

Exposure to radiation therapy is associated with female reproductive health among childhood cancer survivors: a meta-analysis study

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Abstract

Background and aims Many epidemiological studies have revealed a positive correlation between medical radiation exposure and the reproductive health in female childhood cancer survivors. However, because of variations in the samples size, such studies showed partly inconsistent conclusions. The aim of this meta-analysis was to clarify the association between radiotherapy and the risk of reproductive health impairment for female who survived from childhood cancer.

Methods Fourteen cohort studies involving childhood radiotherapy were selected as the exposure of interest and the impaired reproductive health condition during the childbearing age as the outcome. Among meta-analysis of observational studies found in Pubmed and Embase from 1900 to 2014, we evaluated those relevant observational studies which surveyed the association of medical radiation and reproductive health in female childhood cancer survivors. Review Manager 5.2 and STATA 12.0 software were used to perform the meta-analysis. Study-specific estimations for each outcome were combined into a pooled relative risk (RR) with 95 % confidence interval (CI) by a meta-analytic approach.

Capsule Childhood radiotherapy is significantly associated with female infertility, acute ovarian failure, low AMH value, stillbirth of the mothers. Also, it is significantly associated with low birth weight of the offspring. Childhood radiotherapy is not significantly associated with abortion or congenital malformation of the offspring.

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Results Based on a random-effects meta-analysis, significant association between infertility (RR=1.28, 95 % CI=1.16–1.42), acute ovarian failure (AOF) (RR=9.51, 95 % CI=5.03–17.96), low level of anti mullerian hormone (AMH) (<1 ng/mL) (RR=14.79, 95 % CI=3.36–66.64), stillbirth (RR=1.19, 95 % CI=1.02–1.39) and low birth weight (RR=2.22, 95 % CI=1.55–3.17) were identified. Conversely, no significant results were found in abortion and congenital malformations.

Conclusions To the best of our knowledge, this is the first meta-analysis assessing the effect of medical radiation on female childhood cancer survivors' reproductive capability and pregnancy outcomes. Although there were some limitations, our meta-analysis further supported that radiotherapy was a risk factor for reproductive health problems of female who survived from childhood cancer.

Keywords Radiotherapy · Infertility · Reproductive capability · Pregnancy outcomes · Meta-analysis

Introduction

People are exposed to ionizing radiation every day from the food, building materials, soil and air from outer space [1]. In addition to the natural radiation, people might also be exposed to the radiation from medical tests and treatments. Although in developed countries, childhood cancer is the second most common cause of death [2]. In recent years, radiotherapy has become increasingly a successful tool for the treatment of cancers in children, providing high survival rate expectations for many years after treatment.

Increasing attention has been paid on the reproductive health of women who survived from childhood cancer. Radiotherapy impacts all aspects of female reproductive system, including hypothalamic, pituitary gland and endometrial receptivity. Childhood radiotherapy increases the risk of damage

to the hypothalamus and pituitary gland, decreasing the pituitary gonadotropins with subsequent ovaries dysfunction and highly likely leading to infertility. In Simone Reinmuth's epidemiological study, women treated with radiotherapy during childhood showed high rate of infertility (31 %) [3]. The human oocyte is exquisitely sensitive to radiation. In childhood cancer survivors who have received radiotherapy, the diminished ovarian reserve was detected by an AMH value <1 ng/mL [4]. AMH, which is a sensitive indicator of the longitudinal decline of ovarian reserve, is produced in the granulosa cells in late preantral and small antral follicles and plays an essential role in the regulation of egress from the primordial follicle pool adjusting the follicles reentering the meiosis. The serum AMH declines with age and is an important and sensitive predictor of menopause. In vivo studies have shown that ionizing radiation may cause low level of serum AMH. In Yasmen and colleagues' study, the serum level of AMH was found to decrease in rats treated with total body gamma radiation [5]. Conversely, as another aspect of the ability of female fertility, the proportion of abortion in cancer survivors was similar to the population from control subjects. Moreover, the risk of low birth weight and stillbirth increased among the offspring of females who received radiotherapy during childhood [6]. Until now, no evidences have suggested the role of childhood radiotherapy on congenital malformation.

Because most of the studies are focused on the effects of radiation on the fathers or female patients with cancer in offspring, there is a lack of consistency on the effects of childhood radiotherapy on female reproductive health condition. The objective of this study was to comprehensively and systematically review the epidemiological studies and to evaluate the association between childhood medical radiation and female reproductive health conditions.

Methods

Publications screening We searched published studies in Pubmed and Embase databases updated to May 2014 with the following search terms: radiation therapy AND (fertility OR infertility OR reproduction OR pregnancy) AND (female OR women) AND (case control OR case-control OR cohort). Furthermore, reference lists of main reports and review articles were also reviewed to identify additional relevant publications. Our study was conducted and reported following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines.

Selection criteria Two authors (W.G and J.L.) reviewed the retrieved titles and abstracts to identify the eligible studies for our meta-analysis. Published studies were included based on the following criteria: 1, written and published in English; 2, case-control study or cohort study; 3, studies about radiation therapy

and fertility in female; 4, study about childhood cancer survivors; 5, entire paper with sufficient data on the relationship between radiation therapy and fertility. We excluded studies with the following criteria: 1, written and published in a language other than English; 2, not a case-control study or cohort study; 3, studies with no sufficient data on the relationship between radiation therapy and fertility; 4, studies that are not related to childhood cancer survivors; 5, review articles without original data; 6, a commentary, letter to the editor, or monograph.

Data extraction Two authors (W.G and J.L.) performed the data evaluation independently. The following data were extracted from each study: the first author's last name; publication year; country; number of enrolled patients; fertility factors (infertility, stillbirth, spontaneous abortion, congenital anomaly, low birth weight, AMH value, AOF and preterm birth).

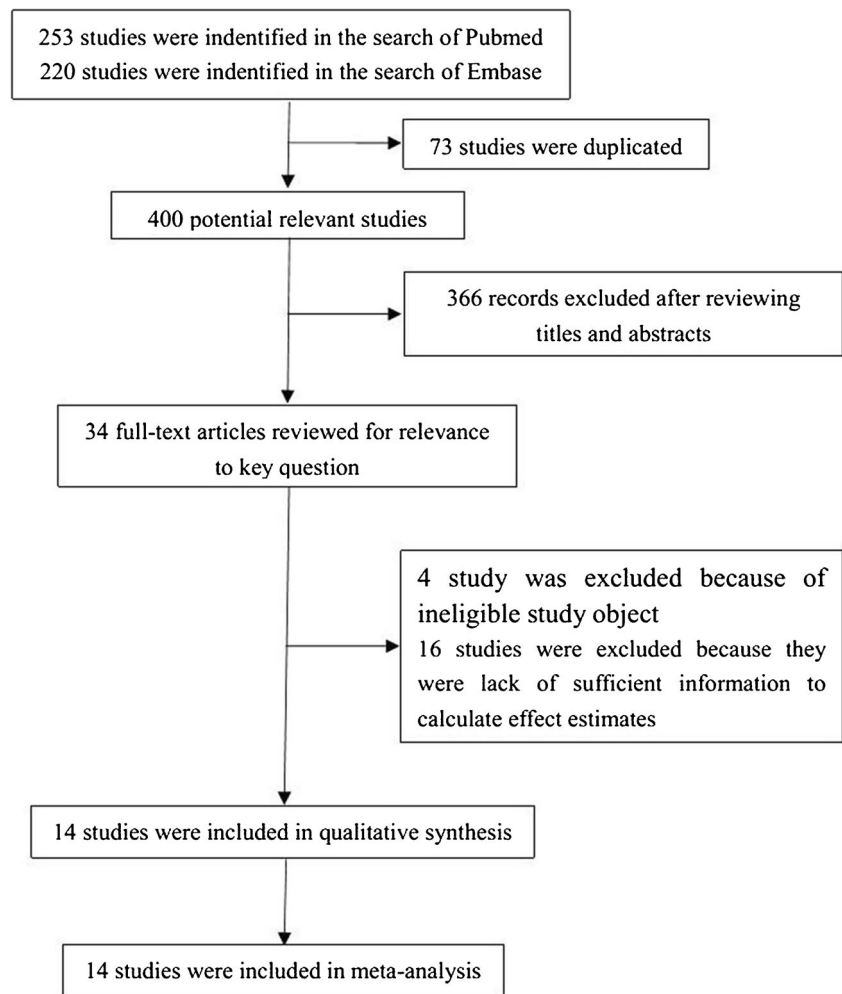
Quality assessment The quality of eligible studies was estimated by two authors (W.G and J.L.), and the disagreements were discussed and resolved by the reviewer (Q.Y.). The appraisal followed the guidelines of the modified Newcastle-Ottawa Quality Assessment Scale (NOS) documents.

Data synthesis and statistical analysis Exposure to radiotherapy was analyzed as dichotomous variables, as high-dose exposure versus non- or low-dose exposure. The fertility factors were also conducted as dichotomous variables (with vs. without) or (high vs. low). These data were analyzed by random-effect method, and were measured in RR with 95 % CI. Statistical heterogeneity was estimated by means of Cochran's Q test and *I*-squared test. The *I*-squared test represents the percentage of variation to heterogeneity, which is categorized as low (0–40 %), moderate (40–60 %), high (60–90 %), and very high (>90 %). To identify any potential publication bias, we used Begg's test and Egger's test. All statistical analyses were performed with Review Manager 5.2 and STATA 12.0.

Results

Systematic review Among the 400 studies selected, only 34 matched to our strategy with inclusion criteria and content (Fig. 1). After reviewing full text, 4 of the 34 studies were excluded because of ineligible study objects; 16 studies were excluded because lacking sufficient information for effects estimations. We reviewed reference lists of these articles, and there were no additional relevant publications to be included. Finally, we identified 14 studies for analysis [4, 6–18] (Table 1).

Detailed characteristics of these studies are provided in Table 1. The included studies were published between 1999 and 2014, and all of them were cohort studies [4,

Fig. 1 Flow chart of the literature search and article selection

6–18]. A total of 10,717 women with radiation therapy and 11,128 women without radiation therapy from 13 studies were evaluated [4, 6–15, 17, 18]. Among the 14 studies analyzed, 1 study did not have the exact number of included participants, but only had effect estimates [16]. A total of 10 studies were performed in North America [4, 6–8, 10, 11, 13–15, 18], and 4 studies in Europe [9, 12, 16, 17]. In fertility factors, 5 studies were described about infertility [6, 9, 12, 14, 18], 2 studies were based on AMH values [4, 17], 2 studies on AOF [10, 16], 3 studies on stillbirth or neonatal death [7, 8, 13], 2 studies on spontaneous abortion [7, 12], 2 studies on congenital anomaly [7, 15], 2 studies on low birth weight [7, 11] and 1 study on preterm birth [11]. In radiation therapy methods, 4 studies were performed in radiation therapy without specific description [10, 12, 16, 2], 2 studies on abd-pelvic radiation [6, 7], 2 studies on ovarian radiation [8, 15] and each of the 6 last studies were performed on pelvic radiation [4], abdominal or total body radiation [17], hypothalamic or pituitary radiation [14], nasopharyngeal radium irradiation [9], uterus radiation [11], uterus and ovarian radiation [13].

The NOS quality point of included studies is provided in Table 1. We defined the NOS quality point >6 as higher

quality and ≤6 as lower quality. All of included studies were higher quality.

Infertility Among the 5 included studies that identified the relationship between radiotherapy and infertility [6–10], the study-specific RRs for infertility range were from 1.20 to 1.54. The pooled RR (exposed to radiotherapy vs. non-exposed) for infertility was 1.28 (95 % CI was 1.16–1.42) with low heterogeneity ($I^2=24.9\%$) (Fig. 2a). There was no indication of publication bias with Begg’s test ($p=0.327$) and Egger’s test ($p=0.180$).

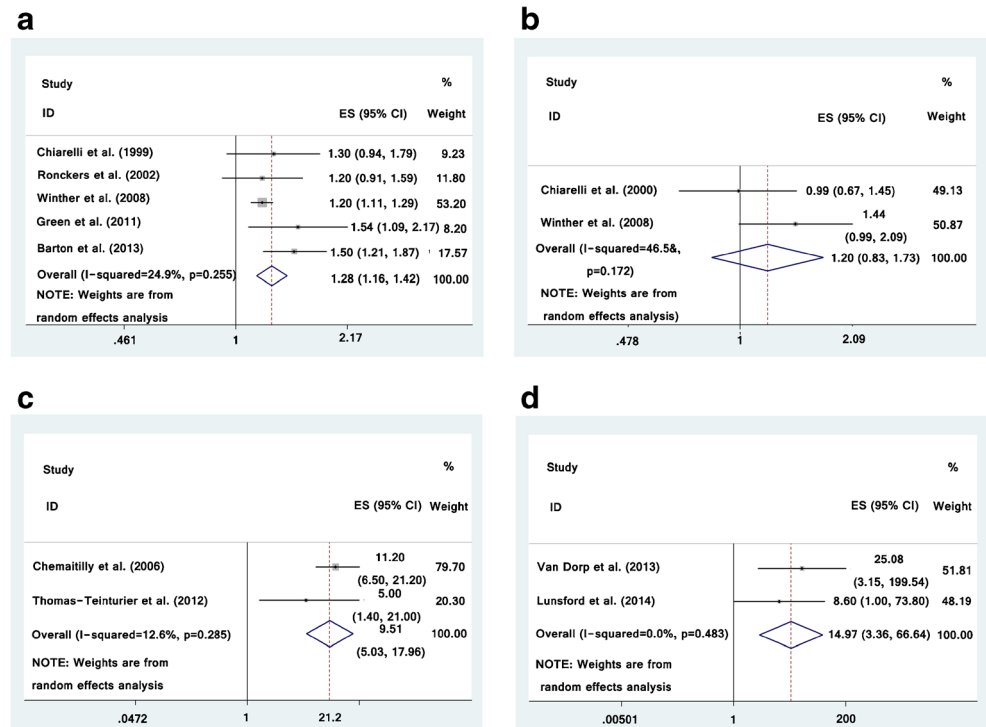
Abortion Two studies demonstrated the relationship between radiotherapy and spontaneous abortion [7, 12] and the study-specific RRs for spontaneous abortion range were from 0.99 to 1.44. The pooled RR (exposed to radiotherapy vs. non-exposed) for spontaneous abortion was 1.20 (95 % CI was 0.83–1.73) with significantly heterogeneity ($I^2=46.5\%$) (Fig. 2b).

AOF Two studies identified the relationship between radiotherapy and AOF [10, 16]. The pooled RR (exposed to

Table 1 Characteristics of studies included in the systematic review and meta-analysis of radiotherapy and risk of reproductive health impairment

The first author's last name (year) [reference]	Study design	Country	Target population	Comparison group	Study sample size (exposed/unexposed)	Fertility factors	Radiation therapy methods	NOS score
Chiarelli (1999) [6]	Cohort	Canada	Childhood cancer survivors	Childhood cancer survivors without radiation therapy	225/494	Infertility	Abd-pelvic radiation	7
Chiarelli (2000) [7]	Cohort	Canada	Childhood cancer survivors	Childhood cancer survivors without radiation therapy	70/165	Congenital anomaly, spontaneous abortion, low birth weight, stillbirth or neonatal death	Abd-pelvic radiation	9
Green (2002) [8]	Cohort	United States	Childhood cancer survivors	Childhood cancer survivors without radiation therapy	232/1937	Stillbirth or neonatal death	Ovarian radiation	7
Ronekers (2002) [9]	Cohort	Netherlands	Childhood cancer survivors	Nonexposed subjects	1178/1057	Infertility	NRI	9
Chemaitilly (2006) [10]	Cohort	United States	Childhood cancer survivors	Childhood cancer survivors without radiation therapy	2110/961	Acute ovarian failure	Radiation therapy	7
Signorello (2006) [11]	Cohort	United States	Childhood cancer survivors	Childhood cancer survivors without radiation therapy	1116/622	Preterm birth, low birth weight	Uterus radiation	9
Winther (2008) [12]	Cohort	Denmark	Childhood cancer survivors	Childhood cancer survivors without radiation therapy	578/1082	Infertility, spontaneous abortion	Radiation therapy	8
Signorello (2010) [13]	Cohort	United States	Childhood cancer survivors	Childhood cancer survivors without radiation therapy	1713/1075	Stillbirth or neonatal death	Uterus and ovarian radiation	7
Green (2011) [14]	Cohort	United States	Childhood cancer survivors	Childhood cancer survivors without radiation therapy	258/1960	Infertility	Hypothalamic/pituitary radiation	7
Signorello (2012) [15]	Cohort	United States and Canada	Childhood cancer survivors	Childhood cancer survivors without radiation therapy	1020/607	Congenital anomaly	Ovarian radiation	8
Thomas-Teinturier (2012) [16]	Cohort	French	Childhood cancer survivors	Childhood cancer survivors with low dose radiation therapy	NA	Acute ovarian failure	Radiation therapy	7
Van Dorp (2013) [17]	Cohort	Netherlands	Childhood cancer survivors	Childhood cancer survivors without radiation therapy	12/164	Anti-müllerian hormone	Abdominal or total body radiation	9
Barton (2013) [18]	Cohort	United States	Childhood cancer survivors	Childhood cancer survivors without radiation therapy	2194/962	Infertility	Radiation therapy	7
Lunsford (2014) [4]	Cohort	United States	Childhood cancer survivors	Childhood cancer survivors without pelvic radiation	11/42	Anti-müllerian hormone	Pelvic radiation	7

Fig. 2 Forest plot for the meta-analysis of the association between radiotherapy during childhood and risk of infertility (a), abortion (b), AOF (c) and low AMH value (d)



radiotherapy vs. non-exposed) for AOF was 9.51 (95 % CI was 5.03–17.96) with low heterogeneity ($I^2=12.6\%$) (Fig. 2c).

Low AMH values Two studies described the influence of radiotherapy exposure in AMH concentration [4, 17]. The pooled RR (exposed to radiotherapy vs. non-exposed) for low level of AMH was 14.97 (95 % CI was 3.36–66.64) with low heterogeneity ($I^2=0.0\%$) (Fig. 2d).

Stillbirth Three studies described radiotherapy associated with stillbirth or neonatal death [7, 8, 13], the study-specific RRs for stillbirth or neonatal death range were from 1.16 to 1.59. The pooled RR (exposed to radiotherapy vs. non-exposed) for stillbirth or neonatal death was 1.19 (95 % CI was 1.02–1.39) with significantly heterogeneity ($I^2=0.0\%$) (Fig. 3a). There was no indication of publication bias with Begg’s test ($p=0.602$) and Egger’s test ($p=0.185$).

Low birth weight Two included studies identified radiotherapy associated with low birth weight [7, 11], the study-specific RRs for low birth weight range were from 2.06 to 2.79. The pooled RR (exposed to radiotherapy vs. non-exposed) for low birth weight was 2.22 (95 % CI was 1.55–3.17) with low heterogeneity ($I^2=0.0\%$) (Fig. 3b).

Congenital malformation Two included studies identified radiotherapy associated with congenital malformation [7, 15], the study-specific RRs for congenital anomaly range were from 0.84 to 0.87. The pooled RR (exposed to radiotherapy

vs. non-exposed) for congenital anomaly was 0.84 (95 % CI was 0.58–1.23) with low heterogeneity ($I^2=0.0\%$) (Fig. 3c).

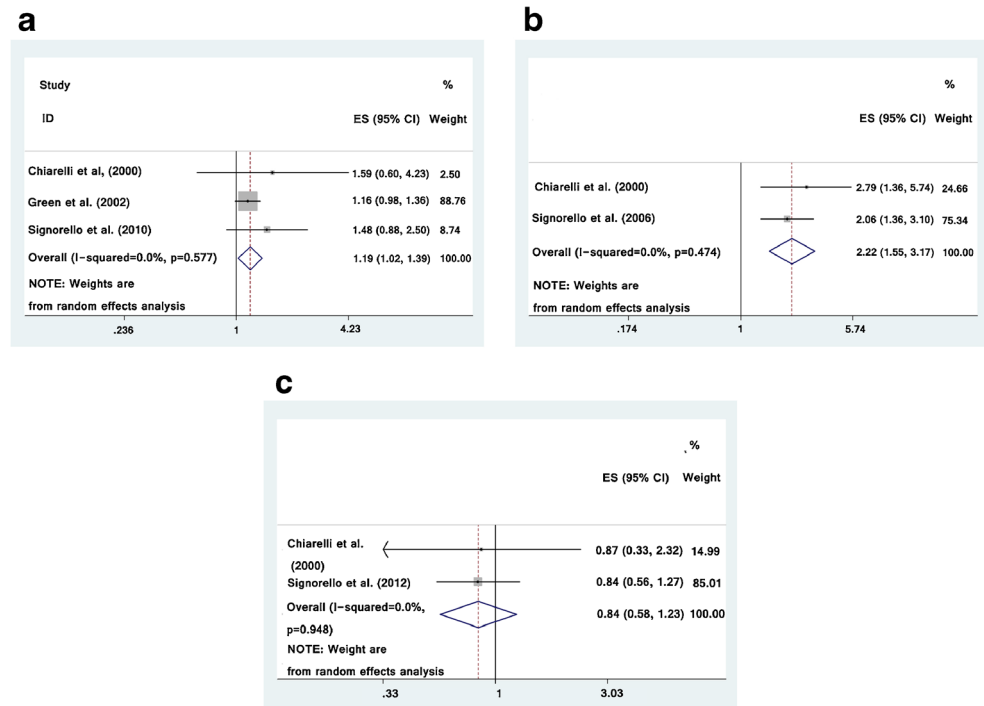
There was 1 study which described the effect of radiation therapy in preterm birth [19], the RR of preterm birth was 1.83 (95 % CI was 1.37–2.46). Because of the limitation of the studies, the meta-analysis for these factors could not be proceeded.

Discussion

Receiving radiotherapy during childhood may cause late effects of ionizing radiation and this was demonstrated by studies on childhood cancer survivors who received thoracic radiation, high rate of right ventricular dysfunction and restrictive lung disease [20]. Increasing attention has been paid to the radiation-induced damage to human health, especially to reproductive health. Radiation affecting ovarian and uterine functions has been linked to pregnancy complications including infertility, spontaneous abortion, acute ovarian failure, low birth weight and stillbirth. Also, sexual malfunction among female survivors of childhood cancers was partially related to cranial radiation treatment [21].

The most important issue for female reproductive health is the ability to successfully conceive a pregnancy and give birth to healthy children. To our knowledge, this is the first meta-analysis evaluating the effect of medical radiation on the reproductive capability and pregnancy outcomes of female childhood cancer survivors. We identified and reviewed 14

Fig. 3 Forest plot for the meta-analysis of the association between radiotherapy during childhood and risk of stillbirth (a), low birth weight (b) and congenital malformation (c) in offspring



studies with a total of >20,000 female childhood cancer survivors.

Reproductive capability Infertility is known as the impossibility of conceiving after unprotected intercourse. Approximately 8–12 % of couples with women at child-bearing age carry this condition [22]. It is reported that radiotherapy during childhood is associated with abnormal female reproductive capability which can be related with ovarian, endometrial or unexplained causes. In Xing and colleagues' follow up study, women who suffered from acute radiation sickness showed severe ovarian failure and uterine dysfunction [23]. Our meta-analysis suggests high frequency of infertility among women who received radiotherapy during childhood (Fig. 2a). However, there is no significant association between abortion and childhood radiation. Among the potential late effects of radiotherapy, evaluation of ovarian function remains to be one of the most important aspects of the survivors' management. Childhood radiotherapy increases the risk of hypothalamus and pituitary gland damages and results in decreased pituitary gonadotropins subsequently leading to ovaries dysfunction [24]. Ovarian radiation results in loss of hormone production and infertility because the normal hormone level is critical for the ootid development and plays an essential role in the maturation of the primary follicle [25]. Our meta-analysis also demonstrated the significant association between AOF and radiotherapy during childhood (Fig. 2c). AOF is a potential impairment factor for female reproductive health, and radiation is known as a potent ovotoxicants capable of accelerating ovarian reserve depletion. AMH, a predictor of

menopause, is a sensitive indicator of the longitudinal decline of ovarian reserve. The diminished ovarian reserve was diagnosed when AMH value is less than 1 ng/mL [4]. We found that childhood radiation is associated with low level (ovarian reserve) of AMH value (Fig. 2d). The association of childhood radiotherapy and ovarian failure is only found in limited meta-analyses. Our study comprehensively assessed the significant association between radiotherapy and ovarian dysfunction among female childhood cancer survivors.

Pregnancy outcomes Previous studies on the effects of childhood radiation in stillbirth, low birth weight and congenital malformation were inconsistent. In this study, we employed meta-analysis to comprehensively assess the association between female childhood radiotherapy and pregnancy outcomes. The association between childhood radiation and stillbirth, as well as low birth weight has been previously described [26]. From Signorello and colleagues' analysis [13], radiation-induced toxicity to the uterus was the main cause of stillbirth. The underlying mechanism by which the radiation was most likely leading to low birth weight is the radiation induced somatic damage to the women's abdominopelvic structures such as uterine vascular insufficiency and fibrosis [7]. From our meta-analysis, we found an increased risk of stillbirth and low birth weight in offspring of women who received radiotherapy during childhood. In the meantime, interestingly, we found the pooled RR for congenital anomaly on childhood radiotherapy was 0.84. This indicates that childhood radiotherapy may not be associated with increased risk of congenital anomaly. Findings of our study are coterminous

with Nori Nakamura's study, which demonstrated that no increased risk of malformation was observed in the offspring of the childhood cancer survivors [27].

Limitation

Several limitations of this meta-analysis should be noted. First, all published studies and papers were written in English. Some related published or unpublished studies that meet the inclusion criteria were missed, because edited in other languages. Second, the number of available references was limited. Third, there were insufficient data to allow subgroup analysis, most of the studies selected in our meta-analysis failed to provide the dose degree of radiation. Therefore, we were unable to conduct a dose–response analysis to assess the association between radiotherapy and female reproductive health. More studies about radiotherapy and reproductive health among females survived from childhood cancer should also be considered in the future.

Conclusion

The female reproductive health is one of great significance for familial and social harmony. It is predicted that girls who accepted radiotherapy treatment are at high risk of ovarian failure, which results in the increase of infertility, incidence of stillbirth and low birth weight among offspring. We found that childhood radiation is not a significant risk factor for abortion or congenital malformation of the offspring. Whether the doses of radiation, time post radiation, the individual differences or other unknown causes are also involved, still needs to be further explored. Our meta-analysis provided an important significance on counseling and management of the childbearing aged women who received radiotherapy during childhood, and called attention for the preservation of childrens who are suffering from unavoidable radiation impair during radiotherapy. Patients and physicians must be aware of the potential side effects which may affect the offspring.

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The quality of eligible studies was estimated by two authors (W.G and J.L), and the disagreements were discussed and resolved by the reviewer (Q.Y).

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