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Male-origin microchimerism and risk of cancer: a systematic review and meta-analysis

Jun Li[1†], Tingting Shao[1†], Junyan Kou[1] and Liwei Ni[1*]

Abstract

Background Many women carry male cells of presumed fetal origin–so-called male-origin microchimerism (MOM) in their circulation and tissues. The association between MOM and cancer risk remains unclear. We aim to evaluate the effect of MOM on cancer risk among postpartum women.

Methods A comprehensive literature search was conducted to identify relevant articles in databases of PubMed, EMBASE, and Web of Science. The data were extracted from eligible studies on the relationship between MOM and cancer risk. A random-effects model was applied to obtain the pooled relative risks (RRs) with 95% confidence intervals (95%CIs). Subgroup analysis, sensitivity analysis and publication bias and were also conducted.

Results Twelve studies involving 3078 participants were enrolled in the pooled analysis. Data on the risk of breast, colon, ovarian, endometrial, thyroid, and brain cancer were collected for quantitative analysis. Pooled analysis showed a significantly reduced rate of cancer (pooled RR = 0.51, 95%CI 0.32–0.82) among MOM-positive women.

Conclusions Individuals harboring MOM exhibits a significantly low risk of cancer.

Keywords Microchimerism, Cancer risk, Meta-analysis

Introduction

Cancer is one of the most common diseases and a crucial contributor to economic burden worldwide [1]. In 2020, the global incidence of cancer in men was reported at 222.0 per 100,000, while the incidence rate in women was 186.0 per 100,000 individuals. An estimated 19.3 million new cancer cases occurred in 2020. Humans face a marked escalation in cancer development with expectations of reaching 28.4 million cases worldwide by 2040 [2]. Various risk factors for cancer have been found, some of which exert adverse effects on tumorigenesis [3]. Therefore, cooperation is needed to identify reliable biomarkers for cancer and clarify their specific molecular mechanisms on tumorigenesis for further promoting the prevention, screening, and control of cancer.

Microchimerism is defined as the existence of two separately derived populations of cells. Fetal cells originating from males can be present in the peripheral blood of women and can infiltrate all tissues in the mother's body [4]. This phenomenon is known as male-origin microchimerism (MOM). Apart from the rare cases where MOM in females may originate from spermatozoa of the partner, an older brother, or a vanishing male twin, the predominant source of MOM is pregnancy with a male fetus [5]. Quantitative Polymerase Chain Reaction (qPCR)

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amplification of Y-chromosome specific genes, including SRY and DYS14, represents a sensitive and feasible approach for assessing the MOM level [6].

The first evidence of MOM detected in maternal blood using Y-chromosome specific probes was reported in 1979 [7]. Throughout the 1990s, research confirmed that MOM could persist for decades, suggesting long-term biological significance. By the 2000s, studies explored the clinical implications of MOM, linking it to autoimmune diseases, tissue repair, and cancer [5]. Recent researchers have further explored the dual role of MOM in cancer and investigated the mechanisms by which MOM could modulate cancer risk [8]. The results of epidemiological studies for specific tumor types were incompatible. Compared with MOM-negative women, women testing positive for MOM face a reduced risk of breast cancer involving both blood [9] and tissue specimens [10]. Likewise, ovarian cancer risk is reduced by 56% among women testing positive for MOM in their circulation [11]. Paradoxically, detection of MOM is strongly associated with an increased risk of developing colon cancer [9]. These contradictory findings have triggered debates on the relationship between MOM and cancer incidence. Hence, we performed this meta-analysis to evaluate the predictive value of MOM for cancer risk among postpartum women.

Methods

Literature search

This study was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [12]. A literature search in PubMed, EMBASE, and ISI Web of Science was conducted to identify relevant studies on the association between MOM and cancer risk. The following MeSH terms and keywords were used: "chimerism" [Mesh], "fetal microchimerism" "carcinoma" [Mesh], "carcinoma*", "malignant tumor", "cancer," "malignant neoplasm," "incidence" [Mesh], "risk", and "prevalence". We restricted searches to capture articles published in English from the database up to February 6, 2024. Moreover, a manual search was performed to update relevant articles in the reference lists.

Inclusion/exclusion criteria

The original articles were screened by Two investigators (Jun Li and Tingting Shao) independently and an agreement was reached on the final enrollment of publications. Eligible studies must meet the following criteria: (1) be full-text searchable in English; (2) designed as a retrospective or prospective study; (3) the methods for detection of MOM were elucidated, (4) the presence of MOM was determined with a qPCR assay for the Y chromosome gene; and (5) incidence [reported as relative risks (RRs) or odds ratios (ORs) or hazard ratios (HRs) with 95% confidence intervals (95%CIs)] of cancer were recorded or could be obtained by calculation. Abstracts, reviews, editorials, meetings, case reports, and laboratory studies were excluded. EndNote X8 software was used to search for eligible articles and omit incompatible studies. Cohen's kappa statistic was applied to assess inter-rater reliability (SPSS version 23. 0, SPSS Inc, Chicago, IL, USA).

Data extraction and quality assessment

Two authors (Junyan Kou and Tingting Shao) independently extracted data from the enrolled studies. The obtained variables were following: the first name of the first author, publication year, country or region, study design, sample size, follow-up period, age of patients, types of cancer, methods used for detection of Y chromosome, sample type, and ORs or HRs with corresponding 95%CIs. The quality of included studies was measured by the Newcastle–Ottawa Quality Assessment Scale (NOS, scores of 0–9 stars), and studies with NOS ≥ 6 were regarded as high – quality [13]. Two reviewers assessed each study independently and finally reached a consensus.

Statistical analysis

ORs or HRs were converted into RRs with a low incidence of cancer in women, thereby providing a reasonable basis for ignoring the difference in cancer risk measurement [14]. The pooled RRs with 95%CIs were calculated to assess the effect of MOM on cancer incidence. Infrequently, a 2-by-2 contingency table was applied to calculate RRs with original data from the enrolled article [15]. Moreover, we also calculated the pooled RRs of site-specific cancers. The Chi-square test and I^2 statistic were used to evaluate the statistical heterogeneity among studies. $P < 0.10$ and $I^2 > 50\%$ indicated significant heterogeneity, and the random-effects model was applied to calculate the pooled RR [16]. Subgroup analyses and sensitivity analyses were performed to reduce and explain the statistical heterogeneity. Funnel plots were illustrated to visually inspect asymmetry to assess the potential publication bias and Egger's test was conducted to quantify asymmetry [17]. A two-tailed P values less than 0.05 was considered statistically significant. Statistical analyses were performed by using Stata 14.0 (Stata Corporation, College Station, TX, USA).

Results

Literature search

The flow diagram illustrates the process of literature selection (Fig. 1). Initially, 328 articles were identified by searching PubMed, EMBASE, and Web of Science. Then, 86 duplicate articles were found and deleted. After

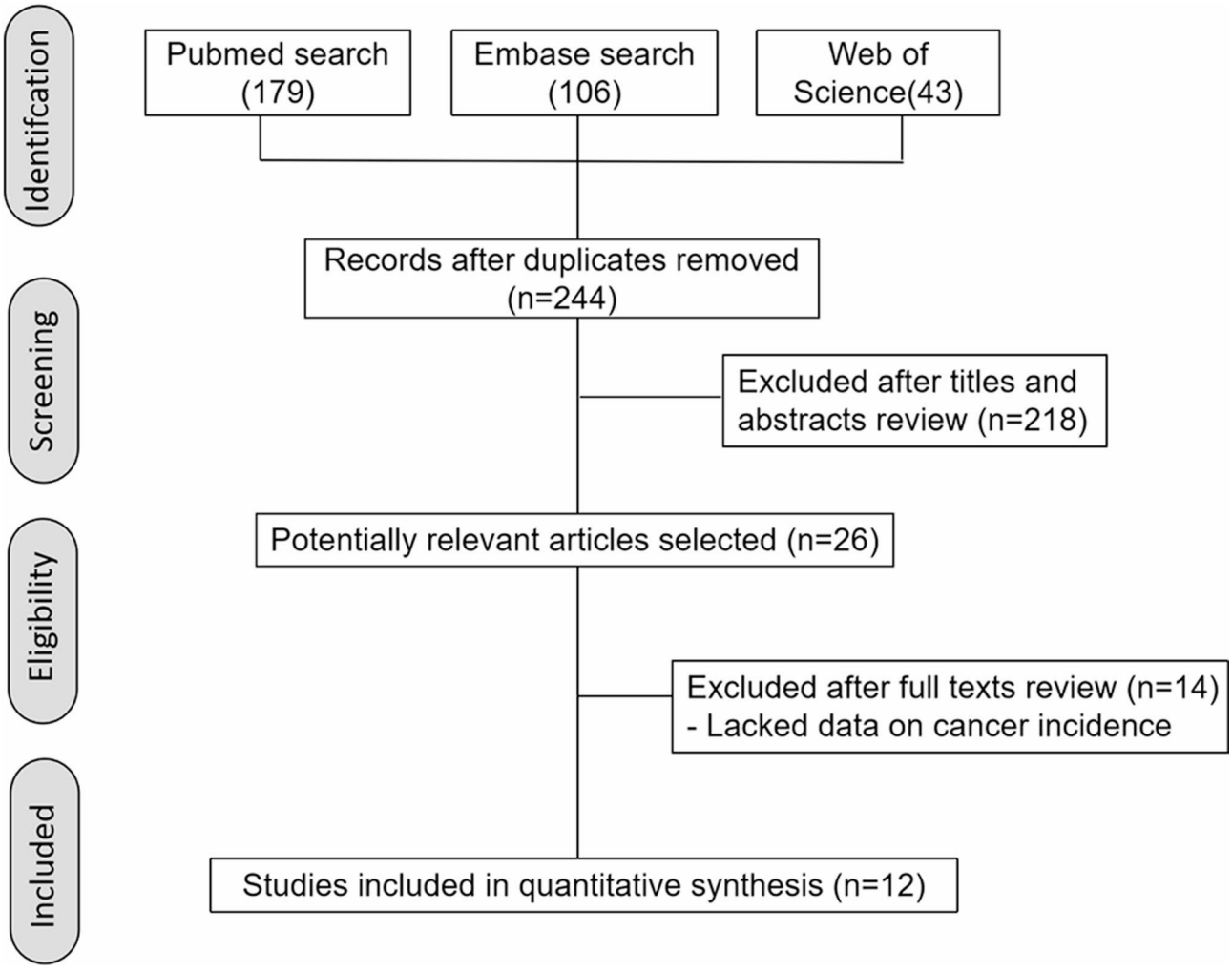

Fig. 1 The literature search process

scaning the titles and abstracts, 26 records remained for inclusion. After full-text screening, 14 publications were excluded due to lacking documents on cancer incidence. Finally, twelve articles were enrolled. The kappa statistic indicated satisfactory agreement between the two reviewers (kappa = 0.86).

Study characteristics and quality assessment

The characteristics of the enrolled publications are described in Table 1. Twelve publications consisted of 3078 participants involving breast [9, 10, 18–21], ovarian [11], endometrial [22, 23], thyroid [24, 25], colon [9], and brain cancer [26]. Mads et al. reported the detected MOM exerted inhibitory effects on breast cancer incidence, yet manifested stimulatory effects on colon cancer. Three studies reported HR for cancer incidence, and nine publications reported OR. Blood samples were obtained for the detection of MOM in nine articles, while tissue samples were extracted in three studies. Y chromosome gene DYS14 was applied for identifying MOM in nine studies and SRY quantitative polymerase chain reaction was used to detect microchimerism in three articles. Two studies reported similar HRs for the association between MOM and the risk of ovarian or endometrial cancer across different hormonal status exposures [11, 22]. Additionally, the NOS scores of the included studies were ≥ 6, thus indicating high quality (Table S1).

Relationship between MOM and cancer risk

A random-effects model was applied to calculate the pooled estimate due to the presence of substantial heterogeneity among the included studies. The combined analysis of ten studies showed that compared with MOM-negative women, positive women faced low risk of developing cancer (pooled RR = 0.51, 95%CI 0.32–0.82, Fig. 2).

Based on the cancer type of enrolled studies, we calculated the pooled estimates of site-specific cancers, including breast, endometrial, and thyroid cancer. The meta-analysis of six studies revealed that MOM-positive

Table 1 The characteristics of the included studies

Author, year, region	Study design	Follow-up time	Number	Age	Tumor type	Detected gene located in Y chromosome	Sample type	Risk of cancer (RRs and 95%CIs)	NOS scores
Mads, 2022,Denmark	Prospective	Median, 21.2 years	578	Median, 56(cancer); 56.6(control)	Brain cancer	DYS14	Blood	HR, 0.50 (0.33–0.77)	7
Sara, 2022, Denmark	Prospective	Median, 21 years	581	50–64	Endometrial cancer	DYS14	Blood	HR, 0.73(0.47–1.15)	7
Sara, 2020, Denmark	Prospective	Median, 17 years	592	Median, 56(cancer); 57(control)	Ovarian cancer	DYS14	Blood	HR, 0.44 (0.29–0.68)	7
Valentina, 2015, Italy	Retrospective	NA	153	NR	Papillary thyroid cancer	SRY	Blood	OR, 0.37(0.19–0.68)	6
Ilona, 2014, USA	Retrospective	NA	126	Mean, 65.5 (cancer);52.4(control)	Endometrial cancer	SRY	Tissue	OR, 0.325 (0.144–0.733)	6
Eugen, 2013, Czech Republic	Retrospective	NA	182	Mean, 48.6(cancer);48.42(control)	Breast cancer	DYS14	Tissue	OR, 4.75 (2.34–9.69)	6
Jinny, 2013, USA	Retrospective	2004–2010	177	NR	Breast cancer in situ	DYS14	Blood	OR, 0.26(0.12–0.56)	6
Mads, 2012,Denmark	Prospective	1993–2006	428	Median, 57 (breast cancer); 59 (colon cancer)	Breast cancer; colon cancer	DYS14	Blood	OR, 0.30 (0.17–0.52) for breast cancer; 3.9 (1.6–9.5) for colon cancer	7
Vijayakrishna, 2009, USA	Prospective	NA	38	NR	Breast cancer	DYS14	Tissue	OR, 0.21 (0.05–0.83)	6
Valentina, 2009, Italy	Retrospective	NA	106	Median,54	Papillary thyroid cancer	SRY	Blood	OR, 0.28(0.12–0.65)	6
Vijayakrishna, 2008, USA	Retrospective	NA	99	21–45	Breast cancer	DYS14	Blood	OR, 0.29(0.11–0.83)	6
Vijayakrishna, 2007, USA	Prospective	NA	82	Median, 42(cancer); 50(control)	Breast cancer	DYS14	Blood	OR, 0.23(0.06–0.75)	7

NA not available, *RR* relative risk, *CI* confidence interval, *HR* hazard ratio, *OR* odd ratio

women had a significantly reduced rate of breast cancer (pooled RR = 0.51, 95%CI 0.31–0.71, Fig. 3). The pooled RR for developing thyroid cancer was 0.33 (95%CI 0.20–0.56, Fig. 4) for MOM presence. Two articles separated Type 1 endometrial cancer from other types of endometrial cancer. We found a reduced risk of Type 1 endometrial cancer (pooled RR = 0.54, 95% CI: 0.35–0.82, Fig. 5) in MOM-positive women, while no obvious association was found between MOM and other types of endometrial cancer (pooled RR = 0.68, 95% CI: 0.33–1.40, Fig. 5). The overall estimated RR for endometrial cancer was 0.57 (95%CI 0.40–0.82, Fig. 5).

Heterogeneity and subgroup analysis

Considering the substantial heterogeneity observed in the pooled RR for developing cancer (I^2 = 84.2%, Fig. 2), we performed subgroup analyses to identify the source of heterogeneity. When stratified on basis of cancer type, the overall estimate for women malignant tumors (RR = 0.45, 95% CI = 0.25–0.83) were similar to the pooled analysis of subgroups (Fig. S1). Test for heterogeneity between subgroups was invalid with I^2 for women malignant tumors increasing to 85.0% and for other tumors increasing to 86.7% (p = 0.726, Fig. S1). Based on the detection gene of MOM, the combined estimates for SRY (RR = 0.33, 95% CI = 0.21–0.51) and for DYS14 were discrepant. I^2 decreased to 0.0% in SRY group and it slightly increased to 87.2% in DYS14 group (p = 0.021, Fig. S2). The detected gene in Y chromosome was likely to be a source of heterogeneity. The RRs for Denmark group, for Italy group, and for USA group were 0.66 (95% CI = 0.37–1.17) and 0.33 (95% CI = 0.20–0.56), 0.45 (95% CI = 0.11–1.89),

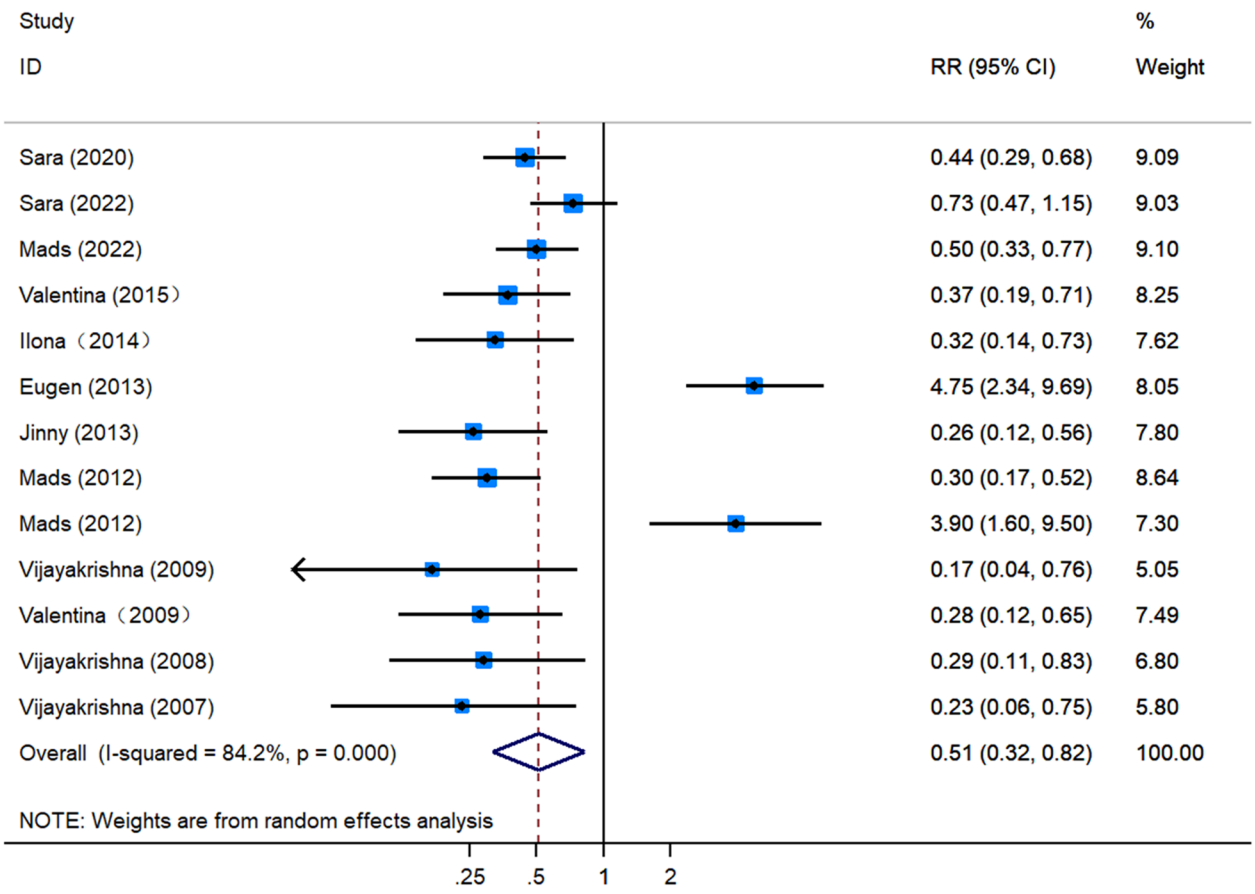

Fig. 2 Meta-analysis of impact of MOM on cancer risk of women

respectively ($P=0.105$, Fig. S3). The results of heterogeneity analysis were unstable with I^2 increasing in Denmark and USA groups. In subgroup analysis stratified by study design, considerable heterogeneity was observed in retrospective and prospective groups ($P=0.942$, Fig. S4). When stratified on sample type, I^2 decreased slightly to 73.8% in blood group and it increased to 93.6% in tissue group (Fig. S5), indicating that sample type did not significantly make a difference to the heterogeneity.

Sensitivity analysis and publication bias

The stability of pooled estimate was measured using the trim-and-fill method. No remarkable changes were identified between the previous and newly pooled RRs (Fig. S6). Additionally, the new RR did not significantly alter regardless of which publication was omitted(Fig. S7). The sensitivity analysis revealed that none of the involved studies influenced the stability of the combined estimate. Furthermore, we measured the potential publication bias. Most of the involved studies were approximately symmetrical in the funnel plots (Fig. 6). Moreover, Egger's test was conducted and no apparent publication bias was found ($P=0.245$).

Discussion

In this meta-analysis, we demonstrated a reduced risk of cancer in MOM-positive women. The pooled analysis revealed that MOM was inversely related with risk of breast, thyroid, and endometrial cancer. Notably, the subgroup analysis implied 43% reduced risk of developing Type 1 endometrial cancer among MOM-positive women, while no significant relationship was observed between MOM and other types of endometrial cancer.

The correlation between MOM and decreased incidence of breast cancer was identified in both peripheral blood [9] and tissue [10] samples and demonstrated in women with in situ [18] and invasive tumors [9]. This pooled analysis revealed that MOM-positive women exhibited a lower rate of breast cancer, which might be a possible elucidation for the relationship between the

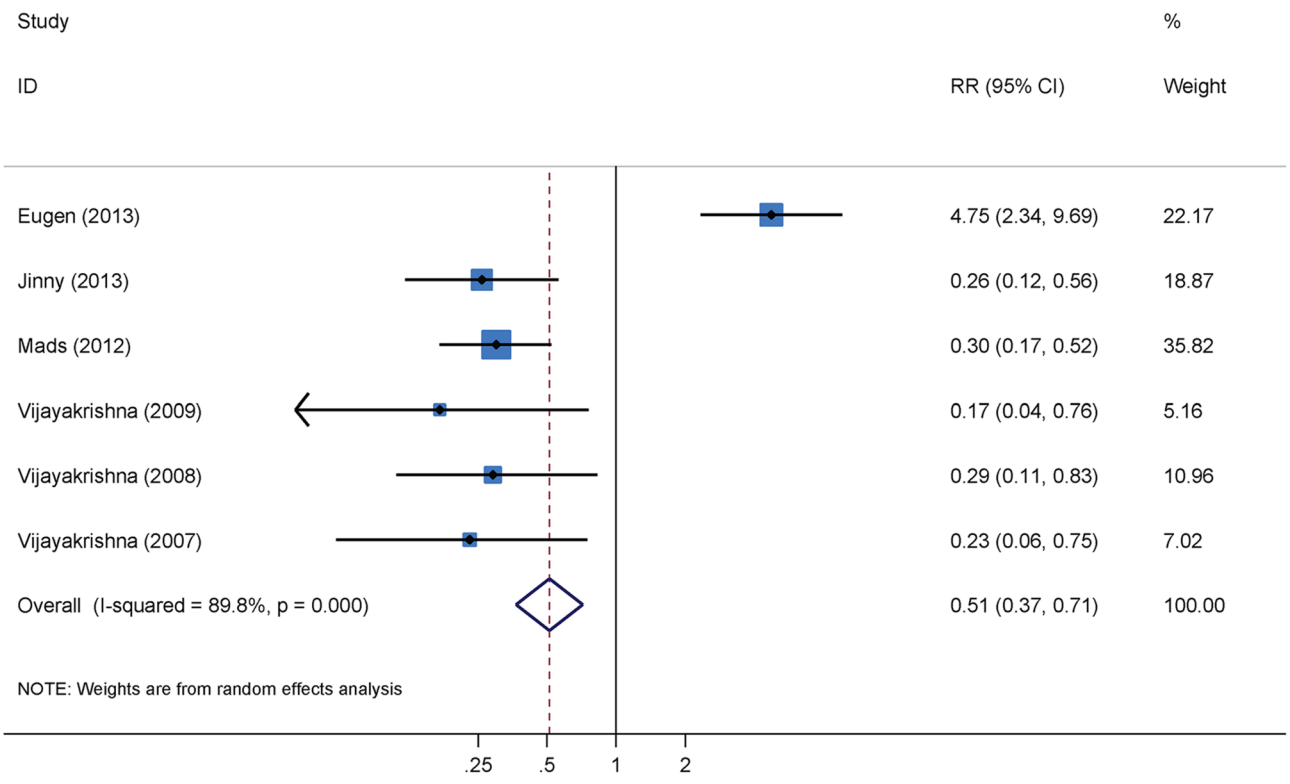

Fig. 3 Meta-analysis of impact of MOM on risk of breast cancer

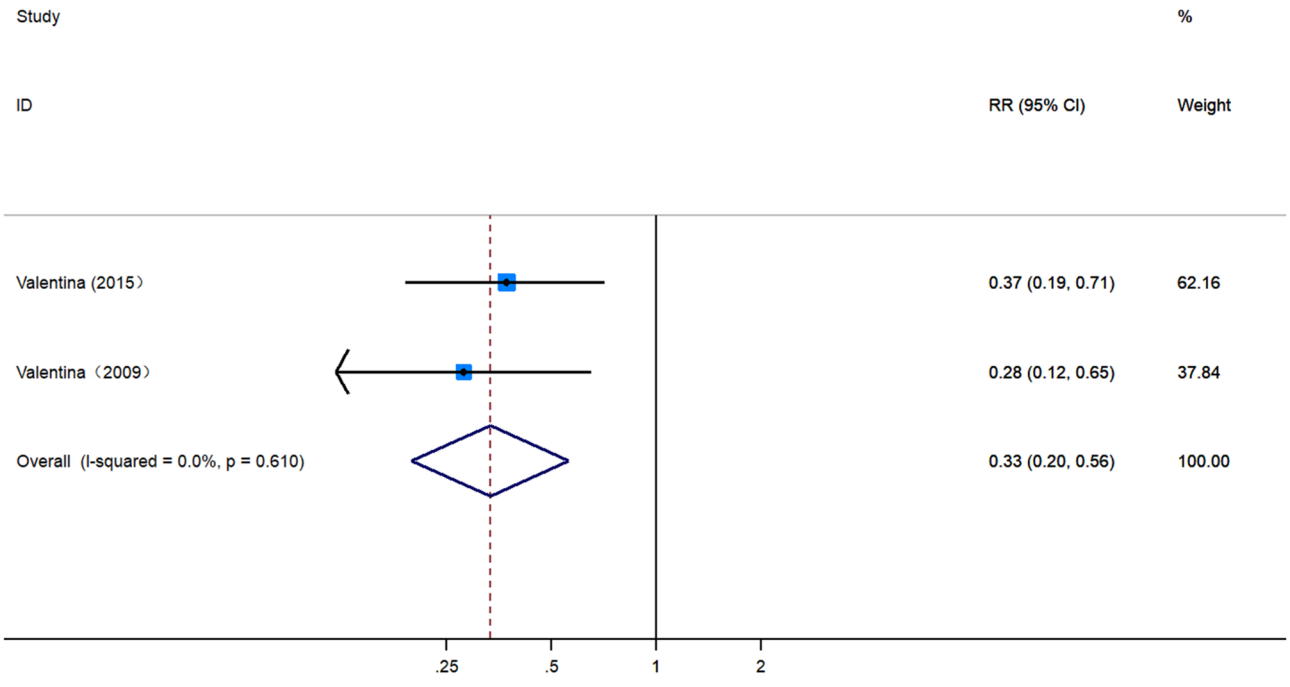

Fig. 4 Meta-analysis of impact of MOM on risk of thyroid cancer

increased number of pregnancies and reduced risk of breast cancer [27]. Similarly, a higher number of deliveries was remarkably related with a lower risk of endometrial [28], colon and rectal cancer [29]. Ovarian cancer risk was reduced in women who gave birth to a child at older ages [30], owing to higher levels of MOMs compared with women pregnant at younger ages [31]. Differentially, older age at first pregnancy were associated

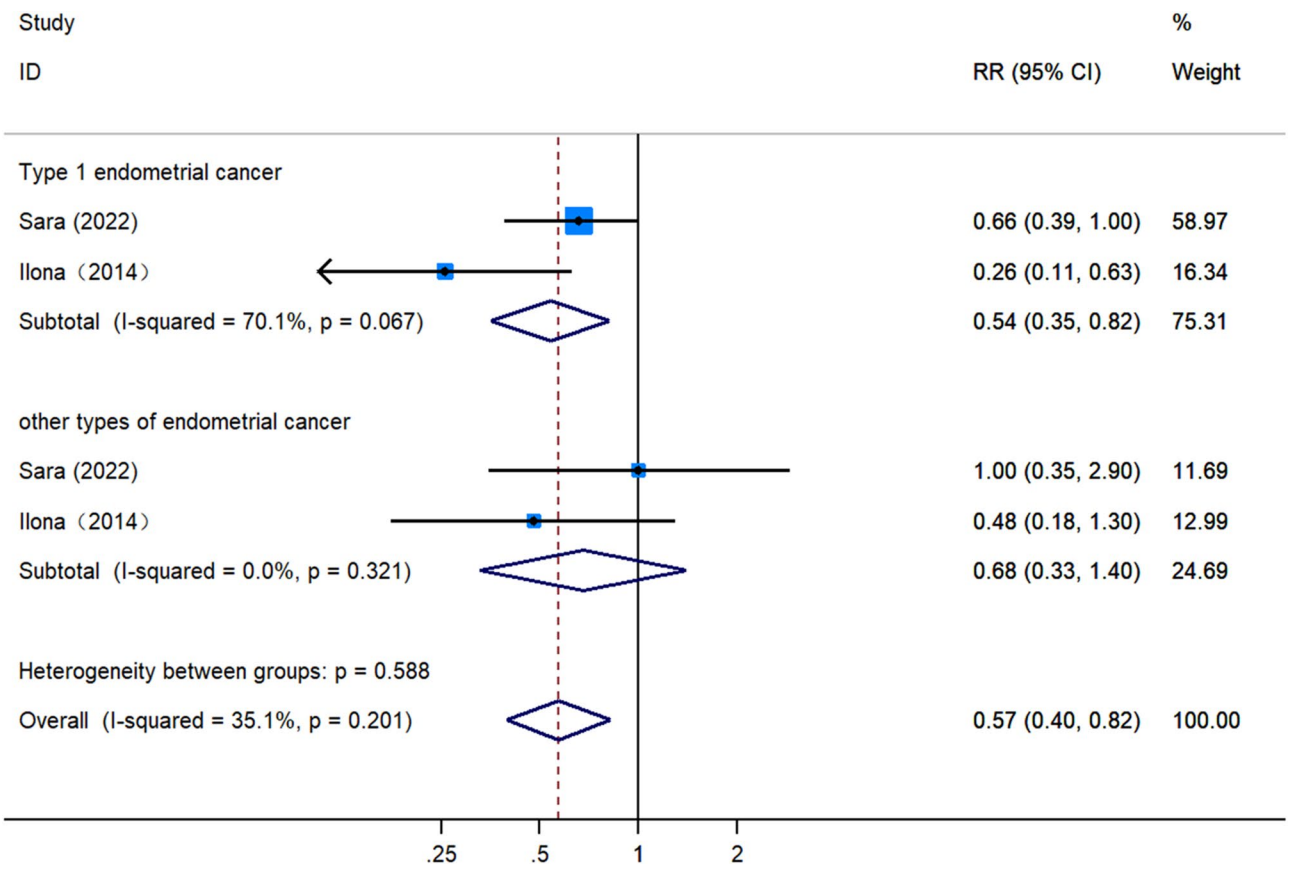

Fig. 5 Meta-analysis of impact of MOM on risk of endometrial cancer

with increased thyroid cancer risk with the underlying mechanisms including iodine deficiency or thyroid autoimmunity [32]. Increasing levels of estrogens not simultaneously opposed by progesterone interact to promote proliferation and growth of the endometrial lining eventually inducing cancer development [33]. The reduced risk of Type 1 endometrial cancer is associated with the protective effect of progesterone during pregnancy [34] and the presence of MOM in women after childbirth. Generally, MOM might be a mediator for the effect of pregnancy on cancer risk in women.

MOM confers a detrimental effect on cancer development. One prominent hypothesis that has been proposed is that fetal microchimerism cells provide enhanced immune surveillance of cancerous cells or participate in cancer suppression through response to tissue injury [35]. Microchimeric cells, endowed with dual immunologic and stem cell-like properties, have the capacity to enhance the immune response, potentially allowing the host to better identify and combat neoplastic cells [36]. A clinical trial (NCT04903990: 2021-05-14) is currently underway to identify the subsets of circulating fetal immune cells that may influence the carcinogenic process of cancer in the context of fetal microchimerism. Techniques such as qPCR for Y-chromosome specific sequences, fluorescence in situ hybridization (FISH), and flow cytometry have been employed to detect and quantify MOM [37]. Studying MOM poses several challenges, including the low abundance of male cells in women and the need for highly sensitive detection methods. Additionally, distinguishing MOM from other sources of microchimerism, such as blood transfusions, organ transplants, or older siblings, complicates interpretation. Variability in MOM levels among individuals and over time further adds to the complexity [38]. These challenges highlight the need for standardized methodologies and larger longitudinal studies to better understand the role of MOM in health and disease.

This meta-analysis reveals that MOM-positive women face a significantly lower risk of cancer. The enrolled studies are high–quality with high NOS scores. The combined estimate of twelve studies weakens the shortcoming of a limited sample size in a single study, which presents high statistical power. Additionally, no publication bias was found across the involved publications, which consolidates the reliability of the pooled analysis. Moreover, quantitative evaluation was performed to expatiate the influence of MOM on risk of site-specific cancers.

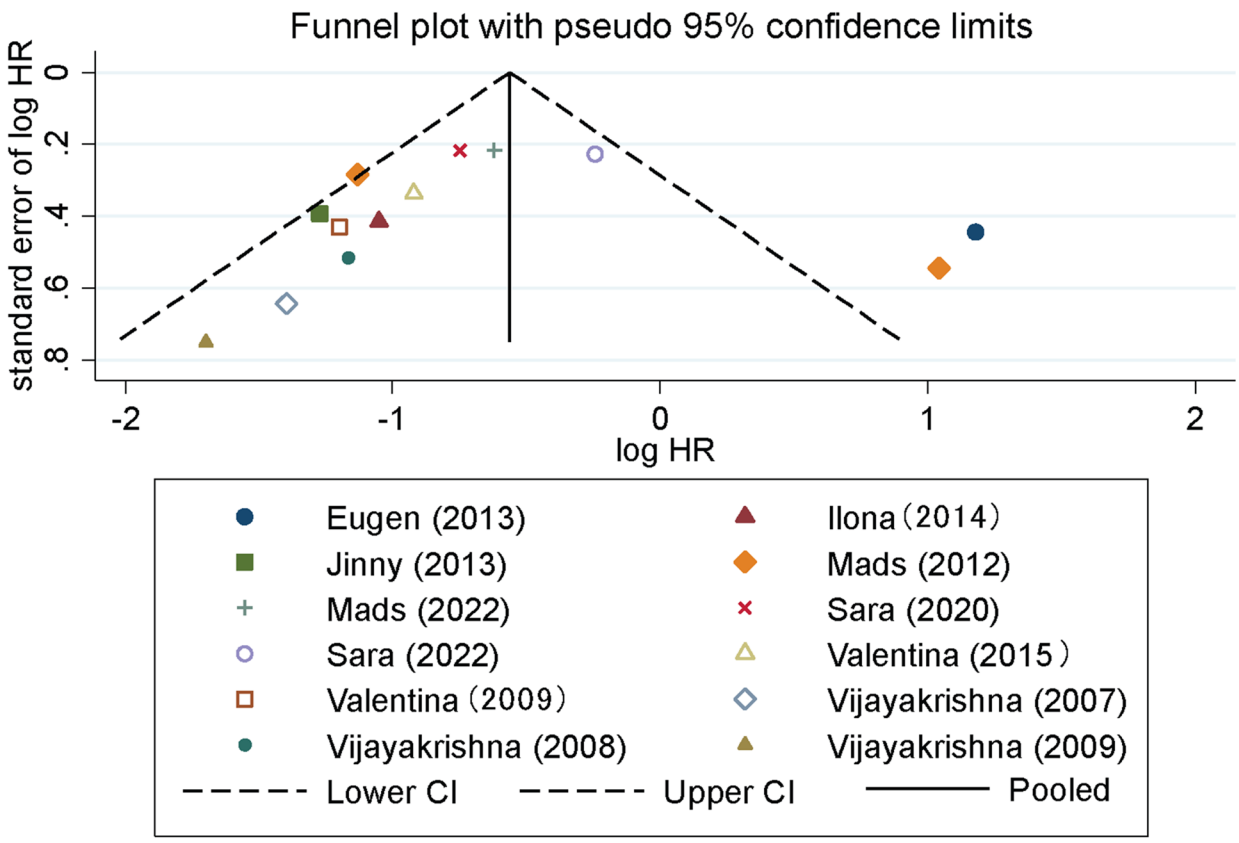

Fig. 6 The funnel plot for measuring the publication bias of enrolled studies

Some limitations are worthy of attention in this study. First, in light of the low prevalence of MOM and cancer, we ignored the difference in the measurement of incidence and then converted ORs and HRs into RRs, which might present a slight bias [14]. Second limitation is that the enrolled population is concentrated on women who have given birth to sons, as female fetal origin microchimerism cannot be detected. Consequently, only half of the pregnancies can be evaluated using FCM. Third, unadjusted factors from the included observational studies could lead to bias. Fourth, different cancer types of involved studies might be a source of selection bias. Finally, although we performed subgroup analyses and sensitivity analyses to explore uncertainties among enrolled publications, notable heterogeneity existed in the combined estimate. Moreover, small sample size results in the lack of power to substantiate the effect of microchimerism on subtypes of certain cancer. There are no technical conditions to determine the specific phenotypes of detected male cells, and thus the biological mechanisms underlying the association remain uncertain.

Conclusion

Despite some limitations, our meta-analysis demonstrates that MOM-positive women had decreased cancer risk. MOM was inversely related with risk of breast, thyroid, and endometrial cancer. Our findings emphasize that clinicians need not only to be aware of the detrimental effect of MOM on cancer risk, but also to recognize the differences in incidence of site-specific cancer, even subtypes of cancer.

To determine a more potent impact of MOM on cancer incidence, more prospective research with enlarged sample sizes and adjusted covariates is needed to survey various site-specific cancers. Technological advances facilitate us to determine the phenotypes of detected male cells, and thus explore the biological mechanisms underlying the association between microchimerism and cancer.

Abbreviations

MOM	Male-origin microchimerism
RRs	Relative risks
cis	Confidence intervals
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
ORs	Odds ratios
HRs	Hazard ratios

NOS Newcastle–Ottawa Quality Assessment Scale

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12885-025-14860-z.

Supplementary Material 1: Table S1 Quality assessment of eligible studies with Newcastle–Ottawa Scale

Supplementary Material 2: Fig. S1 Meta-analysis of the association between MOM and cancer risk stratified by cancer type.

Supplementary Material 3: Fig. S2 Meta-analysis of the association between MOM and cancer risk stratified by detection gene

Supplementary Material 4: Fig. S3 Meta-analysis of the association between MOM and cancer risk stratified by country or region.

Supplementary Material 5: Fig. S4 Meta-analysis of the association between MOM and cancer risk stratified by study design.

Supplementary Material 6: Fig. S5 Meta-analysis of the association between MOM and cancer risk stratified by sample type.

Supplementary Material 7: Fig. S6 Metatrim test of studies on the association between MOM and cancer risk.

Supplementary Material 8: Fig. S7 Metaninf test of studies on the association between MOM and cancer risk.

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Author contributions
Jun Li analyzed the data, and wrote the manuscript. Tingting Shao and Jun Li formulated inclusion and exclusion criteria, searched the databases. Tingting Shao and Junyan Kou extracted the data, assessed the quality of studies. Liwei Ni designed this research, supervised the study, and revised the manuscript. All authors contributed to this systematic review and meta-analysis.

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Data availability
The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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