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ORIGINAL RESEARCH

Predictive value of single nucleotide polymorphisms in XRCC1 for radiation-induced normal tissue toxicity

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Purpose: X-Ray Repair Cross Complementing 1 (XRCC1) functioning in the base excision repair pathway plays an important role in the repair of DNA single-strand breaks caused by ionizing radiation. The relationship between XRCC1 polymorphisms and the risk of radiationinduced side effects on normal tissues remains controversial. Therefore, we performed a comprehensive meta-analysis to elucidate these associations.

Materials and methods: A systematic literature search was carried out in PubMed, Medline (Ovid), Embase, Web of Science, Cochrane database, and the references of relevant studies. The pooled odds ratios (ORs) with corresponding 95% confidence intervals (CIs) were calculated to evaluate the strength of the association.

Results: A total of 40 studies including 6,682 patients were eventually identified in this metaanalysis. Pooled results suggested that rs25487 Arg399Gln polymorphism significantly increased the risk of acute radiation-induced side effects (OR=1.29, 95% CI: 1.10-1.52, P=0.002), especially acute mucositis (OR=1.91, 95% CI: 1.17-3.11, P=0.01) and acute gastrointestinal and genitourinary toxicity (OR=1.49, 95% CI: 1.04-2.11, P=0.03). Furthermore, patients who received head and neck irradiation with rs25487 Arg399Gln polymorphism were more likely to experience radiotherapy (RT)-induced side effects (OR=1.46, 95% CI: 1.12–1.90, P=0.005). However, no statistically significant correlations were identified between rs25487 polymorphism and any late side effects and other irradiation areas. Likewise, no significant associations were detected between rs25489, rs1799782, or rs3213245 polymorphism and RT-induced toxicity. Conclusion: Our meta-analysis demonstrated that XRCC1 rs25487 Arg399Gln polymorphism had a significant predictive value and might predict a risk of severely acute RT-induced adverse effects, especially in acute mucositis and acute gastrointestinal and genitourinary toxicity, or in patients with head and neck irradiation. However, large-scale and well-designed studies are required to further evaluate the predictive value of XRCC1 variations on radiation-induced side effects in order to identify radiosensitive patients and predict radiotoxicity.

Keywords: XRCC1, polymorphism, radiotherapy, side effect

Introduction

Radiotherapy (RT) is a common and indispensable method in cancer treatment, which may result in a spectrum of normal tissue side effects.¹ Although improvements in precise RT techniques such as three-dimensional conformal radiotherapy and intensity-modulated radiotherapy have increased the possibility of dose escalation in tumor targets,² the implementation of radiation dose is still limited by the tolerance of normal tissues in and adjacent to the irradiation field.³ However, patients exhibit substantially different degrees of normal tissue toxicity even with the same treatment

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OncoTargets and Therapy downloaded from https://www.dovepress.com/ For personal use only regimen, varying from mild to severe and occasionally lethal. Acute adverse effects may lead to unanticipated RT breaks and then remarkably affect adequate treatment delivery,^{4,5} and late adverse effects markedly influence patients' quality of life.⁶ It is important to predict a predisposition of severe RT-induced adverse effects in normal tissues for making personal and optimized treatment decision, particularly in those with "high–intermediate risk".

The severity of RT-induced complication is associated with many factors including irradiated dose, volume of normal tissues, fractionation schedule, combined with chemotherapy, as shown by Stone et al,⁷ but they cannot fully explain patient-to-patient differences. Recent studies indicate that genetic component may contribute to the clinical radiosensitivity and radiation adverse effects.⁸⁻¹⁰ DNA is considered to be the main target of RT, which causes cell death by inducing base damage, single-strand breaks (SSBs), and double-strand breaks.11 So, inter-individual differences in DNA repair capacity may determine varying degrees of the normal tissue response. Extensive researches have been conducted in order to identify some genetic markers such as single nucleotide polymorphisms (SNPs) as predictive factors for the risk of radiation-induced normal tissue toxicity.¹⁰ SNPs in DNA damage and repair genes may alter the amino acid composition of encoded proteins, which play a role in individual's radiation response and capacity of DNA damage repair. The protein encoded by X-Ray Repair Cross Complementing 1 (XRCC1) gene, which functions in the base excision repair (BER) pathway, involves in the efficient repair of DNA SSBs caused by exposure to ionizing radiation.¹² The XRCC1 gene is mapped at human chromosome 19q13.2-13.3. The most common variants of XRCC1 gene are rs25487 Arg399Gln in exon 10, rs25489 Arg280His in exon 9, and rs1799782 Arg194Trp in exon 6.13-15

Although several studies have investigated the association of *XRCC1* polymorphisms with clinically observed normal tissue adverse effects, the results are not consistent. It is not sufficient to form a reliable conclusion and consequently limit their clinical applicability as biomarkers. So, we performed a systematic review to investigate these associations. This is, to our knowledge, the first comprehensive meta-analysis of genetics studies on the association between *XRCC1* polymorphisms and radiation-related adverse effects.

Materials and methods Search strategy

A systematic literature search in PubMed, Medline (Ovid), Cochrane, Embase, Web of Science database, and the references of relevant articles was carried out to identify studies involving *XRCC1* polymorphisms and the risk of radiation-related normal tissue adverse effects (last search was updated on June 1, 2017). The search terms used were as follows: "*XRCC1* or X-Ray Repair Cross Complementing 1" in combination with "SNP or polymorphism or variant or variation or mutation or haplotype" and "radiotherapy or radiation or irradiation" and "side effect or adverse effect or complication or injury or toxicity or reaction or response or radiotoxicity or radiosensitivity or morbidity or normal tissue". All the search terms were restricted to studies in human subjects and in English language.

Inclusion criteria

Studies included in the current meta-analysis met the following inclusion criteria: 1) evaluation of the association between *XRCC1* SNPs and radiation-induced normal tissue adverse effects; 2) the design has to be a cohort study or case control study; 3) sufficient published data (genotype distributions of each groups) to estimate an odds ratio (OR) with 95% CI.

Exclusion criteria

Studies were excluded if one of the following existed: 1) data of genotype frequencies of each group were not reported and 2) case reports, reviews, editorials, and repeat studies. If there were more than one study published by the same authors based on the same populations, the one providing the most comprehensive information was included.

Data extraction

Two investigators collected the data independently in duplicate according to the inclusion criteria listed above using a standardized data extraction form. The following items were extracted from each study: first author, publication date, original country, ethnicity, cancer type, subtype of SNP in *XRCC1*, normal tissue toxicity, sample size, treatment, type of study, genotyping method, genotype number, and total number in cases and controls.

Statistical analysis

ORs and 95% CIs were used to assess the strength of association between genetic polymorphisms and the risk of RTinduced adverse effects. The pooled OR was calculated by a fixed-effects model or a random-effects model according to the heterogeneity. Heterogeneity among eligible studies was measured by χ^2 -based *Q*-test and I^2 statistical test.¹⁶ If *Q*-test *P*<0.1 and *I*²-value \geq 50%,¹⁶ the heterogeneity was considered statistically significant, and the assumption

of homogeneity was deemed invalid and the pooled OR was calculated by random-effects model after exploring the cause of heterogeneity. Otherwise, the fixed-effects model was used. Findings of our meta-analysis are shown in forest plots. The two-tailed P<0.05 was considered statistically significant. To evaluate the tolerance of different normal tissues and the occurrence time of side effects, subgroup analysis was conducted by early or late adverse effect, special types of side effects, and irradiation area. Sensitivity analysis was performed to confirm the stability and reliability of the pooled results by excluding each study individually and recalculating the pooled ORs and 95% CIs. If the number of included studies were >10, the possible publication bias and the degree of asymmetry were examined by Begg's funnel plot and Egger's test.^{17,18} If publication bias existed, the "trim and fill" method¹⁹ was used to estimate the number of missing studies and to adjust the pooled result. Statistical analysis was performed using Revman 5.3 and STATA 14.0 software.

Results Study characteristics

A total of 40 studies including 6,682 patients were eventually identified in this meta-analysis for further analysis (Figure 1). The baseline characteristics of each included study are listed in Table 1. These studies were published from 2003 to 2017, and the sample size ranged from 34 to 579. Most of these studies included mainly Caucasian patients, and nine studies included Asian patients, of which five studies are on Chinese.^{15,20–23} The cancer categories included head and neck cancer (8 studies),^{20,21,23–27} breast cancer (18 studies),^{15,28–44} prostate cancer (5 studies),^{14,45–48} cervical endometrial



Figure I Flow diagram of study search and screening for the meta-analysis. Abbreviations: RT, radiotherapy; SNP, single nucleotide polymorphism.

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	^z alvo et al, ³⁴ 2012	Italy	Caucasian	Breast	rs25487	57	Late: fibrosis, fat necrosis	CTCAE v3.0 ≥G2	21 Gy/f	Yes	Cohort	PCR

			0			LENT-SOMA ≥G2	boost of 15 Gv/5f]
	Asian	Cervical	rs25487	208	Acute: diarrhea	CTCAE v2.0 ≥G2	EBRT 50.6 Gy Brachytherapy 24.0 Gy	Yes	Cohort	PCR
Austria	Caucasian	Prostate	rs25487, rs25489, rs1799782	579	Late: bladder or rectal toxicity	RTOG/EORTC ≥G2	66-70.4 Gy	оХ	Cohort	PCR
China	Asian	NPC	rs25487, rs1799782	4	Acute: mucositis, dermatitis	CTCAE v3.0 ≥G3	50–70 Gy	Yes	Cohort	PCR-RFLP
	Caucasian	Breast	rs25487, rs1799782	87	Acute: skin reaction	CTCAE v2.0 ≥G2c	50 Gy/25f, 44 Gy/16f	Yes	Cohort	PCR
France	Caucasian	Breast	rs 25487, rs 25489, rs 1799782	254	Acute and Late	EORTC	50 Gy, tumor bed boost 10 Gy	AN	Cohort	PCR
India	Asian	Breast	rs25487	126	Acute: skin reaction	RTOG ≥G2	50 Gy, tumor bed boost 10 Gy for 26 patients	Yes	Cohort	PCR
Germany	Caucasian	Prostate	rs 25487, rs 25489, rs 1799782	405	Acute: proctitis cystitis	CTCAE v2.0 ≥G3	61–72 Gy	°Z	Cohort	Sequence- specific hybridization probes
Italy	Caucasian	HNC	rs25487	101	Acute: mucositis, skin erythema	CTCAE v3.0 ≥G2	Mean 62 Gy (54–70 Gy)	Yes	Case-control	PCR-RFLP
Germany	Caucasian	Breast	rs25487	83	Acute: erythema	RTOG ≥G2	50-50.4 Gy	٩N	Cohort	PCR-RFLP, MALDI-TOF
Japan	Asian	Bladder	rs25487	95	Acute: gastrointestinal toxicity	CTCAE v3.0 ≥G2	Median 48.6 Gy (30.0–60.4 Gy)	Yes	Cohort	PCR-RFLP
America	Mixed	Rectal	rs25487	165	Acute: gastrointestinal and genitourinary toxicity (diarrhea, proctitis, cystitis)	CTCAE v3.0 ≥G3	Median 50.4 Gy	Yes	Cohort	PCR, MALDI- TOF
Japan	Asian	Breast	rs25487	399	Acute: skin reaction	CTCAE v2.0 ≥G2	46–60 Gy	Yes	Cohort	PCR
Italy	Caucasian	Breast	rs 25487, rs 1799782, rs 32 1 3245	286	Acute: skin reaction	RTOG ≥G2	50–50.4 Gy, tumor bed boost 9–16 Gy	Yes	Cohort	PCR-RFLP
Italy	Caucasian	Breast	rs25487, rs1799782	237	Late: fibrosis	LENT-SOMA ≥G2	50–50.4 Gy, tumor bed boost 9–16 Gy	Yes	Cohort	PCR-RFLP
NSA	Caucasian	NSCLC	rs25487	141	Late: radiation pneumonitis	CTCAE v3.0 ≥G3	Median 63 Gy (50.4–72 Gy)	Yes	Cohort	PCR-RFLP
Canada	Caucasian	Prostate	rs25487	217	Late: urinary toxicity	RTOG ≥G2	I 25I ≥I 45 Gy	No	Cohort	PCR

		EUNICITY	Disease	SNP	Sample size (N)	Adverse effect	Assessment	KI dose	involved	Study decien	Genotyping
					111 2710					Incongi	
Venkatesh Inc	India	Caucasian	HNC	rs25487,	183	Acute: mucositis, skin	RTOG ≥G3	60-70 Gy	Yes	Cohort	PCR-RFLP
et al, ²⁷ 2014				rs25489,		reaction					
				rs I 799782,							
				rs3213245							
Yin et al, ⁵⁵ US	USA	Mixed	NSCLC	rs25487	165	Late: radiation	CTCAE v3.0 ≥G2	Median 63 Gy	Yes	Cohort	PCR-RFLP
2011						pneumonitis		(50.4-84.0 Gy)			
Yoon et al, ⁵⁶ US	USA	Mixed	Esophageal	rs25487	60	Acute: dysphagia	CTCAE v2.0 ≥G3	45 Gy	Yes	Cohort	PCR,
2011			adenocarcinoma								MALDI-TOF
Xian et al, ²² Ch	China	Asian	Esophageal	rs25487	118	Acute: esophagitis	CTCAE ≥G3	Median 60 Gy	Yes	Cohort	PCR
2015			squamous cell					(45–66 Gy)			
			carcinoma								
Zhai et al, ²³ Ch	China	Asian	NPC	rs25487	60	Acute and Late: skin,	RTOG ≥G2	66–76 Gy	Yes	Cohort	PCR-LDR
2016						mucosa, salivary gland					
Zhou et al, ¹⁵ Ch	China	Asian	Breast	rs25487,	611	Acute: skin reaction	CTCAE v3.0 ≥G2	46–54 Gy	No	Cohort	PCR-RFLP
2010				rs25489,							
				rs I 799782,							
				rs3213245							
Zschenker Ge	Germany	Caucasian	Breast	rs25487	69	Late: fibrosis	LENT-SOMA ≥G2	54-55 Gy	Yes	Cohort	PCR-RFLP,
et al,41 2010											MALDI-TOF

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cancer (2 studies),^{49,50} bladder cancer (1 study),⁵¹ rectal cancer (2 studies),^{52,53} non-small-cell lung cancer (NSCLC; 2 studies),^{54,55} esophageal cancer (2 studies),^{22,56} and one mixed cancers (mainly breast cancer and head and neck cancer).⁵⁷ Four subtypes of SNPs in *XRCC1* were analyzed in this meta-analysis. Thirty-six studies were identified for rs25487, 12 studies for rs25489, 17 studies for rs1799782, and 6 studies for rs3213245. Subgroup analyses of radiationinduced adverse effects were performed on acute or late side effects, special types of side effects, and irradiation area. The genotype distributions analyzed in each study were in Hardy–Weinberg equilibrium with P>0.05. All the included eligible reports were written in English language.

Meta-analysis results

XRCC1 rs25487 polymorphism

Overall, *XRCC1* rs25487 Arg399Gln G>A polymorphism was significantly associated with acute normal tissue injury after RT. Specifically, rs25487 "Gln" allele increased the risk of acute radiation-induced adverse effects (for GA+AA versus GG, OR=1.29, 95% CI: 1.10-1.52, *P*=0.002; Figure 2).

Subgroup analysis by specific adverse effect

Because most studies investigated several different adverse effects, subgroup analysis was conducted by specific adverse effect. The results indicated that rs25487 Arg399Gln "Gln" allele carriers significantly increased acute mucositis (OR=1.91, 95% CI: 1.17-3.11, P=0.01) and acute gastrointestinal and genitourinary toxicity (OR=1.49, 95% CI: 1.04-2.11, P=0.03; Figure 3). No statistically significant associations were identified between rs25487 polymorphism and any late radiation-induced adverse effects (Figure 4).

Subgroup analysis by radiotherapy area

Subgroup analysis was conducted by different irradiation area irrespective of the type of adverse effect. The rs25487 Arg399Gln polymorphism was significantly associated with a higher risk of adverse effects induced by head and neck irradiation (OR=1.46, 95% CI: 1.12-1.90, *P*=0.005), whereas the correlation was not significant for breast or pelvic irradiation (breast, OR=1.13, 95% CI: 0.95-1.33, *P*=0.18; pelvic, OR=1.20, 95% CI: 0.94-1.54, *P*=0.14, respectively; Figure 5).

XRCC1 rs25489, rs1799782, and rs3213245 polymorphisms

Although no statistically significant associations were identified, the rs25489 Arg280His polymorphism seemed to indicate a protective effect against radiotoxicity (OR=0.78, 95% CI: 0.58-1.06, P=0.11), especially in acute adverse effects (OR=0.66, 95% CI: 0.38-1.14, P=0.14, Figure 6) or in breast irradiation area (OR=0.71, 95% CI: 0.47-1.06, P=0.10, Figure 7). No significant associations were detected between rs1799782 or rs3213245 polymorphism and RT-induced toxicity (Figures 8 and 9).

Heterogeneity and sensitivity analyses

The heterogeneities between studies of most analyses were not significant except for three subgroup analyses, the evaluation on radiation pneumonitis of rs25487 ($I^2=79\%$, $\chi^2 P=0.03$), late side effect ($I^2=48\%$, $\chi^2 P=0.05$), and pelvic irradiation ($I^2=55\%$, $\chi^2 P=0.04$) of rs25489. The pooled OR calculated by random-effects model of these subgroup analyses had no statistically significant associations, and the pooled results were stable in the sensitivity analysis.

Publication bias

The distribution of all analyzed studies for rs25487 in Begg's funnel plot was visually asymmetrical and the P-value of Egger's test was significantly <0.05. However, we noticed that many included studies assessed several endpoints and different adverse effects, resulting in these studies being evaluated several times in Begg's funnel plot, which led to an inaccurate result of the publication bias. So, in order to avoid "multiple testing problem", we reevaluated the publication bias for each subgroup analysis if >10 studies were included based on the results above in the form of one study emerged only one time. The P-value of Egger's test of rs25487 for RT-induced acute skin toxicity was 0.245 (Figure 10), which indicates no publication bias. No publication bias was identified in other subgroup analysis of rs25487, and in rs25489, rs1799782, rs3213245 genetic models, and the P-values of Egger's test were all >0.05, which suggested that there was no obvious risk of publication bias in the meta-analysis.

Discussion

The protein encoded by *XRCC1* gene functions in the efficient repair of base damage and *DNA* SSBs formed by ionizing radiation and alkylating agents. This protein interacts with *DNA* ligase III, polymerase-beta, and poly (ADP-ribose) polymerase to participate in the BER pathway.⁵⁸ Polymorphisms in this gene are associated with varying radiosensitivity of cancer patients. Association studies on *XRCC1* genetic variations and the risk of RT-induced normal tissue injuries can help us to identify markers predicting occurrence of side effects, but previous studies reported inconsistent findings.

Acute averse effects 	Study or subgroup	Case GA+AA	Total	Control GA+AA	Total	Weight (%)	Odds ratio M–H, fixed, 95% Cl	Odds ratio M–H, fixed, 95% Cl
Dubulse et al. ² 2013 (a) 22 24 70 108 04 557 (13-26.77) Liet al. ² 2013 (a) 14 24 77 90 13 201 (80-5.00) Liet al. ² 2013 (a) 14 24 77 90 13 201 (80-5.00) Liet al. ² 2013 (a) 14 24 77 90 13 201 (80-5.00) Liet al. ² 2013 (a) 14 24 77 90 13 20 40 138 (0.58-7.61) Mampeder al. ^a 2017 (a) 5 7 26 54 0.3 209 (0.48-15.10) Mambeder al. ^a 2010 (a) 37 54 215 33 0.3 24 09 (0.48-15.10) Pendenia (al. ^a 2017 (a) 27 46 20 37 19 12 (10.52-26) Pendenia (al. ^a 2017 (a) 27 46 20 37 19 12 (10.52-26) Salano e al. ^a 2000 (a) 14 9 32 85 0.7 1.35 (0.34-5.40) Salano e al. ^a 2017 (a) 12 14 89 118 106 5.9 1.02 (0.61-1.30) Pendenia (al. ^a 2017 (a) 12 14 89 118 106 5.9 1.02 (0.61-7.0) Salano e al. ^a 2017 (a) 13 13 91 12 127 22 20 73 1.17 (10.75-18.2) Terrazzino et al. ^a 2017 (a) 13 39 112 127 22 20 73 1.17 (10.75-18.2) Terrazzino et al. ^a 2016 (a) 13 39 112 127 22 20 73 1.17 (10.75-18.2) Terrazzino et al. ^a 2016 (a) 13 39 112 127 22 20 2.2 0.22 (0.26-1.70) Venkates et al. ^a 2016 (a) 13 39 112 127 22 20 2.2 0.2 20 2.2 0.14 (a) 0.45-20 (a) 0.45-	Acute adverse effects							
Liskaw ed. J ² 2011 (ab.2) 27 56 67 150 4.0 1.08 (ab.2)-1.90 List al. 2013 (ab) 14 24 77 90 1.3 201 (ab.2)	Changclaude et al,33 2005 (a1)	46	77	219	369	6.2	1.02 (0.62–1.68)	_
Liskaw ed. J ² 2011 (ab.2) 27 56 67 150 4.0 1.08 (ab.2)-1.90 List al. 2013 (ab) 14 24 77 90 1.3 201 (ab.2)	Duldulao et al,52 2013 (a3)	22	24	70	108	0.4	5.97 (1.33-26.77)	
List al. 2013 (a) 14 24 37 90 1.3 2.01 (a) 5.00 (b) 15 7 26 54 0.3 2.69 (a) 46-15.10 17 (a) 7-3.54 (b) 15 7 26 54 0.3 2.69 (a) 46-15.10 17 (a) 27-3.54 (b) 16 17 (a) 16 7 26 54 0.3 2.69 (a) 46-15.10 17 (a) 16 17 (a) 16 12 15 33 0.5 24 (a) 0.24 (a) 3-17 (a) 16 12 (a) 15 33 0.5 24 (a) 0.24 (a) 3-17 (a) 16 12 (a) 15 33 0.5 24 (a) 0.24 (a) 3-17 (a) 16 12 (a) 15 33 0.5 24 (a) 0.24 (a) 3-17 (a) 16 12 (a) 15 (a) 15 (a) 16 (a							. ,	_
Li et al." 2013 (a2) 25 46 26 66 2.1 LT (7 0.79-5.4) Mumbers et al." 2017 (a1) 23 43 44 76 3.0 0.94 (0.39-17.5) Protest et al." 2017 (a1) 23 43 44 76 3.0 0.94 (0.39-17.5) Protest et al." 2017 (a1) 23 43 44 76 3.0 0.94 (0.39-17.5) Protest et al." 2017 (a1) 8 12 15 331 3.7 1.38 (0.75-2.6) Protest et al." 2017 (a1) 8 12 50 89 0.8 1.66 (0.4-5.50) Protest et al." 2017 (a1) 4 9 12 250 89 0.8 1.56 (0.4-5.50) Protest et al." 2017 (a1) 4 9 132 80 0.7 1.13 (0.4-5.40) Staken et al." 2017 (a1) 4 9 132 80 0.7 1.13 (0.4-5.40) Staken et al." 2017 (a1) 4 9 132 80 0.7 1.13 (0.4-5.40) Staken et al." 2017 (a1) 4 9 132 80 0.7 1.13 (0.4-5.40) Staken et al." 2017 (a1) 4 89 116 160 5.0 100 122 200 7.3 1.17 (0.75-182) Staken et al." 2017 (a1) 3 39 112 127 22 0.52 (0.20-1.34) Venketsh et al." 2016 (a1) 31 39 112 127 22 0.52 (0.20-1.34) Venketsh et al." 2016 (a1) 48 54 57 66 12 31 66 0.4-6.20 Protest et al." 2016 (a1) 48 54 45 76 68 1.23 (1.40.39-6.60) Venketsh et al." 2016 (a1) 48 54 45 76 68 1.23 (1.40.39-6.40) Venketsh et al." 2016 (a1) 48 54 45 76 68 1.23 (1.40.03-6.40) Venketsh et al." 2016 (a1) 48 54 47 19 10 1.56 (0.4-6.22) Protest et al." 2016 (a1) 48 54 47 19 10 1.63 (0.5-4.49) State et al." 2016 (a1) 48 54 47 19 10 1.63 (0.5-4.49) Von et al." 2008 (b1) 5 30 10 30 1.7 0.40 (0.12-1.36) Andreasen et al." 2003 (b1) 1 12 20 9 120 120 20 (0.27-3.15) Andreasen et al." 2003 (b1) 1 12 20 9 120 120 20 (0.27-3.15) Andreasen et al." 2003 (b1) 1 12 20 9 120 120 20 (0.22-2.50) Andreasen et al." 2003 (b1) 1 12 20 9 120 120 120 20 20 20.72-3.15) Andreasen et al." 2003 (b1) 1 12 20 12 120 11 11 130 (0.3-3.5) Et al. 2007 (b1) 1 3 15 24 122 1.11 1.13 (0.3-3-3.5) Et al. 2007 (b1) 1 40 70 12 25 03 22 0.75 (0.3-1.59) Et al. 2007 (b1) 1 40 70 12 25 03 22 0.75 (0.3-1.59) Et al. 2007 (b1) 1 42 24 13 1.5 0.07 (0.2-1.30) Andreasen et al." 2003 (b1) 77 127 164 276 0.2 106 10 10 10 10 10 10 10 10 10 10 10 10 10							· · · ·	
Mangpoint et al.** 2011 (a1) 5 7 20 54 0.3 2.00 (0.43-15.10) Popanda et al.** 2007 (a1) 3 4.3 4.4 76 3.0 0.44 (0.39-176) Preate et al.** 2017 (a1) 8 12 15 33 0.5 4.20 (1.16-13.90) Preate et al.** 2017 (a1) 2.7 46 2.0 89 9.8 1.56 (0.44-6.56) Preate et al.** 2017 (a1) 2.7 4 3.2 2.8 2.1 0.69 (0.22-2.44) Sakano et al.** 2010 (a2-1) 4 13 2.2 1.2 0.69 (0.22-2.44) Sakano et al.** 2010 (a2-1) 4 13 2.2 1.2 0.69 (0.22-2.40) Sige et al.** 2010 (a2-1) 4 1.4 1.4 1.60 (0.4-1.93)								
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Protesi et al, ¹⁰ 2011 (a2) Protesi et al, ¹⁰ 2012 (a1) Protesi et al, ¹⁰ 2010 (a3-2) Sakano et al, ¹⁰ 2010 (a3-1) Sakano et al, ¹⁰ 2010 (a3-1) Sakano et al, ¹⁰ 2010 (a3-1) Sakano et al, ¹⁰ 2012 (a1) Sakano et al, ¹⁰ 2014 (a2) Sakano et al, ¹⁰ 2	Popanda et al,47 2009 (a3)	37	54	215	351	3.7	1.38 (0.75-2.54)	—
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Smith et al ² 2017 (a); 12 14 89 151 0.4 418 (0.00-19.3); Terrazzino et al. ² 2017 (a); 50 109 122 20 7.3 1.7 (0.75-1.82) Terrazzino et al. ² 2014 (a) 13 09 112 127 22 0.52 (0.20-1.34) Venkatesh et al. ² 2014 (a) 13 09 112 127 22 0.52 (0.20-1.34) Venkatesh et al. ² 2014 (a) 13 09 112 127 22 0.52 (0.20-1.34) Venkatesh et al. ² 2015 (a) 6 10 31 63 0.7 155 (0.40-5.02) Zinai et al. ² 2015 (a) 6 10 14 28 13 32 12 1.44 (0.53-4.07) Zinai et al. ² 2016 (a) 20 41 7 19 10 126 0.54 4.619 Zinou et al. ² 2016 (a) 20 41 7 19 10 126 0.54 4.619 Zinou et al. ² 2010 (a) 30 69 14 33 2.2 1.44 (0.53-4.07) Zinai et al. ² 2016 (a) 20 41 7 19 10 126 0.54 4.619 Zinou et al. ² 2010 (a) 30 69 14 33 2.2 1.44 (0.54-4.61) Zinou et al. ² 2010 (a) 30 69 14 33 2.2 1.44 (0.54-4.61) Zinou et al. ² 2010 (a) 30 69 14 33 2.2 1.44 (0.54-4.61) Zinou et al. ² 2010 (a) 30 69 14 33 2.2 1.74 (0.645-2.41) Zinou et al. ² 2010 (a) 30 69 14 33 2.2 0.75 (0.64-1.62) Zinou et al. ² 2010 (a) 30 69 14 33 2.2 0.75 (0.24-1.64) Andressene facts Aladesene et al. ² 2010 (b) 15 26 16 28 1.4 0.65 (0.28-2.68) Andressene, ² 2006 (b) 11 12 3 9 18 1.1 0.92 (0.27-3.15) Andressene, ² 2006 (b) 11 12 3 9 18 1.1 0.92 (0.27-3.15) Andressene, ² 2006 (b) 17 127 164 276 2.2 1.05 (0.84-1.42) Enterazione et al. ² 2006 (b) 17 127 174 27 6.2 1.05 (0.84-1.62) Cheuk et al. ² 2016 (b) 1 14 2.9 14 91 2.1 1.14 (0.49-2.63) Ent et al. ² 2016 (b) 1 14 2.8 14 2.9 1.4 1.07 (0.38-3.03) Giotopoulos et al. ² 2016 (b) 1 15 2.2 2.4 0.1 1.15 (0.68-1.62) Cheuk et al. ² 2014 (b) 11 13 54 67 0.3 6.51 (0.32-3.04) Faive et al. ² 2016 (b) 1 4 6 2.3 54 0.3 2.70 (0.45-1.60) Zina et al. ² 2016 (b) 1 77 77 77 78 9 4.56 0.52 (0.27-1.03) Toker et al. ² 2016 (b) 1 77 727 2.20 45.8 1.05 (0.87-2.82) Subtocal (6% C) 70 70 184 3.8 1.65 (0.87-2.82) Total events 4.49 20.	Sakano et al, ⁵¹ 2010 (a3-1)	4	9	32	86	0.7	1.35 (0.34-5.40)	
Smith et al ² 2017 (a), 12 14 89 151 0.4 4 18 (0.00-19.3), Terrazzio et al. ² 2017 (a) 54 89 118 196 5.9 122 (0.61-170), Winkateh et al ² 2014 (a) 13 39 112 127 22 0.52 (0.20-1.34), Winkateh et al ² 2014 (a) 13 39 112 127 22 0.52 (0.20-1.34), Winkateh et al ² 2014 (a) 13 39 112 127 22 0.52 (0.20-1.34), Winkateh et al ² 2016 (a) 6 10 31 63 0.7 155 (0.40-5.02) Zhai et al ² 2016 (a) 14 28 13 32 12 1.44 (0.53-4.07), Zhai et al ² 2016 (a) 20 41 7 19 10 26 0.9 209 (0.72-6.10), Zhai et al ² 2016 (a) 20 41 7 19 10 126 0.54 4.69), Zhou et al. ⁴ 2010 (a) 30 69 14 33 22 14 (0.54-4.69), Zhou et al. ⁴ 2010 (a) 554 1.458 Heterogeneity, z ^k =21.80, <i>d</i> =24 (<i>P</i> =0.59), <i>P</i> =0/k Test for versall effect Andressen et al. ⁴ 2010 (b) 15 26 16 28 14 0.65 (0.28-2.48), Andressen et al. ⁴ 2000 (b) 15 26 16 22 1.1 1.13 (0.54-4.61), Andressen et al. ⁴ 2000 (b) 15 26 16 22 1.4 0.45 (0.28-2.48), Andressen et al. ⁴ 2000 (b) 15 26 16 22 1.4 0.45 (0.28-2.48), Andressen et al. ⁴ 2000 (b) 17 127 143 15 0.67 (0.21-2.08), Changelaude et al. ⁴ 2000 (b) 17 127 144 276 82 1.05 (0.88-1.62), Entre et al. ⁴ 2006 (b) 17 17 127 144 276 82 1.05 (0.68-1.62), Changelaude et al. ⁴ 2010 (b) 13 15 34 67 0.3 6.37 (0.33-0.33), Globopulo (c) 21 7 13 61 22 34 01.1 1.15 (0.53-4.73), Entre et al. ⁴ 2001 (b) 13 15 34 67 0.3 6.31 (1.23-0.014), Entre et al. ⁴ 2001 (b) 13 15 34 67 0.3 6.31 (1.23-0.304), Changelaude et al. ⁴ 2011 (b) 25 29 11 233 484 8.0 0.67 (0.53-1.37), Falvo et al. ⁴ 2011 (b) 14 28 14 29 1.4 1.07 (0.38-3.65), Entrematione et al. ⁴ 2011 (b) 13 15 34 67 0.3 6.31 (1.23-0.014), Entrematione et al. ⁴ 2011 (b) 13 17 77 52 2.06 3.30 (0.75-5.88), Unmani et al. ⁴ 2003 (b) 13 15 34 67 0.3 6.31 (1.23-0.014), Tall events 449 1.3 1.15 (0.04-3.65), Tall events 449 1.3 1.15 (0.04-3.65), Tall events 449 1.3 1.17 (2.04-2.65), Tall events 449 1.3 1.17 (2.04-2.65), Tall events 449 20 (1.11) 17 72 52 2.06 3.30 (0.67-5.31), Tall events 449 200 (b) 13 17 77 72 2.06 33.20 (0.04-5.60), Zhal et al. ⁴ 2010 (b) 13 17	Sakano et al. ⁵¹ 2010 (a3-2)	4	13	32	82	1.2	0.69(0.20-2.44)	
Suga et al. 2007 (a1) 50 109 122 200 7.3 1.17 (0.75-182) terrazino et al. 2012 (a1) 31 39 112 127 2.2 0.52 (0.261-170) winkaten et al. 2014 (a2) 48 54 57 66 12 1.26 (0.242-360) Wonkaten et al. 2014 (a2) 48 54 57 66 12 1.26 (0.242-360) Wonkaten et al. 2014 (a2) 48 54 57 66 10.3 1.63 0.7 1.55 (0.40-6.02) Zhai et al. 2016 (a1) 14 28 13 32 1.2 1.46 (0.53-4.07) Zhai et al. 2016 (a2) 17 30 10 26 0.9 2.00 (0.72-6.10) Zhai et al. 2016 (a) 17 30 10 26 0.9 2.00 (0.72-6.10) Zhai et al. 2016 (a) 20 41 7 19 1.0 163 (0.57-4.69) Subtool (95% CI) 944 2.665 50.4 1.29 (1.04-5.24) Heterogeneity: $z^{-2}18.0$ $z^{-2}10.2$ (2.40-3.80) Andreassen et al. 2005 (b1) 15 26 16 28 1.4 0.85 (0.27-3.15) Andreassen et al. 2005 (b2.1) 3 6 66 129 0.6 0.95 (0.19-4.91) Burri et al. 2005 (b2.1) 3 6 66 129 0.6 0.95 (0.19-4.91) Burri et al. 2005 (b2.1) 3 6 6 61 29 0.6 0.95 (0.19-4.91) Burri et al. 2005 (b2.1) 3 6 6 61 29 0.6 0.95 (0.19-4.91) Burri et al. 2005 (b2.1) 3 6 6 61 29 0.6 0.95 (0.19-4.91) Burri et al. 2005 (b2.1) 3 6 6 61 29 0.6 0.95 (0.19-4.91) Burri et al. 2005 (b2.1) 3 6 6 61 29 0.6 0.95 (0.19-4.91) Burri et al. 2005 (b2.1) 3 6 6 61 29 0.6 0.95 (0.19-4.91) Burri et al. 2005 (b2.1) 3 6 6 61 29 0.6 0.95 (0.19-4.91) Burri et al. 2005 (b2.1) 3 6 82 1.25 0.07 (0.21-2.08) Chaude (a2) 2014 (b1-1) 14 29 41 91 2.1 1.14 (0.49-2.63) Derive et al. 2005 (b2.2) 7 13 62 122 34 0.0 1.1 1.58 (0.68-1.62) Chaude (a2) 2014 (b1-1) 14 28 14 20 1.4 1.07 (0.38-3.03) Gloppoulos et al. 2012 (b1-1) 14 28 14 20 1.4 1.07 (0.38-3.03) Gloppoulos et al. 2014 (b1-1) 14 28 14 3.8 1.65 (0.87-2.82) Take or evand effect 2-17.17 (e-2.08) Chaude (a2) 2014 (b1-1) 14 28 14 3.8 1.65 (0.87-2.82) Take or evand effect 2-17.17 (e-0.09) Take al. 2016 (b1) 17 7 72 72 2.06 3.3 0.10 (0.45-1.60) Zal et al. 2016 (b1) 17 7 70 126 12.7 0.3 (0.31 (1.23-0.014) Autom et al. 2016 (b1) 17 7 70 126 12.7 0.3 (0.45-1.60) Zal et al. 2016 (b1) 17 7 70 126 12.7 0.3 (0.45-1.60) Zal et al. 2016 (b2) 17 70 126 12.7 0.4 1.1 1.18 (0.48-2.53) Data et al. 2016 (b2) 17 70								
Terrazzno et al. ¹² 2014 (a1) 31 39 Wenkalesh et al. ¹⁷ 2014 (a1) 31 39 Wenkalesh et al. ¹⁷ 2014 (a1) 31 39 Wenkalesh et al. ¹⁷ 2014 (a1) 31 Wenkalesh et al. ¹⁷ 2016 (a1) 14 24 48 33 21 21 21 21 21 21 21 21 21 21								· · · ·
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Venkatesh et al." 2014 (a) 48 54 57 66 1.2 1.26 (0.42-3.80) Xian et al." 2015 (a) 6 10 31 63 0.7 1.55 (0.40-6.02) Zhai et al." 2016 (a) 14 28 13 32 12 1.46 (0.53-6.07) Zhai et al." 2016 (a) 17 30 10 28 0.9 2.09 (0.72-6.10) Zhai et al." 2010 (a) 30 69 14 33 2.2 1.04 (0.45-2.41) Subtotal (5% CI) 944 2.665 50.4 1.29 (1.10-1.52) Subtotal (5% CI) 944 2.665 50.4 1.29 (1.10-1.52) Tal et al." 2010 (b) 1 5 30 10 30 1.7 0.40 (0.12-1.36) Andreassen 4.27 2030 (b) 1 15 28 16 28 1.4 0.85 (0.26-2.58) Marriet al." 2005 (b) 1 15 28 16 28 1.4 0.85 (0.26-2.58) Marriet al." 2005 (b) 1 15 26 16 28 1.4 0.85 (0.26-2.58) Marriet al." 2006 (b:2) 9 17 27 43 15 0.57 (0.34-1.58) Marriet al." 2006 (b:2) 9 17 27 43 15 0.67 (0.21-2.08) Marriet al." 2006 (b:2) 9 17 27 43 15 0.67 (0.21-2.08) Marriet al." 2006 (b:2) 9 17 27 43 15 0.67 (0.21-2.08) Marriet al." 2006 (b:2) 9 17 27 43 15 0.67 (0.21-2.08) Marriet al." 2006 (b:2) 9 17 27 43 15 0.67 (0.21-2.08) Changeduade et al." 2016 (b) 1 13 29 41 91 2.1 1.14 (0.49-263) Changeduade et al." 2016 (b) 1 13 15 34 67 0.3 6.37 (0.35-1.58) Marriet al." 2006 (b:2) 9 17 27 43 15 0.67 (0.21-2.08) Changeduade et al." 2016 (b) 1 13 15 34 67 0.3 6.37 (0.21-2.08) Marriet al." 2006 (b) 15 22 2.3 40 1.1 1.58 (0.53-47.3) Giotopoulos et al." 2016 (b) 1 13 15 34 67 0.3 6.37 (0.25-3.1) Changeduade et al." 2017 (b) 13 15 34 67 0.3 6.37 (0.25-3.1) Marriet al." 2016 (b) 1 3 2 28 78 113 1.1 2.06 (0.75-5.8) Marriet al." 2016 (b) 1 3 15 34 67 0.3 6.37 (0.25-3.1) Marriet al." 2016 (b) 1 3 15 34 67 0.3 6.37 (0.25-3.1) Marriet al." 2016 (b) 1 14 28 13 34 1.1 1.88 (0.67-5.31) Tracker al." 2016 (b) 1 3 15 34 67 0.3 2.70 (0.45-16.00) Zachencker al." 2016 (b) 1 3 15 34 67 0.3 2.70 (0.45-16.00) Zachencker al." 2016 (b) 1 3 17 27 52 0.6 3 0.10 (8.7-10.46) Marriet al." 2016 (b) 1 14 28 13 34 1.1 1.88 (0.67-5.31) Tracker al." 2016 (b) 1 14 28 13 34 1.55 (0.33-2.92) Matriet al." 2016 (b) 1 13 17 27 52 0.6 3 0.10 (8.7-10.46) Marriet al." 2016 (b) 1 4 6 23 54 0.3 2.70 (0.45-16.00) Zachencker at al." 201	Terrazzino et al,39 2012 (a1)	54	89	118	196	5.9	1.02 (0.61–1.70)	_
Venkatesh et al. ²⁷ 2014 (a) 48 54 57 66 1.2 1.26 (0.42-3.80) Xian et al. ²⁷ 2015 (a) 6 10 31 63 0.7 1.55 (0.40 (0.39-5.00) Zhai et al. ²⁷ 2016 (a) 14 28 13 32 12 1.44 (0.53-4.00) Zhai et al. ²⁷ 2016 (a) 17 30 10 28 0.9 2.09 (0.72-6.10) Zhai et al. ²⁷ 2010 (a) 30 69 14 33 2.2 1.04 (0.45-2.41) Subtotal (95% CI) 944 2.665 50.4 1.28 (1.10-1.52) Tast at al. ²⁷ 2010 (b)-1 5 30 10 30 1.7 0.40 (0.12-1.36) Andreassen 41 al. ²⁷ 2010 (b)-1 5 30 10 30 1.7 0.40 (0.12-1.36) Andreassen 41 al. ²⁷ 2010 (b)-1 15 26 14 0.86 (0.24-2.58)	Venkatesh et al,27 2014 (a1)	31	39	112	127	2.2	0.52 (0.20-1.34)	
Yoon et al [®] 2011 (a4) 7 12 24 48 0.8 1.40 (0.39-5.03) Zhai et al [®] 2016 (a1) 14 28 13 32 12 1.46 (0.53-6.03) Zhai et al [®] 2016 (a2) 14 28 13 32 1.2 1.46 (0.53-4.07) Zhai et al [®] 2016 (a2) 14 7 19 1.0 1.63 (0.54-4.98) Subtotal (95% CI) 30 60 1.42 33 2.2 1.04 (0.45-2.41) Subtotal (95% CI) 30 61 4.33 2.2 1.04 (0.45-2.41) Andressen et al. [®] 2000 (b1-1) 5 30 10 30 1.7 0.40 (0.12-1.36) Andressen et al. [®] 2000 (b1-1) 1 2.9 18 1.1 0.92 (0.27-3.15) Andressen et al. [®] 2000 (b2.1) 3 6 66 129 1.6 0.5 (0.1+0.1) Andressen et al. [®] 2000 (b2.1) 7 13 62 1.6 1.4 0.48 (0.2-2.58) Burri et al. [®] 2000 (b2.1) 7 127 14 17.0							, ,	
Xian et al " 2016 (a4) 6 0 0 31 63 0.7 1 55 (040-6.0.2) Zhai et al " 2016 (a1) 14 28 13 32 12 146 (0.53-0.7) Zhai et al " 2016 (a2) 17 30 10 26 0.9 2.06 (0.72-6.10) Zhai et al " 2016 (a5) 20 41 7 19 10 16 30 0.47-0.48) Zhou et al " 2010 (a1) 30 69 14 233 2.2 1.04 (0.45-2.41) Zhou et al (95% CI) 544 7.456 50.4 1.23 (1.19-1.52) Total events 554 1.456 Heterogeneity: $z^{+2}21.8$, $0.6^{+2}2(P=0.59)$; Pers% Test for overall effect: $Z=3.04$ ($P=0.02$): Late adverse effects Adversame 12 2010 (b1) 1 5 30 10 30 1.7 0.40 (0.12-1.36) Andreassen 41 22010 (b1) 1 15 26 16 26 1.4 0.85 (0.28-2.58) Andreassen 41 22005 (b1) 1 15 26 16 220 1.4 0.85 (0.28-2.58) Andreassen 41 22005 (b2) 1 3 6 66 129 0.6 0.95 (0.19-4.91) Burri et al "2006 (b2-1) 3 6 66 129 0.6 0.95 (0.19-4.91) Burri et al "2006 (b2-1) 1 3 6 66 129 0.6 0.95 (0.19-4.91) Burri et al "2006 (b2-1) 1 4 22 41 91 2.1 1.14 (0.49-2.63) Changdaud et al "2006 (b2-1) 1 14 22 41 91 2.1 1.14 (0.49-2.63) Changdaud et al "2006 (b1) 15 22 23 40 0.1.1 1.50 (0.53-4.73) De Ruyck et al "2014 (b1-1) 14 28 14 29 1.4 1.07 (0.38-3.03) Changdaud et al "2007 (b1) 13 15 34 67 0.3 6.31 (1.32-30.14) Langeneiher et al "2016 (b1) 14 28 17 1.14 (0.49-2.63) Terrazzino et al "2016 (b1) 14 28 17 1.14 (0.67-3.31) Terrazzino et al "2016 (b1) 14 28 17 1.11 1.50 (0.67-5.31) Terrazzino et al "2016 (b1) 14 28 17 1.11 1.50 (0.67-5.31) Terrazzino et al "2016 (b1) 13 15 34 67 0.3 6.31 (1.32-30.14) Langeneiher et al "2016 (b1) 13 15 34 67 0.3 (6.31 (0.32-30.14) Langeneiher et al "2016 (b1) 14 28 13 34 1.1 1.88 (0.67-5.31) Terrazzino et al "2016 (b1) 14 28 13 34 1.1 1.88 (0.67-5.31) Tai et al "2016 (b1) 14 28 13 34 1.1 1.18 (0.67-5.31) Tai et al "2016 (b1) 14 28 13 34 1.1 1.18 (0.67-5.31) Tai et al "2016 (b1) 14 28 13 34 1.1 1.18 (0.67-5.31) Tai et al "2016 (b1) 14 28 13 34 1.1 1.18 (0.67-5.31) Tai et al "2016 (b1) 14 28 14 22 1.44 1.25 (0.44-5.55) Tai et al "2016 (b1) 14 28 14 2.208 40 3.270 (0.45-6.00) Tai et al "2016 (b1) 14 6 70 99 46 3.06 (0.32.70 (0.45-6.00) Tai et a							, ,	
$\begin{aligned} \begin{aligned} & \text{The if all $^2} 2016 (a1) & 14 & 28 & 13 & 32 & 12 & 146 (6.053-4.07) \\ & \text{The if all $^2} 2016 (a2) & 17 & 30 & 10 & 26 & 0.9 & 2.06 (0.72-6.10) \\ & \text{The if all $^2} 2016 (b2) & 20 & 41 & 7 & 19 & 10 & 163 (0.54-4.98) \\ & \text{The if all $^2} 2016 (b1) & 30 & 69 & 14 & 33 & 2.2 & 1.04 (0.45-2.41) \\ & \text{Total events} & 554 & 1.456 \\ & \text{Hetrogeneticy $_{2}^{+2.1} 2.0, df=2.4 (P=0.59); F=0^{+5} \\ & \text{Test for overall effect: $2-3.04 (P=0.002) \\ & \text{Late adverse effects} \\ & Andreassen $^2 2016 (b1-1) $5 & 30 & 10 & 30 & 1.7 & 0.40 (0.12-1.36) \\ & \text{Andreassen $^2 2016 (b1-1) $1 & 23 & 9 & 18 & 1.1 & 0.92 (0.27-3.15) \\ & \text{Andreassen $^2 2005 (b1-1) $1 & 23 & 9 & 18 & 1.1 & 0.92 (0.27-3.15) \\ & \text{Andreassen $^2 2005 (b1-1) $1 & 23 & 6 & 66 & 129 & 0.6 & 0.95 (0.16-4.81) \\ & \text{Burri et all $^2 2006 (b2-2) $7 & 13 & 62 & 122 & 1.1 & 1.13 (0.36-3.55) \\ & \text{Burri et all $^2 2006 (b2-2) $7 & 13 & 62 & 122 & 1.1 & 1.13 (0.36-3.55) \\ & \text{Burri et all $^2 2006 (b2-2) $9 & 17 & 27 & 43 & 1.5 & 0.67 (0.21-2.08) \\ & \text{Changedauce et al $^2 2004 (b1-1) $14 & 29 & 41 & 91 & 2.1 & 1.14 (0.49-2.63) \\ & \text{Burri et all $^2 2002 (b1-1) $13 & 15 & 44 & 67 & 0.3 & 6.31 (1.32-3.014) \\ & \text{Langenehener et all $^2 2012 (b1-1) $14 & 28 & 144 & 29 & 1.4 & 10.07 (0.38-3.03) \\ & \text{Glopoulos et all $^2 2012 (b1-1) $13 & 15 & 44 & 67 & 0.3 & 6.31 (1.32-6.014) \\ & \text{Langenehener et all $^2 2012 (b1-1) $13 & 17 & 27 & 52 & 0.6 & 3.01 (0.87-1.63) \\ & \text{Treat all $^2 2016 (b1-1) $14 & 28 & 143 & 29 & 1.4 & 1.50 (0.69-4.63) \\ & \text{Treat all $^2 2016 (b1-1) $14 & 26 & 13 & 34 & 1.1 & 1.88 (0.67-5.31) \\ & \text{Treat all $^2 2016 (b1-1) $14 & 26 & 13 & 34 & 1.1 & 1.80 (0.67-5.31) \\ & \text{Treat all $^2 2016 (b1-1) $14 & 26 & 13 & 34 & 1.1 & 1.80 (0.67-5.31) \\ & \text{Treat all $^2 2016 (b1-1) $14 & 26 & 13 & 34 & 1.1 & 1.80 (0.67-5.31) \\ & \text{Treat all $^2 2016 (b1-1) $14 & 26 & 13 & 34 & 1.1 & 1.80 (0.67-5.31) \\ & \text{Treat all $^2 2016 (b1-1) $14 & 26 & 13 & 34 & 1.1 & 1.80 (0.67-5.31) \\ & \text{Treat all $^2 2016 (b1-1) $14 & 26 & 13 & 34 & 1.1 & 1.80 ($, ,	
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$								— • — –
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	Zhai et al,23 2016 (a1)	14	28	13	32	1.2	1.46 (0.53–4.07)	
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	Zhai et al,23 2016 (a2)	17	30	10	26	0.9	2.09 (0.72-6.10)	
Zhou et al." 2010 (a1) 30 69 14 33 2.2 104 $(0.45-2.41)$ Subtoal (95% CI) 944 2,665 50.4 1.29 $(1.10-1.52)$ Total events 554 1,458 Heterogeneity: $z^2=1.80$, $d^{r=24}$ ($P=0.59$); $P=0\%$ Test for overall effect: $Z=3.04$ ($P=0.09$); $P=0\%$ Total events 46 $P=0$ 99 Heterogeneity; $z^2=48.90$, $d=42/7$ ($P=0.09$); $P=0\%$ Total events 46 $P=0.09$; $P=0.62$) Acute an int $Z=0.01$ ($P=0.09$); $P=0.62$ Total events 46 $P=0.00$; $P=0.62$) Acute and intermixed Heterogeneity; $z^2=48.90$, $d=4/2$ ($P=0.09$); $P=0.40$;	,							
Subtool (95% CI) 944 2,665 50.4 1.29 (1.10–1.52) Total events 554 1,458 Heterogeneity: $z^{2}=1.80$, $d^{r=24}$ ($P=0.059$); $z^{r=00}$ Test for overall effect: $z=3.04$ ($P=0.002$) Late adverse effects Andreassen = 0.2010 (b1-1) 5 30 10 30 1.7 0.40 (0.12–1.36) Andreassen = 0.2010 (b1-1) 11 23 9 18 1.1 0.92 (0.27–3.15) Andreassen = 0.2005 (b1) 15 26 16 25 1.4 0.85 (0.28–2.58) Andreassen = 0.2005 (b1) 13 6 66 129 0.6 0.95 (0.19–4.91) Burri et al." 2008 (b2-1) 3 6 66 129 0.6 0.95 (0.19–4.91) Burri et al." 2008 (b2-2) 7 13 62 122 1.1 1.13 (0.36–3.55) Burri et al." 2008 (b2-2) 7 13 62 122 1.1 1.14 (0.49–2.63) Burri et al." 2008 (b2-2) 7 13 62 122 1.1 1.14 (0.49–2.63) Burri et al." 2008 (b2-2) 177 127 164 276 8.2 1.05 (0.68–1.52) Cheaged and et al." 2009 (b1) 15 22 23 40 1.1 158 (0.63–3.473) Falvo et al." 2014 (b1-1) 14 28 14 29 1.4 1.07 (0.38–3.03) Falvo et al." 2012 (b1-1) 13 15 34 67 0.3 6.31 (1.32–30.14) Langeneinhere at							```	
Total events 5 54 1,458 Heterogeneity: $z^2 = 21.80$, $dr = 24$ ($P = 0.59$); $P = 0\%$ Task for overall effect: $Z = 3.04$ ($P = 0.002$) Late adverse effects Alsebin et al. ²¹ 2010 (01-1) 5 30 10 30 1.7 0.40 (0.12-1.36) Andreassen et al. ²² 2005 (01) 15 26 16 26 1.4 0.85 (0.28-2.58) Durri et al. ²¹ 2008 (02-1) 3 6 66 129 0.6 0.95 (0.19-4.91) Burri et al. ²¹ 2008 (02-1) 3 6 66 129 0.6 0.95 (0.19-4.91) Burri et al. ²¹ 2008 (02-1) 3 6 66 129 0.6 0.95 (0.19-4.91) Burri et al. ²¹ 2008 (02-2) 7 13 62 122 1.1 1.13 (0.38-3.55) Durri et al. ²¹ 2008 (02-3) 9 17 27 43 1.5 0.67 (0.21-2.08) Changedude et al. ²² 2009 (01) 77 127 164 276 8.2 1.05 (0.08-1.62) Changedude et al. ²² 2009 (01) 177 127 164 276 8.2 1.05 (0.08-1.62) De Ruyck et al. ²¹ 2005 (02-3) 9 17 27 43 1.1 1.14 (0.49-2.63) De Ruyck et al. ²¹ 2005 (01) 15 22 23 40 1.1 1.15 (0.53-4.73) Terazzino et al. ²¹ 2012 (01-1) 13 15 34 67 0.3 6.31 (1.32-30.14) De Ruyck et al. ²¹ 2012 (01-1) 13 15 34 67 0.3 6.31 (1.32-30.14) Under et al. ²¹ 2012 (01-1) 23 41 119 196 37 0.83 (0.42-1.63) Tucker et al. ²¹ 2012 (01-1) 23 41 119 196 37 0.83 (0.42-1.63) Tucker et al. ²¹ 2012 (01-1) 17 36 10 24 1.3 1.25 (0.44-3.56) Tucker et al. ²¹ 2016 (01) 13 17 27 52 0.6 3.30 (0.67-5.31) Tal et al. ²¹ 2016 (01) 13 17 27 52 0.6 3.30 (0.67-5.51) Tal et al. ²¹ 2016 (01-1) 17 36 10 24 1.3 1.25 (0.44-3.56) Tal et al. ²¹ 2016 (01-1) 17 36 10 24 1.3 1.25 (0.44-3.56) Tal et al. ²¹ 2016 (05) 4 6 23 54 0.3 2.70 (0.45-16.00) Zhai et al. ²¹ 2016 (05) 4 6 23 54 0.3 2.70 (0.45-16.00) Zhai et al. ²¹ 2016 (05) 4 6 23 54 0.3 2.70 (0.45-16.00) Zhai et al. ²² 2016 (0.51) 1 3 17 27 52 0.6 3.30 (0.87-1.26) Total events 46 99 Heterogeneity: $z^2=32.01$, $de=1/(P=0.39)$; $P=0\%$ Tat events 46 99 Heterogeneity: $z^2=3.01$, $de=1/(P=0.39)$; $P=0\%$ Total events 46 99 Heterogeneity: $z^2=3.01$, $de=1/(P=0.39)$; $P=0\%$ Total events 1049 2,868 Heterogeneity: $z^2=3.9.0$, $dr=47$ ($P=0.40$); $P=4\%$		30		14			, ,	
Heterogeneity: $\chi^{1+2}1.80$, $df=24$ ($P=0.59$); $f^{2+0.002}$ Tast for overall effect: 23.04 ($P=0.002$) Late adverse effects Andreassen, $tal^{2}2005$ (h1) 1 1 23 9 18 1.1 0.92 (0.27-3.16) Andreassen, $tal^{2}2005$ (h1) 15 26 16 26 1.4 0.85 (0.28-2.56) Andreassen, $tal^{2}2005$ (h1) 1 3 6 66 129 0.6 0.95 (0.19-4.91) Burri et al. $tal^{2}2006$ (b2-1) 3 6 66 129 0.6 0.95 (0.19-4.91) Burri et al. $tal^{2}2008$ (b2-1) 3 6 66 129 0.6 0.95 (0.19-4.91) Burri et al. $tal^{2}2008$ (b2-1) 7 1 27 43 1.5 0.67 (0.21-2.08) Hangdiaude et $al^{2}203$ (b1) 77 127 164 276 8.2 1.05 (0.68-1.62) Changdiaude et $al^{2}203$ (b1) 1 4 29 41 91 2.1 1.14 (0.49-2.63) Globopoulos et al. $tal^{2}2014$ (b1-1) 14 28 14 29 1.4 107 (0.38-3.03) Globopoulos et al. $tal^{2}2012$ (b1-1) 13 15 34 67 0.3 6.31 (1.32-30.14) Langemelher et al. $tal^{2}2012$ (b1-1) 23 41 119 196 3.7 0.83 (0.42-1.63) Globopoulos et al. $tal^{2}2017$ (b1) 1 23 41 119 196 3.7 0.83 (0.42-1.63) Therazzino et al. $tal^{2}2016$ (b1) 14 26 13 34 1.1 1.88 (0.67-5.31) Therazzino et al. $tal^{2}2016$ (b1) 14 26 13 34 1.1 1.50 (0.49-4.55) The et al. $tal^{2}2016$ (b1) 14 26 13 34 1.1 1.26 (0.47-3.58) Usmani et al. $tal^{2}2016$ (b1) 1 77 25 0.6 3.01 (0.87-1.06) Zhai et al. $tal^{2}2016$ (b1) 1 77 25 2.2,209 45.8 1.05 (0.87-1.26) That et al. $tal^{2}2016$ (b1) 1 7 7 25 2.2,209 45.8 1.05 (0.87-1.26) That et al. $tal^{2}2016$ (b1) 1 7 7 25 2.2,209 45.8 1.05 (0.87-1.26) Total events 449 9 Heterogeneily: $\chi^{2-23.01}$ $df=21$ ($P=0.34$); $P=9\%$ Test for overail effect: $Z=1.71$ ($P=0.09$) Total events 46 9 99 Heterogeneily: $\chi^{2-248.90}$, $df=47$ ($P=0.40$); $P=4\%$	Subtotal (95% CI)		944		2,665	50.4	1.29 (1.10–1.52)	•
Test for overall affect: Z=3.04 (<i>P</i> =0.002) Late adverse effects Alsobelin et al. ¹² 2010 (b1-1) 1 1 23 9 18 1.1 0.92 (0.27-3.15) Andreassen et al. ¹² 2005 (b1) 15 26 16 26 1.4 0.85 (0.28-2.58) Burri et al. ¹² 2008 (b2-1) 3 6 66 129 0.6 0.95 (0.19-4.91) Burri et al. ¹² 2008 (b2-2) 7 13 62 122 1.1 1.13 (0.36-3.55) Burri et al. ¹² 2008 (b2-2) 7 13 62 122 1.1 1.13 (0.49-2.63) Burri et al. ¹² 2008 (b2-2) 7 115 22 23 40 1.1 15 0.87 (0.21-2.08) Changdiaude et al. ¹² 2009 (b1) 77 127 164 276 8.2 1.05 (0.88-3.62) Changdiaude et al. ¹² 2009 (b1) 15 22 23 40 1.1 158 (0.53-4.73) Falvo et al. ¹² 2012 (b1-1) 14 28 14 29 1.4 1.07 (0.38-3.03) Glotopoulos et al. ¹² 2007 (b1) 13 15 34 667 0.3 6.31 (1.32-30.14) Langsentehner et al. ¹² 2011 (b2) 52 91 283 484 8.0 0.87 (0.55-1.37) Tucker et al. ¹² 2011 (b2) 52 91 283 484 8.0 0.87 (0.55-1.37) Tucker et al. ¹² 2012 (b1-1) 13 15 34 667 0.3 6.31 (1.32-30.14) Langsentehner et al. ¹² 2012 (b1-1) 13 15 34 67 0.3 6.31 (1.32-30.14) Langsentehner et al. ¹² 2016 (b1) 13 15 34 067 0.5 99 4.6 0.52 (0.27-1.03) Tucker et al. ¹² 2016 (b1) 14 28 13 34 1.1 1.88 (0.67-5.31) Tucker et al. ¹² 2016 (b1) 14 7 36 10 24 1.3 125 (0.44-3.55) Thr et al. ¹² 2016 (b1) 14 7 36 10 24 1.3 1.25 (0.44-3.55) Thai et al. ¹² 2016 (b1) 17 3 67 99 4.6 0.52 (0.27-1.03) The et al. ¹² 2016 (b1) 17 7 27 52 0.6 3.01 (0.87-1.046) Subtod (195% CI) 70 184 3.8 1.65 (0.93-2.92) Subtod (195% CI) 70 194 40 10 1.19 (1.06-1.35) Total events 4.6 99 Heterogeneity: z ¹ =24.0, df=47 (P=0.40); P=4%	Total events	554		1,458				
Test for overall affect: Z=3.04 (<i>P</i> =0.002) Late adverse effects Alsobelin et al. ¹² 2010 (b1-1) 1 1 23 9 18 1.1 0.92 (0.27-3.15) Andreassen et al. ¹² 2005 (b1) 15 26 16 26 1.4 0.85 (0.28-2.58) Burri et al. ¹² 2008 (b2-1) 3 6 66 129 0.6 0.95 (0.19-4.91) Burri et al. ¹² 2008 (b2-2) 7 13 62 122 1.1 1.13 (0.36-3.55) Burri et al. ¹² 2008 (b2-2) 7 13 62 122 1.1 1.13 (0.49-2.63) Burri et al. ¹² 2008 (b2-2) 7 115 22 23 40 1.1 15 0.87 (0.21-2.08) Changdiaude et al. ¹² 2009 (b1) 77 127 164 276 8.2 1.05 (0.88-3.62) Changdiaude et al. ¹² 2009 (b1) 15 22 23 40 1.1 158 (0.53-4.73) Falvo et al. ¹² 2012 (b1-1) 14 28 14 29 1.4 1.07 (0.38-3.03) Glotopoulos et al. ¹² 2007 (b1) 13 15 34 667 0.3 6.31 (1.32-30.14) Langsentehner et al. ¹² 2011 (b2) 52 91 283 484 8.0 0.87 (0.55-1.37) Tucker et al. ¹² 2011 (b2) 52 91 283 484 8.0 0.87 (0.55-1.37) Tucker et al. ¹² 2012 (b1-1) 13 15 34 667 0.3 6.31 (1.32-30.14) Langsentehner et al. ¹² 2012 (b1-1) 13 15 34 67 0.3 6.31 (1.32-30.14) Langsentehner et al. ¹² 2016 (b1) 13 15 34 067 0.5 99 4.6 0.52 (0.27-1.03) Tucker et al. ¹² 2016 (b1) 14 28 13 34 1.1 1.88 (0.67-5.31) Tucker et al. ¹² 2016 (b1) 14 7 36 10 24 1.3 125 (0.44-3.55) Thr et al. ¹² 2016 (b1) 14 7 36 10 24 1.3 1.25 (0.44-3.55) Thai et al. ¹² 2016 (b1) 17 3 67 99 4.6 0.52 (0.27-1.03) The et al. ¹² 2016 (b1) 17 7 27 52 0.6 3.01 (0.87-1.046) Subtod (195% CI) 70 184 3.8 1.65 (0.93-2.92) Subtod (195% CI) 70 194 40 10 1.19 (1.06-1.35) Total events 4.6 99 Heterogeneity: z ¹ =24.0, df=47 (P=0.40); P=4%	Heterogeneity: $\gamma^2 = 21.80$ df=24 (F	P=0 59) · /2=0	אר					
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Burri et al. ¹⁴ 2008 (b2-1) 3 6 66 129 0.6 0.95 (0.19-91) Burri et al. ¹⁴ 2008 (b2-2) 7 13 62 122 1.1 1.13 (0.36-3.55) Changelaude et al. ²² 2009 (b1) 77 127 164 276 8.2 1.05 (0.68-1.62) Cheuk et al. ²³ 2014 (b1-1) 14 29 41 91 2.1 1.14 (0.49-2.63) De Ruyck et al. ²⁴ 2015 (b) 15 22 23 40 1.1 1.56 (0.53-4.73) Giotopoulos et al. ³² 2017 (b1-1) 14 28 14 29 14 1.07 (0.38-3.03) Giotopoulos et al. ³² 2017 (b1-1) 14 28 14 67 0.3 6.31 (1.32-30.14) Langsenlehner et al. ⁴² 2012 (b1-1) 23 41 119 196 3.7 0.83 (0.42-1.63) Tucker et al. ⁴² 2012 (b1-1) 23 41 119 196 3.7 0.83 (0.42-1.63) Usmani et al. ⁴² 2012 (b1-1) 23 41 119 196 3.7 0.83 (0.42-1.63) Tucker et al. ⁴² 2012 (b1-1) 123 41 119 196 3.7 0.83 (0.42-1.63) Usmani et al. ⁴² 2016 (b1) 14 26 13 34 1.1 1.50 (0.49-4.56) Yin et al. ⁴² 2016 (b1) 14 26 13 34 1.1 1.50 (0.49-4.56) Yin et al. ⁴² 2016 (b1) 14 26 13 34 1.1 1.88 (0.67-5.31) Zhai et al. ²² 2016 (b1) 14 26 13 34 1.1 1.88 (0.67-5.31) Zhai et al. ²² 2016 (b1) 17 36 10 24 1.3 1.25 (0.44-3.55) Zhai et al. ²² 2016 (b1) 17 7 62 2.209 45.8 1.05 (0.87-1.26) Thai et al. ⁴² 2016 (b1-1) 17 7 7 52 0.6 3.01 (0.87-10.46) Zschenker et al. ⁴¹ 2010 (b1-1) 13 17 27 52 0.6 3.01 (0.87-10.46) Subtoal (95% CI) 762 2.209 45.8 1.05 (0.87-1.26) Total events 449 1.311 Heterogeneity: χ^2 =23.01, <i>df</i> =21 (<i>P</i> =0.34); <i>P</i> =9% Test for overall effect: <i>Z</i> =0.50 (<i>P</i> =0.62) Acute and late mixed Moulian et al. ⁴² 2010 (b1-1) 13 17 27 52 0.6 3.01 (0.87-1.26) Total events 449 9 Total events 446 99 Total events 446 99 Heterogeneity: χ^2 =28.90, <i>df</i> =47 (<i>P</i> =0.40); <i>P</i> =4%	Andreassen et al,30 2006 (b1-1)	40	70	32	50	3.2	0.75 (0.36-1.58)	
Burri et al. ¹⁴ 2008 (b2-2) 7 1 3 62 122 1.1 1.13 ($0.38-355$) Burri et al. ¹⁴ 2008 (b2-2) 9 17 27 164 276 8.2 1.05 ($0.88-162$) Changclaude et al. ²⁵ 2009 (b1) 77 127 164 276 8.2 1.05 ($0.68-162$) De Ruyck et al. ³⁶ 2014 (b1-1) 14 29 41 91 2.1 1.14 ($0.49-263$) De Ruyck et al. ³⁶ 2007 (b1) 13 15 34 67 0.3 6.31 ($1.32-30.14$) Glotopoulos et al. ³⁵ 2007 (b1) 13 15 34 67 0.3 6.31 ($1.32-30.14$) Langsenlehner et al. ⁴⁵ 2017 (b1-1) 23 41 119 196 3.7 0.83 ($0.42-1.63$) Tranzio et al. ³⁶ 2011 (b2) 52 91 293 484 8.0 0.87 ($0.55-1.37$) Terrazzino et al. ³⁶ 2012 (b1-1) 23 41 119 196 3.7 0.83 ($0.42-1.63$) Tucker et al. ⁴⁶ 2014 (b2-2) 35 39 152 176 1.1 1.50 ($0.49-4.56$) Yin et al. ³⁶ 2011 (b3) 41 66 75 99 4.6 0.52 ($0.27-1.03$) Zhai et al. ²⁵ 2016 (b1-1) 14 26 13 34 1.1 1.88 ($0.67-5.31$) Zhai et al. ²⁵ 2016 (b1-1) 17 36 10 24 1.3 1.25 ($0.44-3.55$) Zhai et al. ²⁵ 2016 (b1-1) 17 7 52 0.6 3.01 ($0.87-10.46$) Zhai et al. ²⁵ 2016 (b1-1) 13 17 27 52 0.6 3.01 ($0.87-10.46$) Subtoal (95% CI) 7C2 2.09 45.8 1.05 ($0.87-1.26$) Total events 449 1.31 Heterogeneity: $x^2=23.01, df=21 (P=0.34); P=9\%$ Test for overall effect: Z=0.50 (P=0.62) Acute and late mixed Moulian et al. ⁸⁵ 2010 $d-f=21 (P=0.34); P=9\%$ Total events 46 99 Heterogeneity: $x^2=24.90, df=47 (P=0.40); P=4\%$		3	6	66	129	0.6	, ,	
Burri et al, ¹⁴ 2008 (b2-3) 9 17 27 43 1.5 0.67 (0.21-2.08) Changelaude et al, ²² 2009 (b1) 77 127 164 276 8.2 1.05 (0.68-1.62) Cheuk et al, ²² 2014 (b1-1) 14 29 41 91 2.1 1.14 (0.49-2.63) De Ruyck et al, ⁴² 2015 (b) 15 22 23 40 1.1 1.58 (0.53-4.73) De Ruyck et al, ⁴² 2015 (b1) 13 15 34 67 0.3 6.31 (1.32-30.14) Langsenlehner et al, ⁴² 2017 (b1) 13 15 34 67 0.3 6.31 (1.32-30.14) Langsenlehner et al, ⁴² 2012 (b1-1) 23 41 119 196 3.7 0.83 (0.42-1.63) Urcker et al, ⁴² 2012 (b1-1) 23 41 119 196 3.7 0.83 (0.42-1.63) Ursker et al, ⁴² 2013 (b3) 23 28 78 113 1.1 2.06 (0.73-5.88) Usmani et al, ⁴² 2014 (b2-2) 35 39 152 178 1.1 1.50 (0.49-4.56) Uraker et al, ⁴² 2016 (b1) 14 26 13 34 1.1 1.88 (0.67-5.31) Zhai et al, ⁴² 2016 (b1-1) 17 36 10 24 1.3 1.25 (0.44-3.55) Zhai et al, ⁴² 2016 (b1-1) 17 36 10 24 1.3 1.25 (0.44-3.55) Zhai et al, ⁴² 2016 (b1-1) 17 36 10 24 1.3 1.25 (0.44-3.55) Zhai et al, ⁴² 2016 (b1-1) 13 17 27 52 0.6 3.01 (0.87-1.26) Total events 449 1.311 Heterogeneity: χ^2 =23.01, <i>df</i> =21 (<i>P</i> =0.34); <i>I</i> ² =9% Test for overall effect: Z=0.50 (<i>P</i> =0.62) Acute and late mixed Moulian et al, ⁴² 2003 (a+b) 46 70 99 184 3.8 1.65 (0.93-2.92) Subtotal (95% C1) 70 184 3.8 1.65 (0.93-2.92) Total events 46 99 Heterogeneity: χ^2 =248.90, <i>df</i> =47 (<i>P</i> =0.40); <i>I</i> ² =4%							, ,	
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De Ruyck et al, ⁴² 2005 (b) 15 22 23 40 1.1 1.58 ($0.53-4.73$) Falvo et al, ³⁴ 2012 ($01-1$) 14 28 14 29 1.4 1.07 ($0.38-3.03$) Giotopulos et al, ³⁵ 2017 ($b1$) 13 15 34 67 0.3 6.31 ($1.32-30.14$) Langsenlehner et al, ⁴² 2011 ($b2$) 52 91 293 484 8.0 0.87 ($0.55-1.37$) Terrazino et al, ³⁶ 2012 ($b1-1$) 23 41 119 196 3.7 0.83 ($0.42-1.63$) Tucker et al, ⁴² 2013 ($b3$) 23 28 78 113 1.1 2.06 ($0.73-5.86$) Usmani et al, ⁴² 2014 ($b2-2$) 35 39 152 178 1.1 1.50 ($0.49-4.56$) Yin et al, ⁴² 2016 ($b1$) 14 26 13 34 1.1 1.88 ($0.67-5.31$) Zhai et al, ²³ 2016 ($b1$) 14 26 13 34 1.1 1.88 ($0.67-5.31$) Zhai et al, ²³ 2016 ($b1$) 14 26 13 34 1.1 1.88 ($0.67-5.31$) Zhai et al, ²³ 2016 ($b1$) 17 36 10 24 1.3 1.25 ($0.44-3.55$) Zhai et al, ²³ 2016 ($b1$) 1 3 17 27 52 0.6 3.01 ($0.87-10.46$) Zschenker et al, ⁴¹ 2010 ($b1-1$) 13 17 27 52 0.6 3.01 ($0.87-10.46$) Subtotal (95% CI) 762 2.209 45.8 1.05 ($0.87-1.26$) Actua and late mixed Moulian et al, ³² 2030 ($a+b$) 46 70 99 184 3.8 1.65 ($0.93-2.92$) Subtotal (95% CI) 70 184 3.8 1.65 ($0.93-2.92$) Subtotal (95% CI) 70 184 3.8 1.65 ($0.93-2.92$) Subtotal (95% CI) 70 184 3.8 1.65 ($0.93-2.92$) Total events 46 99 Heterogeneity: $x^2=48.90$, $df=47$ ($P=0.40$); $P=4\%$	Cheuk et al,20 2014 (b1-1)	14	29	41	91	2.1	1.14 (0.49-2.63)	
Falvo et al, ³⁴ 2012 (b1-1) 14 28 14 29 1.4 1.07 (0.38-3.03) Glotopoulos et al, ³⁴ 2007 (b1) 13 15 34 67 0.3 6.31 (1.32-30.14) Langsenlehner et al, ⁴⁶ 2011 (b2) 52 91 293 484 8.0 0.87 (0.55-1.37) Terrazzino et al, ³⁹ 2012 (b1-1) 23 41 119 196 3.7 0.83 (0.42-1.63) Usmani et al, ⁴⁹ 2014 (b2-2) 35 39 152 178 1.1 1.50 (0.49-4.56) Usmani et al, ⁴⁹ 2016 (b1) 14 26 13 34 1.1 1.88 (0.67-5.31) Zhai et al, ²⁹ 2016 (b1) 14 26 13 34 1.1 1.88 (0.67-5.31) Zhai et al, ²⁹ 2016 (b1) 14 26 13 34 1.1 1.25 (0.44-3.55) Zhai et al, ²⁹ 2016 (b2) 4 6 23 54 0.3 2.70 (0.45-16.00) Zhai et al, ⁴⁹ 2016 (b5) 4 6 23 54 0.3 2.70 (0.45-16.00) Zschenker et al, ⁴¹ 2010 (b1-1) 13 17 27 52 0.6 3.01 (0.87-1.26) Total events 449 1.311 Heterogeneity: $\chi^2=23.01$, $df=21$ ($P=0.34$); $P=9\%$ Test for overall effect: $Z=0.50$ ($P=0.62$) Acute and late mixed Moullan et al, ³⁹ 2003 (a+b) 46 70 99 184 3.8 1.65 (0.93-2.92) Subtoal (95% CI) 70 184 3.8 1.65 (0.93-2.92) Total events 46 99 Heterogeneity: $\chi^2=48.90$, $df=47$ ($P=0.40$); $P=4\%$	De Ruvck et al 49 2005 (b)	15	22	23	40	11	1 58 (0 53-4 73)	
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Subtotal (95% Cl) 70 184 3.8 1.65 (0.93–2.92) Total events 46 99 Heterogeneity: not applicable 70 1.65 (0.93–2.92) Total events 46 99 Total operation of the second sec	Moullan et al, ³⁶ 2003 (a+b)	46	70	99	184	3.8	1.65 (0.93-2.92)	↓
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Test for overall effect: Z=1.71 (P=0.09) Total (95% Cl) 1,776 5,058 100 1.19 (1.06–1.35) Total events 1,049 2,868 Heterogeneity: χ²=48.90, df=47 (P=0.40); l²=4% 0.05 0.2 1 5 21		46		99				
Total events 1,049 2,868 Heterogeneity: χ^{2} =48.90, <i>df</i> =47 (<i>P</i> =0.40); <i>I</i> ² =4%		0.09)						
Total events 1,049 2,868 Heterogeneity: χ²=48.90, df=47 (P=0.40); l²=4%	Total (95% CI)		1,776		5,058	100	1.19 (1.06-1.35)	
Heterogeneity: χ^2 =48.90, <i>df</i> =47 (<i>P</i> =0.40); <i>l</i> ² =4%		1.040	.,	0.000	0,000			▼
0.05 0.2 1 5 2	iotai events	1,049		2,868				
0.05 0.2 1 5 2	Heterogeneity: χ^2 =48.90, df=47 (F	P=0.40); /2=4	4%					
								0.05 0.2 1 5 20

Figure 2 Forest plot for the association between rs25487 and radiation-induced adverse effects.

Notes: A fixed-effects model was used. The square with the corresponding horizontal line represents the OR and 95% Cl of each study. The area of the square reflects the weight of the study. The diamond represents the pooled OR and 95% Cl. The "case" represents patients with severe radiation-induced side effects and "control" represents patients without or with light radiation-induced side effects. a, acute side effects; a1, skin reactions (dermatitis and erythema); a2, mucositis; a3, gastrointestinal and genitourinary toxicity; a3-1, gastrointestinal reactions (nausea and vomiting); a3-2, gastrointestinal reactions (diarrhea, rectal pain, obstipation, bleeding and proctitis); a4, dysphagia; a5, salivary gland; b, late side effects; b1, skin and subcutaneous reactions (subcutaneous fibrosis, skin telangiectasia and breast appearance); b1-1, subcutaneous fibrosis; b2, gastrointestinal and genitourinary toxicity; b2-3, erectile dysfunction; b3, radiation pneumonitis; b4, mucous membrane; b5, salivary gland. Abbreviations: M–H, Mantel–Haenszel; OR, odds ratio.

Study or Subgroup	Case GA+AA	Total	Control GA+AA	Total	Weight (%)	Odds ratio M–H, fixed, 95% Cl	Odds ratio M–H, fixed, 95% Cl
Skin toxicity							
Changclaude et al, ³³ 2005 (a1)	46	77	219	369	12.2	1.02 (0.62-1.68)	_ _
i et al, ²¹ 2013 (a1)	14	24	37	90	2.6	2.01 (0.80-5.00)	
/angoni et al,43 2011 (a1)	5	7	26	54	0.7	2.69 (0.48-15.10)	
fumbrekar et al,37 2017 (a1)	23	43	44	76	5.9	0.84 (0.39–1.78)	
Pratesi et al, ²⁶ 2011 (a1)	8	12	15	33	1.1	2.40 (0.60–9.56)	
Raabe et al, ⁴⁴ 2012 (a1)	27	46	20	37	3.7	1.21 (0.50–2.89)	
Suga et al. ³⁸ 2007 (a1)	50	109	122	290	14.5	1.17 (0.75–1.82)	
errazzino et al. ³⁹ 2012 (a1)	54	89	118	196	11.6	1.02 (0.61–1.70)	
enkatesh et al, ²⁷ 2014 (a1)	31	39	112	127	4.3	0.52 (0.20–1.34)	
hai et al, ²³ 2016 (a1)	14	28	13	32		1.46 (0.53–4.07)	
				32	2.4	. ,	
hou et al,¹⁵ 2010 (a1) Subtotal (95% Cl)	30	69 543	14	33 1,337	4.3 63.4	1.04 (0.45–2.41) 1.11 (0.90–1.38)	•
otal events	302		740				
leterogeneity: χ²=7.45, df=10 (est for overall effect: Z=0.97 (<i>F</i>		0%					
lucositis							
i et al, ²¹ 2013 (a2)	25	48	26	66	4.2	1.67 (0.79–3.54)	+
Pratesi et al,26 2011 (a2)	15	22	8	23	1.0	4.02 (1.16–13.90)	
/enkatesh et al,27 2014 (a2)	48	54	57	66	2.3	1.26 (0.42–3.80)	_
hai et al,23 2016 (a2)	17	30	10	26	1.9	2.09 (0.72-6.10)	
Subtotal (95% CI)		154		181	9.4	1.91 (1.17-3.11)	
otal events	105		101			,	-
leterogeneity: χ^2 =2.07, df=3 (F		%					
Test for overall effect: $Z=2.58$ (F							
Sastrointestinal and genitour	inary toxici	ty					
Ouldulao et al, ⁵² 2013 (a3)	22	24	70	108	0.9	5.97 (1.33-26.77)	·
shikawa et al, ⁵⁰ 2011 (a3-2)	27	58	67	150	8.0	1.08 (0.59-1.98)	
Popanda et al,47 2009 (a3)	37	54	215	351	7.2	1.38 (0.75-2.54)	
Sakano et al, ⁵¹ 2010 (a3-1)	4	9	32	86	1.4	1.35 (0.34-5.40)	
Sakano et al, ⁵¹ 2010 (a3-2)	4	13	32	82	2.4	0.69 (0.20-2.44)	
Smith et al, ⁵³ 2017 (a3)	12	14	89	151	0.9	4.18 (0.90–19.33)	
Subtotal (95% CI)	.=	172		928	20.8	1.49 (1.04–2.11)	
otal events	106		505	520	20.0	1.40 (1.04-2.11)	-
leterogeneity: χ^2 =7.60, <i>df</i> =5 (<i>F</i> fest for overall effect: <i>Z</i> =2.20 (<i>F</i>	P=0.18); /2=3	4%	000				
) ysphagia							
Pratesi et al, ²⁶ 2011 (a4)	8	12	50	89	1.6	1.56 (0.44–5.56)	—
′oon et al,56 2011 (a4)	7	12	24	48	1.6	1.40 (0.39–5.03)	—— — — — —
(ian et al, ²² 2015 (a4)	6	10	31	63	1.4	1.55 (0.40–6.02)	——————————————————————————————————————
Subtotal (95% CI)		34		200	4.6	1.50 (0.71-3.18)	
otal events	21		105		-		
leterogeneity: χ^2 =0.02, <i>df</i> =2 (<i>F</i> est for overall effect: <i>Z</i> =1.06 (<i>F</i>	P=0.99); /²=0 P=0.29)	%					
	,						
alivary gland	20	41	7	10	2.0	1 62 (0 54 4 00)	
hai et al, ²³ 2016 (a5)	20	41	7	19	2.0	1.63 (0.54–4.98)	
ubtotal (95% CI)	20	41	7	19	2.0	1.63 (0.54–4.98)	
otal events	20		7				
leterogeneity: not applicable est for overall effect: Z=0.86 (<i>F</i>	P=0.39)						
otal (95% CI)		944		2,665	100	1.29 (1.10–1.52)	
Total events	554	v	1,458	2,000			$ \bullet $
leterogeneity: χ^2 =21.80, <i>df</i> =24		=0%	1,-50				
-21.00, d/-24		-0/0					
est for overall effect: Z=3.04 (A	2=0 0021						0.05 0.2 1 5

Figure 3 Forest plot for the association between rs25487 and radiation-induced acute adverse effects by specific side effect.

Notes: The "case" represents patients with severe radiation-induced side effects and "control" represents patients without or with light radiation-induced side effects. a, acute side effects; a1, skin reactions (dermatitis and erythema); a2, mucositis; a3, gastrointestinal and genitourinary toxicity; a3-1, gastrointestinal reactions (nausea and vomiting); a3-2, gastrointestinal reactions (diarrhea, rectal pain, obstipation, bleeding and proctitis); a4, dysphagia; a5, salivary gland. Abbreviation: M–H, Mantel–Haenszel.

The present meta-analysis was performed to comprehensively evaluate the influence of *XRCC1* polymorphisms on the development of radiation-induced normal tissue adverse effects. Four common SNPs of *XRCC1* were analyzed in our meta-analysis: *XRCC1* rs25487 (Arg399Gln, G>A), *XRCC1* rs25489 (Arg280His, G>A), *XRCC1* rs1799782 (Arg194Trp, C>T), and *XRCC1* rs3213245 (-77 T>C). Among these, rs25487 (Arg399Gln, G>A) was the most

tudy or ubgroup	Case GA+AA	Total	Control GA+AA	Total	Weight (%)	Odds ratio M–H, fixed, 95% Cl	Odds ratio M–H, fixed, 95% Cl
kin and subcutaneous toxicity							
lsbeih et al,24 2010 (b1-1)	5	30	10	30	3.7	0.40 (0.12-1.36)	
ndreassen et al,29 2003 (b1-1)	11	23	9	18	2.3	0.92 (0.27–3.15)	
ndreassen,63 2005 (b1)	15	26	16	26	3.0	0.85 (0.28–2.58)	
ndreassen et al, ³⁰ 2006 (b1-1)	40	70	32	50	7.1	0.75 (0.36–1.58)	
hangclaude et al, 32 2009 (b1)	77	127	164	276	18.0	1.05 (0.68–1.62)	
heuk et al, ²⁰ 2014 (b1-1)	14	29	41	91	4.5	1.14 (0.49–2.63)	
alvo et al, ³⁴ 2012 (b1-1)	14	29	14	29	4.5 3.0	1.07 (0.38–3.03)	
		20 15				,	
Biotopoulos et al, ³⁵ 2007 (b1)	13		34	67	0.7	6.31 (1.32–30.14)	· · ·
errazzino et al, ³⁹ 2012 (b1-1)	23	41	119	196	8.0	0.83 (0.42–1.63)	
hai et al,23 2016 (b1)	14	26	13	34	2.3	1.88 (0.67–5.31)	
hai et al,²³ 2016 (b1-1)	17	36	10	24	2.8	1.25 (0.44–3.55)	·
schenker et al,41 2010 (b1-1)	13	17	27	52	1.4	3.01 (0.87–10.46)	+
ubtotal (95% CI)		468		893	56.9	1.09 (0.86–1.39)	◆
otal events	256		489				
leterogeneity: χ^2 =13.02, <i>df</i> =11 (<i>F</i> est for overall effect: <i>Z</i> =0.72 (<i>P</i> =0)		:15%					
astrointestinal and genitourina							
urri et al, ¹⁴ 2008 (b2-1)	3	6	66	129	1.3	0.95 (0.19–4.91)	
urri et al, ¹⁴ 2008 (b2-2)	7	13	62	122	2.4	1.13 (0.36–3.55)	
urri et al, ¹⁴ 2008 (b2-3)	9	17	27	43	3.2	0.67 (0.21–2.08)	
angsenlehner et al,46 2011 (b2)	52	91	293	484	17.6	0.87 (0.55–1.37)	
smani et al,48 2014 (b2-2)	35	39	152	178	2.5	1.50 (0.49-4.56)	——————————————————————————————————————
ubtotal (95% CI)		166		956	27.0	0.93 (0.65-1.33)	
ital events	106		600			,	•
eterogeneity: χ^2 =1.23, df =4 (P =0) est for overall effect: Z=0.39 (P =0)	0.87); /²=0%	6					
adiation pneumonitis							
ucker et al,54 2013 (b3)	23	28	78	113	2.4	2.06 (0.73-5.88)	
n et al,55 2011 (b3)	41	66	75	99	10.1	0.52 (0.27-1.03)	
ubtotal (95% CI)		94		212	12.5	0.83 (0.48-1.42)	
otal events	64		153			,	
eterogeneity: χ^2 =4.67, df =1 (P =0 est for overall effect: Z =0.69 (P =0		9%					
ucous							
hai et al, ²³ 2016 (b4)	4	6	23	54	0.7	2.70 (0.45–16.00)	
ubtotal (95% CI)		6		54	0.7	2.70 (0.45-16.00)	
otal events	4		23				
eterogeneity: not applicable est for overall effect: Z=1.09 (P=0	0.28)						
alivary gland						/- /- /	
nai et al, ²³ 2016 (b5)	4	6	23	54	0.7	2.70 (0.45–16.00)	
ubtotal (95% CI)		6		54	0.7	2.70 (0.45–16.00)	
otal events	4		23				
eterogeneity: not applicable est for overall effect: Z=1.09 (P=	0.28)						
ixed late							
e Ruyck et al,49 2005 (b)	15	22	23	40	2.3	1.58 (0.53–4.73)	— —
ubtotal (95% CI)		22		40	2.3	1.58 (0.53–4.73)	
tal events	15		23			7	
eterogeneity: not applicable est for overall effect: Z=0.82 (P=0			~				
otal (95% CI) otal events	449	762	1,311	2,209	100	1.05 (0.87–1.26)	•
	2=0 34)· 12=	9%					
eterogeneity: χ^2 =23.01, df=21 (F	-0.3+), 7 -	0 /0					
eterogeneity: $\chi^2 = 23.01$, $df = 21$ (F st for overall effect: Z=0.50 (P=0)		070					0.05 0.2 1 5 2

Figure 4 Forest plot for the association between rs25487 and radiation-induced late adverse effects by specific side effect.

Notes: The "case" represents patients with severe radiation-induced side effects and "control" represents patients without or with light radiation-induced side effects. b, late side effects; b1, skin and subcutaneous reactions (subcutaneous fibrosis, skin telangiectasia and breast appearance); b1-1, subcutaneous fibrosis; b2, gastrointestinal and genitourinary toxicity; b2-1, gastrointestinal toxicity; b2-2, genitourinary toxicity; b2-3, erectile dysfunction; b3, radiation pneumonitis; b4, mucous membrane; b5, salivary gland. Abbreviation: M–H, Mantel–Haenszel.

ubgroup	Case GA+AA	Total	Control GA+AA	Total	Weight (%)	Odds ratio M–H, fixed, 95% Cl	Odds ratio M–H, fixed, 95% Cl
lead and neck							
Isbeih et al, ²⁴ 2010 (b1-1)	5	30	10	30	1.7	0.40 (0.12-1.36)	
Cheuk et al,20 2014 (b1-1)	14	29	41	91	2.1	1.14 (0.49–2.63)	
i et al, ²¹ 2013 (a1)	14	24	37	90	1.3	2.01 (0.80-5.00)	
i et al, ²¹ 2013 (a2)	25	48	26	66	2.1	1.67 (0.79-3.54)	
Pratesi et al.26 2011 (a1)	8	12	15	33	0.5	2.40 (0.60-9.56)	
Pratesi et al, ²⁶ 2011 (a2)	15	22	8	23	0.5	4.02 (1.16–13.90)	
Pratesi et al, 26 2011 (a4)	8	12	50	89	0.8	1.56 (0.44–5.56)	
/enkatesh et al, ²⁷ 2014 (a1)	31	39	112	127	2.2	0.52 (0.20–1.34)	
/enkatesh et al, ²⁷ 2014 (a2)	48	54	57	66	1.2	1.26 (0.42–3.80)	-
² (hai et al, ²³ 2016 (a1)	40 14	28	13	32	1.2	1.46 (0.53–4.07)	
Thai et al. 23 2016 (a1)	14	28 30	10	26	0.9		
	20		7	20 19		2.09 (0.72-6.10)	
Chai et al, ²³ 2016 (a5)		41			1.0	1.63 (0.54–4.98)	
hai et al, ²³ 2016 (b1)	14	26	13	34	1.1	1.88 (0.67–5.31)	
hai et al, ²³ 2016 (b1-1)	17	36	10	24	1.3	1.25 (0.44–3.55)	· · · ·
hai et al, ²³ 2016 (b4)	4	6	23	54	0.3	2.70 (0.45–16.00)	
² hai et al, ²³ 2016 (b5)	4	6	23	54	0.3	2.70 (0.45–16.00)	
Subtotal (95% CI)		443		858	18.5	1.46 (1.12–1.90)	◆
otal events	258		455				
Heterogeneity: χ^2 =14.65, <i>df</i> =15 (<i>P</i> Test for overall effect: <i>Z</i> =2.81 (<i>P</i> =0		0					
Breast							
ndreassen et al,29 2003 (b1-1)	11	23	9	18	1.1	0.92 (0.27-3.15)	
ndreassen,63 2005 (b1)	15	26	16	26	1.4	0.85 (0.28-2.58)	
ndreassen et al,30 2006 (b1-1)	40	70	32	50	3.2	0.75 (0.36-1.58)	
Changclaude et al,33 2005 (a1)	46	77	219	369	6.2	1.02 (0.62–1.68)	_
Changclaude et al, ³² 2009 (b1)	77	127	164	276	8.2	1.05 (0.68–1.62)	_ _
alvo et al,34 2012 (b1-1)	14	28	14	29	1.4	1.07 (0.38-3.03)	
Giotopoulos et al,35 2007 (b1)	13	15	34	67	0.3	6.31 (1.32–30.14)	
/angoni et al,43 2011 (a1)	5	7	26	54	0.3	2.69 (0.48-15.10)	
Noullan et al, ³⁶ 2003 (a+b)	46	70	99	184	3.8	1.65 (0.93-2.92)	
/umbrekar et al, ³⁷ 2017 (a1)	23	43	44	76	3.0	0.84 (0.39–1.78)	
Raabe et al, 44 2012 (a1)	27	46	20	37	1.9	1.21 (0.50–2.89)	
Suga et al, ³⁸ 2007 (a1)	50	109	122	290	7.3	1.17 (0.75–1.82)	
errazzino et al, ³⁹ 2012 (a1)	50 54	89	118	196	5.9	1.02 (0.61–1.70)	
	23					, ,	
errazzino et al, ³⁹ 2012 (b1-1)		41	119	196	3.7	0.83 (0.42–1.63)	
hou et al, ¹⁵ 2010 (a1)	30	69	14 27	33 52	2.2	1.04 (0.45–2.41)	
					0.6	3.01 (0.87–10.46)	
schenker et al, ⁴¹ 2010 (b1-1)	13	17	21				▲
Subtotal (95% CI)		857		1,953	50.4	1.13 (0.95–1.33)	◆
otal events	487	857	1,077		50.4	1.13 (0.95–1.33)	•
Subtotal (95% CI) Total events Heterogeneity: χ^2 =13.09, df=15 (P	487 2=0.60); /2=0%	857			50.4	1.13 (0.95–1.33)	•
otal events	487 2=0.60); /2=0%	857			50.4	1.13 (0.95–1.33)	•
Subtotal (95% CI) otal events leterogeneity: χ^2 =13.09, <i>df</i> =15 (<i>P</i> est for overall effect: <i>Z</i> =1.35 (<i>P</i> =0 Pelvic	487 2=0.60); /²=0% 0.18)	857	1,077	1,953			•
Subtotal (95% CI) otal events leterogeneity: $\chi^2=13.09$, $df=15$ (<i>P</i> leterogeneity: $\chi^2=13.09$, $df=15$ (<i>P</i> =0 Pelvic Burri et al, ¹⁴ 2008 (b2-1)	487 2=0.60); /²=0% 0.18) 3	857	1,077	1,953 129	0.6	0.95 (0.19-4.91)	•
Subtotal (95% CI) total events leterogeneity: χ^2 =13.09, df =15 (<i>P</i> east for overall effect: <i>Z</i> =1.35 (<i>P</i> =0 Pelvic Burri et al, ¹⁴ 2008 (b2-1) Burri et al, ¹⁴ 2008 (b2-2)	487 2=0.60); /2=0% 0.18) 3 7	857 6 13	1,077 66 62	1,953 129 122	0.6 1.1	0.95 (0.19–4.91) 1.13 (0.36–3.55)	
Subtotal (95% CI) Total events leterogeneity: χ^2 =13.09, df =15 (<i>P</i> est for overall effect: <i>Z</i> =1.35 (<i>P</i> =0 Pelvic Burri et al, ¹⁴ 2008 (b2-1) Burri et al, ¹⁴ 2008 (b2-2) Burri et al, ¹⁴ 2008 (b2-3)	487 2=0.60); /2=0% 0.18) 3 7 9	857 6 13 17	1,077 66 62 27	1,953 129 122 43	0.6 1.1 1.5	0.95 (0.19–4.91) 1.13 (0.36–3.55) 0.67 (0.21–2.08)	
Subtotal (95% CI) Total events teterogeneity: χ^2 =13.09, df =15 (<i>P</i> rest for overall effect: <i>Z</i> =1.35 (<i>P</i> =0 Pelvic Burri et al. ¹⁴ 2008 (b2-1) Burri et al. ¹⁴ 2008 (b2-2) Burri et al. ¹⁴ 2008 (b2-3) De Ruyck et al. ⁴⁹ 2005 (b)	487 2=0.60); /2=0% 0.18) 3 7 9 15	6 13 17 22	1,077 66 62 27 23	1,953 129 122 43 40	0.6 1.1 1.5 1.1	0.95 (0.19–4.91) 1.13 (0.36–3.55) 0.67 (0.21–2.08) 1.58 (0.53–4.73)	
Subtotal (95% CI) total events leterogeneity: χ^2 =13.09, <i>df</i> =15 (<i>P</i> est for overall effect: <i>Z</i> =1.35 (<i>P</i> =0) Pelvic surri et al. ¹⁴ 2008 (b2-1) surri et al. ¹⁴ 2008 (b2-2) surri et al. ¹⁴ 2008 (b2-3) De Ruyck et al. ⁴⁰ 2005 (b) Juldulao et al. ⁵² 2013 (a3)	487 2=0.60); /2=0%).18) 3 7 9 15 22	6 13 17 22 24	1,077 66 62 27 23 70	1,953 129 122 43 40 108	0.6 1.1 1.5 1.1 0.4	0.95 (0.19–4.91) 1.13 (0.36–3.55) 0.67 (0.21–2.08) 1.58 (0.53–4.73) 5.97 (1.33–26.77)	+
Subtotal (95% CI) total events leterogeneity: χ^2 =13.09, <i>df</i> =15 (<i>P</i> est for overall effect: <i>Z</i> =1.35 (<i>P</i> =0 Pelvic Burri et al. ¹⁴ 2008 (b2-1) surri et al. ¹⁴ 2008 (b2-2) Burri et al. ¹⁴ 2008 (b2-3) be Ruyck et al. ⁴⁹ 2005 (b) Duldulao et al. ⁵² 2013 (a3) shikawa et al. ⁵⁰ 2011 (a3-2)	487 2=0.60); / ² =0% 0.18) 3 7 9 15 22 27	6 13 17 22 24 58	1,077 66 62 27 23 70 67	1,953 129 122 43 40 108 150	0.6 1.1 1.5 1.1 0.4 4.0	0.95 (0.19-4.91) 1.13 (0.36-3.55) 0.67 (0.21-2.08) 1.58 (0.53-4.73) 5.97 (1.33-26.77) 1.08 (0.59-1.98)	
Subtotal (95% CI) otal events leterogeneity: χ^2 =13.09, df =15 (<i>P</i> est for overall effect: <i>Z</i> =1.35 (<i>P</i> =0 Pelvic Burri et al, ¹⁴ 2008 (b2-1) Burri et al, ¹⁴ 2008 (b2-2) Burri et al, ¹⁴ 2008 (b2-3) De Ruyck et al, ⁴⁹ 2005 (b) Duldulao et al, ⁵² 2013 (a3) shikawa et al, ⁵⁰ 2011 (a3-2) .angsenlehner et al, ⁴⁶ 2011 (b2)	487 2=0.60); /2=0% 0.18) 3 7 9 15 22 27 52	6 13 17 22 24 58 91	1,077 66 62 27 23 70 67 293	1,953 129 122 43 40 108 150 484	0.6 1.1 1.5 1.1 0.4 4.0 8.0	0.95 (0.19–4.91) 1.13 (0.36–3.55) 0.67 (0.21–2.08) 1.58 (0.53–4.73) 5.97 (1.33–26.77) 1.08 (0.59–1.98) 0.87 (0.55–1.37)	
Subtotal (95% CI) Total events leterogeneity: χ^2 =13.09, df =15 (<i>P</i> rest for overall effect: <i>Z</i> =1.35 (<i>P</i> =0 Pelvic Burri et al, ¹⁴ 2008 (b2-1) Burri et al, ¹⁴ 2008 (b2-2) Burri et al, ¹⁴ 2008 (b2-3) De Ruyck et al, ⁴⁹ 2005 (b) Duldulao et al, ⁵² 2011 (a3-2) angsenlehmer et al, ⁴⁹ 2001 (b2) Popanda et al, ⁴⁷ 2009 (a3)	487 P=0.60); /2=0% 0.18) 3 7 9 15 22 27 52 37	6 13 17 22 24 58 91 54	1,077 66 62 27 23 70 67 293 215	1,953 129 122 43 40 108 150 484 351	0.6 1.1 1.5 1.1 0.4 4.0 8.0 3.7	0.95 (0.19–4.91) 1.13 (0.36–3.55) 0.67 (0.21–2.08) 1.58 (0.53–4.73) 5.97 (1.33–26.77) 1.08 (0.59–1.98) 0.87 (0.55–1.37) 1.38 (0.75–2.54)	
Subtotal (95% CI) total events leterogeneity: χ^2 =13.09, <i>df</i> =15 (<i>P</i> est for overall effect: <i>Z</i> =1.35 (<i>P</i> =0) Pelvic Surri et al, ¹⁴ 2008 (b2-1) Burri et al, ¹⁴ 2008 (b2-2) Burri et al, ¹⁴ 2008 (b2-3) De Ruyck et al, ⁴² 2005 (b) Duldulao et al, ⁴² 2005 (b) Duldulao et al, ⁵² 2011 (a3-2) angsenlehner et al, ⁴² 2011 (b2) topanda et al, ⁴⁷ 2009 (a3) Sakano et al, ⁵¹ 2010 (a3-1)	487 2=0.60); /2=0% .18) 3 7 9 15 22 27 52 37 4	6 13 17 22 24 58 91 54 9	1,077 66 62 27 23 70 67 293 215 32	1,953 129 122 43 40 108 150 484 351 86	0.6 1.1 1.5 1.1 0.4 4.0 8.0 3.7 0.7	0.95 (0.19-4.91) 1.13 (0.36-3.55) 0.67 (0.21-2.08) 1.58 (0.53-4.73) 5.97 (1.33-26.77) 1.08 (0.59-1.98) 0.87 (0.55-1.37) 1.38 (0.75-2.54) 1.35 (0.34-5.40)	
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Subtotal (95% CI) total events leterogeneity: χ^2 =13.09, <i>df</i> =15 (<i>P</i> est for overall effect: <i>Z</i> =1.35 (<i>P</i> =0) Pelvic Surri et al. ¹⁴ 2008 (b2-1) Burri et al. ¹⁴ 2008 (b2-2) Burri et al. ¹⁴ 2008 (b2-2) Burri et al. ⁴² 2008 (b2-3) De Ruyck et al. ⁴² 2005 (b) Duldulao et al. ⁴² 2011 (a3-2) angsenlehner et al. ⁴² 2011 (a3-2) copanda et al. ⁵¹ 2010 (a3-1) Sakano et al. ⁵¹ 2010 (a3-2) Simith et al. ⁵³ 2017 (a3) Simani et al. ⁴² 2014 (b2-2) Subtotal (95% CI)	487 2=0.60); <i>I</i> ² =0% 0.18) 3 7 9 15 22 27 52 37 4 12 35 227 =0.40); <i>I</i> ² =4%	6 13 17 22 24 58 91 54 9 13 14 39 360	1,077 66 62 27 23 70 67 293 215 32 32 32 32 89 152	1,953 129 122 43 40 108 150 484 351 86 82 151 178	0.6 1.1 1.5 1.1 0.4 4.0 3.7 0.7 1.2 0.4 1.1	$\begin{array}{c} 0.95 & (0.19{-}4.91) \\ 1.13 & (0.36{-}3.55) \\ 0.67 & (0.21{-}2.08) \\ 1.58 & (0.53{-}4.73) \\ 5.97 & (1.33{-}26.77) \\ 1.08 & (0.55{-}1.37) \\ 1.08 & (0.75{-}2.54) \\ 1.35 & (0.34{-}5.40) \\ 0.69 & (0.20{-}2.44) \\ 1.18 & (0.09{-}19.33) \\ 1.50 & (0.49{-}4.56) \end{array}$	
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Figure 5 Forest plot for the association between rs25487 and radiation-induced adverse effects by irradiation area.

Notes: The "case" represents patients with severe radiation-induced side effects and "control" represents patients without or with light radiation-induced side effects. a, acute side effects; a I, skin reactions (dermatitis and erythema); a2, mucositis; a3, gastrointestinal and genitourinary toxicity; a3-I, gastrointestinal reactions (nausea and vomiting); a3-2, gastrointestinal reactions (diarrhea, rectal pain, obstipation, bleeding and proctitis); a4, dysphagia; a5, salivary gland; b, late side effects; b1, skin and subcutaneous reactions (subcutaneous fibrosis, skin telangiectasia and breast appearance); b1-1, subcutaneous fibrosis; b2, gastrointestinal and genitourinary toxicity; b2-1, gastrointestinal toxicity; b2-2, genitourinary toxicity; b2-3, erectile dysfunction; b3, radiation pneumonitis; b4, mucous membrane; b5, salivary gland. Abbreviation: M–H, Mantel–Haenszel.

Study or subgroup	Case GA+AA	Total	Control GA+AA	Total	Weight (%)	Odds ratio M–H, fixed, 95% Cl		Odds rat fixed, 95		
Acute adverse effects										
Changclaude et al,33 2005 (a1)	6	77	44	368	14.3	0.62 (0.26-1.52)			_	
Popanda et al,47 2009 (a3)	4	54	35	351	8.8	0.72 (0.25-2.12)				
Venkatesh et al,27 2014 (a1)	38	39	127	127	2.3	0.10 (0.00-2.52)	←			
Zhou et al, ¹⁵ 2010 (a1)	14	69	8	33	8.8	0.80 (0.30-2.14)				
Subtotal (95% CI)		239		879	34.3	0.66 (0.38-1.14)		•		
Total events	62		214			,		•		
Heterogeneity: χ^2 =1.49, df =3 (P = Test for overall effect: Z=1.49 (P =)%								
Late adverse effects										
Andreassen,63 2005 (b1-1)	4	70	3	50	3.4	0.95 (0.20-4.44)				
Azria et al,57 2008 (b1-1)	8	16	7	18	3.4	1.57 (0.40-6.14)				
Burri et al, ¹⁴ 2008 (b2-1)	0	6	11	129	1.1	0.79 (0.04-14.99)			
Burri et al, ¹⁴ 2008 (b2-2)	1	13	10	122	1.8	0.93 (0.11-7.93)				
Burri et al, ¹⁴ 2008 (b2-3)	4	17	2	43	0.9	6.31 (1.03-38.48)			-
Changclaude et al, ³² 2009 (b1)	9	127	32	276	19.1	0.58 (0.27-1.26)			-	
Damaraju et al,45 2006 (b2)	3	28	3	55	1.8	2.08 (0.39-11.05)			
De Ruyck et al,49 2005 (b)	6	22	4	40	2.1	3.38 (0.84–13.62)	-		
Langsenlehner et al, ⁴⁶ 2011 (b2)	3	91	57	487	17.7	0.26 (0.08–0.84)		_		
Subtotal (95% CI)		390		1,220	51.3	0.84 (0.56-1.28)		•	•	
Total events	38		129			,		•		
Heterogeneity: χ^2 =15.27, <i>df</i> =8 (<i>F</i> Test for overall effect: Z=0.81 (<i>P</i> =		-48%								
Acute and late mixed										
Moullan et al, ³⁶ 2003 (a+b)	10	70	30	184	14.5	0.86 (0.39–1.86)				
Subtotal (95% CI)		70		184	14.5	0.86 (0.39–1.86)				
Total events	10		30							
Heterogeneity: not applicable Test for overall effect: Z=0.39 (P=	=0.69)									
Total (95% CI)		699		2,283	100	0.78 (0.58–1.06)		•		
Total events	110		373					•		
Heterogeneity: χ^2 =17.60, df=13 (P=0.17); I	²=26%					+			
Test for overall effect: Z=1.59 (P=	=0.11)						0.01	0.1 1	10	100
Test for subgroup differences: γ^2 =	,							Favors (case)	Favors (conti	n

Figure 6 Forest plot for the association between rs25489 and radiation-induced adverse effects.

Notes: The "case" represents patients with severe radiation-induced side effects and "control" represents patients without or with light radiation-induced side effects. a, acute side effects; a1, skin reactions (dermatitis and erythema); a3, gastrointestinal and genitourinary toxicity; b, late side effects; b1, skin and subcutaneous reactions (subcutaneous fibrosis and skin telangiectasia); b1-1, subcutaneous fibrosis; b2, gastrointestinal and genitourinary toxicity; b2-1, gastrointestinal toxicity; b2-2, genitourinary toxicity; b2-3, erectile dysfunction.

Abbreviation: M-H, Mantel-Haenszel.

commonly studied polymorphism of *XRCC1* in previous researches. Due to different molecular mechanisms of acute and late radiation effects, we analyzed the acute and late side effects separately.

To date, several systematic reviews have been published on genetic variants and normal tissue toxicities induced by radiation, most of which involved *XRCC1* polymorphism.^{47,59–63} However, due to obvious heterogeneity, it is difficult to draw any definite conclusion. So far, four meta-analyses have been published on *XRCC1* polymorphism and the risk of normal tissue injury after RT, three of which were performed only in breast cancer and one in prostate cancer patients; besides, only one to three polymorphisms have been analyzed in each paper.^{13,46,64,65} A positive association between rs25487 Arg399Gln polymorphism and acute side effect in breast cancer patients,^{64,65} and a negative association between rs25489 Arg280His variant and late side effect in breast cancer and prostate cancer patients^{46,65} have been reported in these meta-analyses.

In our meta-analysis, more specific evidences were provided. For rs25487 Arg399Gln polymorphism, significant associations with seriously acute adverse effects were revealed, especially acute mucositis and acute gastrointestinal and genitourinary toxicity. Subgroup analysis according to irradiated area revealed that rs25487 Arg399Gln significantly correlated with an elevated risk of side effects induced by head and neck irradiation. It indicates that patients with rs25487 variant who receive RT are more likely to experience acute adverse effects, especially in head and neck irradiation. No significant correlation with any late side effects,

Study or subgroup	Case GA+AA	Total	Control GA+AA	Total	Weight (%)	Odds ratio M–H, fixed, 95% C	;	Odds rat M–H, fixe	io ed, 95% Cl	
Breast										
Andreassen et al, ²⁹ 2003 (b1-1)	4	70	3	50	3.4	0.95 (0.20-4.44)				
Changclaude et al, ³³ 2005 (a1)	6	77	44	368	14.3	0.62 (0.26-1.52)			<u> </u>	
Changclaude et al. ³² 2009 (b1)	9	127	32	276	19.1	0.58 (0.27–1.26)			+	
Moullan et al,36 2003 (a+b)	10	70	30	184	14.5	0.86 (0.39–1.86)			-	
Zhou et al, ¹⁵ 2010 (a1)	14	69	8	33	8.8	0.80 (0.30-2.14)			<u> </u>	
Subtotal (95% CI)		413		911	60	0.71 (0.47-1.06)		•		
Total events	43		117			. ,				
Heterogeneity: χ^2 =0.75, <i>df</i> =4 (<i>P</i> = Test for overall effect: <i>Z</i> =1.67 (<i>P</i> =)%								
Pelvic										
Burri et al,14 2008 (b2-1)	0	6	11	129	1.1	0.79 (0.04–14.99)				
Burri et al,14 2008 (b2-2)	1	13	10	122	1.8	0.93 (0.11–7.93)				
Burri et al,14 2008 (b2-3)	4	17	2	43	0.9	6.31 (1.03–38.48)				-
Damaraju et al,45 2006 (b2)	3	28	3	55	1.8	2.08 (0.39–11.05)			+ .	
De Ruyck et al,49 2005 (b)	6	22	4	40	2.1	3.38 (0.84–13.62)				
Langsenlehner et al, ⁴⁶ 2011 (b2)	3	91	57	487	17.7	0.26 (0.08-0.84)				
Popanda et al,47 2009 (a3)	4	54	35	351	8.8	0.72 (0.25–2.12)			<u> </u>	
Subtotal (95% CI)		231		1,227	34.3	0.88 (0.53–1.45)				
Total events	21		122							
Heterogeneity: χ^2 =13.45, <i>df</i> =6 (<i>P</i> Test for overall effect: <i>Z</i> =0.52 (<i>P</i> =		=55%								
Head and neck										
Venkatesh et al,27 2014 (a1)	38	39	127	127	2.3	0.10 (0.00-2.52)	←		<u> </u>	
Subtotal (95% CI)		39		127	2.3	0.10 (0.00–2.52)				
Total events	38		127							
Heterogeneity: not applicable Test for overall effect: Z=1.40 (P=	=0.16)									
Mixed										
Azria et al,57 2008 (b1-1)	8	16	7	18	3.4	1.57 (0.40–6.14)			+	
Subtotal (95% CI)		16		18	3.4	1.57 (0.40-6.14)				
Total events	8		7							
Heterogeneity: not applicable										
Test for overall effect: Z=0.65 (P=	=0.52)									
Total (95% CI)		699		2,283	100	0.78 (0.58–1.06)		•		
Total events	110		373							
Heterogeneity: χ^2 =17.60, df=13 (²=26%								
Test for overall effect: Z=1.59 (P=							0.01		1 10	100
Test for Subgroup differences: χ^2	=2.98, df=3	3 (<i>P</i> =0.3	39); /²=0%				Fa	vors (case)	Favors (con	trol)

Figure 7 Forest plot for the association between rs25489 and radiation-induced adverse effects by irradiation area.

Notes: The "case" represents patients with severe radiation-induced side effects and "control" represents patients without or with light radiation-induced side effects. a, acute side effects; a1, skin reactions (dermatitis and erythema); a3, gastrointestinal and genitourinary toxicity; b, late side effects; b1, skin and subcutaneous reactions (subcutaneous fibrosis and skin telangiectasia); b1-1, subcutaneous fibrosis; b2, gastrointestinal and genitourinary toxicity; b2-1, gastrointestinal toxicity; b2-2, genitourinary toxicity; b2-3, erectile dysfunction.

Abbreviation: M-H, Mantel-Haenszel.

or with breast, pelvic, or thoracic irradiation, was observed in rs25487 polymorphism. For rs25489 Arg280His variant, inconsistent with previous results reported, no statistically significant associations were identified, but rs25489 seemed to indicate a protective effect against radiotoxicity, especially in acute adverse effects or in breast irradiation. *XRCC1* SNPs appear to be more likely to correlate with acute RT-induced side effects, but the reason is unclear. Radiation causes *DNA* strand breaks in normal cells, most of the cells die and cannot renew in time leading to acute side effects, accompanied by responses of *DNA* damage repair. Late side effects refer to the cells unable to regenerate after exhausted by radiation and eventually lead to fibrosis instead. The *XRCC1* protein functions in the efficient repair of *DNA* SSBs; thus, we speculate that *XRCC1* may participate in the *DNA* damage repair mainly in the period of RT-induced acute reactions.

No significant associations were detected between rs1799782 or rs3213245 polymorphism and RT-induced toxicity in the overall or the subgroup analyses. However, Moullan et al³⁶ and Mangoni et al⁴³ indicated that the rs1799782194Trp variant was associated with an increased risk of RT-induced adverse response when analyzed in combination with the rs25487 399Gln variant in breast cancer patients. No definite conclusion can be made for rs25489, rs1799782, or rs3213245 polymorphisms, may be due to the relatively small number of identified studies.

Study or subgroup	Case CT+TT	Total	Control CT+TT	Total	Weight (%)	Odds ratio M–H, fixed, 95% Cl	Odds ratio fixed, 95%	
Acute adverse effects								
Changclaude et al,33 2005 (a1)	7	77	40	366	6.7	0.81 (0.35–1.89)		_
Li et al, ²¹ 2013 (a1)	10	24	49	90	6.4	0.60 (0.24–1.49)		
Li et al, ²¹ 2013 (a2)	24	48	35	66	7.8	0.89 (0.42-1.86)		_
Mangoni et al,43 2011 (a1)	1	7	4	54	0.4	2.08 (0.20–21.83)		
Popanda et al,47 2009 (a3)	10	54	47	351	5.4	1.47 (0.69–3.12)	+	<u> </u>
Terrazzino et al,39 2012 (a1)	10	89	22	196	6.5	1.00 (0.45–2.21)		_
Venkatesh et al,27 2014 (a1)	8	39	32	127	6.3	0.77 (0.32-1.84)		_
Venkatesh et al,27 2014 (a2)	14	54	18	66	6.4	0.93 (0.41–2.11)		_
Zhou et al,15 2010 (a1)	31	63	21	39	7.0	0.83 (0.37-1.85)		_
Subtotal (95% CI)		455		1,355	52.9	0.91 (0.68–1.21)	♦	
Total events	115		268					
Heterogeneity: χ^2 =3.19, <i>df</i> =8 (<i>P</i> = Test for overall effect: <i>Z</i> =0.65 (<i>P</i> =		•0%						
Late adverse effects	0.01)							
Andreassen et al, ³⁰ 2006 (b1-1)	3	70	3	50	1.8	0.70 (0.14–3.63)		
Burri et al, ¹⁴ 2008 (b2-1)	0	6	3 7	129	0.4	1.26 (0.06–24.48)		
Burri et al, ¹⁴ 2008 (b2-2)	1	13	6	129	0.4	1.61 (0.18–14.52)		
Burri et al, ¹⁴ 2008 (b2-3)	1	17	1	43	0.0	2.63 (0.15–44.53)		
Changelaude et al, 32 2009 (b1)	10	127	32	43 274	0.3 9.9	0.65 (0.31–1.36)		•
Cheuk et al, ²⁰ 2014 (b1-1)	13	29	32 39	274 91	9.9 5.5	()	-	
						1.08 (0.47–2.51)		
Damaraju et al, 45 2006 (b2)	5	28 22	9	55	2.6	1.11 (0.33–3.70)		
De Ruyck et al, ⁴⁹ 2005 (b)	0		10	40	3.9	0.06 (0.00–1.16)	•	
Falvo et al, ³⁴ 2012 (b1-1)	1 11	19 91	12 65	38 486	4.0	0.12 (0.01–1.01) –	•	
Langsenlehner et al, ⁴⁶ 2011 (b2)					9.6	0.89 (0.45–1.76)		-
Terrazzino et al, ³⁹ 2012 (b1-1)	5	41	23	196	3.7	1.04 (0.37–2.93)		
Subtotal (95% CI)		463	~~~	1,524	42.2	0.75 (0.53–1.06)		
Total events	50		207					
Heterogeneity: χ^2 =8.87, <i>df</i> =10 (<i>H</i>) Test for overall effect: Z=1.63 (<i>P</i>)	<i>,</i> ,	² =0%						
Acute and late mixed								
Moullan et al, ³⁶ 2003 (a+b)	14	70	21	184	4.9	1.94 (0.92-4.07)	+	- -
Subtotal (95% CI)		70		184	4.9	1.94 (0.92–4.07)		
Total events	14		21					
Heterogeneity: not applicable Test for overall effect: Z=1.75 (P	=0.08)							
Total (95% CI)		988		3,063	100	0.89 (0.73–1.10)	•	
Total events	179		496	-		. ,	1	
Heterogeneity: χ^2 =16.12, df=20		/ ² =0%				í –		
Test for overall effect: $Z=1.05$ (P	• • • • •	,,				0.01	0.1 1	10 10

Figure 8 Forest plot for the association between rs1799782 and radiation-induced adverse effects.

Notes: The "case" represents patients with severe radiation-induced side effects and "control" represents patients without or with light radiation-induced side effects. a, acute side effects; a l, skin reactions (dermatitis and erythema); a 2, mucositis; a 3, gastrointestinal and genitourinary toxicity; b, late side effects; b l, skin and subcutaneous reactions (subcutaneous fibrosis and skin telangiectasia); b l - l, subcutaneous fibrosis; b 2, gastrointestinal and genitourinary toxicity; b 2- l, gastrointestinal toxicity; b 2- 2, genitourinary toxicity; b 2- 3, erectile dysfunction.

Abbreviation: M–H, Mantel–Haenszel.

Although a series of studies have been made to evaluate the association between SNPs and RT-induced adverse effects, no SNPs have been thoroughly identified to have the predictive power in clinical practice. Moreover, most studies assessed the individual effect of selected SNPs,^{59,61-63} and the original researches available on combined effect of multiple SNPs are less and not enough to make a metaanalysis. Further studies are needed to elucidate the selection criteria and predictive effect for SNP combinations. In addition, genome-wide association study (GWAS) is more credible due to the comprehensive genetic coverage. Barnett et al⁶⁶ presented the largest GWAS in which 1217 breast cancer patients received adjuvant RT and 633 prostate cancer patients received radical RT. Quantile–quantile plot results provided evidence for the true association between common genetic variants and late toxicity, and associations with late toxicity appeared to be tumor site-specific.

The main source of heterogeneity in such meta-analysis is the overall assessment of all kinds of side effects in various cancer types. However, there are two types of RT-induced adverse effects; acute side effects can be observed during RT and within several weeks after RT, while late side effects occur months to years later.³ Furthermore, different RT-induced side effects may occur in the same irradiation

Study or subgroup	Case TC+CC	Total	Control TC+CC	Total	Weight (%)	Odds ratio M–H fixed, 95% Cl	,	Odds ra fixed, 9	itio M–H, 5% Cl	
Acute adverse effects										
De Ruyck et al,25 2013 (a4)	36	53	103	136	12.6	0.68 (0.34-1.36)			+-	
Terrazzino et al,39 2012 (a1)	57	89	130	196	19.9	0.90 (0.54-1.53)			.	
Venkatesh et al,27 2014 (a1)	18	39	69	127	11.9	0.72 (0.35-1.48)			+	
Venkatesh et al,27 2014 (a2)	27	54	38	66	11.6	0.74 (0.36-1.52)			+	
Zhou et al,15 2010 (a1)	24	69	4	33	2.4	3.87 (1.22-12.30))		·	_
Subtotal (95% CI)		304		558	58.4	0.91 (0.67–1.23)	,	•		
Total events	162		344							
Heterogeneity: χ^2 =7.41, <i>df</i> =4 (<i>F</i> Test for overall effect: Z=0.63 (<i>F</i>		=46%								
Late adverse effects										
Changclaude et al, ³² 2009 (b1)	84	127	181	275	26.4	1.01 (0.65–1.58)		_	• -	
Subtotal (95% CI)		127		275	26.4	1.01 (0.65–1.58)		•	►	
Total events	84		181							
Heterogeneity: not applicable Test for overall effect: Z=0.06 (A	P=0.95)									
Acute and late mixed										
Brem et al,31 2006 (a+b)	42	66	115	181	15.2	1.00 (0.56-1.80)			_	
Subtotal (95% CI)		66		181	15.2	1.00 (0.56-1.80)				
Total events	42		115			, ,			T	
Heterogeneity: not applicable Test for overall effect: Z=0.01 (A	P=0.99)									
Total (95% CI)		497		1,014	100	0.95 (0.75–1.20)		•	•	
Total events	288		640							
Heterogeneity: χ^2 =7.74, df=6 (F		=23%					+		+ + +	
Test for overall effect: Z=0.44 (H	,	0 (D 0	00) 12 CO				0.05	0.2	1 5	20
Test for subgroup difference: χ^2	=0.21, df=	2 (P=0.	90); /2=0%)				Favors (case)	Favors (contro	51)

Figure 9 Forest plot for the association between rs3213245 and radiation-induced adverse effects.

Notes: The "case" represents patients with severe radiation-induced side effects and "control" represents patients without or with light radiation-induced side effects. a, acute side effects; al, skin reactions (dermatitis and erythema); a2, mucositis; a4, dysphagia; b, late side effects; bl, skin and subcutaneous reactions (subcutaneous fibrosis and skin telangiectasia).

Abbreviation: M–H, Mantel–Haenszel.

area, while the same type of side effect can occur in different irradiation areas with the same histological structure. Hence, it is rational to make subgroup analysis in acute or late side effects, the special type of side effects, and irradiation areas.⁶⁷ The subgroup analyses evaluating the effect of rs25487 on



 $Figure \ 10$ Begg's funnel plot for the effect of rs25487 on radiation-induced skin toxicity.

Note: Circles represent the actually included studies. **Abbreviations:** OR, odds ratio; SE, standard error. radiation pneumonitis or on thoracic irradiation yielded significant heterogeneity, because the only two identified studies on NSCLC reached contrary conclusions. The evaluations of rs25489 on late side effects and pelvic irradiation as well as rs3213245 on acute side effects also yielded significant heterogeneity. The presence of heterogeneity may be caused by the differences in study characteristics such as treatment regimen, evaluation endpoint, and genotyping method. The results are reliable because the pooled results calculated by random-effects model are stable in the sensitivity analysis.

Limitations

Several limitations of the present meta-analysis should be considered. First, many included studies assessed multiple different endpoints, resulting in the same study being evaluated more than one time in one analysis. The "multiple testing problem" reduced the statistical power. Second, the number of trails in some of the subgroups and the sample sizes of some of the studies were relatively small, which also restricted the statistical power. Third, eight studies without sufficient data could not be evaluated by weight in the pooled result, which may cause some potential bias. Furthermore, data analyses were not stratified by other confounding factors such as ethnicity, genotyping method, radiation dose, or chemotherapy status because of insufficient information from the primary publications.

Conclusion

The present study, to our knowledge, is the first comprehensive meta-analysis of genetics studies on the association between XRCC1 polymorphisms and radiation-related adverse effects. In conclusion, the meta-analysis suggests that rs25487 Arg399Gln polymorphism is significantly associated with the risk of acute RT-induced adverse effects such as acute mucositis and acute gastrointestinal and genitourinary toxicity. Patients who received head and neck irradiation with rs25487 Arg399Gln polymorphism were more likely to experience RT-induced side effects. The present study also indicates a radioprotective effect for rs25489 polymorphism, especially in acute side effects or in breast irradiation, but without statistical significance. Well-designed studies with large sample size are needed to be performed to assess the value of XRCC1 polymorphisms on radiation-induced adverse effects, which can be used clinically to identify radiosensitive patients and predict radiotoxicity.

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Disclosure

The authors report no conflicts of interest in this work.

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