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Assisted reproduction technology and risk of malignancy among offspring: a meta-analysis

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ABSTRACT

Background: With the popularization of assisted reproductive technology (ART), the question of whether ART increases the risk of malignancy in offspring has received increasing attention. Although many studies have explored the relationship between ART use and malignancy in offspring, the results remain controversial.

Materials and methods: Two authors used the Embase, Web of Science, PubMed, and the Cochrane Library databases to conduct a systematic search of published studies on the effects of ART on the risk of malignancy in offspring. Odds ratios (OR) and 95% confidence intervals were used for the analysis.

Results: Twenty cohort and four case-control studies were included in this review. ART did not increase the risk of overall malignancy in the offspring (OR, 1.04)

compared with natural pregnancy (NP). However, the subgroup analysis showed that the offspring in the ART group had a higher risk of leukaemia (OR, 1.24), soft tissue tumours (OR, 1.35), hepatic tumours (OR, 2.10), and epithelial tumours and melanoma (OR, 1.50). The risks of lymphoma, retinoblastoma, central nervous system tumours, neuroblastoma, renal tumours, germ cell and gonad tumours, and embryonic tumours did not differ between the ART and NP groups. Subgroup analysis based on ART type showed that in vitro fertilisation, intracytoplasmic sperm injection, frozen embryo transfer, and intrauterine insemination or ovulation did not increase the risk of overall malignancy compared to the NP group.

Conclusions: ART may not be associated with the risk of overall malignancy in offspring. However, we found that ART may be associated with an increased risk of leukaemia, soft tissue tumours, hepatic tumours, epithelial tumours, and melanoma.

Keywords: Assisted reproductive technology; In vitro fertilization; Intracytoplasmic sperm injection; Frozen embryo transfer; Paediatric malignancy

Highlights:

- ART may not be associated with an increased risk of overall malignancy.
- ART may be associated with an increased risk of leukaemia, soft tissue tumours, hepatic tumours, epithelial tumours, and melanoma.
- Subgroup analyses based on different ART types found that IVF, ICSI, FET, and OI/IUI may not be associated with an increased risk of overall malignancy.

INTRODUCTION

On 25 July 1978 the first in vitro fertilization (IVF) baby was born. Forty-six years later, over 10 million babies have been born worldwide with the use of assisted reproductive technology (ART) [1]. However, after decades of follow-up observations, health issues among ART offspring have gradually surfaced, including malformations [2], malignant tumours [3], premature births [4], and more. However, the relationship

between ART and the risk of malignancy in offspring remains contentious.

Results from the Swedish National Health Register, studied by Kallen et al., indicated that ART did not affect the incidence of malignant tumours in offspring with a sample size of 16,280 [5]. Conversely, a cohort study by Rios et al. showed that both frozen and fresh embryo transfers with ART increased the risk of acute lymphoblastic leukaemia; this study included 8,526,306 children with a median follow-up time of 6.7 years [6]. Although five meta-analyses were conducted, the results were contradictory. A meta-analysis by Raimondi et al. found no evidence that ART increased the risk of tumours in children [7]. However, a meta-analysis by Hargreave et al. revealed that children born after fertility treatment (including ART and medication) had an increased risk of overall malignancy, haematological tumours, central nervous system (CNS) tumours, and other solid tumours. The subgroup analysis also showed an increased risk of leukaemia, neuroblastoma, and retinoblastoma [8]. A meta-analysis by Wang et al. suggested a possible association between post-fertility treatment (including ART and drug therapy) and an increased risk of overall tumours, haematological malignancies, other solid tumours, leukaemia, and hepatic tumours in offspring [9]. In contrast, a meta-analysis by Gilboa et al. based on extensive data found that ART, particularly IVF, was not associated with an overall increased risk of childhood tumours [10]. In 2020, Zhang et al.'s meta-analysis, which included studies published up until January 2020, found that most types of fertility treatments, including IVF, intracytoplasmic sperm injection (ICSI), and fertility drugs, were not associated with an increased risk of childhood cancer. However, the meta-analysis suggested that frozen embryo transfer might be linked to a higher incidence of childhood cancer [11]. Since 2020, several high-quality cohort studies have been conducted on this topic. Several studies have shown that ART is associated with an increased risk of tumours in offspring [6,12-15]. The addition of a large body of new evidence may update the conclusions of the previous meta-analyses.

Therefore, to explore the relationship between ART and the risk of malignancy in the offspring, we combined all existing observational studies and conducted subgroup analyses based on the type of ART and malignancy to draw more reliable conclusions.

It is reasonable to believe that the results of this meta-analysis may prompt clinicians to re-evaluate the relationship between ART and malignant tumours in the offspring.

METHODS

Search strategy

This meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Supplementary Methods 1[16] and A Measurement Tool to Assess Systematic Reviews 2 (AMSTAR2) (Supplementary Methods 2) [17].

Two authors independently carried out a systematic search of the Embase, Web of Science, PubMed, and Cochrane Library databases for studies published from the inception to May 4, 2024 (updated on 20 October 2024), by using the following search strings: ((assisted reproductive technology) OR (ART) OR (intrauterine insemination) OR (IUI) OR (in vitro fertilization) OR (IVF) OR (intracytoplasmic sperm injection) OR (ICSI) OR (preconception genetic diagnosis) OR (PGD) OR (oocyte in vitro maturation) OR (IVM)) AND ((children) OR (offspring) OR (adolescent) OR (paediatric)) AND ((cancer) OR (tumours) OR (neoplasm)) (Table 1). No language restrictions were imposed. A list of references for relevant reviews and the included studies was also searched.

Study selection

The inclusion criteria were:

(P) Children;

(I) Children born through ART - in vitro fertilization (IVF), intracytoplasmic sperm injection (ICSI)，preconception genetic diagnosis (PGD), intrauterine insemination (IUI), ovulation (OI) and frozen embryo transfer (FET);

(C) Children who were conceived naturally were regarded as control cohorts, and case-control studies that included tumour and non-tumour groups.

(O) Outcomes of interest included overall malignancy, CNS tumours, neuroblastoma, leukaemia, lymphoma, retinoblastoma, hepatic tumours, renal tumours, soft tissue tumours, germ cell and gonad tumours, epithelial neoplasm and melanoma, and

embryonic tumours.

(S) Cohort or case control studies.

Reviews, experimental or qualitative studies, conference abstracts, case reports, reviews, and duplicate publications were excluded.

Data extraction

Data including the first author, year, country, study design, sample size, ART details, and tumour type were extracted from each study by two authors. The research team contacts the corresponding author of the study directly when the necessary information is not available.

Quality assessment

For non-randomised controlled trials, the Newcastle-Ottawa Scale (NOS) is utilised to evaluate quality, with a total score of nine points, and a score of ≥ 6 being indicative of high quality. Two authors independently performed literature search, study selection, data extraction, and quality assessment. Discrepancies between both authors were resolved by a third author.

GRADE assessment

The GRADEpro online tool (https://gradepro.org/) was used to assess evidence quality. The GRADE consists of four grades: very low, low, medium, and high. Two researchers independently assessed the quality of evidence. Any disputes between them will be discussed and resolved.

Statistical analysis

The odds ratios (OR) and 95% confidence intervals (CI) were calculated as qualitative variables. Heterogeneity among studies was quantified using I^2 statistics. $I^2 \leq 50\%$ was considered as low heterogeneity, a fixed effect model was applied. Otherwise, if I^2 was > 50%, a random-effects model was used. To ensure the robustness of our findings, we conducted sensitivity analysis by sequentially removing each study to

assess its impact on the overall effect size. Subgroup analyses were conducted based on ART type, tumor type, region and publication time. The entire analysis was performed using RevMan 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration 2014; Copenhagen, Denmark). Publication bias was assessed using Egger's test and a funnel plot if more than ten studies were identified. Statistical significance was set at $p < 0.05$.

RESULTS

Literature search

A total of 3,897 related articles were retrieved, of which 855 duplicates were excluded. After reviewing the titles and abstracts, we excluded 3,008 articles that did not meet the inclusion criteria. We evaluated the full text of the remaining 34 articles and finally included 24 studies for the meta-analysis (Fig 1) [6,10,12-15,18-35]. Ten studies were excluded for the following reasons: no control group (n = 7), inability to extract data (n = 2), or the use of fertility drugs (n = 1). The corresponding authors of these two studies were contacted; however, the data were not available.

Study characteristics

Table 2 summarises the basic characteristics of the 24 included studies [6,10,12-15,18-35]. These studies were published between 2001 and 2024, and encompassed 31,810,095 participants (1,283,508 in the ART group and 30,526,587 in the natural pregnancy (NP) group). Four were case-control studies and the remaining 20 were cohort studies. The geographical distributions of the studies included four from France, three from the United States, three from the Netherlands, four from Israel, four from Denmark, three from Sweden, one from Greece, one from Norway, and one from China.

Methodological quality

Twenty cohort studies and four case-control studies were of good quality, with scores of six or more [6,10,12-15,18-35]. The methodological quality of each study is summarised in Table 3.

Meta-analysis

Overall malignancy

Twenty-four studies were utilised to evaluate the impact of ART on the risk of malignancy in the offspring of the participants [6,10,12-15,18-35]. There was no significant difference in the risk of malignancy between the ART group and the NP group (OR 1.04, 95% CI 0.86, 1.27; Heterogeneity: I^2 = 92%, P < 0.00001) (Fig 2). Table 4 summarises the results of the meta-analysis.

Subgroup analysis

In addition, subgroup analysis according to tumour type showed that receiving ART was associated with a higher OR of leukaemia in children (OR 1.24, 95% CI 1.03, 1.50), with a high degree of heterogeneity across studies (I^2 = 59%, P = 0.003) (Fig 3A) [6,12,14,15,24,26,29-35]. The risk of soft tissue tumours was higher in patients receiving ART than in those with NP (OR 1.35, 95% CI 1.08, 1.68), and there was no heterogeneity in the study (I^2 = 38%, P = 0.12) (Fig 3B) [6,12,14,15,29,31,33-35]. Seven studies reported the association between ART and the risk of hepatic tumours, and the combined results showed that ART significantly increased the OR of hepatic tumours compared with NP (OR 2.10, 95% CI 1.15, 3.85), with significant heterogeneity across studies (I^2 = 71%, P = 0.002) (Fig 3C) [6,14,15,29,31,33,34]. Three studies provided data on epithelial tumours and melanoma for ART, with significant differences between ART and NP (OR 1.50, 95% CI 1.12, 1.99) and no significant heterogeneity between studies (I^2 = 3%, P = 0.36) (Fig 3D) [6,14,34].

Ten studies reported data on ART and lymphoma risk, and the combined results showed no significant difference in OR (OR 0.96, 95% CI 0.65, 1.43; Heterogeneity: I^2 = 68%, P = 0.0009) (Fig 4A) [6,12,14,26,29,31-35]. The pooled results of the ten studies showed no significant difference in the risk of retinoblastoma with ART compared to that with NP (OR 1.12, 95% CI 0.69, 1.81; Heterogeneity: I^2 = 57%, P = 0.01) (Fig 4B [6,14,15,18,19,24,29,31,33,34]. There was no significant difference in the risk of CNS tumours between ART and NP (OR 1.14, 95% CI 0.86, 1.51; Heterogeneity: I^2 = 74%, P < 0.0001) (Fig. 4C) [6,14,15,25,29,31-35]. Seven studies compared the risk of neuroblastoma in

NP, and the combined effect size showed that ART was not associated with an increase in OR of neuroblastoma (OR 1.24, 95% CI 0.67, 2.28; Heterogeneity: I^2 = 78%, P = 0.0001) (Fig 4D) [14,15,29,31,33-35]. There was no significant difference between ART and NP in renal tumours (OR 1.13, 95% CI 0.69, 1.84; Heterogeneity: I^2 = 73%, P = 0.002) (Fig 5A) [6,14,15,29,33,34]. Six studies compared ART and NP data and found no significant difference in the OR of germ cells and gonad tumours between both groups (OR 1.11, 95% CI 0.46, 2.73; Heterogeneity: I^2 = 82%, P < 0.0001) (Fig 5B) [6,14,15,29,33,34]. There was no significant increase in OR of embryonal tumours in ART group (OR 1.62, 95% CI 0.61, 4.28), and the heterogeneity was high (I^2 = 98%, P < 0.00001) (Fig 5C) [6,33].

Subgroup analysis results based on ART type showed that the pooled data of 7,613,937 patients in 13 studies showed no significant difference in the OR of overall malignancy risk compared to NP with IVF (OR 1.25, 95% CI 0.84, 1.84; Heterogeneity: I^2 = 88%, P < 0.00001) (Fig 6A) [10,12,18-22,24,26,27,30,33,35]. Two studies reported the association of ICSI with overall malignancy risk, and the combined results showed no significant difference in OR compared to NP (OR 1.18, 95% CI 0.84, 1.67; Heterogeneity: I^2 = 0%, P = 0.51) (Fig 6B) [20,27]. Two studies described data on the overall malignancy risk between FET and NP, and the difference was not statistically significant (OR 1.23, 95% CI 0.49, 3.12; Heterogeneity: I^2 = 90%, P = 0.002) (Fig 6C) [6,20]. Compared with NP, OI/IUI did not significantly increase the OR of overall malignancy risk (OR 1.03, 95% CI 0.40, 2.66; Heterogeneity: I^2 = 50%, P = 0.16) (Fig 6D) [13,19]. In addition to ART type, we conducted subgroup analyses stratified by geographical region and publication period to further explore potential sources of heterogeneity.

Region-specific results revealed marked differences. In the Asia, pooled data from five studies (n = 3,085,111) demonstrated no significant increase in malignancy risk among ART offspring compared to NP (OR 1.09, 95% CI 0.93, 1.24; Heterogeneity: I^2 = 0%, P = 0.48) [10,12,15,23,35]. In North America, pooled data from three studies (n = 4,231,015) indicated a statistically significant association between ART and malignancy risk (OR 2.00, 95% CI 1.14, 3.53), accompanied by a high level

of heterogeneity (Heterogeneity: I^2 = 95%, P < 0.00001) [13,18,33]. Meanwhile, pooled results from 16 European studies involving 22,652,262 individuals showed no statistically significant association (OR 0.88, 95% CI 0.76, 1.03; Heterogeneity: I^2 = 75%, P < 0.00001) [6,14,19-22,24-32,34]. Temporal trends were also assessed by stratifying studies according to their year of publication. For studies published on or before 2010 (7 studies, n = 3,362,855), the pooled OR was 0.99 (95% CI 0.52, 1.90; Heterogeneity: I^2 = 55%, P = 0.04) [18,21,22,24,25,27,28]. Those published between 2010 and 2020 (11 studies, n = 8,507,257) yielded an OR of 1.09 (95% CI 0.78, 1.51; Heterogeneity: I^2 = 94%, P < 0.00001) [10,19,20,23,26,29,30,32-35], while studies published after 2020 (6 studies, n = 19,939,983) reported an OR of 0.99 (95% CI 0.79, 1.26; Heterogeneity: I^2 = 90%, P < 0.00001) [6,12-15,31].

Sensitivity analysis and publication bias

Sensitivity analysis showed that no single study affected the overall effect size of malignancy, retinoblastoma, lymphoma, CNS tumours, neuroblastoma, renal tumours, germ cell and gonad tumours, or IVF. The size of the pooled effect of leukaemia was influenced by the findings of a study by Petridou et al. (OR 1.19, 95% CI 0.98, 1.45; Heterogeneity: I^2 = 58%, P = 0.006) [26]. The overall effect size for soft tissue tumours changed in the study by Spector et al. (OR 1.18, 95% CI 0.92, 1.52; Heterogeneity: I^2 = 0%, P = 0.76) [33]. The size of the pooled effect of hepatic tumours was influenced by the findings of a study by Weng et al. (OR 1.89, 95% CI 0.90, 3.97; Heterogeneity: I^2 = 76%, P = 0.001) [15]. According to the funnel plots and Egger's tests, no evidence of publication bias was found for overall malignancy (Fig 7A), leukaemia (Fig 7B), or IVF (Fig 7C) (p = 0.464, p = 0.683, and p = 0.178, respectively).

GRADE analysis

In this study, we graded the quality of each piece of evidence. Some of the evidences (epithelial tumours and melanoma, retinoblastoma, ICSI, OI/IUI) were at a medium level, ten (overall malignancy, leukaemia, soft tissue tumours, hepatic tumours, lymphoma, CNS tumours, neuroblastoma, renal tumours, germ cells, and gonad

tumours, IVF) were low, two (embryonal tumours, FET) were very low. Table 5 summarises the results of the GRADE analysis.

DISCUSSION

Based on the current evidence, our meta-analysis suggests that while ART may not be associated with an increased overall risk of malignancy, it may be linked to elevated risks of certain tumour types, including leukaemia, soft tissue tumours, hepatic tumours, epithelial tumours, and melanoma. Subgroup analyses by ART modality, geographic region, and publication period provided further context for these associations. No significant association was found between IVF, ICSI, FET, or OI/IUI and overall malignancy risk. Regional analyses indicated a possible increased risk in North America, though this finding was marked by high heterogeneity. Temporal subgroup analyses revealed no significant trend over time. These findings underscore the importance of tumour-specific surveillance strategies, particularly for leukaemia and soft tissue tumours, and caution against overgeneralizing the conclusion of "no overall increase." Regional, temporal, and tumour-specific factors should be carefully considered in both clinical decision-making and future research.

Although the results of the comprehensive analysis are valid, it is still unclear whether ART or other factors in the recipients themselves increase the risk of tumour development. Adverse outcomes associated with ART can depend on several factors, including the underlying cause of infertility, drugs used to induce superovulation and maintain the early stages of pregnancy, and the processes involved in IVF or ICSI techniques. Examples include sperm preparation, embryo freeze-thaw, medium, conditions used for embryo growth, and delayed fertilization [36]. It is well known that tumours are closely related to genes. Disrupted gene expression and the deletion of gene imprinting have been observed in various childhood tumours. Drugs and procedures involved in ART can cause epigenetic modification of DNA and alter imprinted gene expression, which may lead to tumours in the offspring [37]. Current studies have not included the risk of tumours in children with PGD, and some recessive genetic problems cannot be ruled out. Therefore, further research is needed

to investigate the potential impact of infertility on the risk of tumours in the offspring.

Although ART may not be associated with an increased risk of overall malignancy, there was high heterogeneity among the studies. This may be related to the different types of tumours assessed in the different studies. Sixteen studies evaluated multiple tumours [6,10,12,14,15,20-22,27-29,31-35] (including CNS tumours, neuroblastoma, leukaemia, lymphoma, retinoblastoma, hepatic tumours, renal tumours, soft tissue tumours, germ cells and gonad tumours, epithelial neoplasm and melanoma, and embryonal tumours), two studies evaluated only retinoblastoma [18,19], and two studies evaluated only haematological tumours [26,30]. Therefore, we assessed ART separately based on the risk of specific tumours in the offspring. The risks of ART and different tumour types may differ. Our results suggest that ART may not be associated with the risk of overall malignancy but may be associated with the risk of leukaemia, soft tissue tumours, hepatic tumours, epithelial tumours, and melanoma. In addition, we did not find heterogeneity between the studies on soft tissue tumours, epithelial neoplasms, and melanoma. The publication time of the included studies spanned more than two decades, from 2001 to 2024, during which ART practices have undergone considerable evolution. Substantial variations have emerged both within and between laboratories—for example, in culture media composition, oxygen tension, and embryo cryopreservation techniques. Differences in temporal context and geographical region may also contribute to variability in clinical protocols, laboratory standards, and cancer surveillance systems, potentially influencing the observed outcomes. To investigate these potential sources of heterogeneity, we conducted subgroup analyses by geographical region and publication period. While the regional analysis suggested a statistically significant association in the North American subgroup, the limited number of studies and extremely high heterogeneity ($I^2 = 95\%$) warrant cautious interpretation. In contrast, no significant differences were observed across subgroups defined by publication period, indicating that temporal variation alone is unlikely to explain the observed heterogeneity. In addition, frozen or fresh embryo transfers may also contribute to heterogeneity, and a meta-analysis by Zhang et al. suggested that FET was associated with an increased incidence of childhood

tumours [11]. There is a large difference in sample size among studies, ranging from dozens to millions of cases, and the difference in sample size affects the incidence of tumours. In addition, the length of follow-up was inconsistent between the studies, and the probability of tracking tumours during the study period varied greatly.

Of the five previously published meta-analyses, two showed that ART was associated with an increased risk of tumours in children. The meta-analysis categorised children with overall malignancy, haematological tumours, CNS tumours, and other tumours but did not specifically differentiate between tumours [20]. A meta-analysis was based on overall tumours, haematological malignancies, leukaemia, and hepatic tumours [9]. Consistent with the results of a previous meta-analysis, the results of our meta-analysis indicate that ART may be associated with an increased risk of leukaemia and hepatic tumours. In addition, we performed a more detailed differentiation of tumour types and found that ART may be associated with an increased risk of soft tissue tumours, epithelial tumours, and melanoma. However, there were also three meta-analyses that only analysed ART and overall malignancy without detailed differentiation of tumour types, and there were many confounding factors, which may explain why these studies finally reached the conclusion that ART was not associated with an increased risk of tumours in children [7,10,11].

The strength of our study is that 24 studies were included. The studies were of high quality and included a large sample size, totalling 31,810,095, in favour of providing more reliable and accurate risk estimates. Moreover, we performed subgroup analyses for tumour and ART types while controlling for confounding factors. The sensitivity analysis results also supported the robustness of the observed association between ART and risk of malignancy in children. Moreover, there was no publication bias in the included studies and the comprehensive evaluation results were reliable.

Although we did our best to search for all relevant studies and evaluate the robustness of the results from various perspectives, certain limitations remain. In addition to soft tissue tumours, ICSI, epithelial tumours, and melanoma, other indicators (leukaemia, lymphoma, retinoblastoma, CNS tumours, neuroblastoma,

renal tumours, germ cell and gonad tumours, embryonal tumours, IVF, FET, and OI/IUI) are highly heterogeneous. Sensitivity analyses revealed that the results for leukaemia, soft tissue tumours, and hepatic tumours were not robust. The number of studies on epithelial and melanoma, embryonic tumours, ICSI, FET, and OI/IUI indicators is insufficient, resulting in small sample sizes. Therefore, these results need to be further studied. Given the paucity of studies on epithelial and melanoma tumours, embryonic tumours, ICSI, FETs, and OI/IUI, their association with malignancy risk should be treated with caution.

CONCLUSIONS

This study found that ART may not be associated with the risk of overall malignancy, and that different types of ART may not be associated with the risk of overall malignancy. However, through subgroup analysis, we found that ART may be associated with the risk of leukaemia, soft tissue tumours, hepatic tumours, epithelial tumours, and melanoma. This suggests that we may need to pay more attention to screening for ART progeny leukaemia, soft tissue tumours, hepatic tumours, epithelial tumours and melanoma. Epithelial and melanoma tumours, as well as embryonic tumours, ICSI, FET, and OI/IUI, have been poorly studied, and their association with malignancy risk needs to be treated with caution; more research is needed to explore their relationship. Conduct larger prospective studies on specific tumor types like epithelial and melanoma, embryonic tumours, focusing on the long-term tumor risks associated with different ART techniques, and strengthen long-term follow-up and tumor registration integration.

Provenance and peer review

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Figure legends

Figure 1. PRISMA flow diagram

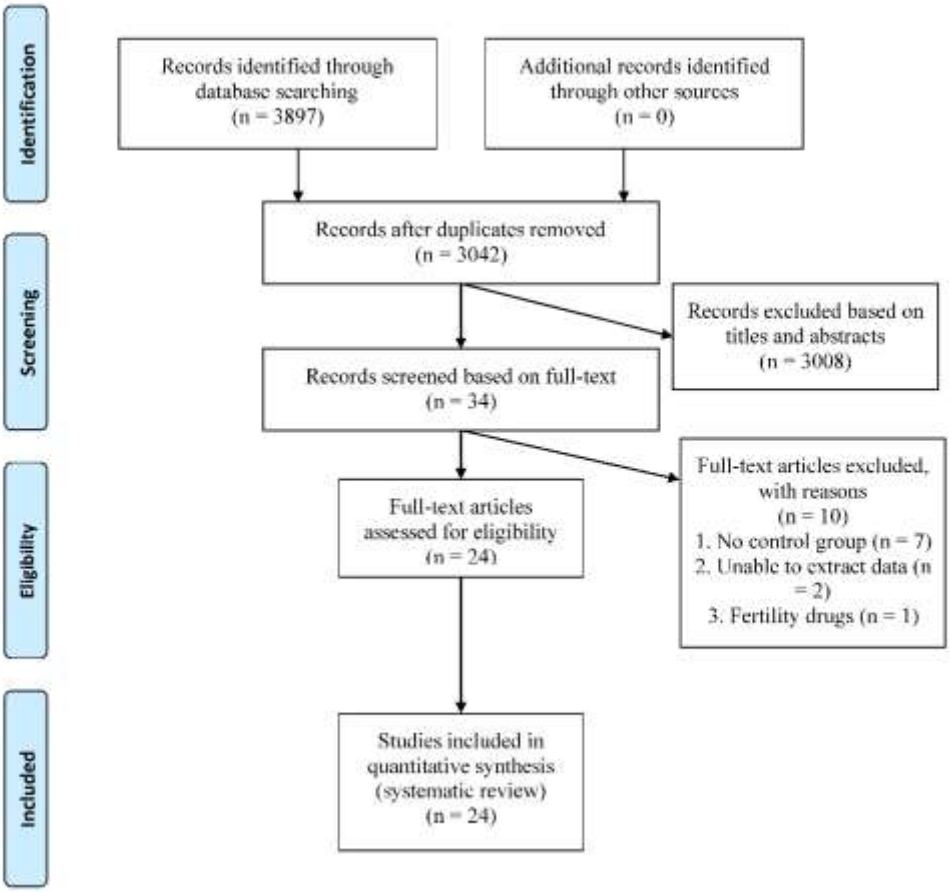

Figure 2. Forest plot of overall malignancy for ART versus NP.

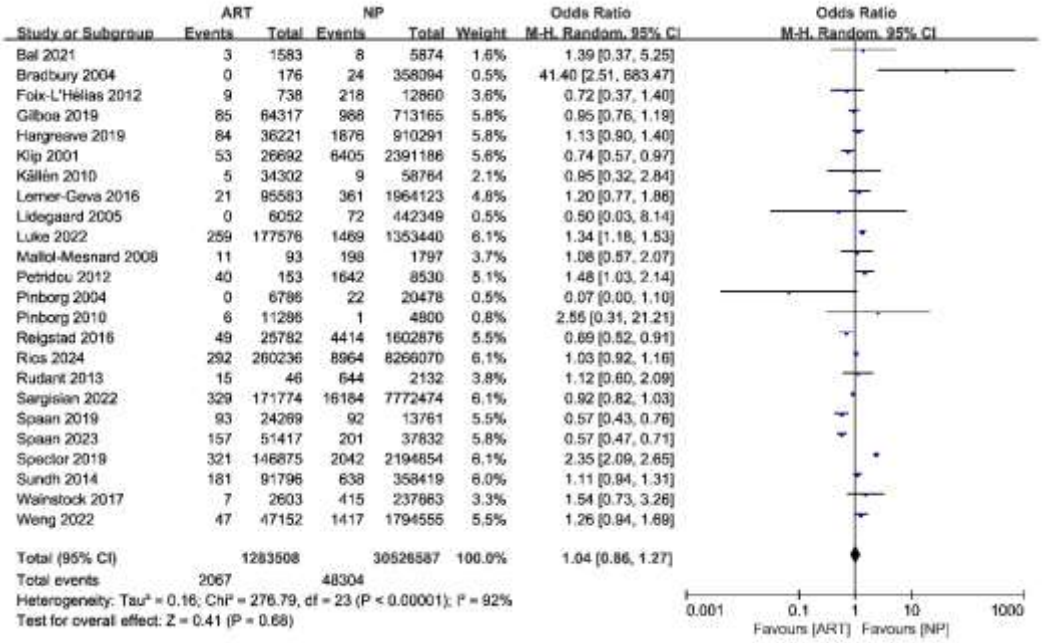

Figure 3. Forest plot of A. leukaemia, B. soft tissue tumours, C. hepatic tumours, D. epithelial tumours, and melanoma for ART versus NP.

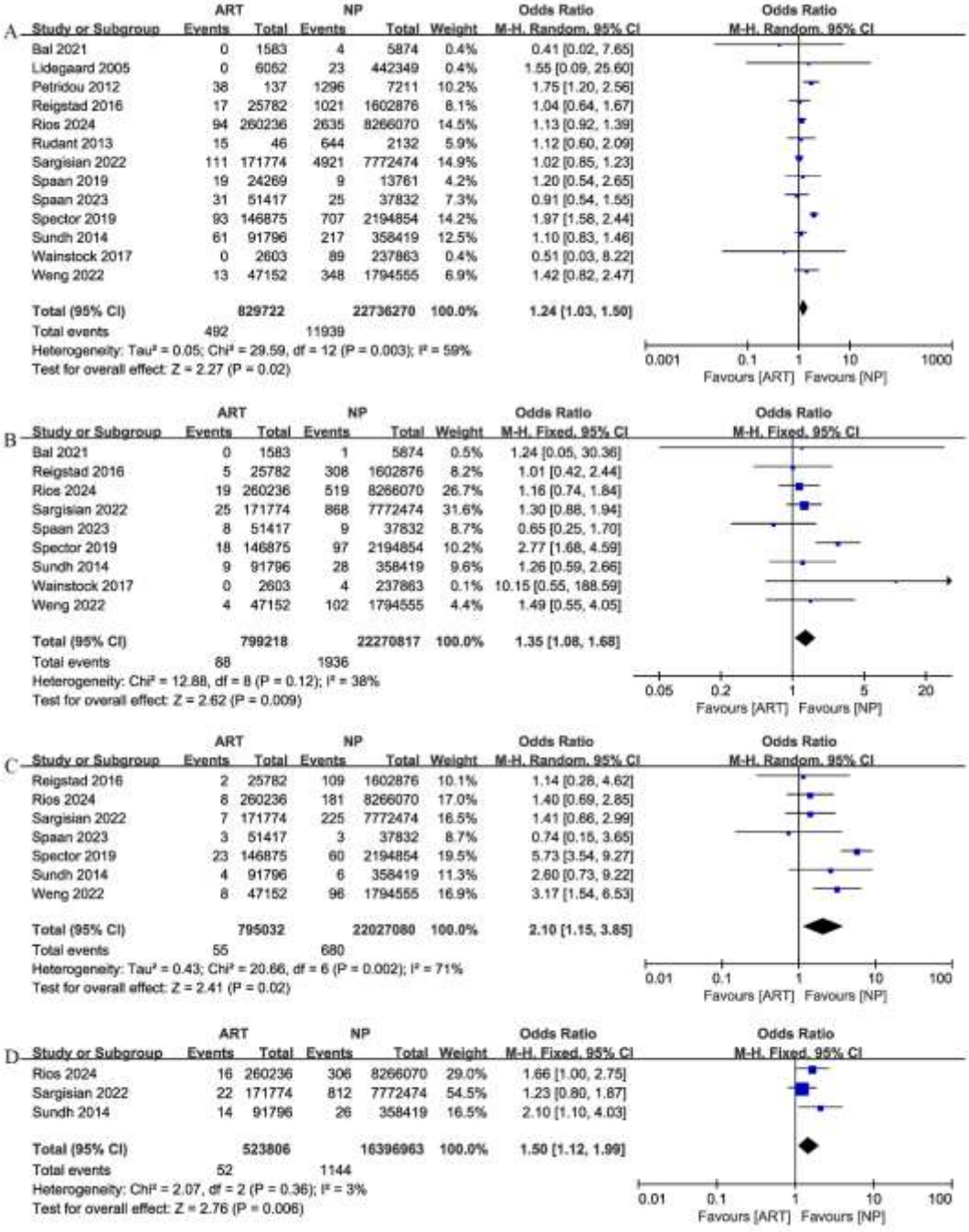

Figure 4. Forest plots of A. lymphoma, B. retinoblastoma, C. central nervous system, and D. neuroblastoma for ART versus NP

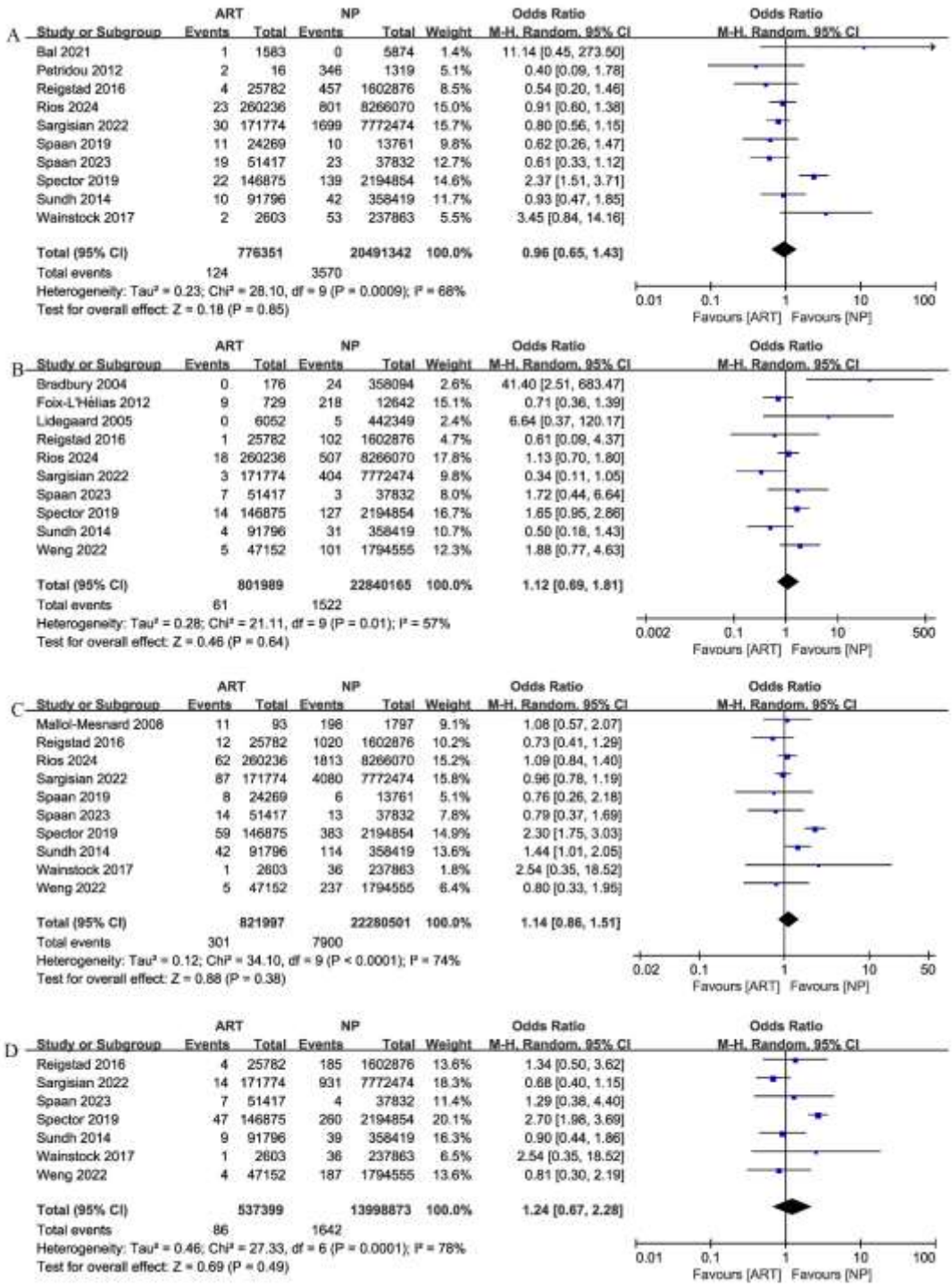

Figure 5. Forest plot of A. renal tumours, B. germ cell and gonad tumours, and C. embryonal tumours for ART versus NP

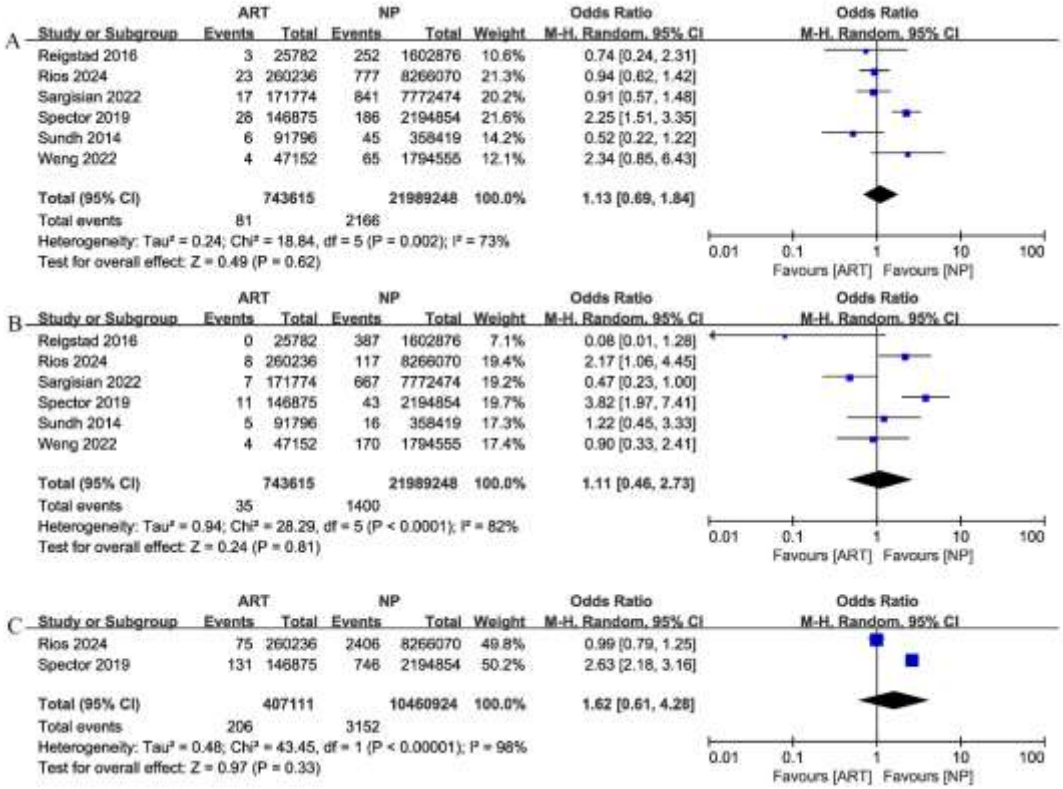

Figure 6. Forest plots of A. IVF, B. ICSI, C. FET, and D. OI/IUI with overall malignancy

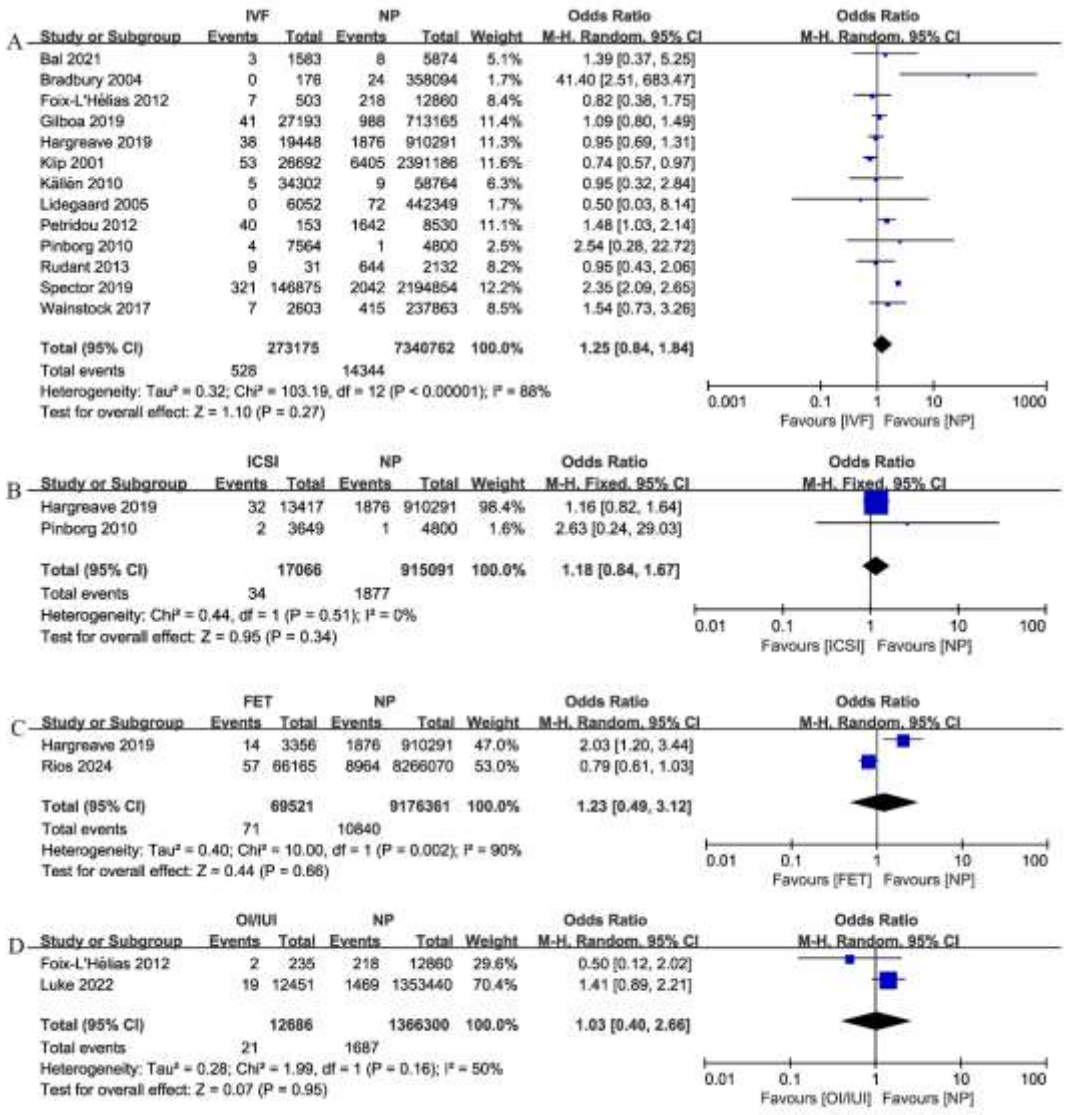

Figure 7. Funnel plots of A. overall malignancy, B. leukaemia, and C. IVF

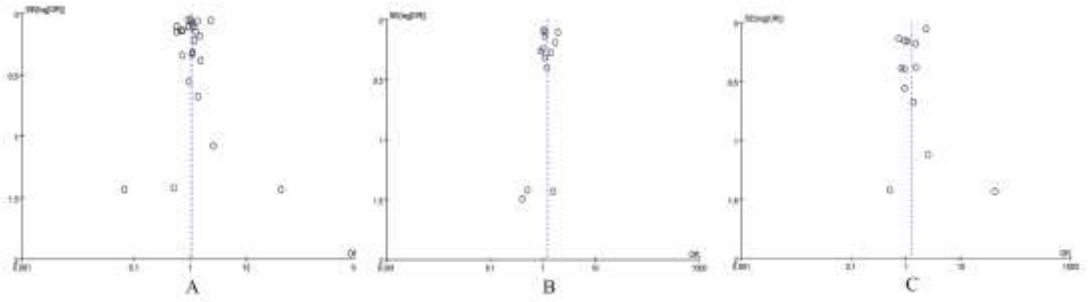

Table 1. Electronic search strategy.

Database	Search term	Number
PubMed (Title/Abstract)	#1: ((assisted reproductive technology) OR (ART) OR (Intrauterine insemination) OR (IUI) OR (in vitro fertilization) OR (IVF) OR (intracytoplasmic sperm	#1: 225682

	injection) OR (ICSI) OR (preconception genetic diagnosis) OR (PGD) OR (Oocyte in vitro maturation) OR (IVM))	
	#2: ((children) OR (offspring) OR (adolescent) OR (pediatric))	#2: 1699068
	#3: ((cancer) OR (tumor) OR (neoplasm))	#3: 3190528
	#4: #1 AND #2 AND #3	#4: 741
Embase (ab,ti.)	#1: ((assisted reproductive technology) OR (ART) OR (Intrauterine insemination) OR (IUI) OR (in vitro fertilization) OR (IVF) OR (intracytoplasmic sperm injection) OR (ICSI) OR (preconception genetic diagnosis) OR (PGD) OR (Oocyte in vitro maturation) OR (IVM))	#1: 293482
	#2: ((children) OR (offspring) OR (adolescent) OR (pediatric))	#2: 2143291
	#3: ((cancer) OR (tumor) OR (neoplasm))	#3: 4322834
	#4: #1 AND #2 AND #3	#4: 1280
Cochrane (MeSH)	#1: ((assisted reproductive technology) OR (ART) OR (Intrauterine insemination) OR (IUI) OR (in vitro fertilization) OR (IVF) OR (intracytoplasmic sperm injection) OR (ICSI) OR (preconception genetic diagnosis) OR (PGD) OR (Oocyte in vitro maturation) OR (IVM))	#1: 31327
	#2: ((children) OR (offspring) OR (adolescent) OR (pediatric))	#2: 331060
	#3: ((cancer) OR (tumor) OR (neoplasm))	#3: 265199
	#4: #1 AND #2 AND #3	#4: 373
Web of Science (TS)	#1: ((assisted reproductive technology) OR (ART) OR (Intrauterine insemination) OR (IUI) OR (in vitro fertilization) OR (IVF) OR (intracytoplasmic sperm	#1: 1009546

	injection) OR (ICSI) OR (preconception genetic diagnosis) OR (PGD) OR (Oocyte in vitro maturation) OR (IVM))	
	#2: ((children) OR (offspring) OR (adolescent) OR (pediatric))	#2: 2685995
	#3: ((cancer) OR (tumor) OR (neoplasm))	#3: 4528682
	#4: #1 AND #2 AND #3	#3: 1730

Table 2. Study characteristics and outcomes.

First author, year	Country	Study design	Details of ART	No. of cases (Treated/total)	No. of control (Treated/total)	Type of tumor
Bal 2021	Israel	retrospective cohort study	IVF	17/1,583	29/5,874	Leukemia; lymphoma; brain and spinal cord tumors (medulloblastoma or Astrocytoma); connective tissue or skin; adrenal or kidney; bone cancer (osteosarcoma or Ewing sarcoma); ophthalmic
Bradbury 2004	USA	retrospective	IVF	0/176	24/358,094	Retinoblastoma

		cohort study				
Foix-L'Hélias 2012	France	case–control study	IVF IUI	9/729	218/12,642	Retinoblastoma
Gilboa 2019	Israel	prospective cohort study	IVF ICSI FET IUI	85/64,317	988/713,165	Overall malignancy
Hargreave 2019	Denmark	retrospective cohort study	IVF ICSI FET	84/36,221	1,876/910,291	Leukemia; lymphoma; central nervous system tumors; sympathetic nervous system tumors; other types of cancer
Källén 2010	Sweden	prospective cohort study	IVF	53/26,692	6,405/2,391,186	Hematologic neoplasms; histiocytosis; central nervous system or eye neoplasms; soft tissue neoplasms; adenocarcinomas
Klip 2001	The Netherlands	retrospective cohort	IVF	5/34,302	9/58,764	Keukemia; lymphoma; central nervous

		study				system tumors; sympathetic nervous system tumors; renal tumors; wilms' tumors; malignant bone tumors; soft-tissue, germ-cell, and gonadal tumors
Lerner-Geva 2016	Israel	retrospective cohort study	IVF ICSI	21/95,583	361/1,964,123	Retinoblastoma; renal tumor; leukemia; lymphoma; other types of cancer
Lidegaard 2005	Denmark	prospective cohort study	IVF	0/6052	72/442,349	Kidney cancer; retinoblastoma; acute myeloblastic leukemia
Luke 2022	USA	retrospective cohort study	IVF ICSI OI/IUI	259/177,576	1,469/ 1,353,440	Leukemia; central nervous system tumors; embryonal tumors; solid tumors
Mallol-Mesnard 2008	France	case–control study	NA	11/93	198/1,797	Central nervous system tumors

Petridou 2012	Greece	case–control study	IVF	40/153	1,642/8,530	Leukemia; lymphoma
Pinborg 2010	Denmark	prospective cohort study	IVF ICSI	12/10,329	1/4800	Overall malignancy
Pinborg 2004	Denmark	prospective cohort study	IVF ICSI	0/6,786	22/20,478	Acute lymphoblastic leukemia; astrocytoma; nonspecific tumors of the heart, brain, adrenal glands, and soft tissues
Reigstad 2016	Norway	prospective cohort study	IVF ICSI	49/25,782	4,414/1,602,876	Leukemia; lymphoma; central nervous system tumors; neuroblastoma; retinoblastoma; nonspecific tumors of the renal, hepatic, bone, germ cell and soft tissues
Rios 2024	France	retrospective	fresh ET	292/260,236	8,964/8,266,070	Leukemia; lymphoma;

		cohort study	FET AI			central nervous system tumors; embryonal tumor; retinoblastoma; epithelial neoplasm and melanoma; malignant bone tumor; soft tissue sarcoma; germ cell and gonad tumor
Rudant 2013	France	case–control study	IVF AI	30/61	342/784	Acute leukemia
Sargisian 2022	Sweden	retrospective cohort study	fresh ET FET IVF	329/171,774	16,184/ 7,772,474	Leukemia; lymphoma; central nervous system tumors; neuroblastoma and other peripheral nervous cell tumors; retinoblastoma; renal tumors, hepatic and bone tumors; soft tissue sarcomas; germ

						cell and gonad tumor; epithelial neoplasm and melanoma
Spaan 2023	The Netherlands	prospective cohort study	FET IVF ICSI	157/51,417	201/37,832	Head, neck, salivary glands, digestive organs, bone, joints, soft tissue, skin, melanoma, breast, female genital tract, male genital tract, urinary tract, eye, adnexa, brain, endocrine glands, and other parts of central nervous system tumors; kaposi sarcoma; lymphohematopoietic malignancies
Spaan 2019	The Netherlands	prospective cohort study	IVF ICSI	93/24,269	92/13,761	Head, neck, salivary glands, digestive organs, bone,

					joints, soft tissue, skin, melanoma, breast, female genital tract, male genital tract, urinary tract, eye, adnexa, brain, endocrine glands, and other parts of central nervous system tumors; kaposi sarcoma; lymphohemato poietic malignancies
Spector 2019	USA	retrospective cohort study	IVF	321/146,875	2,042/2,194,854	Leukemia; lymphoma; central nervous system tumors; astrocytoma; ependymoma; intracranial embryonal tumors; neuroblastoma; retinoblastoma; renal, hepatic, germ cell and

						soft tissues tumors; embryonal tumors
Sundh 2014	Sweden	retrospective cohort study	FET IVF ICSI	181 /91,796	638/358,419	Leukemia; lymphoma; central nervous system tumors; neuroblastoma and peripheral nervous cell tumors; retinoblastoma; renal, hepatic, germ cell, bone, and soft tissues tumors; embryonal tumors; other malignant epithelial neoplasms
Wainstock 2017	Israel	retrospective cohort study	IVF	29/2603	1450/237,863	Head, neck, salivary glands, digestive organs, bone, joints, soft tissue, skin, melanoma, breast, female genital tract,

						male genital tract, urinary tract, eye, adnexa, brain, endocrine glands, and other parts of central nervous system tumors; leukemia; lymphoma; hemangioma
Weng 2022	China Taiwan	retrospective cohort study	FET IVF ICSI	47/47,152	1,417/1,794,555	Leukemia; lymphoma; hepatic tumors; central nervous system tumors; neuroblastoma; retinoblastoma; renal, germ cell, bone, and soft tissues tumors;

ART, assisted reproductive technology; FET, frozen embryo transfer; ICSI, intracytoplasmic sperm injection; IUI, intrauterine insemination; IVF, in-vitro fertilization; OI, ovulation

Table 3. Outcome of assessment of the quality of non-randomized studies using the Newcastle-Ottawa scale.

Coho	Selection	Comparability	Outcome

rt studies	Representative-ness of the exposed cohort	Selection of non-exposed cohort	Ascertainment of exposure	Outcome not presented at the start	age	Most of additional factors	Assess-ment of outcome	Follow-up long enough	Adequacy of follow up	Total score
Bal 2021	*	*	*	*	*	Delivery and newborn characteristics	*	*	*	8/9
Bradbury 2004	*	*	*	*	*	-	*	*	*	8/9
Gilboa 2019	*	*	*	*	-	-	*	*	*	7/9
Hargreave 2019	*	*	*	*	*	*	*	*	*	9/9
Källén 2010	*	*	*	*	*	*	*	*	*	9/9
Klip 2001	*	*	*	*	-	-	*	*	*	7/9
Lerner-Gev	*	*	*	*	-	-	*	*	*	7/9

a 2016										
Lidegaard 2005	*	*	*	*	-	-	*	*	*	7/9
Luke 2022	*	*	*	*	-	*	*	*	*	8/9
Pinborg 2010	*	*	*	*	-	*	*	*	*	8/9
Pinborg 2004	*	*	*	*	-	-	*	*	*	7/9
Reigstad 2016	*	*	*	*	-	-	*	*	*	7/9
Rios 2024	*	*	*	*	-	*	*	*	*	8/9
Sargisian 2022	*	*	*	*	-	*	*	*	*	8/9
Spaan 2023	*	*	*	*	-	-	*	*	*	7/9
Spaan 2019	*	*	*	*	-	-	*	*	*	7/9
Spector 2019	*	*	*	*	-	-	*	*	*	7/9
Sundh	*	*	*	*	*	*	*	*	*	9/9

2014 Wainstock 2017	*	*	*	*	-	-	*	*	*	7/9
Weng 2022	*	*	*	*	*	*	*	*	*	9/9
Case-control studies	Selection Is the case definition adequate?	Representativeness of the cases	Selection of Controls	Definition of Controls	Comparability age	Most of additional factors	Outcome Assessment of outcome	Same method of ascertainment for cases and controls	Non-Response rate	Total score
Mallol-Mesnard 2008	*	*	*	*	-	-	*	*	*	7/9
Petridou 2012	*	*	*	*	*	*	*	*	*	9/9
Rudant 2013	*	*	*	*	-	*	*	*	-	7/9
Foix-	*	*	*	*	*	*	*	*	*	9/9

L'Hélias 2012					

A single asterisk (*) indicates 1 score, and dash (-) indicates 0 score.

Table 4. Summary of the results of the meta-analysis.

	No. of studies			Test of heterogeneity	
Outcome		OR (95% CI)	p value	I^2	p value
Overall malignancy	24	1.04 (0.86, 1.27)	0.68	92%	< 0.00001
Leukemia	13	1.24 (1.03, 1.50)	0.02	59%	0.003
Soft tissue tumors	9	1.35 (1.08, 1.68)	0.009	38%	0.12
Hepatic tumors	7	2.10 (1.15, 3.85)	0.09	71%	0.002
Epithelial tumors and melanoma	3	1.50 (1.12, 1.99)	0.006	3%	0.36
Lymphoma	10	0.96 (0.65, 1.43)	0.85	68%	0.0009
Retinoblastoma	10	1.12 (0.69, 1.81)	0.64	57%	0.01
CNS tumors	10	1.14 (0.86, 1.51)	0.38	74%	< 0.0001
Neuroblastoma	7	1.24 (0.67, 2.28)	0.49	78%	0.0001
Renal tumors	6	1.13 (0.69, 1.84)	0.62	73%	0.002
Germ cells and gonad tumors	6	1.11 (0.46, 2.73)	0.81	82%	< 0.0001
Embryonal tumors	2	1.62 (0.61, 4.28)	0.33	98%	< 0.00001
IVF	13	1.25 (0.84, 1.84)	0.27	88%	< 0.00001
ICSI	2	1.18 (0.84, 1.67)	0.34	0	0.51
FET	2	1.23 (0.49, 3.12)	0.66	90%	0.002
OI/IUI	2	1.03 (0.40, 2.66)	0.95	50%	0.16
Asia	5	1.09 (0.93, 1.24)	0.31	0%	0.48
North America	3	2.00 (1.14, 3.53)	0.02	95%	<

					0.00001
Europe	16	0.88 (0.76, 1.03)	0.11	75%	< 0.00001
Before 2010	7	0.99 (0.52, 1.90)	0.99	55%	0.04
Between 2010 and 2020	11	1.09 (0.78, 1.51)	0.62	94%	< 0.00001
After 2020	6	0.99 (0.79, 1.26)	0.96	90%	< 0.00001

CNS, central nervous system; FET, frozen embryo transfer; ICSI, intracytoplasmic sperm injection; IUI, intrauterine insemination; IVF, in-vitro fertilization; OI, ovulation

Table 5. Summary of the results of the GRADE analysis.

Outcomes	**Anticipated absolute effects*** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
	Risk with Non ART	**Risk with ART**			
Overall malignancy	2 per 1,000	**2 per 1,000** (1 to 2)	**OR 1.04** (0.86 to 1.27)	31810095 (24 non-randomised studies)	⨁⨁◯◯ Low[a]
Leukemia	1 per 1,000	**1 per 1,000** (1 to 1)	**OR 1.24** (1.03 to 1.50)	23565992 (13 non-randomised studies)	⨁⨁◯◯ Low[b]
Soft tissue tumors	0 per 1,000	**0 per 1,000** (0 to 0)	**OR 1.35** (1.08 to 1.68)	23070035 (9 non-randomised studies)	⨁⨁◯◯ Low[b]
Hepatic tumors	0 per 1,000	**0 per 1,000** (0 to 0)	**OR 2.10** (1.15 to 3.85)	22822112 (7 non-randomised studies)	⨁⨁◯◯ Low[b,c]
Epithelial tumors and melanoma	0 per 1,000	**0 per 1,000** (0 to 0)	**OR 1.50** (1.12 to 1.99)	16920769 (3 non-randomised studies)	⨁⨁⨁◯ Moderate
Lymphoma	0 per 1,000	**0 per 1,000** (0 to 0)	**OR 0.96** (0.65 to 1.43)	21267693 (10 non-randomised studies)	⨁⨁◯◯ Low[d]

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
	Risk with Non ART	**Risk with ART**			
Retinoblastoma	0 per 1,000	**0 per 1,000** (0 to 0)	**OR 1.12** (0.69 to 1.81)	23642154 (10 non-randomised studies)	⨁⨁⨁◯ Moderate
CNS tumors	0 per 1,000	**0 per 1,000** (0 to 1)	**OR 1.14** (0.86 to 1.51)	23102498 (10 non-randomised studies)	⨁⨁◯◯ Low[e]
Neuroblastoma	0 per 1,000	**0 per 1,000** (0 to 0)	**OR 1.24** (0.67 to 2.28)	14536272 (7 non-randomised studies)	⨁⨁◯◯ Low[f]
Renal tumors	0 per 1,000	**0 per 1,000** (0 to 0)	**OR 1.13** (0.69 to 1.84)	22732863 (6 non-randomised studies)	⨁⨁◯◯ Low[g]
Germ cells and gonad tumors	0 per 1,000	**0 per 1,000** (0 to 0)	**OR 1.11** (0.46 to 2.73)	22732863 (6 non-randomised studies)	⨁⨁◯◯ Low[h]
Embryonal tumors	0 per 1,000	**0 per 1,000** (0 to 1)	**OR 1.62** (0.61 to 4.28)	10868035 (2 non-randomised studies)	⨁◯◯◯ Very low
IVF	2 per 1,000	**2 per 1,000** (2 to 4)	**OR 1.25** (0.84 to 1.84)	7613937 (13 non-randomised studies)	⨁⨁◯◯ Low[i]
ICSI	2 per 1,000	**2 per 1,000** (2 to 3)	**OR 1.18** (0.84 to 1.67)	932157 (2 non-randomised studies)	⨁⨁⨁◯ Moderate
FET	1 per 1,000	**1 per 1,000** (1 to 4)	**OR 1.23** (0.49 to 3.12)	9245882 (2 non-randomised studies)	⨁◯◯◯ Very low
OI/IUI	1 per 1,000	**1 per 1,000** (0 to 3)	**OR 1.03** (0.40 to 2.66)	1378986 (2 non-randomised studies)	⨁⨁⨁◯ Moderate

Explanations

a. Downgraded because the I^2 value was 92%
b. Sensitivity analysis showed that the robustness of the results was affected by individual study
c. Downgraded because the I^2 value was 71%
d. Downgraded because the I^2 value was 68%
e. Downgraded because the I^2 value was 74%
f. Downgraded because the I^2 value was 78%
g. Downgraded because the I^2 value was 73%
h. Downgraded because the I^2 value was 82%
i. Downgraded because the I^2 value was 88%

Highlights:

- ART may not be associated with an increased risk of overall malignancy.
- ART may be associated with an increased risk of leukaemia, soft tissue tumours, hepatic tumours, epithelial tumours, and melanoma.
- Subgroup analyses based on different ART types found that IVF, ICSI, FET, and OI/IUI may not be associated with an increased risk of overall malignancy.

Supplementary Methods 1: http://links.lww.com/JS9/E195

Supplementary Methods 2: http://links.lww.com/JS9/E196