 1.10 to 1.62, $P = 0.003$) in cancer patients, but not for fatal infections (RR 1.62, 95%CI: 0.81 to 3.26, $P = 0.18$). Meta-regression indicated the infections might possibly occur early in the treatment with anti-EGFR MoAbs. On sub-group analysis, the risk of severe infections significantly varied with tumor type ($P = 0.001$). When stratified by specific anti-EGFR MoAbs, a significantly increased risk of infections with cetuximab was observed ($P < 0.001$), but not for panitumumab ($P = 0.98$). Additionally, the use of anti-EGFR MoAbs significantly increased the risk of severe infections when used in conjunction with cisplatin (RR 1.48, 95%CI 1.22 to 1.79, $P < 0.001$) or irinotecan (RR 1.53, 95%CI 1.12 to 2.10, $P = 0.008$). When stratified by specific infectious events, anti-EGFR-MoAbs significantly increased the risk of developing severe sepsis (RR 4.30, 95%CI: 1.80 to 10.27; $P = 0.001$).

Conclusions: Anti-EGFR MoAbs treatment significantly increases the risk of developing severe infectious events in cancer patients. The risk may vary with tumor types. Clinicians should be aware of the risks of severe infections with the administration of these drugs in cancer patients.

Keywords: Cetuximab, Panitumumab, Anti-EGFR monoclonal antibody, Infections, Cancer, Meta-analysis

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Background

The epidermal growth factor receptor (EGFR) signal pathway plays an essential role in tumor proliferation, differentiation, anti-apoptosis and metastasis [1-3]. For this reason, EGFR and the process of its receptor binding are regarded as attractive therapeutic targets in the treatment of cancers. Currently, two monoclonal antibodies (MoAbs) targeted at EGFR, the chimeric immunoglobulin G1 (IgG1) MoAb cetuximab and the fully humanized IgG2 MoAb panitumumab, have shown a relevant clinical effect in the treatment of a variety of malignancies. Cetuximab has been approved by the US Food and Drug Administration (FDA) for the treatment of metastatic colorectal cancer [4] and recurrent or metastatic head and neck cancer [5]. Panitumumab is approved by the FDA for the indication of advanced colorectal cancer [6].

In contrast with traditional chemotherapy agents, anti-EGFR-MoAbs do not usually produce systemic toxicities such as nausea, vomiting, diarrhea, alopecia, and bone marrow suppression. However, anti-EGFR-MoAbs exhibit some unique toxicities including rash [7,8], hypomagnesemia [9-11], hypokalemia [12] and venous and arterial thromboembolic events [11]. Specifically, severe infections (≥grade 3) are reported in both cetuximab and panitumumab trials as a common side effect, as a cause of treatment disruption, and in some cases led to fatalities [13-15]. However, to the best of our knowledge, the incidence and risk of severe infections with these drugs have not been systematically defined. Therefore, we performed this up-to-date meta-analysis of randomized controlled trials to determine whether the addition of anti-EGFR-MoAbs to therapies increases the risk of severe and fatal infections in cancer patients.

Methods
Data sources

We searched the PubMed (data from 2000 to May 2014), Embase (data from 2000 to May 2014) and the Cochrane Library electronic databases. Key words were 'cetuximab', 'Erbitux', 'panitumumab', 'Vectibix', 'cancer', 'carcinoma', 'neoplasm', 'randomized controlled trial' and 'infections'. The search was limited to prospective randomized clinical trials published in English. We also searched abstracts containing the term 'cetuximab' and 'panitumumab' that were presented at the American Society of Clinical Oncology (ASCO) and European Society of Medical Oncology (ESMO) annual meetings from 2004 to 2014 to identify relevant studies. Additionally, we searched the clinical trial registration website [16] to obtain information on registered prospective trials. Each publication was reviewed and in cases of duplicate publications only the most complete, recent and updated report of the clinical trial was included in the meta-analysis.

Study selection

The primary goal of our study was to determine the overall incidence of severe and fatal infections (≥grade 3) associated with approved anti-EGFR-MoAbs (cetuximab and panitumumab) and establish the association between treatment with anti-EGFR-MoAbs and the risk of developing severe and fatal infections. Thus, only prospective randomized controlled phase II and III trials evaluating approved anti-EGFR-MoAbs (cetuximab and panitumumab) in cancer patients with adequate data on severe or fatal infections were incorporated in the analysis. Phase I and single-arm phase II trials were excluded due to lack of control groups. Clinical trials that met the following criteria were included: (1) prospective randomized controlled phase II or III trials involving cancer patients; (2) participants assigned to treatment with or without approved anti-EGFR-MoAbs (cetuximab and panitumumab) in addition to concurrent chemotherapy, radiotherapy or biological agent; and (3) available data regarding events or incidence of severe or fatal infections and sample size.

Data extraction and clinical end point

Data abstraction was conducted independently by two investigators (WXQ and SF), and any discrepancy between the reviewers was resolved by consensus. For each study, the following information was extracted: first author's name, year of publication, phase of trials, number of enrolled subjects, treatment arms, number of patients in treatment and control groups, underlying malignancy, median age, median treatment duration, median progression-free survival, median overall survival and adverse outcomes of interest (severe and fatal infections). The following adverse outcomes were considered as infectious events and were included in the analyses: infections (not specified), febrile neutropenia, sepsis, septic shock, and pneumonia. Adverse events of severe infections (≥grade 3), as assessed and recorded according to the National Cancer Institute's common terminology criteria (NCI-CTC) version 2 or 3 [17], which has been widely used in cancer clinical trials, were extracted for analysis.

Statistical analysis

For the calculation of incidence, the number of patients with infections in the anti-EGFR-MoAbs group and the total number of patients receiving anti-EGFR-MoAbs were extracted from the selected clinical trials; the proportion of patients with infections and 95% confidence interval (CI) were derived for each study. To calculate relative risk (RR), patients assigned to anti-EGFR-MoAbs were compared only with those assigned to control treatment in the same trial. For one study that reported zero events in the treatment or control arm, we applied the classic half-integer correction to calculate the RR and variance [18]. We also conducted the following pre-specified subgroup analyses to

find the potential risk factor of infections: tumor types, anti-EGFR-MoAbs, concomitant therapies and phase of trials. To assess the stability of results, sensitivity analysis was performed by sequential omission of individual studies. Additionally, to test whether effect sizes were moderated by differences in length of treatment, we have carried out meta-regressions with the difference in median length of experimental treatments (expressed in weeks) as the predictor and RR as the dependent variable. Between-study heterogeneity was estimated using the χ^2-based Q statistic [19]. Heterogeneity was considered statistically significant when $P_{heterogeneity} <0.1$. If heterogeneity existed, the pooled estimate calculated based on the random-effects model was reported using the DerSimonian *et al.* method [20]. In the absence of heterogeneity, the pooled estimate calculated based on the fixed-effects model was reported using the inverse variance method. A statistical test with a *P*-value less than 0.05 was considered significant. The presence of publication bias was evaluated by using the Begg and Egger tests [21]. All statistical analyses were performed by using Version 2 of the Comprehensive MetaAnalysis program (Biostat, Englewood, NJ, USA) and Open Meta-Analyst software version 4.16.12 (Tufts University, Medford, MA, USA).

Results

Search results

Our search yielded 190 clinical studies relevant to cetuximab and panitumumab. After excluding review articles, phase I studies, single-arm phase II trials, case reports, editorials, meta-analyses and systematic reviews (Figu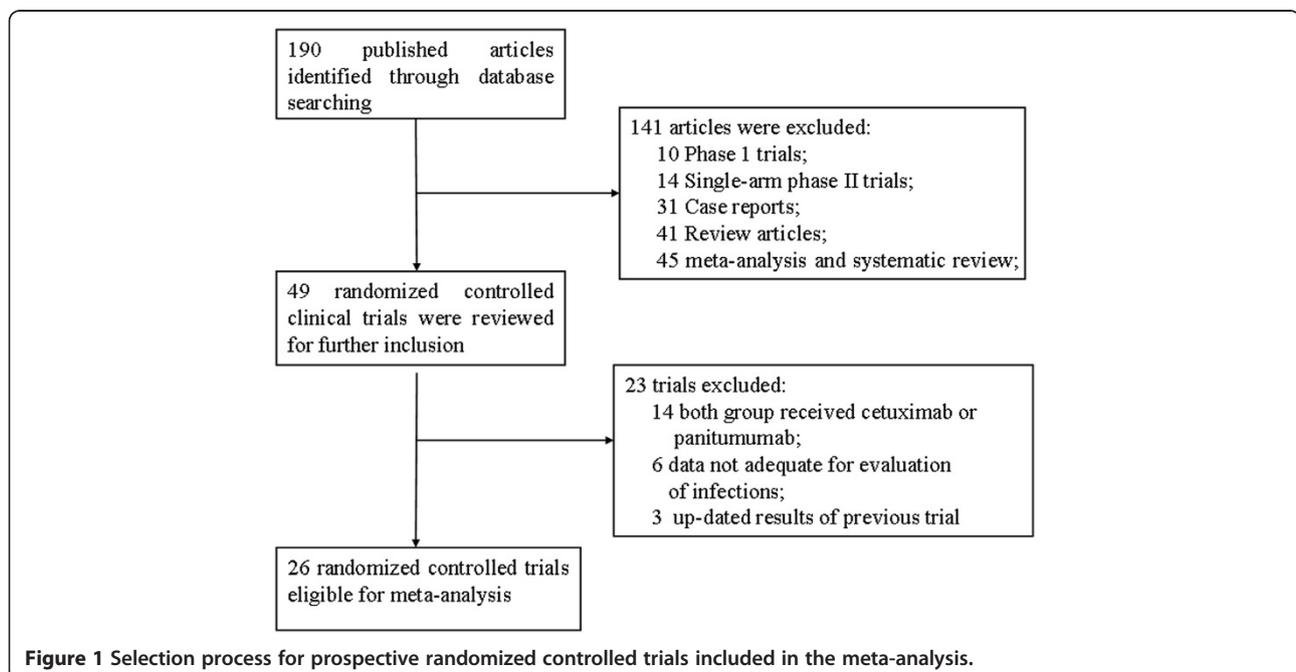re 1), we selected 26 randomized controlled trials (RCTs), which included 17 phase III and 9 phase II trials. A total of 14,060 patients from 26 RCTs were included for analysis. The characteristics of the patients and studies are listed in Table 1. According to the inclusion criteria of each trial, patients were required to have adequate hepatic, renal and hematological function. Underlying malignancies included colorectal cancer (eleven trials) [14,15,22-31], non-small-cell lung cancer (seven trials) [32-38], head and neck cancer (four trials) [5,13,39,40], breast cancer (one trial) [41], urothelial carcinoma (one trial) [42], pancreatic cancer (one trial) [43] and esophagogastric cancer (one trial) [44].

Overall incidence of severe and fatal infections

For calculating the incidence of severe infections, a total of 6,446 patients from 26 RCTs who received anti-EGFR-MoAbs were included for analysis. Using a random-effects model, the summary incidence of severe infection was 8.1% (95%CI, 6.0 to 10.9%). In addition, severe infections can be fatal in many instances. A total of 5,239 patients from 16 RCTs were included for analysis of fatal infections. Fatal infections occurred in 24 patients, representing a total incidence of 0.8% (95%CI: 0.5% to 1.2%). Among patients with anti-EGFR MoAbs-associated severe infections, meta-analysis showed that the mortality of severe infections associated with anti-EGFR MoAbs was 4.0% (95%CI: 2.7 to 5.9%).

Relative risk of severe and fatal infections

To determine the specific contribution of anti-EGFR MoAbs to the development of infections and to exclude the effect of any confounding factors, we calculated the

Figure 1 Selection process for prospective randomized controlled trials included in the meta-analysis.

Table 1 Baseline characteristics of 26 randomized controlled trials in the meta-analysis (number = 14,060)

Authors/year/phase	Histology	Patients enrolled	Treatment aim	Median age, years	Median duration, weeks	Median PFS, m	Median OS, m	Number for analysis	Severe infections	Reported infectious events
Burtness B. et al./2005/III	Head and neck cancer	117	Cetuximab + DDP	60.6	4.5	4.2	9.2	58	15	Infections
			Placebo + DDP	58.3	3	2.7	8	58	10	
Bonner J.A. et al./2006/III	Head and neck cancer	424	Cetuximab + radiotherapy	56	8	24.4	49	208	1	Infections
			Radiotherapy	58	NR	14.9	29.3	212	1	
Jonker D. J. et al./2007/III	CRC	572	Cetuximab + BSC	63	8.1	NR	6.1	288	37	Infections
			BSC	63.6	NR	NR	4.6	274	15	
Borner M. et al./2008/II	CRC	74	Cetuximab + oxaliplatin + capecitabine	60	18	7.2	20.5	37	0	Febrile neutropenia
			Oxaliplatin + capecitabine	63	18	5.8	16.5	37	0	
Rosell R. et al./2008/II	NSCLC	86	Cetuximab + NVB + DDP	58	13.6	5	8.3	42	7	Infections
			NVB + DDP	57	12	4.6	7.3	43	2	
Sobrero A.F. et al./2008/III	CRC	1298	Cetuximab + irinotecan	61	14	4	10.7	638	49	Febrile neutropenia
			Irinotecan	62	13.1	2.6	10	629	39	
Vermorken J.B. et al./2008/III	Head and neck cancer	422	Cetuximab + platinum + FU	56	18	5.6	10.1	219	28	Febrile neutropenia, pneumonia, sepsis
			Platinum + FU	57	15	3.3	7.4	215	15	
Lienbaum R. et al./2009/II	NSCLC	64	Cetuximab + PTX	NR	16	3.4	NR	30	1	Infections
			Bortezomib + PTX	NR	8	1.9	NR	29	1	
Pirker R.et al./2009/III	NSCLC	1125	Cetuximab + NVB + DDP	59	18	NR	11.3	548	129	Febrile neutropenia, sepsis
			NVB + DDP	60	14	NR	10.1	562	90	
Tol J. et al./2009/III	CRC	755	Cetuximab + capecitabine + oxaliplatin + Bev	62	30	10.7	20.3	366	22	Infections
			Capecitabine + oxaliplatin + Bev	62	25.7	9.4	19.4	366	25	
Lynch T.J. et al./2010/III	NSCLC	676	Cetuximab + chemotherapy	64	13	4.4	9.69	325	15	Febrile neutropenia
			Chemotherapy	65	12	4.24	8.38	320	11	
Govindan R. et al./2011/II	NSCLC	101	Cetuximab + chemoradiotherapy	66	NR	12.3	22.2	53	9	Febrile neutropenia, pneumonia,
			Chemoradiotherapy	65	NR	12.6	22.4	50	10	
Alberts S.R. et al./2012/III	CRC	2686	Cetuximab + FOLFOX	NR	NR	NR	NR	931	96	Infections, febrile neutropenia, pneumonia
			FOLFOX	NR	NR	NR	NR	894	45	

Table 1 Baseline characteristics of 26 randomized controlled trials in the meta-analysis (number = 14,060) *(Continued)*

Dewdney A. *et al.*/2012/II	CRC	165	Cetuximab + capecitabine + oxaliplatin + radiotherapy	65	NR	NR	NR	83	1	Febrile neutropenia
			Capecitabine + oxaliplatin + radiotherapy	61	NR	NR	NR	81	1	
Saltz L. *et al.*/2012/III	CRC	247	Cetuximab + Bev + FOLFOX	63.2	NR	8.3	19.5	121	1	Sepsis
			Bev + FOLFOX	61.2	NR	11	21.3	118	1	
Baselga J. *et al.*/2013/II	MBC	181	Cetuximab + DDP	53	13.6	3.7	12.9	114	2	Sepsis
			DDP	52	13.1	1.5	9.4	57	0	
Kim E.S. *et al.*/2013/III	NSCLC	605	Cetuximab + Pemetrexed	64	NR	2.9	6.9	292	35	Infections, lung infections, sepsis
			Pemetrexed	65	NR	2.8	7.8	289	23	
Burtness B. *et al.*/2014/II	Pancreatic cancer	87	Cetuximab + Doc + irinotecan	60	16.5	4.5	6.5	45	5	Febrile neutropenia, infections
			Doc + irinotecan	60	14.5	3.9	5.3	46	4	
Huang J. *et al.*/2014/III	CRC	146	Cetuximab + FOLFIRI	57	NR	NR	NR	40	3	Infections, febrile neutropenia
			FOLFIRI	59	NR	NR	NR	106	3	
Hussain M. *et al.*/2014/II	Urothelial carcinoma	88	Cetuximab + GEM + DDP	60.9	21.4	7.6	14.3	59	7	Infections, pneumonia
			GEM + DDP	65.8	21.4	8.5	17.4	28	3	
van den Heuval M.M. *et al.*/2014/II	NSCLC	102	Cetuximab + chemoradiotherapy	62	NR	NR	NR	51	3	Pneumonia
			Chemoradiotherapy	63	NR	NR	NR	51	0	
Douillard J.Y. *et al.*/2010/III	CRC	1183	Panitumumab + FOLFOX4	NR	20	9.6	23.9	539	15	Febrile neutropenia
			FOLFOX4	NR	NR	8.6	19.7	545	14	
Peeters M. *et al.*/2010/III	CRC	1186	Panitumumab + FOLFIRI	NR	NR	5.9	14.5	539	9	Febrile neutropenia
			FOLFIRI	NR	NR	3.9	12.5	540	16	
Seymour M. T. *et al.*/2013/III	CRC	460	Panitumumab + irinotecan	64	12	NR	10.4	219	42	Infections
			Irinotecan	63	12	NR	10.5	218	22	
Vermorken J.B. *et al.*/2008/III	Head and neck cancer	657	Panitumumab + DDP + FU	58	18.3	5.8	11.1	325	20	Febrile neutropenia
			DDP + FU	59	NR	4.6	9	325	17	
Waddell T. *et al.*/2013/III	Esophagogastric cancer	553	Panitumumab + epirubicin + oxaliplatin + capecitabine	63	15	7.4	8.8	276	48	Infection, febrile neutropenia
			Epirubicin + oxaliplatin + capecitabine	62	15	6	11.3	266	70	

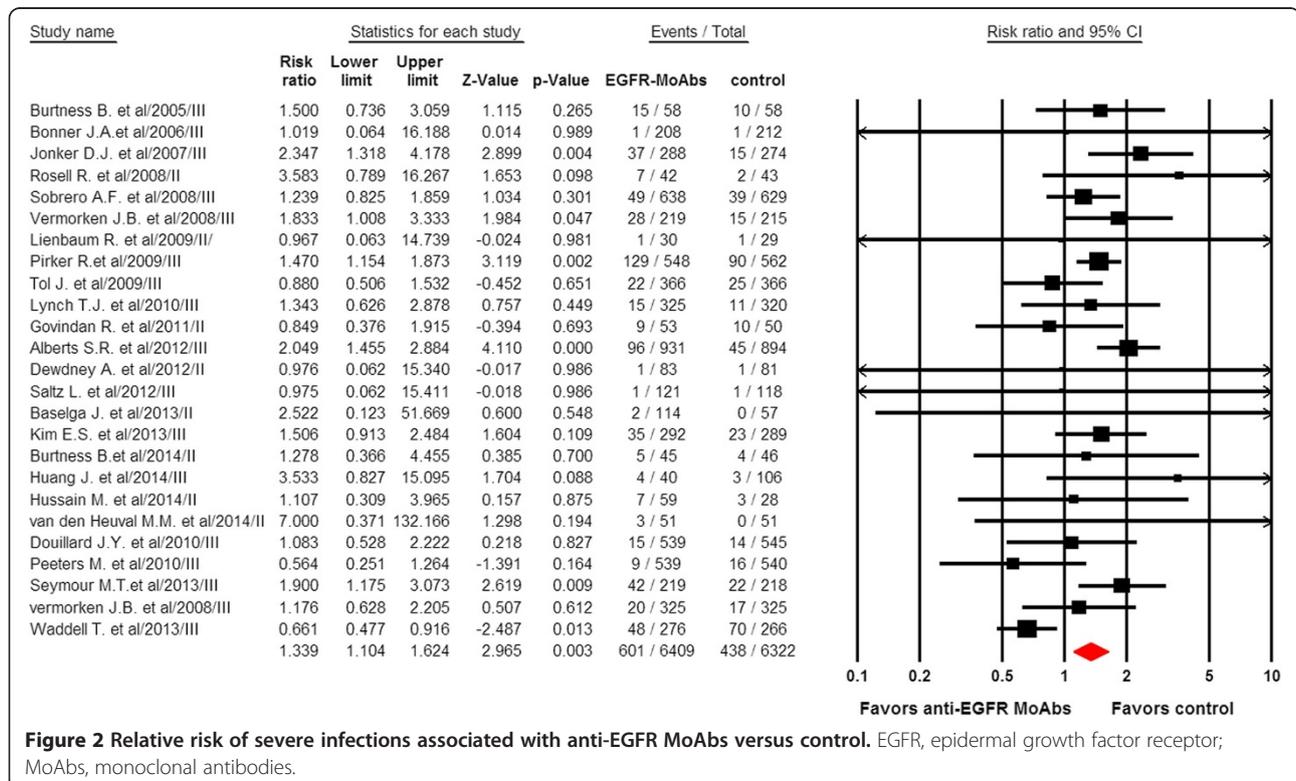Bev, bevacizumab; BSC, best support care; CRC, colorectal cancer; DDP, cisplatin; Doc, docetaxel; FOLFIRI, folinic acid (leucovorin), fluorouracil and irinotecan; FOLFOX, folinic acid (leucovorin), fluorouracil and oxaliplatin; Fu, fluorouracil; MBC, metastatic breast cancer; NR, not reported; NSCLC, non-small-cell lung cancer; NVB, vinorelbine; OS, overall survival; PTX, paclitaxel; PFS, progression free survival.
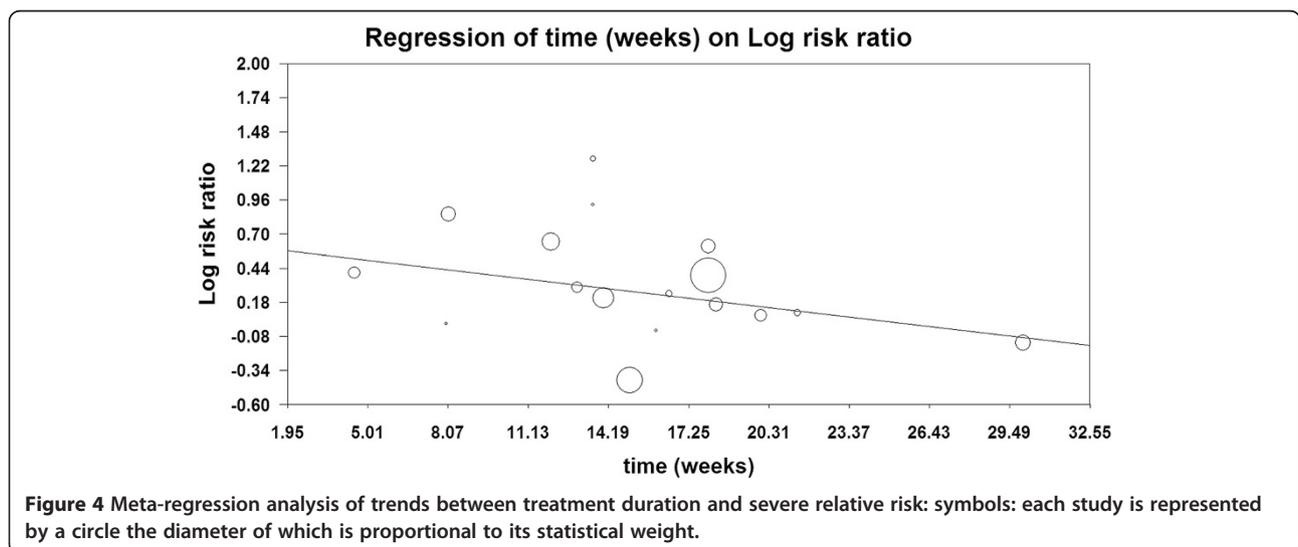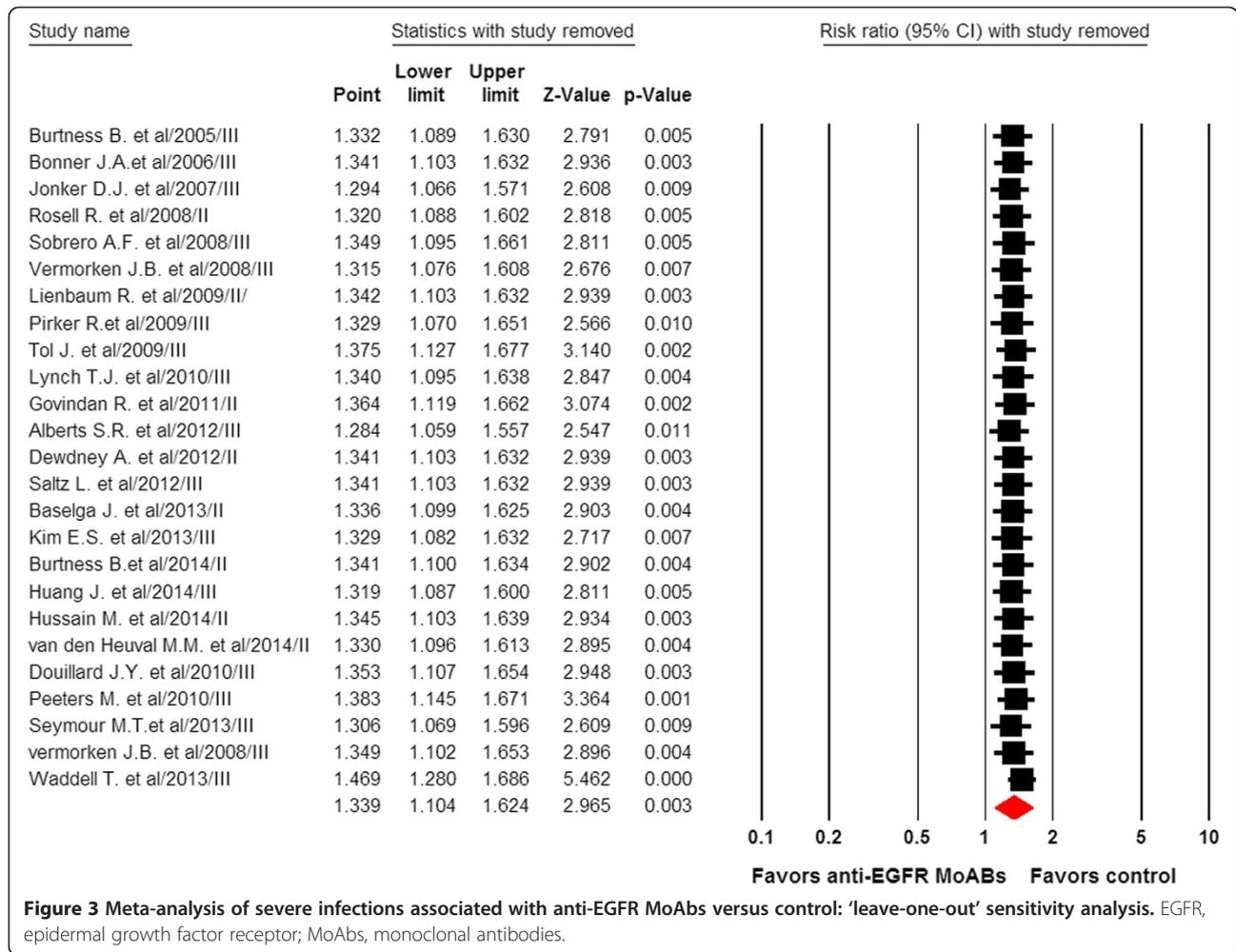
overall RR of infections from these RCTs. For calculating RR of severe infections, 26 RCTs, representing 14,060 patients, were included. Among the 6,446 patients treated with anti-EGFR MoAbs, 601 presented with severe infections, whereas 438 of 6,359 patients in control groups had a severe infectious event. This conferred an overall RR of developing severe infections of 1.34 (95%CI, 1.10 to 1.62; $P = 0.003$; Figure 2). Significant heterogeneity was observed in the RR analysis of severe infectious events (Q = 44.99; $P = 0.006$; $I^2 = 46.7\%$). Considering fatal infectious events, 24 of 5,239 patients treated with anti-EGFR MoAbs and 11 of 4,940 patients in control arms experienced a fatal infection. This conferred an overall RR of 1.61 (95%CI, 0.81 to 3.25; $P = 0.18$). No significant heterogeneity was observed in the RR analysis of fatal infections (Q = 6.64; $P = 0.88$; $I^2 = 0\%$). We also performed a sensitivity analysis to examine the stability and reliability of pooled severe RRs by sequential omission of individual studies. The results indicated that the significance estimate of pooled severe RRs was not significantly influenced by omitting any single study (Figure 3). Additionally, a meta-regression analysis was carried out to test whether the RR of severe infections varied as a function of difference in the length of the experimental treatments. The result indicated that the RR of severe infections tended to be lower in the study in which the experimental treatment was longer, and this effect was statistically significant ($P = 0.02$, Figure 4).

Sub-group analysis for relative risk of severe infections

To determine whether the observed increase in RRs of developing severe infections was the result of confounding bias, we performed subgroup analyses according to the underlying malignancy, anti-EGFR-MoAbs, concomitant drugs and phase of trials. When stratified by tumor types, a significantly increased risk of severe infections was observed in colorectal cancer (RR1.42, 95%: 1.05 to 1.93, $P = 0.024$), non-small-cell lung cancer (RR1.45, 95%: 1.19 to 1.77, $P <0.001$) and head and neck cancer (RR1.48, 95%: 1.02 to 2.13, $P = 0.037$), while the risk of severe infections was decreased in other tumor types (RR 0.72, 95%CI: 0.53 to 0.97, $P = 0.033$, Table 2). In addition, significant differences in RRs of severe infections were found among these tumor types ($P = 0.001$). However, clinicians should be cautious when interpreting these results due to limited RCTs of other tumor types included for the RR calculation.

The risk of severe infections might be related to different anti-EGFR MoAbs. Our results demonstrated that the use of cetuximab significantly increased the risk of severe infections (RR 1.52, 95%CI: 1.33 to 1.75, $P <0.001$), while the use of panitumumab did not increase the risk of severe infections (RR 0.99, 95%CI: 0.62 to 1.60, $P = 0.98$). Then, we also carried out a subgroup risk analysis stratified according to concomitant therapies with anti-EGFR-MoAbs. A significantly increased risk of severe infections with anti-EGFR-MoAbs was observed when used in conjunction with

Study name	Risk ratio	Lower limit	Upper limit	Z-Value	p-Value	Events / Total EGFR-MoAbs	control
Burtness B. et al/2005/III	1.500	0.736	3.059	1.115	0.265	15 / 58	10 / 58
Bonner J.A.et al/2006/III	1.019	0.064	16.188	0.014	0.989	1 / 208	1 / 212
Jonker D.J. et al/2007/III	2.347	1.318	4.178	2.899	0.004	37 / 288	15 / 274
Rosell R. et al/2008/II	3.583	0.789	16.267	1.653	0.098	7 / 42	2 / 43
Sobrero A.F. et al/2008/III	1.239	0.825	1.859	1.034	0.301	49 / 638	39 / 629
Vermorken J.B. et al/2008/III	1.833	1.008	3.333	1.984	0.047	28 / 219	15 / 215
Lienbaum R. et al/2009/II/	0.967	0.063	14.739	-0.024	0.981	1 / 30	1 / 29
Pirker R.et al/2009/III	1.470	1.154	1.873	3.119	0.002	129 / 548	90 / 562
Tol J. et al/2009/III	0.880	0.506	1.532	-0.452	0.651	22 / 366	25 / 366
Lynch T.J. et al/2010/III	1.343	0.626	2.878	0.757	0.449	15 / 325	11 / 320
Govindan R. et al/2011/III	0.849	0.376	1.915	-0.394	0.693	9 / 53	10 / 50
Alberts S.R. et al/2012/III	2.049	1.455	2.884	4.110	0.000	96 / 931	45 / 894
Dewdney A. et al/2012/II	0.976	0.062	15.340	-0.017	0.986	1 / 83	1 / 81
Saltz L. et al/2012/III	0.975	0.062	15.411	-0.018	0.986	1 / 121	1 / 118
Baselga J. et al/2013/II	2.522	0.123	51.669	0.600	0.548	2 / 114	0 / 57
Kim E.S. et al/2013/III	1.506	0.913	2.484	1.604	0.109	35 / 292	23 / 289
Burtness B.et al/2014/II	1.278	0.366	4.455	0.385	0.700	5 / 45	4 / 46
Huang J. et al/2014/III	3.533	0.827	15.095	1.704	0.088	4 / 40	3 / 106
Hussain M. et al/2014/II	1.107	0.309	3.965	0.157	0.875	7 / 59	3 / 28
van den Heuval M.M. et al/2014/II	7.000	0.371	132.166	1.298	0.194	3 / 51	0 / 51
Douillard J.Y. et al/2010/III	1.083	0.528	2.222	0.218	0.827	15 / 539	14 / 545
Peeters M. et al/2010/III	0.564	0.251	1.264	-1.391	0.164	9 / 539	16 / 540
Seymour M.T.et al/2013/III	1.900	1.175	3.073	2.619	0.009	42 / 219	22 / 218
vermorken J.B. et al/2008/III	1.176	0.628	2.205	0.507	0.612	20 / 325	17 / 325
Waddell T. et al/2013/III	0.661	0.477	0.916	-2.487	0.013	48 / 276	70 / 266
	1.339	1.104	1.624	2.965	0.003	601 / 6409	438 / 6322

Figure 2 Relative risk of severe infections associated with anti-EGFR MoAbs versus control. EGFR, epidermal growth factor receptor; MoAbs, monoclonal antibodies.

Study name	Statistics with study removed					Risk ratio (95% CI) with study removed
	Point	Lower limit	Upper limit	Z-Value	p-Value	
Burtness B. et al/2005/III	1.332	1.089	1.630	2.791	0.005	
Bonner J.A.et al/2006/III	1.341	1.103	1.632	2.936	0.003	
Jonker D.J. et al/2007/III	1.294	1.066	1.571	2.608	0.009	
Rosell R. et al/2008/II	1.320	1.088	1.602	2.818	0.005	
Sobrero A.F. et al/2008/III	1.349	1.095	1.661	2.811	0.005	
Vermorken J.B. et al/2008/III	1.315	1.076	1.608	2.676	0.007	
Lienbaum R. et al/2009/II/	1.342	1.103	1.632	2.939	0.003	
Pirker R.et al/2009/III	1.329	1.070	1.651	2.566	0.010	
Tol J. et al/2009/III	1.375	1.127	1.677	3.140	0.002	
Lynch T.J. et al/2010/III	1.340	1.095	1.638	2.847	0.004	
Govindan R. et al/2011/II	1.364	1.119	1.662	3.074	0.002	
Alberts S.R. et al/2012/III	1.284	1.059	1.557	2.547	0.011	
Dewdney A. et al/2012/II	1.341	1.103	1.632	2.939	0.003	
Saltz L. et al/2012/III	1.341	1.103	1.632	2.939	0.003	
Baselga J. et al/2013/II	1.336	1.099	1.625	2.903	0.004	
Kim E.S. et al/2013/III	1.329	1.082	1.632	2.717	0.007	
Burtness B.et al/2014/II	1.341	1.100	1.634	2.902	0.004	
Huang J. et al/2014/III	1.319	1.087	1.600	2.811	0.005	
Hussain M. et al/2014/II	1.345	1.103	1.639	2.934	0.003	
van den Heuval M.M. et al/2014/II	1.330	1.096	1.613	2.895	0.004	
Douillard J.Y. et al/2010/III	1.353	1.107	1.654	2.948	0.003	
Peeters M. et al/2010/III	1.383	1.145	1.671	3.364	0.001	
Seymour M.T.et al/2013/III	1.306	1.069	1.596	2.609	0.009	
vermorken J.B. et al/2008/III	1.349	1.102	1.653	2.896	0.004	
Waddell T. et al/2013/III	1.469	1.280	1.686	5.462	0.000	
	1.339	1.104	1.624	2.965	0.003	

0.1   0.2   0.5   1   2   5   10

Favors anti-EGFR MoABs   Favors control

Figure 3 Meta-analysis of severe infections associated with anti-EGFR MoAbs versus control: 'leave-one-out' sensitivity analysis. EGFR, epidermal growth factor receptor; MoAbs, monoclonal antibodies.

Figure 4 Meta-regression analysis of trends between treatment duration and severe relative risk: symbols: each study is represented by a circle the diameter of which is proportional to its statistical weight.

Table 2 Relative risk of severe infectious events with EGFR-MoAbs according to tumor types, EGFR-MoAbs, concomitant therapies and phases of trials

Groups	Studies, number	Severe infectious events, number/total, number		RR (95%CI)	P value	P value for group difference
		EGFR-MoAbs	Control			
Tumor types						
CRC	11	276/3801	181/3808	1.42 (1.05 to 1.93)	0.024	0.001
NSCLC	7	199/1341	137/1344	1.45 (1.19 to 1.77)	<0.001	
Head and neck cancer	4	64/810	43/810	1.48 (1.02 to 2.13)	0.037	
Others	4	62/494	77/397	0.72 (0.53 to 0.97)	0.033	
Anti-EGFR MoAbs						
Cetuximab	21	467/4548	299/4465	1.52 (1.33 to 1.75)	<0.001	0.092
Panitumumab	5	134/1898	139/1894	0.99 (0.62 to 1.60)	0.98	
Concomitant therapies						
Cisplatin	8	233/1690	148/1608	1.48 (1.22 to 1.79)	<0.001	0.30
Irinotecan	4	100/942	68/999	1.53 (1.12 to 2.10)	0.008	
Oxaliplatin	8	192/2892	172/2847	0.97 (0.58 to 1.61)	0.90	
Radiotherapy	3	13/312	11/313	0.99 (0.47 to 2.10)	0.98	
Others	3	73/610	39/592	1.80 (1.24 to 2.62)	0.002	
Phases of trials						
Phase II	9	35/514	21/422	1.26 (0.75 to 2.12)	0.39	0.82
Phase III	17	566/5932	417/593	1.34 (1.08 to 1.67)	0.008	
Overall	26	601/6446	438/6359	1.34 (1.10 to 1.62)	0.003	NA

CI, confidence interval; CRC, colorectal cancer; EGFR, epidermal growth factor receptor; MoAbs, monoclonal antibodies; NA, not available; NSCLC, non-small-cell lung cancer; RR, relative risk.

cisplatin (RR 1.48, 95%CI: 1.22 to 1.79, *P* <0.001) and irinotecan (RR 1.53, 95%CI: 1.12 to 2.10, *P* = 0.008), while anti-EGFR-MoAbs in combination with oxaliplatin (RR 0.97, 95%CI: 0.58 to 1.61, *P* = 0.90) and radiotherapy (RR 0.99, 95%CI: 0.47 to 2.10, *P* = 0.98) did not increase the risk of severe infections. However, no significant difference in RRs of severe infections was found among these concomitant therapies (*P* = 0.30). Additionally, we did sub-group analysis according to the phase of trials (phase II versus phase III). Patients from phase III trials had an RR of 1.34 (95%CI: 1.08 to 1.67, *P* = 0.008), while patients from phase II studies had an RR of 1.26 (95%CI: 0.75 to 2.12, *P* = 0.39, Table 2).

Risk of severe and fatal infections by specific types
Individual specified and non-specified causes of severe and fatal infections are listed in Table 3. Of those severe infections that were specified, the most common events for severe infections were febrile neutropenia (47.8%). We then calculated the risk of severe infections stratifying trials according to specific type of infections. Our results showed that the use of anti-EGFR MoAbs significantly increased the risk of severe sepsis (RR 4.30, 95%CI: 1.80 to 10.27, *P* = 0.001), while a non-significantly increased risk of febrile neutropenia (RR 1.09, 95%CI: 0.86 to 1.38, *P* = 0.68) and pneumonia (RR 1.11, 95%CI: 0.72 to 1.70,

P = 0.64) was observed. Of the 24 fatal infections on the treatment arms and 11 fatal infections on the control arms, 33.3% and 18.2% were of non-specified etiology, respectively. Of those fatal infections that were specified, the most common events for fatal infections were sepsis (37.5%). When we calculated the risk of fatal infections, stratifying trials according to specific types of infections, a non-significantly increased risk of pneumonia (RR 1.46, 95%CI: 0.39 to 5.48, *P* = 0.56) and sepsis (RR 1.54, 95%CI: 0.50 to 4.74, *P* = 0.45) was observed (Table 3).

Publication bias
No publication bias was detected for the primary endpoint of this study (RR of severe infections) by the funnel plot (Figure 5), Egger's test and Begg's test (RR of severe infections: Begg's test *P* = 0.98; Egger's test *P* = 0.73).

Discussion
Infections are emerging complications of many MoAbs and concerns have arisen regarding the risk of infections with the use of these drugs. In 2007, Rafailidis *et al.* [45] performed a systematic review to investigate the incidence of infectious complications of several MoAbs including trastuzumab, alemtuzumab, bevacizumab, cetuximab and rituximab. Based on a single trial, there was a higher rate of severe infections in patients receiving cetuximab. Then,

**Table 3 Severe and fatal infectious events with EGFR-MoAbs by specific types**

	Infectious events, number/total, number		RR (95%CI)	*P* value
	EGFR-MoAbs	**Control**		
Severe infections				
Unspecified	236/2844	144/2829	1.57 (1.16 to 2.13)	0.004
Specified	365/7450	294/7347	1.18 (0.95 to 1.47)	0.14
Febrile neutropenia	287/4551	221/4579	1.09 (0.86 to 1.38)	0.68
Pneumonia	45/1605	37/1527	1.11 (0.72 to 1.70)	0.64
Sepsis	33/1294	6/1241	4.30 (1.80 to 10.27)	0.001
Fatal infections				
Unspecified	8/1471	2/1424	2.39 (0.58 to 9.83)	0.23
Specified	16/2486	9/2305	1.43 (0.64 to 3.18)	0.38
Pneumonia	6/1336	3/1261	1.46 (0.39 to 5.48)	0.56
Febrile neutropenia	1/321	1/321	1.00 (0.11 to 9.51)	1.00
Sepsis	9/829	5/732	1.54 (0.50 to 4.74)	0.45

CI, confidence interval; EGFR, epidermal growth factor receptor; MoAbs, monoclonal antibodies; RR, relative risk.

Lee *et al.* [46] in 2012 conducted a national cohort study of 1,083 head and neck cancer patients and found that cetuximab therapy was not statistically associated with an increased infection rate in head and neck cancer patients. As a result, the incidence and risk of infections associated with anti-EGFR MoAbs has not been well defined.

Our meta-analysis includes a total of 14,060 patients from twenty six RCTs investigating anti-EGFR MoAbs for the treatment of cancers. To the best of our knowledge, this is the first large study of RCTs demonstrating a significant increase in the risk of severe infections (≥grade 3) with the use of anti-EGFR MoAbs in cancer patients. Our analysis finds that the risk of developing a severe infection is 1.34-fold higher in patients treated with anti-EGFR MoAbs, while the use of anti-EGFR MoAbs does not significantly increase the risk of fatal infections.

Sensitivity analysis indicates that the significance estimate of pooled RRs of severe infection is stable and reliable. We also performed a meta-regression analysis to investigate the association between cumulative anti-EGFR MoAbs exposure and severe infections. The result indicates that severe infections might possibly occur early in the treatment with anti-EGFR MoAbs. In contrast with our result, the study conducted by Burtness *et al.* [5] showed that the increased risk of neutropenia with cetuximab/cisplatin compared with placebo/cisplatin was associated with longer duration of therapy. As a result, further prospective studies are still needed to address this issue. We also investigated the outcome of anti-EGFR MoAbs-associated severe infections. Our study shows that the overall incidence of fatal infections with anti-EGFR MoAbs is 0.8%. Given that the absolute risk of fatal infections is low, the

Figure 5 Funnel plot of standard error by log-odds ratio for severe infections.
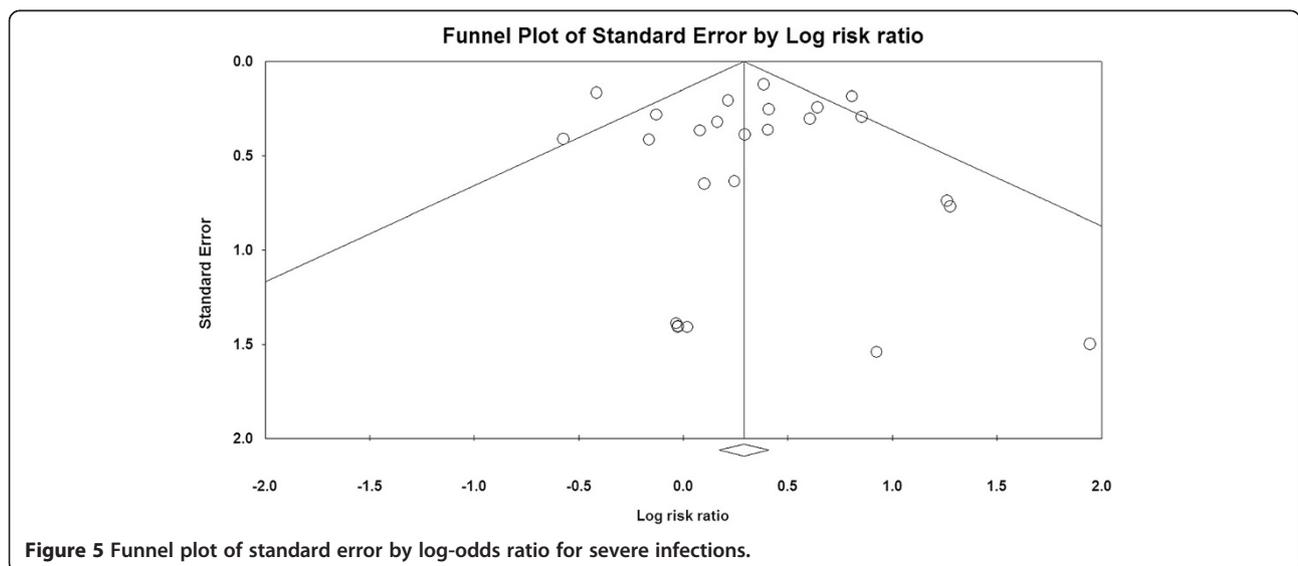
use of anti-EGFR-MoAbs should be considered in the context of overall survival benefits. Because anti-EGFR MoAbs are increasingly used in cancer patients, it is particularly important for all health care practitioners and patients to understand and recognize the risk of severe and fatal infection.

Because risk factors for severe infections with anti-EGFR MoAbs are poorly understood, we carried out a subgroup analysis to identify potential risk factors for anti-EGFR MoAbs related-infections. When stratified by tumor type, a significantly increased risk of severe infections with anti-EGFR MoAbs is observed in colorectal cancer, non-small-cell lung cancer, and head and neck cancer. Interestingly, no increased risk of severe infections is observed in patients with other tumor types receiving anti-EGFR MoAbs. The risk of severe infections varies significantly with different tumor types ($P = 0.001$), reflecting the nature of the underlying tumor biology or associated treatment. Notably, our study shows that anti-EGFR MoAbs significantly increase the risk of severe infections when used in conjunction with cisplatin or irinotecan. This result may reflect an interaction between anti-EGFR MoAbs and certain chemotherapeutic agents in causing severe infections. However, the risk of severe infections dose not significantly vary with concomitant therapies ($P = 0.30$). We also performed sub-group analysis according to anti-EGFR MoAbs and demonstrated that the use of cetuximab significantly increases the risk of severe infections, but this was not the case with panitumumab. Additionally, no significant differences in the risk of severe infections with anti-EGFR MoAbs were observed according to the phase of the trials. Based on our findings, the following approaches may be considered to reduce the association of anti-EGFR MoAbs with risk of severe infections. Before the initiation of anti-EGFR MoAbs, clinicians must fully treat patients with any active infection and must monitor patients during the course of anti-EGFR MoAbs treatment. Clinicians should be cautious when adding anti-EGFR MoAbs to the therapies for the treatment of colorectal cancer, non-small-cell lung cancer, and head and neck cancer, especially when used in conjunction with cisplatin or irinotecan.

Despite the size of this meta-analysis, our study has several limitations. First, all included studies were conducted at major academic institutions among patients with adequate major organ function and may not reflect the general patient population in the community or patients with organ dysfunction. It is conceivable that the true incidences and risk of treatment-related infections from this study may be underestimated. Second, these studies were conducted at various institutions by different investigators internationally and may have potential bias in reported incidences or specification of severe infections. Severe infections are not primary outcome measures in the included studies. The reported incidence of severe infections has significant heterogeneity among the included studies. Nevertheless, we attempted to adjust for the heterogeneity using a random-effects model to calculate the incidence of severe and fatal infections. Third, our study shows that the RR of fatal infection is higher in patients receiving anti-EGFR MoAbs than in controls, but is not statistically significant. This observation might be limited by sample size. Finally, this is a meta-analysis at study level; therefore, confounding factors at the patient level cannot be assessed properly and incorporated into the analysis.

Conclusions

In conclusion, this study has demonstrated that the addition of anti-EGFR MoAbs to concurrent antineoplastic therapy is associated with an increased risk of severe infections in cancer patients. The use of cisplatin or irinotecan may increase the risk of severe infections associated with anti-EGFR MoAbs. The increased risk of severe infections associated with anti-EGFR MoAbs may vary with tumor types. Early detection and effective management of infections that can occur with anti-EGFR MoAbs is crucial for safer use of this drug. Further studies are still recommended to investigate risk reduction and the possible mechanism of anti-EGFR MoAbs induced infections.

Abbreviations
ASCO: American Society of Clinical Oncology; CIs: confidence intervals; EGFR: epidermal growth factor receptor; ESMO: European Society of Medical Oncology; FDA: Food and Drug Administration; IgG1: immunoglobulin G1; MoAbs: monoclonal antibodies; NCI-CTC: National Cancer Institute's common terminology criteria; RCTs: randomized controlled trials; RRs: relative risks; VEGF: vascular endothelial growth factor.

Competing interests
All authors declare that they have no competing interests.

Authors' contributions
Concept and design: XMG and SF. Search and collection of data: XMG and SF. Analysis of data and interpretation: QZ and XMG. Tables and figures: WXQ. Writing the manuscript and review: WXQ and SF. All authors read and approved the final manuscript.

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