

Does Fingolimod have anticancer effects? A meta-analysis and systematic review based on experimental animal models of various cancers

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Abstract

Background: Numerous studies have explored the anticancer effect of FTY720 (Fingolimod) in animal models, a sphingosine-1-phosphate (S1P) receptor antagonist and an immunosuppressant, but little clinical evidence guides the use of FTY720 in cancer patients.

Methods: Strictly, only related published articles about the treatment with FTY720 for various cancers *in vivo* from January 1998 to January 2020 were selected from PubMed, Web of Science, Ovid, Embase, CNKI and Cochrane databases, and which were qualified. We acquired agreement through discussion. Then, we conducted meta-analysis, subgroups analysis, publication bias analysis and sensitivity analysis based on selected studies. In the last two sections, we summarized and compared side effects, drug combination effects and molecular pathways from selected studies.

Results: In the 31 articles included from 2002 to 2019, FTY720 was found to reduce tumor volume (SMD = -2.58, 95% CI: -3.42, -1.75, Z = 6.09, P = 0.000), tumor weight (SMD = -3.69, 95% CI: -5.17, -2.21, Z = 4.88, P = 0.000) and body weight (SMD = -0.86, 95% CI: -1.61, -0.11, Z = 2.23, P = 0.025) in 14 types of cancer. Relevant frequent signal pathways include the Akt pathway, S1PRs-Caspase pathway and the STAT3-PP2A pathway. FTY720 has significant independent or in combination anticancer effects and a lower toxicity in renal cell carcinoma and neuroblastoma mice models. However, it should be noted that FTY720 achieved a significant therapeutic effect in immunodeficient mice, not in immunocompetent mice. Also, the dosage-safety of FTY720 alone in clinical use is a noteworthy issue. In mouse models, the mechanism of the FTY720 treatment of tumors lies in inducing the tumor cells apoptosis through important signaling molecules.

Conclusions: FTY720 alone or in combination exerted significant anti-tumor effects for neuroblastoma and renal cell carcinoma, however not for melanoma. Due to insufficient evidence, more specific studies of FTY720 only and in combination included in immunity, inflammation and melanoma should be carried out in the future preclinical and clinical studies.

1. Background

Sphingosine-1-phosphate, abbreviated as S1P, is an active form of sphingolipids and is exported to outside of cells after synthesized in nuclear. Some excellent reviews have summarized the roles of S1P in inflammatory and allergic responses and cancer (Hait and Maiti 2017; Maceyka et al. 2012; Pyne et al. 2016). S1P lyase or phosphatases and sphingosine kinases (SphKs) balance the S1P metabolism in plasma membrane, cytoplasm and outside of cells. S1P can target these signal molecules as Ras, PI3K, and Rho etc by binding S1P receptors, S1PR1-5, a kind of G protein-coupled receptors (GPCRs) (Ogretmen 2018).

There have been exciting animal experiments that explored sphingolipid metabolism and signaling involved in carcinogenesis and tumor metastasis. Recently, target sphingolipid signaling are developing in anti-cancer therapy, however unavailable SphK1 inhibitors were clinically adopted.

FTY720 (chemical name: 2-amino-2-[2-(4-octylphenyl)-1,3-propanediol hydrochloride) is a prescription drug for multiple sclerosis (MS) treatment. S1PR1 is the main target of FTY720. Mechanismly, FTY720 stably downregulates S1PR1 in a unique way of internalization while transiently suppressing S1PR3, 4, 5. A transient heart rate decrease has been reported as a major clinical side effect of FTY720 on the first day at 5 mg/day oral for 7

consecutive days (Koyrakh et al. 2005). Another experiment reported that FTY720 at 2.5 mg/kg/day with intraperitoneal injection (ip) for more than two weeks induced a moderate lymphopenia of nude mice (Pchejetski et al. 2010). In addition, weight loss or inflammation was not observed in healthy volunteers (5 mg/day for one week, oral) or in animals treated with FTY720 at 2.5 mg/kg/day (Kovarik et al. 2004).

Phosphorylated FTY720 inhibit lymphocytes egress of lymphoid tissues, acted as a potential immunosuppressant. However, three main ways of FTY720 in tumor suppress were reported. Huwiler et al. and White C. et al. studies suggested that non-phosphorylated FTY720 displayed anti-cancer properties mainly via a SphK1 downregulation cascade reaction, inducing tumor cell apoptosis, inhibition of tumor cell proliferation, migration and tumor vessel density (Huwiler and Zangemeister-Wittke 2018; White et al. 2016). FTY720 also can be phosphorylated by SK2, and FTY720-P induces internalization of S1PR1 as an antagonist and exerts function of tumor suppress (Pyne and Pyne 2010). Non-phosphorylated FTY720 can target at non-receptor molecular such as PP2A to achieve its anti-cancer role (Perrotti and Neviani 2013). More interestingly, single FTY720 or combined with gefitinib treatment did not suppress the immune system of mice and conversely improved treatment in breast cancer (Martin et al. 2017). The anticancer effect of FTY720 in patients has rarely been reported. It is worth evaluating its potential anticancer function and the clinical safe dosage of oral FTY720. Therefore, we built this systematic review to assess how effective FTY720 is in treating diverse types of cancer and its dosage evaluation.

2. Methods

2.1. A survey of references and Selection criteria

Our References between 1998 and 2020 came from PubMed, Ovid, Embase, Web of Science, CNKI and Cochrane databases. These references were no a language limit. This search used these mesh terms: "fingolimod" OR "FTY720" AND/OR "animals" AND/OR "cancer" in PubMed. Keyword "FTY720 cancer" was used in Ovid, Web of Science and Embase and "FTY720" in CNKI and the Cochrane library. We reviewed the titles, abstracts, main text and even references identified in the search and built the exclusion standard, including (a) reviews, letters, abstracts, editorials and expert opinions; (b) articles without data; (c) repetitive or similar studies; and (d) non-animal based studies. Additionally, we set inclusion parameters, such as: (1) animals: experimental mouse without complication; (2) FTY720 only and in combination; (3) outcomes measures (at the end of experiment or the day of death of all animals in a group): tumor volume, tumor weight and body weight were evaluated. When different doses were used in the same experiment, the highest dose of FTY720 was adopted.

2.2. Meta-analysis data processing

Data extraction contained some routine parameter set, such as first author, year, country, tumor type, animals' strain and age, dosage, frequency, duration, cell lines and numbers, location, administration and therapeutics outcomes (tumor volume, tumor weight) and side effect evaluation (body weight). We extracted the data by using standard form. Values for data were expressed in graph only, values were read off the graphics by using CorelDraw 2019 software.

When a control group shared more than one experiment group, we adjusted the numbers of animals in control group according to a practical guide on PROSPERO. When there was a lack of valid data in a study, review authors acquired the original data from the articles' author by E-mail or phone.

2.3. Assessment of data quality and risk of bias

The SYRCLE's risk for bias tool was utilized to assess the preclinical animal studies quality and evaluate the risk bias of individual animal model studies (Hooijmans et al. 2014). Considering for publication bias and selective results among studies, subgroup analysis, funnel plot analysis, and sensitive analysis were carried out. We evaluated the factors of bias for each study individually in this process.

2.4. Statistical analysis

Our manuscript utilized the STATA software (Stata Corporation, College Station, TX, version 14.0). Tumor volume and weight were taken as an evaluation of the anticancer efficacy of FTY720, conversely body weight as an index of toxicity. The mean value standard difference (SD), standard mean difference (SMD) and 95% confidence interval (CI) in each group were collected. I² test illustrate the heterogeneity among studies and a funnel plot evaluated the possible publication bias. More accurately, Eggers's regression was finished following funnel plots. In our article, P < 0.05 was set as statistically significant by two-sided test.

3. Results

- *Literature screening and the summary of 31 studies*

Using "FTY720" or/and "animals" or/and "cancer" as the index, only 31 studies including 44 experiments of a total of 1485 research papers met our research criteria. The flow diagram for meta-analysis in detail was displayed in Fig. (Alshaker et al. 2017; Azuma et al. 2002; Chen et al. 2014; Chua et al. 2005; Estrada-Bernal et al. 2012; Gstalder et al. 2016; Hait et al. 2015; Ho et al. 2005; Katsuta et al. 2017; Kreitzburg et al. 2018; Lankadasari et al. 2018; Lee et al. 2004; Lee et al. 2005; Leu et al. 2016; Li et al. 2013; Li et al. 2018; Li et al. 2017; Lifshitz et al. 2017; Liu et al. 2015; Liu et al. 2014; Markovsky et al. 2019; Martin et al. 2017; Mousseau et al. 2012; Muroyama et al. 2017; Nagahashi et al. 2016; Pchejetski et al. 2010; Rosa et al. 2013; Schmid et al. 2007; Szymiczek et al. 2017; Woo et al. 2015; Xu et al. 2015).

Table S1 discussed study characteristics of 31 published articles from 1998 to 2019. 14 types of cancer were involved, such as colorectal cancer, breast cancer, pancreatic cancer, lung cancer, ovarian cancer, mesothelioma, glioblastoma, melanoma, neuroblastoma, renal cell carcinoma, prostate cancer, adrenocortical carcinoma, acute myelogenous leukemia and hepatocellular carcinoma. Animal models were mostly used via subcutaneous (sc) or orthotopic tumor implantation. The dose ranges of FTY720 were between 1 mg/kg and 10 mg/kg. Almost all studies adopted FTY720 intraperitoneal injection (ip), gavage (po) or vein injection (iv) daily on specific time. The minimum size of the study sample was 3 and the maximum was 30. Animal experiment times were set from 10 days to nearly a month. Cell number from 1×10^4 to 1×10^7 were observed. Table S2 made a bias assessment followed by SYRCLE's risk tool. Above all, our inclusion studies are of standard quality.

- *Evaluation of the antitumor effect of FTY720 only or in combination*

Here, we measured the therapeutic efficacy of FTY720 by tumor volume and weight. 44 experiments contained in all of the 31 articles observed the tumor volume in animal models with FTY720 treatment (Alshaker et al. 2017; Azuma et al. 2002; Chen et al. 2014; Chua et al. 2005; Estrada-Bernal et al. 2012; Gstalder et al. 2016; Hait et al. 2015; Ho et al. 2005; Katsuta et al. 2017; Kreitzburg et al. 2018; Lankadasari et al. 2018; Lee et al. 2004; Lee et al. 2005; Leu et al. 2016; Li et al. 2013; Li et al. 2018; Li et al. 2017; Lifshitz et al. 2017; Liu et al. 2015; Liu et al. 2014;

Markovsky et al. 2019; Martin et al. 2017; Mousseau et al. 2012; Muroyama et al. 2017; Nagahashi et al. 2016; Pchejetski et al. 2010; Rosa et al. 2013; Schmid et al. 2007; Szymiczek et al. 2017; Woo et al. 2015; Xu et al. 2015). Fig. 2 showed that FTY720 was statistically significant in decreasing tumor volume evaluated by the overall pooled effect value (SMD = -2.58, 95% CI: -3.42, -1.75, Z = 6.09, P = 0.000), especially these subgroups, such as neuroblastoma (SMD = -2.70, 95% CI: -4.21, -1.19, Z = 3.51, P = 0.000), renal cell carcinoma (SMD = -3.65, 95% CI: -4.99, -2.32, Z = 5.36, P = 0.000), breast cancer (SMD = -2.90, 95% CI: -4.25, -1.55, Z = 4.20, P = 0.000), hepatocellular carcinoma (SMD = -3.96, 95% CI: -5.13, -2.79, Z = 6.64, P = 0.000) and prostate cancer (SMD = -5.69, 95% CI: -9.17, -2.22, Z = 3.21, P = 0.001). However, there was no statistical significance in lung cancer (SMD = -1.72, 95% CI: -5.18, 1.74, Z = 0.97, P = 0.331), colorectal cancer (SMD = 1.13, 95% CI: -4.15, 6.41, Z = 0.42, P = 0.675) and melanoma (SMD = 2.66, 95% CI: -0.98, 6.30, Z = 1.43, P = 0.152). Upon further investigation, we found that two different cell lines, human A549 and murine LLC cells in lung cancer or human GEO-CR cells and murine CT26 cells in colorectal cancer, which were respectively used in these studies, brought the opposite experimental outcomes. For melanoma, two of the three studies showed a negative antitumor effect of FTY720. However, it is worth noting that some clinical cases in the treatment of MS reported that FTY720 might cause skin cancers such as melanoma in condition of long-term treatment (FTY720 daily for 62 months) and should pay more attention in the future application.

Heterogeneity in over all types of cancer was $I^2 = 91.1\%$, $P = 0.000$. No or low heterogeneity which were found in renal cell carcinoma ($I^2 = 0.0\%$, $P = 0.424$) and neuroblastoma ($I^2 = 46.8\%$, $P = 0.153$) revealed that FTY720 can significantly reduce tumor volume in these two cancers. Whereas I^2 of some cancers were missed due to there only being one study, including pancreatic cancer, ovarian cancer, mesothelioma, adrenocortical carcinoma, glioblastoma and acute myelogenous leukemia, many more studies should be carried out to verify the antitumor effect of FTY720 in these 6 types of cancer. Obvious heterogeneity existed in breast cancer ($I^2 = 90.7\%$, $P = 0.000$), hepatocellular cancer ($I^2 = 70.2\%$, $P = 0.009$), and prostate cancer ($I^2 = 85.6\%$, $P = 0.001$). Hence, 7 potential heterogeneity factors were utilized to make a subgroup meta-analysis, including cell lines derivation, strain of animal, immunology function of animal model, administration, tumor location, three dosage range of FTY720 (≤ 25 mg/kg/w, 25 mg/kg/w~ 50 mg/kg/w, and ≥ 50 mg/kg/w) and animal age (Table S3). The results showed that cell lines derivation and animal age should be vital factors of heterogeneity in breast cancer mouse models. Transplant tumor location is an obvious factor of heterogeneity in hepatocellular carcinoma mouse models. Due to the limited study number, we failed in finding the heterogeneous factors in prostate cancer mouse models.

Only eight experiments reported tumor weight (Chen et al. 2014; Gstalder et al. 2016; Katsuta et al. 2017; Li et al. 2013; Liu et al. 2015; Liu et al. 2014; Szymiczek et al. 2017; Xu et al. 2015). Fig. 3A showed that FTY720 reduced tumor weight the overall pooled effect values (SMD = -3.69, 95% CI: -5.17, -2.21, Z = 4.88, P = 0.000) and however existed high heterogeneity ($I^2 = 83.2\%$, $P = 0.000$). In the subgroup analysis, FTY720 slowed down the growth of tumors in lung cancer with low heterogeneity (SMD = -7.35, 95% CI: -9.27, -5.43, Z = 7.49, P = 0.000, $I^2 = 0.0\%$, $P = 0.478$), however, other groups with only one study can't offer pooled effect values. Regrettably, heterogeneity analysis could not be finished in neuroblastoma, renal cell carcinoma, mesothelioma, acute myelogenous leukemia, adrenocortical carcinoma and breast cancer without the value of I^2 due to limited number.

Intriguingly, FTY720 exhibited outstanding anticancer effect in co-treatment with other drugs or radiotherapy (Table S4). 18 of 31 articles about FTY720 in combination treatment reported the improvement of the therapeutic efficacy (Alshaker et al. 2017; Estrada-Bernal et al. 2012; Gstalder et al. 2016; Hait et al. 2015; Katsuta et al. 2017; Kreitzburg et al. 2018; Lankadasari et al. 2018; Li et al. 2013; Lifshitz et al. 2017; Liu et al. 2014; Markovsky et al.

2019; Martin et al. 2017; Mousseau et al. 2012; Muroyama et al. 2017; Pchejetski et al. 2010; Rosa et al. 2013; Szymiczek et al. 2017; Woo et al. 2015). The reported chemotherapy drugs included tamoxifen, carboplatin, gemcitabine or radiotherapy.

- *Evaluation of the side effect of FTY720 only or in combination*

Eight experiments reported that FTY720 might reduce animal body weight (SMD = -0.86, 95% CI: -1.61, -0.11, Z = 2.23, P = 0.025, Fig. 3B), especially in prostate cancer (SMD = -1.45, 95% CI: -2.46, -0.44, Z = 2.81, P = 0.005) with low heterogeneity ($I^2 = 0.0\%$, P = 0.920) (Alshaker et al. 2017; Chua et al. 2005; Ho et al. 2005; Lee et al. 2005; Leu et al. 2016; Szymiczek et al. 2017; Xu et al. 2015). And, no statistical significance was shown in hepatocellular carcinoma (SMD = 0.00, 95% CI: -0.97, 0.97, Z = 0.00, P = 0.999). Due to limitations of the number and experimental groups of studies, SMD and I^2 was missed in adrenocortical carcinoma, breast cancer and mesothelioma.

More deeply, we summarized the toxicity reaction of FTY720 alone or in combination from every original study in Table S4. 16 of the total 31 articles related to side effect of FTY720, and showed no obvious side effects in mice and rats during their experiment (Alshaker et al. 2017; Chua et al. 2005; Gstalder et al. 2016; Hait et al. 2015; Ho et al. 2005; Katsuta et al. 2017; Lee et al. 2004; Lee et al. 2005; Leu et al. 2016; Li et al. 2017; Lifshitz et al. 2017; Martin et al. 2017; Pchejetski et al. 2010; Rosa et al. 2013; Szymiczek et al. 2017; Xu et al. 2015). The remaining 15 articles didn't document explicitly for the potential side effects of FTY720. Co-treatment with gefitinib, doxorubicin and docetaxel showed lower toxicity than by themselves.

- *Publication bias and sensitivity analysis*

First, SYRCLE's tool from PRSPERO is set to evaluate quality of studies, detail data was listed in Table S2. Then, we used funnel plots to assess publication for meta-analysis and tested by Egger's regression for tumor volume only, due to the limitation of the number of studies. It suggested that the majority of researches were approximately symmetrical (Fig. 4), and Egger's regression for all types of cancer in tumor volume (P = 0.235), tumor weight (P = 0.018) and body weight (P = 0.172) suggested that the publication bias were not obvious in tumor volume and body weight, but in tumor weight. For the sensitivity analysis, Fig. 5 showed that the pooled SMD in the rest of the studies were still significant although one individual research was deleted once.

- *Signaling pathway related with FTY720 anticancer mechanism*

Finally, the anticancer related molecular signals of FTY720 alone or in combination with chemical drug in total 26 articles were summarized in Table 1. The main molecular mechanism was focused on apoptosis which was discussed by 20 articles, including non-small lung cancer, pancreatic cancer, mesothelioma, breast cancer, renal cell carcinoma, colorectal cancer, adrenocortical carcinoma, acute myeloid leukemia, neuroblastoma, glioblastoma, prostate cancer, and hepatocellular carcinoma (Alshaker et al. 2017; Chen et al. 2014; Chua et al. 2005; Estrada-Bernal et al. 2012; Gstalder et al. 2016; Ho et al. 2005; Lankadasari et al. 2018; Lee et al. 2004; Lee et al. 2005; Li et al. 2013; Li et al. 2017; Lifshitz et al. 2017; Liu et al. 2015; Martin et al. 2017; Mousseau et al. 2012; Pchejetski et al. 2010; Rosa et al. 2013; Szymiczek et al. 2017; Woo et al. 2015; Xu et al. 2015). In the remaining signal pathway, six involved metastasis (pancreatic cancer, breast cancer, pancreatic cancer, non-small cell lung cancer, hepatocellular carcinoma and androgen-independent prostate cancer) (Azuma et al. 2003; Chua et al. 2005; Lankadasari et al. 2018; Lee et al. 2005; Liu et al. 2014; Nagahashi et al. 2016), four involved cell cycle

arrest (androgen-independent prostate cancer, acute myeloid leukemia, hepatocellular carcinoma) (Chua et al. 2005; Ho et al. 2005; Lee et al. 2004; Lee et al. 2005), four involved angiogenesis (hepatocellular carcinoma, Lewis lung cancer, androgen-independent prostate cancer, breast cancer) (Chua et al. 2005; Ho et al. 2005; Mousseau et al. 2012; Schmid et al. 2007), two involved invasion (non-small lung cancer, adrenocortical carcinoma) (Liu et al. 2015; Xu et al. 2015), one involved histone acetylation (breast cancer) (Hait et al. 2015) and one involved autophagy pathways (lung cancer) (Li et al. 2018) respectively. The frequent targeted molecules were SphK1, PP2A, S1PR1, STAT3, VEGF, EGFR, caspases. This evidence suggests that the sphingosine signaling pathway is one of importance in various types of cancer and mainly induces apoptosis of tumor cells after interfering it.

3. Discussion

First, in our systematic review, we evaluated the treatment efficacy of SphK1 inhibitor- FTY720 alone or in combination in 14 types of cancers. Undoubtedly, both FTY720 alone and in combination have an anticancer function with statistical significance, especially in neuroblastoma (SMD = -2.70, 95% CI: -4.21, -1.19, Z = 3.51, p = 0.000, $I^2 = 46.8\%$, P = 0.153 in tumor volume), renal cancer (SMD = -3.65, 95% CI: -4.99, -2.32, Z = 5.36, p = 0.000, $I^2 = 0.0\%$, P = 0.424 in tumor volume) and lung cancer (SMD = -7.35, 95% CI: -9.27, -5.43, Z=7.49, P = 0.000, $I^2 = 0.0\%$, P = 0.478 in tumor weight). Due to obvious heterogeneity, these types of cancer are controversial in treatment efficacy, including breast cancer ($I^2 = 90.7\%$, P = 0.000), hepatocellular cancer ($I^2 = 70.2\%$, P = 0.009), and prostate cancer ($I^2 = 85.6\%$, P = 0.001). After investigating seven potential influencing factors cell lines derivation, strains of animal, immunology function of animal models, administration, tumor location, three dosage range of FTY720 and animal age were recognized as vital factors for heterogeneity of breast cancer mouse models, and tumor transplant location for heterogeneity of hepatocellular carcinoma mouse models. However, the heterogeneous factors in prostate cancer mice models cannot be concluded because of the number of valid studies. Interestingly, Pchejetski et al. reported that FTY720 enhanced the sensitivity to radiotherapy for nude mice of hormone-independent metastatic prostate cancer (Pchejetski et al. 2011). Besides, the total pooled results showed that SMD was -2.58, 95% CI: -3.42, -1.75, Z = 6.09, P = 0.000 with statistical significance, for other cancers which included ovarian cancer, mesothelioma, pancreatic cancer, glioblastoma, adrenocortical carcinoma and acute myelogenous leukemia, suggesting potential treatment value of FTY720 for them, and should give more evidences in the future. For total pooled results of tumor weight showed that SMD = -3.69, 95% CI: -5.17, -2.21, Z = 4.88, P = 0.000) and however existed high heterogeneity ($I^2 = 83.2\%$, P = 0.000). In subgroup analysis, FTY720 slowed down the growth of tumor in lung cancer with low heterogeneity (SMD = -7.35, 95% CI: -9.27, -5.43, Z=7.49, P = 0.000, $I^2 = 0.0\%$, P = 0.478). Same, other groups with only one study can't offer pooled effect values and more studies should be conducted.

Next, our discussion focused on the side effects of FTY720 alone or in combination at a potent pharmaceutical dose. Only eight experiments of 31 articles discussed issues regarding reducing experimental animal body weight of FTY720 at the dosage range from 3 mg/kg, 2 weeks, biweekly to 10mg/kg /day, and only one study in prostate cancer reported a significant weight loss (SMD = -1.45, CI: -2.46, -0.44, Z = 2.81, P = 0.005) with low heterogeneity ($I^2 = 0.0\%$, P = 0.920). Although total pooled values (SMD = -0.86, 95% CI: -1.61, -0.11, Z = 2.23, P = 0.025) suggested that there is a tendency in reducing body weight in the included eight experiments, therefore conclusions cannot be drawn in these studies, such as adrenocortical carcinoma, breast cancer, and mesothelioma due to the low number of studies. Additionally, because of the different combinations, we adopted the method of single literature summary to discuss the toxicity reaction of FTY720 in combination or alone in

Table S4. 16 out of 29 articles did not suggest any side effects in mice and rats and conversely increased anticancer efficacy, especially co-treatment with gefitinib, doxorubicin and docetaxel. Actually, there exists some controversial conclusions about FTY720 side effects. For example, moderate lymphopenia was observed in prostate cancer models treated with FTY720 at the dose of 2.5 mg/kg/day (Pchejetski et al. 2011). Additionally, healthy volunteers treated by 5 mg/day FTY720 oral for one week showed no toxic effects, however FTY720 might cause skin cancers which was reported in clinical therapy (Michiels et al. 2019; Robinson and Guo 2016). Hence, the dosage-safety of FTY720 in clinical use is still a noteworthy issue. Another controversial results of animals immune system condition suggested significant anticancer effect in immunocompromised mice (SMD = -3.35, 95% CI: -4.17, -2.53, Z = 8.02, P = 0.000, I² = 87.7%, p = 0.000 for tumor volume), not in immunocompetent mice (SMD = -0.67, 95% CI: -2.80, 1.46, Z = 0.62, P = 0.537, I² = 94.5%, p = 0.000 for tumor volume) (Fig S1). The author analyze that This result shows FTY720 may have side effect in immune system against its anti-cancer function. Only one study paradoxically investigated more efficacy of FTY720 on immunocompetent mice than on immunocompromised mice, due to intratumoral T cells activation (Martin et al. 2017). Conflicting research demonstrated FTY720 in combination showed better therapeutic efficacy and did not inhibit the function of the immune system.

At last, to further understand the significance of sphingolipids, especially S1P in diverse cancers, we analyzed the molecular targets of FTY720 alone or in combination in detail in Table 1. 20 out of 31 articles explained that FTY720-induced cell cycle arrest of tumor cells and apoptosis are one of the main anticancer mechanisms in these cancer types, as is non-small lung cancer, pancreatic cancer, mesothelioma, breast cancer, renal cell carcinoma, colorectal cancer, adrenocortical carcinoma, acute myeloid leukemia, neuroblastoma, glioblastoma, prostate cancer, and hepatocellular carcinoma. These classic signal cascades mediated apoptosis including SphK1/S1PR1/STAT3/Ki67 or CycD1 or β -catenin or c-Myc or PP2A; FTY720-P/S1PR1/JAK2/STAT3/caspase-3 or PARP-1 or Bcl-2; SphK2/Akt or BAD /Cyt c; S1PR1/ERK; PI3K/Akt/caspases or MAPK/caspase cascades, et al, suggesting the close association between S1PR1 and important molecules such as Akt, STAT3, VEGF, EGFR, SphK 1, SphK 2, PP2A et al.

Conclusion

According to the data meta-analysis, we suggest that FTY720 alone or in combination may be a candidate for the treatment of certain cancers, especially for neuroblastoma and renal cell carcinoma, however not for melanoma. Considering higher dosage of FTY720 in animal experiments and a few case reports of the side effects in MS, we recommend that more specific studies of FTY720 only and in combination focus on immunity, inflammation and melanoma be carried out in the future preclinical studies.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

All data generated or analysed during this study are included in this published article.

Competing Interests: The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Authors' contributions GYZ and ZP collected and analyzed the data. GYZ drafted the manuscript. KL designed this study and interpreted the data and revised the manuscript. All authors have read and approved the manuscript.

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Tables

Table 1 Summarized signal molecules and pathways of FTY720 alone or in combination

Literature	Drugs	Diseases	signal molecules and cluster pathways
Yang Li 2018	FTY720 and cisplatin	Non-small lung cancer	FTY720→Bcl-2↓→ Bax↑ cleaved caspase 9↑ (apoptosis↑) FTY720→Atg7↓ Ki67↓ (autophagy↑)
Manendra Babu Lankadasari 2018	FTY720 FTY720 and gemcitabine	Pancreatic cancer	FTY720→S1PR1/STAT3↓→ Ki67↓ Cyclin D1↓ β-catenin↓ C-Myc↓ (apoptosis↑) FTY720→PP2A↑ (apoptosis↑) FTY720→S1PR1/STAT3↓→E-cadherin↑ N-cadherin↓ Vimentin↓ Snail↓ Slug↓ Twist1↓ Twist2↓ IL-6 ↑ (metastasis↓(EMT)) FTY720→S1PR1/STAT3↓→SHH↓ Gli1↓ Gli3↑ CXCR4↓ CXCL12↓ HIF1α↓ (desemoplasia↓) →gemcitabine accumulation↑→ABCC5↓ CDA↓ DCK↓ DCTD↓ RRM1↓ RRM2↓ NF-κB↓ TNF-α↓ p65↓ (gemcitabine sensitivity↑)
Agata Szymiczek 2017	FTY720	Mesothelioma	FTY720→SET↓→PP2A↑→AKT phosphorylation↓→Bcl2↓ caspase 3↑ PARR↑→Cyt-c↓→AIF in mitochondrial fraction↓→Cyt-c&AIF in cytoplasm↑ AIF in nuclear fraction↑ (apoptosis↑)
Janet L. Martin 2017	FTY720 and gefitinib	Breast cancer (Triple negative breast cancer)	SphK1↓ (inhibited by FTY720) or/ and phospho-EGFR↓ (tyrosine kinase inhibited by gefitinib)→ cleaved caspase 3↑ Ki67↓ IGFBP-3↓→CD44↓ (apoptosis↑)
Veronica Lifshitz 2017	FTY720 and etoposide	Neuroblastoma	FTY720→SphK2→FTY720-P→S1PR1-JAK2-STAT3↓ etoposideresistance↓→cleavage caspase-3 ↑ PARP-1↑ STAT3 phosphorylation↓ Bcl-2↓ (apoptosis↑)
Eriko Katsuta 2017	FTY720 and doxorubicin	Breast cancer	Doxorubicin→STAT3↑ SphK1↑ S1PR1↑ IL6↑→FTY720→NF-κB↑ IL6↓ STAT3↓ SphK1↓ S1PR1↓ (mitigate toxicity of doxorubicin)
Heba Alshaker 2017	FTY720-docetaxel nanoparticles	Breast cancer (in triple negative breast cancer)	FTY720&docetaxel→SphK1↓ VEGF↓ caspase 3↑ caspase 7↑ (apoptosis↑)
Masayuki Nagahashi 2016	FTY720	Breast cancer	FTY720→SphK1↓→S1P and dihydro-S1P in tumor IF↓ (hypothesis: metastasis↓)
Cecile Gstalder 2016	FTY720	Renal cell carcinoma	FTY720→S1PR1↓ SphK1↓ H1Fa↓ H2Fa↓ VEGF↓ CD34↓ (remodel tumor vasculature and tumor oxygenation on intratumoral hypoxia) FTY720→ cleaved caspase 3↑ Ki67↓ (apoptosis↑)
NC Hait 2015	FTY720	Breast cancer (in triple negative breast cancer and hormonal therapy - resistant breast cancer)	FTY720→SphK2↑→FTY720-P↑→HDACs↓→acetylation of histone H3-K9, H4-K5 and H2B-K12↑→ERα↑ (histone acetylations↑)
Seon Min Woo 2015	FTY720	Renal cell carcinoma	FTY720→DR-5↑ Mcl-1↓ (TRAIL mediated apoptosis↑)

		Breast cancer	
		Colorectal cancer	
Hao Liu 2015	FTY720	Non-small lung cancer	FTY720→SET↓→PP2A↑→AKT& ERK dephosphorylation↑→Cyclin D1↓ MMP9↓ p27↓ (apoptosis↑ and invasion↓)
Yunze Xu 2015	FTY720	Adrenocortical carcinoma	Fty720→SphK1↓→PI3k& AKT&ERKphosphorylation↓ MAPK↓ (apoptosis↑)
Hao Liu 2014	FTY720 and cisplatin	Non-small cell lung cancer	FTY720→SET↓→PP2A↑→c-myc↑→NDRG1↓ increased levels of AKT phosphorylation↓ N-cadherin↓ vimentin↓ E-cadherin↑ GSK-3β/β-catenin signaling↓ Snail↓ (EMT↓ metastasis↓ invasion↓)
Limen Chen 2014	FTY720	Acute Myeloid Leukemia	FTY720→DEGS1↑SMPD1↑SMPD3↑ GBA↑→cearmides accumulation↑→MOMP↑ and I2PP2A/SET↓→PP2A↑→cleaved caspase3↑ cleaved caspase8↑ cleaved caspase 9↑ Cyt c↑ (apoptosis↑) FTY720→AML1-ETO↓→G0/G1 cell cycle arrest↑ (cell cycle arrest↑) FTY720→ErbB2 Interacting Protein (ERBB2IP)↑ Lymphocyte Antigen 9 (LY9)↑ Modulator of apoptosis1 (MOAP1)↑ NFE2↑ →AML1↑
Roberta Rosa 2013	FTY720 and cetuximab	Colorectal cancer	FTY720→SPHK2→FTY720-P→SphK1↓→EGFR↓→AKT/MAPK/mTOR and Ras/MAPK phosphorylation↓→resensitization to cetuximab↑ (cetuximab sensitivity↑ apoptosis↑)
Mei-Hong Li 2013	FTY720	Neuroblastoma	FTY720→SphK2↓→Akt&BAD dephosphorylation↑→Cyt c↑ (apoptosis↑)
Adriana Estrada-Bernal 2012	FTY720 and temozolomide	Glioblastoma	FTY720→S1PR1↓→ ERK↓ ERK-P↑ (spectulated in PP2A pathway)→BH3-only protein Bim↑→cleaved caspase 9↑ cleaved caspase 7↑ cleaved caspase 3↑ (apoptosis↑)
Dmitri Pchejetski 2010	FTY720 and radiotherapy	Prostate cancer	FTY720→SphK1↓→cleaved caspase 3↑ cleaved caspase 7↑ (apoptosis↑), FTY720→radio sensitization↑ (no mention mechanism)
Gerald Schmid 2007	FTY720	Lewis lung cancer	FTY720→S1PR1→CXCR4↓ (angiogenesis↓)
Terence K. Lee 2005	FTY720	Hepatocellular carcinoma	FTY720→Rac↓→VEGF↓ CD34↓→vascular permeability ↓ (metastasis↓)
Joanna W.Y. Ho 2005	FTY720	Hepatocellular carcinoma	FTY720 →G1 arrest↑ (cell cycle arrest↑) FTY720→cleaved caspase 3↑ (apoptosis↑) FTY720→angiogenesis↓ (no mention mechanism)
Yoanne Mousseau 2012	FTY720 and sunitinib	Breast cancer	FTY720→S1PR1↓ S1PR3↓→S1P/PDGF-B pathway↓ VEGF pathway↓ (VSMCs spatial organization↓ angiogenesis↓, better result with sunitinib, no mention mechanism) FTY720→SphK1↓ (apoptosis↑)

Chee-Wai Chua 2005	FTY720	Androgen-independent prostate cancer	<p>FTY720→cell cycle inhibitors such as p21Waf1↑ (cell cycle arrest↑)</p> <p>FTY720→apoptosis regulators such as Bcl-2↓ and caspases↑ (apoptosis↑)</p> <p>FTY720→angiogenesis promoting factor, VEGF↓ (angiogenesis↓)</p> <p>FTY720→PCNA and Ki-67↓ (apoptosis↑)</p> <p>FTY720→E-cadherin and β-catenin translocate from cytoplasm to membrane (metastasis↓)</p>
Haruhito Azuma 2002	FTY720	Breast cancer	<p>Fty720→expression of integrins, especially VLA1, VLA2, and VLA6 (both are ligands for laminin and collagen type I)↓→decreased the ability of cancer cells to adhere to ECM components, especially laminin↓ (metastasis↓)</p>
Terence K.Lee 2004	FTY720	Hepatocellular carcinoma	<p>FTY720→PI3-K↓→Akt dephosphorylation↑→p22/p44&FKHR&GSK-3β dephosphorylation → p27↑ Cyclin D1↓→G1 arrest (cell cycle arrest↑)</p> <p>FTY720→PI3-K↓→Akt dephosphorylation↑→caspase 9 dephosphorylation↑→cleaved caspase 9↑ cleaved caspase 3↑ (apoptosis↑)</p>

FTY720-p, phospholated FTY720; BTSCs, brain tumor stem cells, refer to BTCS9, BTSC44, BTSC57 and BTSC61; EGFR vIII, a kind of epithelial growth factor receptor (EGFR) receptor mutant; VSMCs, vascular smooth muscle cells; EGFR-TKI, epidermal growth factor receptor kinase blockade; BTSCs, brain tumor stem cells, refer to BTCS9, BTSC44, BTSC57 and BTSC61; EGFR vIII, a kind of epithelial growth factor receptor(EGFR) receptor mutant; VSMCs, vascular smooth muscle cells; IF, interstitial fluid; Cyt-c, cytochrome c; AIF, apoptosis inducing factor; DCK, deoxycytidine kinase; DCTD, deoxycytidine monophosphate deaminase; CDA, cytidine deaminase; RRM1, ribonucleotide reductases M1; Shh, sonic hedgehog; IGFBP-3, insulin-like growth factor binding protein-3; EGFR, epidermal growth factor receptor; HDACs, class I histone deacetylases; DR-5, death receptor 5; EMT, epithelial-to-mesenchymal transition; NDRG1, N-myc downstream regulated gene1; MOMP, mitochondria outer membrane permeabilization; PCNA, proliferating cell nuclear antigen; Akt, serine/threonine kinase; PI3K, phosphatidylinositol 3-kinase;

ERK, extracellular regulated MAP kinase; BAD, Bcl2 associated death protein; MAPK, mitogen-activated protein kinase; VEGF, vascular endothelial growth factor; JAK2, Janus Kinase 2; STAT3, signal transducer and activator of transcription 3; PARP-1, poly (ADP-ribose) polymerase 1

Figures

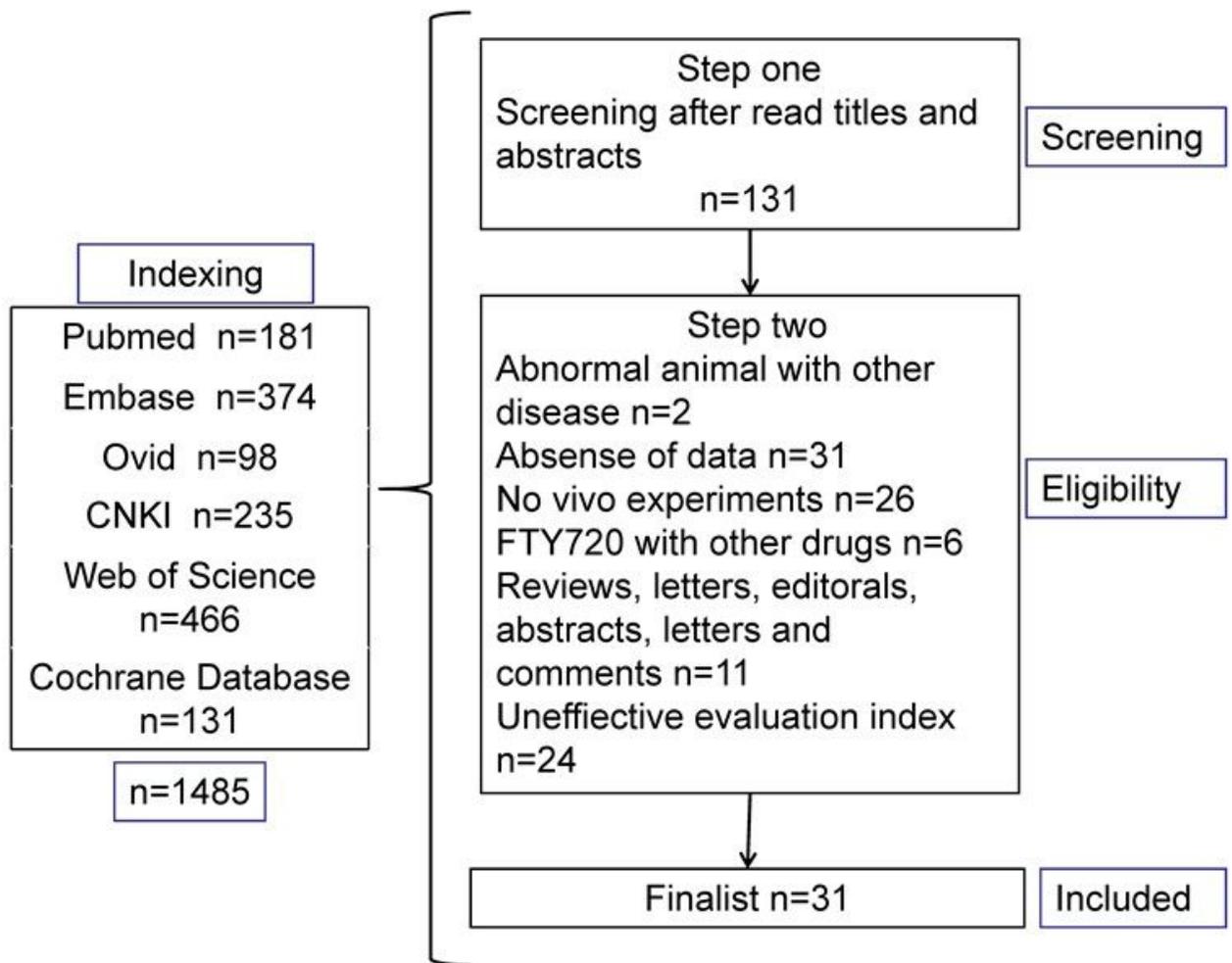


Figure 1

The screened diagram of meta-analysis articles.

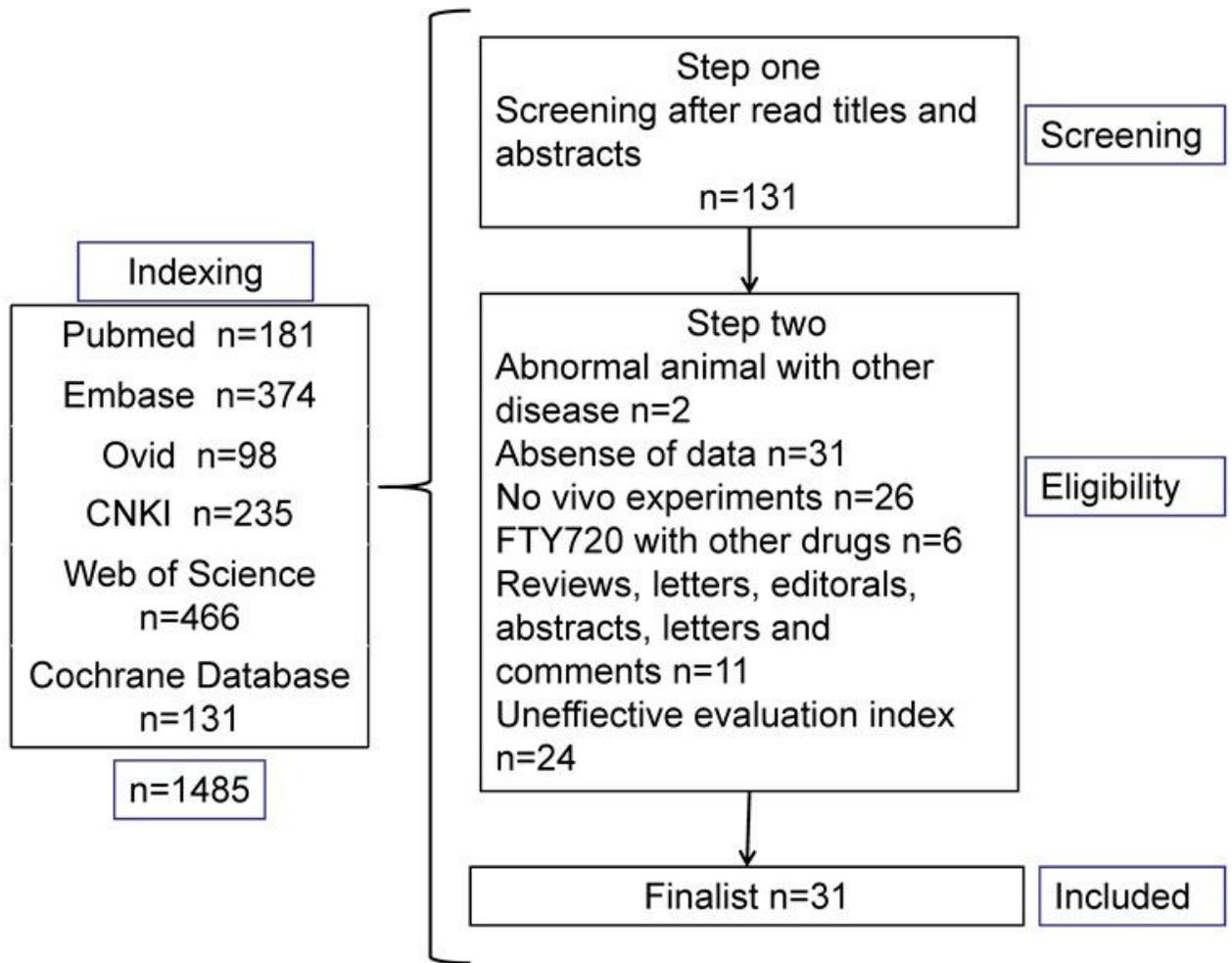


Figure 1

The screened diagram of meta-analysis articles.

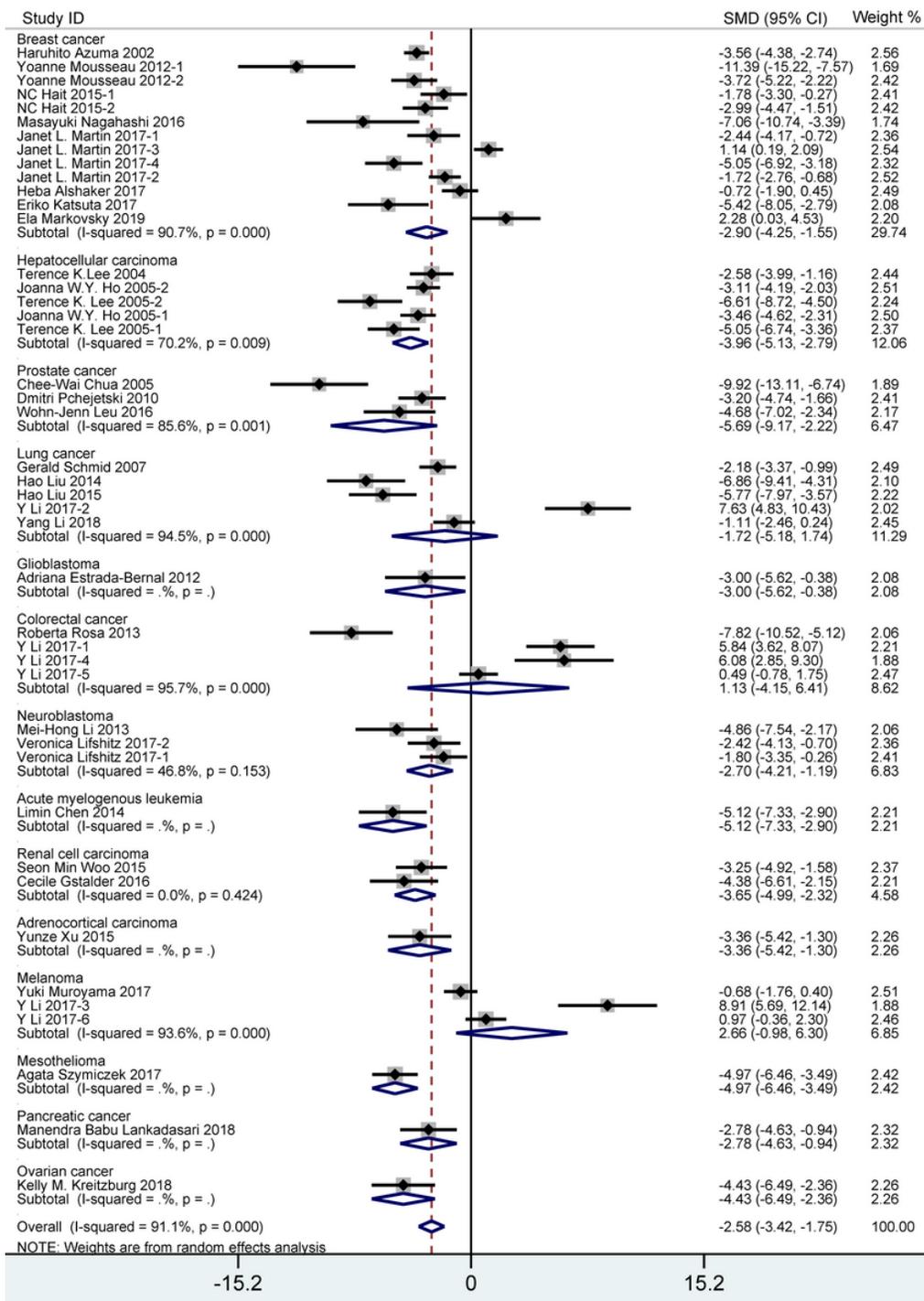


Figure 2

Forest diagram demonstrated the tumor volumes in the different cancer models treated with FTY720.

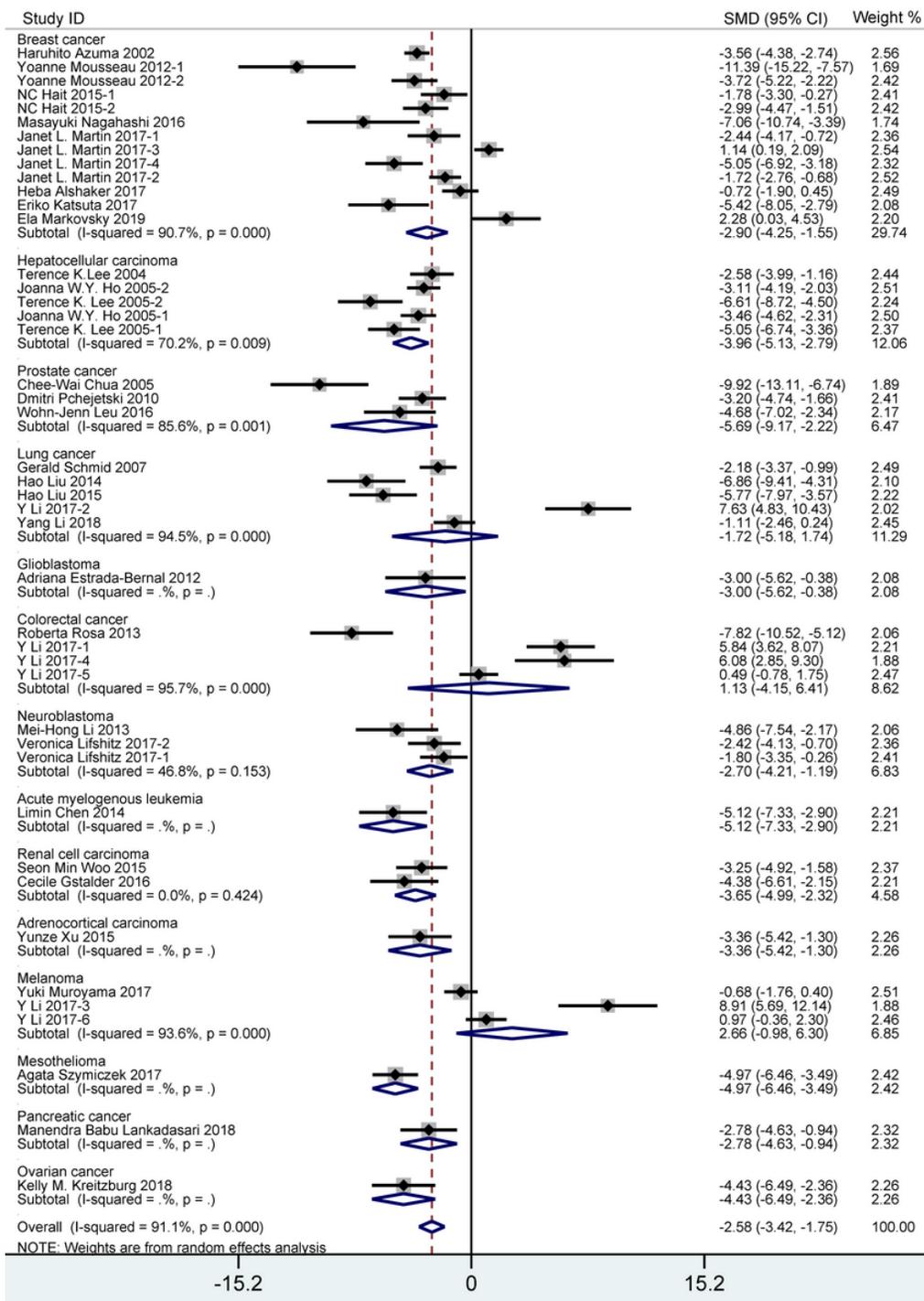


Figure 2

Forest diagram demonstrated the tumor volumes in the different cancer models treated with FTY720.

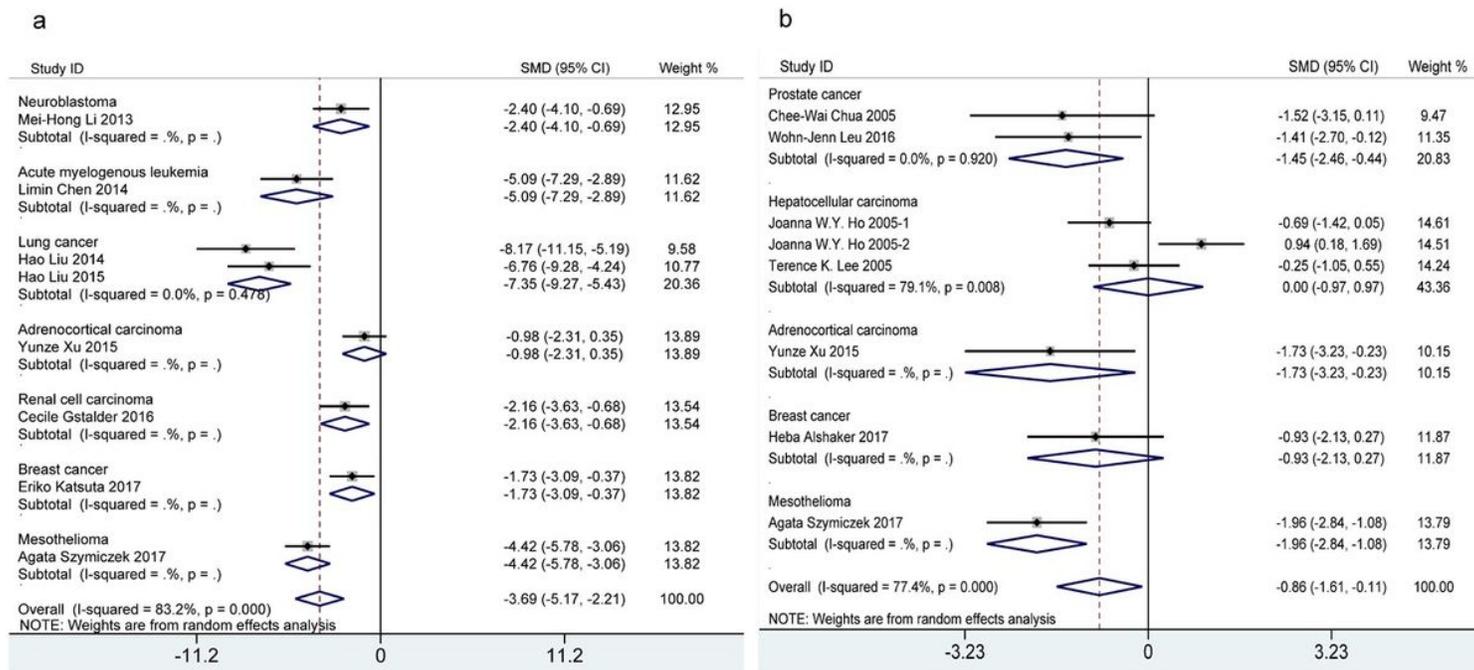


Figure 3

Forest diagram demonstrated the tumor weight (a) and the body weight (b) in various cancer models treated with FTY720.

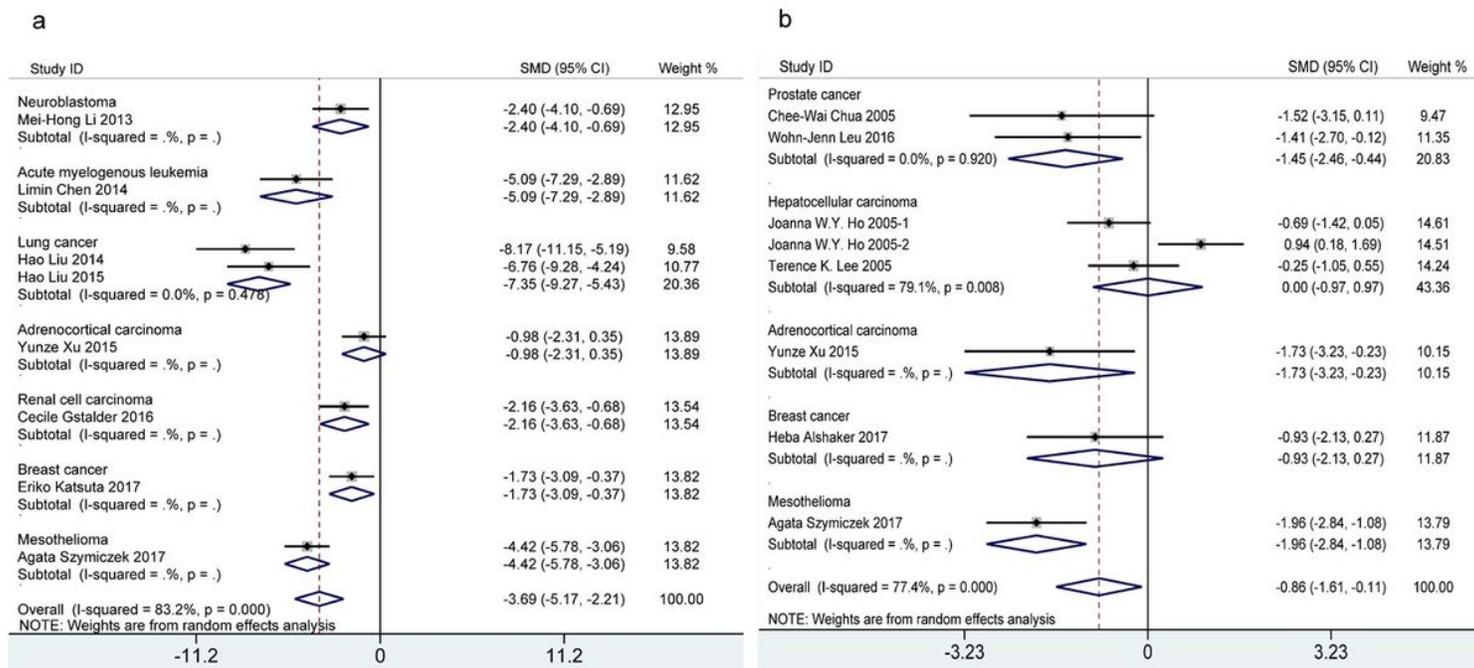


Figure 3

Forest diagram demonstrated the tumor weight (a) and the body weight (b) in various cancer models treated with FTY720.

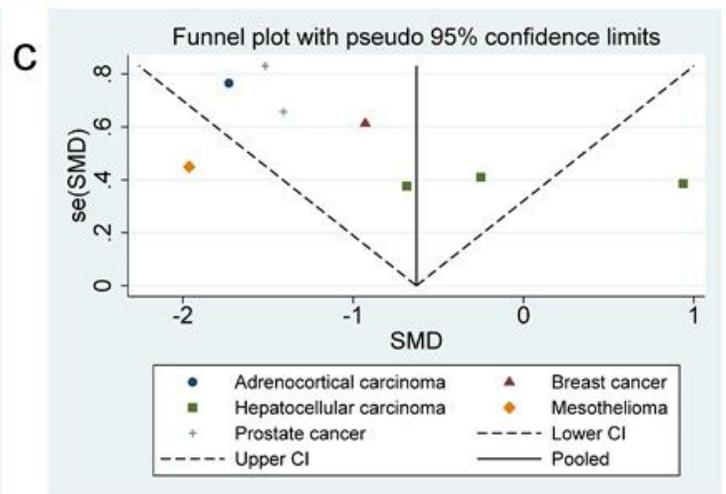
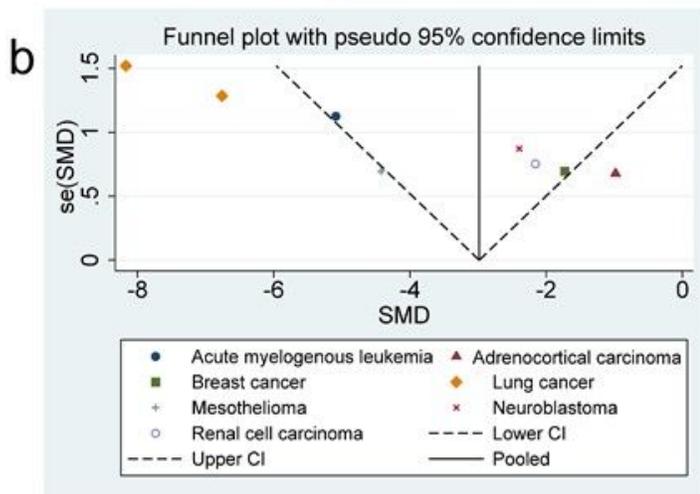
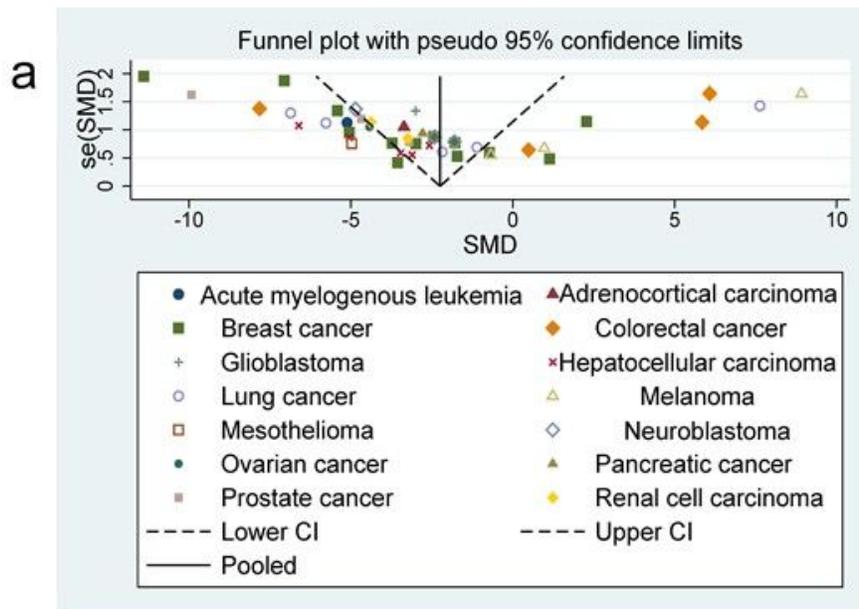


Figure 4

Funnel diagram demonstrated tumor volume outcome (a) and tumor weight outcome (b) and body weight outcome (c).

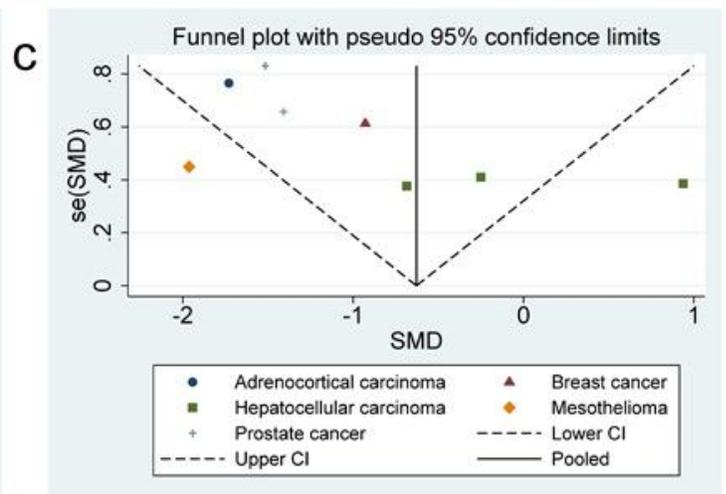
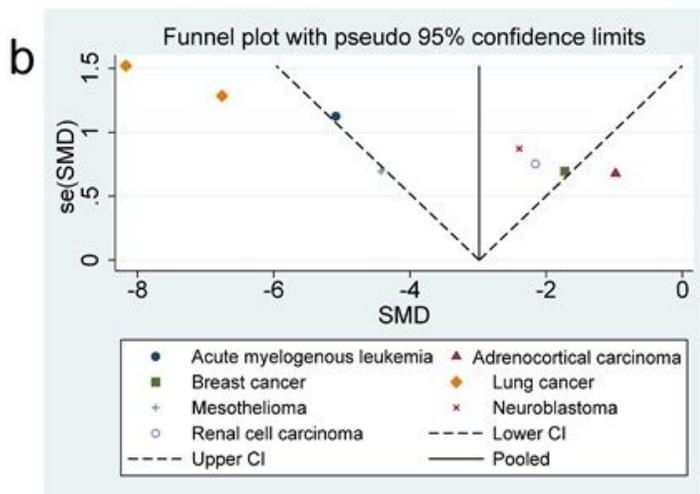
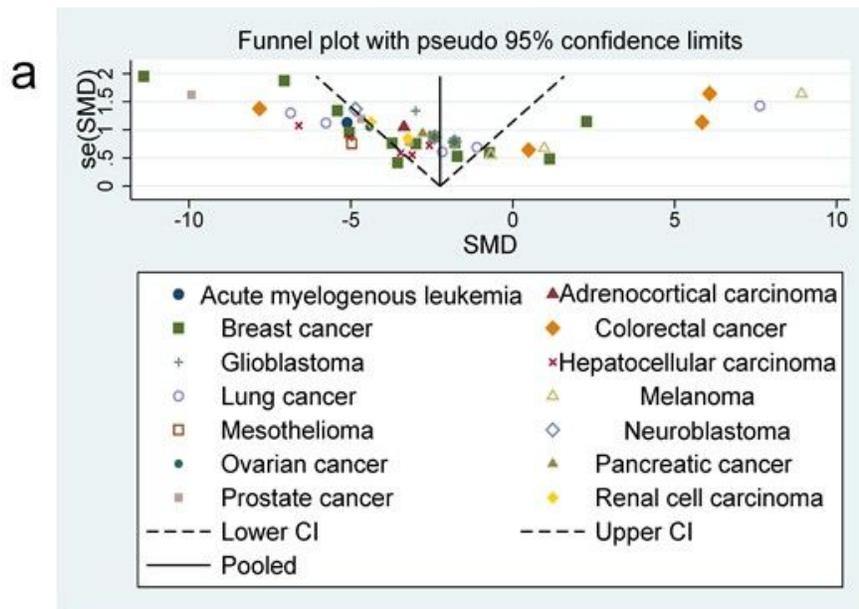


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Funnel diagram demonstrated tumor volume outcome (a) and tumor weight outcome (b) and body weight outcome (c).

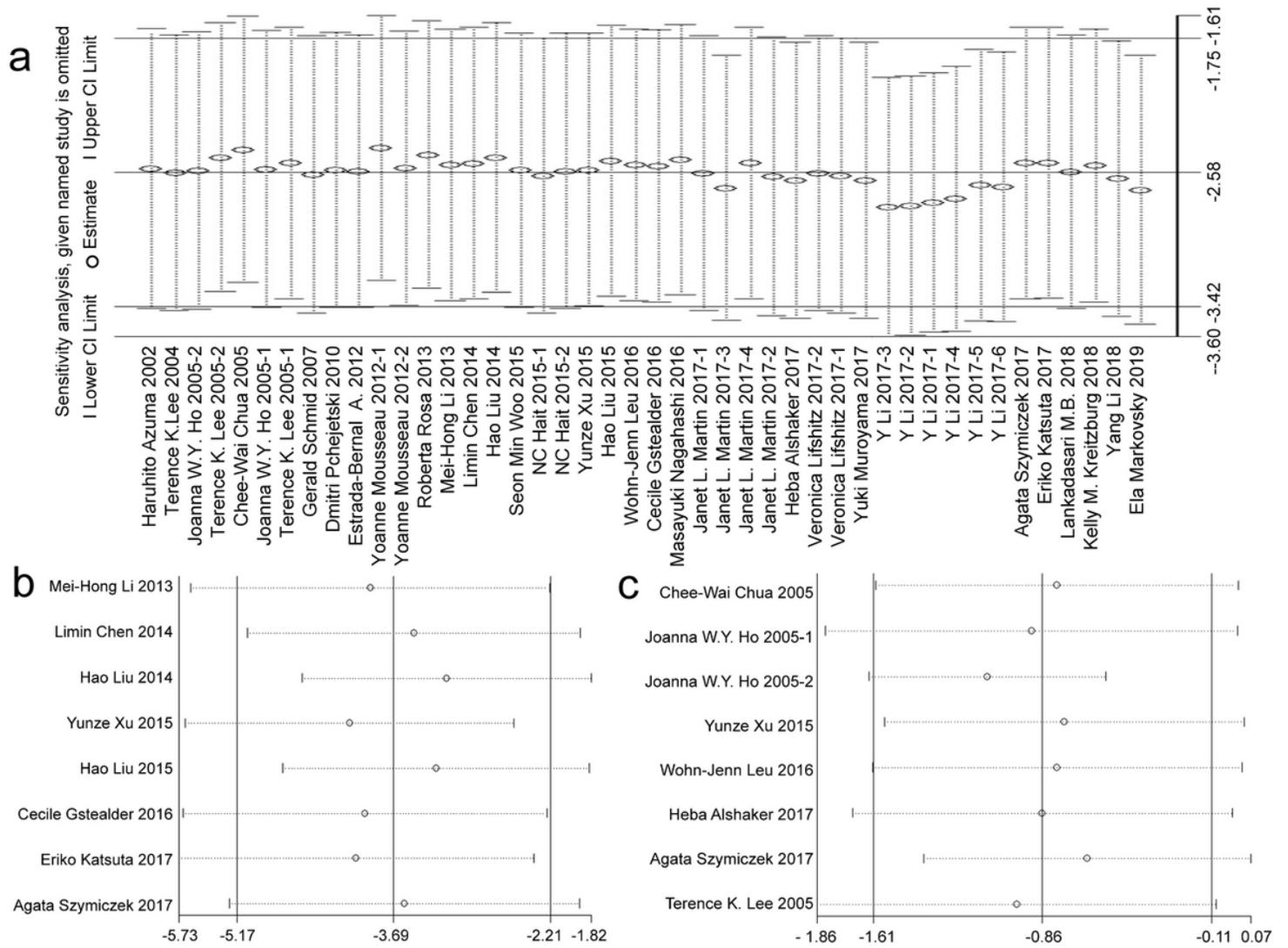


Figure 5

Metaninf diagram demonstrated tumor volume outcome (a) and tumor weight outcome (b) and body weight outcome (c).

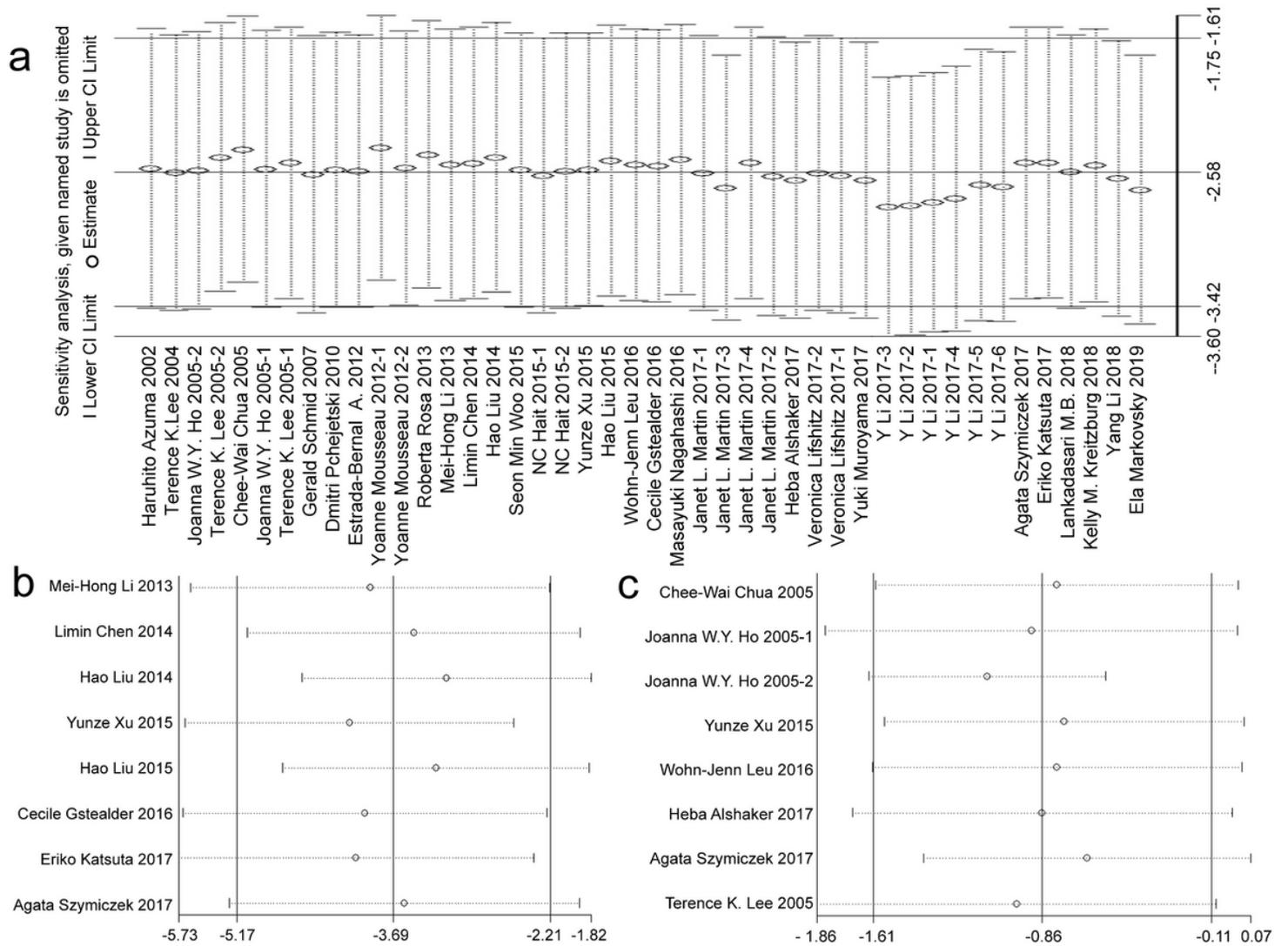


Figure 5

Metaninf diagram demonstrated tumor volume outcome (a) and tumor weight outcome (b) and body weight outcome (c).

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