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Original Research

Perinatal complications in female survivors of cancer: a systematic review and meta-analysis

Anne-Lotte L.F. van der Kooi [a,b], Tom W. Kelsey [c], Marry M. van den Heuvel-Eibrink [b], Joop S.E. Laven [a], W. Hamish B. Wallace [d], Richard A. Anderson [e,*]

[a] *Department of Obstetrics and Gynecology, Erasmus MC – Sophia Children's Hospital, Rotterdam, the Netherlands*
[b] *Prinses Máxima Centrum for Pediatric Oncology, Utrecht, the Netherlands*
[c] *School of Computer Science, University of St. Andrews, North Haugh, St. Andrews, UK*
[d] *Department of Oncology and Haematology, Royal Hospital for Sick Children, Sciennes Road, Edinburgh Scotland, United Kingdom*
[e] *MRC Centre for Reproductive Health, University of Edinburgh, Edinburgh, UK*

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Congenital abnormalities

Abstract ***Background:*** Observational studies have suggested that perinatal outcomes are worse in offspring of cancer survivors. We conducted a systematic review and meta-analysis to examine the risks of perinatal complications in female cancer survivors diagnosed before the age of 40 years.

Methods: All published articles on pregnancy, perinatal or congenital risks in female cancer survivors were screened for eligibility. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines were followed.

Results: Twenty-two studies met the inclusion criteria. Meta-analysis indicates that offspring of cancer survivors are at increased risk of prematurity (relative risk [RR]: 1.56; 95% confidence interval [CI] 1.37–1.77) and low birth weight (RR 1.47; 95% CI 1.24–1.73) but not of being small for gestational age (RR 0.99; 95% CI 0.81–1.22). Cancer survivors have higher rates of elective (RR: 1.38; 95% CI 1.13–1.70) and emergency caesarean section (RR: 1.22; 95% CI 1.15–1.30) as well as assisted vaginal delivery (RR: 1.10; 95% CI 1.02–1.18) and are at increased risk of postpartum haemorrhage (RR: 1.18; 95% CI 1.02–1.36). The risk of congenital abnormalities also appears increased (RR 1.10; 95% CI 1.02–1.20), but this is likely to be an artefact of analysis. Although meta-analysis of the effects of radiotherapy was not possible for all outcomes, there was an increased risk of prematurity (RR 2.27; 95% CI 1.34–3.82) and consistent findings of low birth weight (RR 1.38–2.31). Risk of being small for gestational age was increased only after high uterine radiotherapy dosage.

* *Corresponding author*: MRC Centre for Reproductive Health, University of Edinburgh Edinburgh, UK.
E-mail address: Richard.anderson@ed.ac.uk (R.A. Anderson).

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Conclusion: The increased perinatal risks warrant a proactive approach from healthcare providers in both counselling and management of perinatal care for cancer survivors.

1. Introduction

Around 5% of all cancers are diagnosed before the age of 40 years [1], and survival rates after cancer in children and young adults are relatively high, with approximately 80% being alive 5 years after the diagnosis [2]. Building a family may be part of their future, and as societal changes have led women to delay childbirth, an increasing number of survivors have not started a family at the time of diagnosis. Future fertility prospects may be affected by the administered cancer treatment, and pregnancy chances are about a third lower in cancer survivors compared with the general population [3]. Nevertheless, many female survivors have the wish and the potential to become pregnant [4–7].

Several studies have evaluated complications during pregnancy and labour in female cancer survivors in comparison to siblings or the general population. Increased risks for preterm birth were reported in the US Childhood Cancer Survivors Study (CCSS) and the British Childhood Cancer Survivors Study (BCCSS) [8,9], as well as in other large populations, with survivors diagnosed in their reproductive life [10,11]. However, contrasting findings were observed for the risk of offspring being small for gestational age [8,11,12]. Despite being an important landmark in pregnancy planning for psychological reasons, less is known about the method of delivery in cancer survivors. Nonetheless, the largest studies showed decreased rates of spontaneous vaginal delivery and increased rates of caesarean section [9,12–14]. Some early studies suggested an increased relative risk (RR) of congenital abnormalities in the offspring of cancer survivors [15,16]. These findings have not been confirmed in more recent analyses [9,12,17,18]. Owing to the low prevalence of both cancer in children and young adults and of some pregnancy and labour complications, evaluation of these data benefits from large number of subjects being involved, giving increased statistical power. To synthesise the available data across studies, we performed a systematic review and meta-analysis.

2. Methods

This review and meta-analysis was registered in PROSPERO (CRD42017078007), and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses were followed [19].

The databases Embase, MEDLINE (via OvidSP), Web of Science, Cochrane and Google Scholar were used for the systematic search. Details of the full search strategy for each database are included in Appendix A (online only). In brief, we searched for articles reporting on any perinatal outcomes (maternal and foetal/neonatal) in survivors of any cancer until the age of 40 years. The search was limited to the following criteria: reported between 1990 and September 2018 and published in English. All titles and abstracts were reviewed to select potentially eligible studies by two independent reviewers (A.L.F.v.d.K. and T.W.K.). Full-text articles were retrieved to assess fulfilment of the selection criteria. Studies reporting on pregnancies and/or births of less than 50 cancer survivors and cohort studies that did not include a control group were excluded, as well as opinion articles or reviews. Cross-reference check of the retrieved studies was performed to identify additional studies that were overlooked during the initial search.

The critical appraisal skills programme (CASP, https://casp-uk.net/) provides tools for a structured approach to find evidence and appraise the evidence based on methodology and validity. The standardised checklist for cohort studies consists of 11 questions within three parts: 'Are the results of the study valid' (section A, focussing on bias and confounding), 'What are the results' (section B, on strength and precision) and 'Will the results help locally' (section C, on generalisability). This assessment was performed by three independent authors (A.L.F.v.d.K., T.W.K. and R.A.A.) and disagreements were discussed and resolved among them.

Outcome measures that were included were the following: low birth weight (<2500 g), preterm birth (<37 weeks gestation), small for gestational age (<10th percentile), spontaneous vaginal delivery, assisted vaginal delivery, elective caesarean section, emergency caesarean section, antepartum haemorrhage (as defined by the authors of included studies, including placenta praevia, placental abruption and other bleeding), postpartum haemorrhage and congenital abnormalities.

For all outcomes, incidence or prevalence numbers were extracted for both the cancer survivor group and the control group. In addition, incidence or prevalence numbers from survivors treated with abdominal radiotherapy were extracted or 'any radiotherapy' if no more details were available. Heterogeneity between the eligible studies was assessed using the I^2 statistic, with $I^2 > 80\%$ indicating high variation between included studies, I^2 between 50% and 80% indicating moderate variation and $I^2 < 50\%$ indicating sufficient similarity

between the studies to ensure that pooling was valid. When heterogeneity was considerable (i.e., $I^2 \geq 50\%$ and $p < 0.05$), pooled estimates based on the random effects model were presented. Otherwise, pooled fixed effects were presented. Meta-analysis was only performed if more than two studies were available for the meta-analysis. Funnel plots were created to evaluate the possibility of publication bias. This type of graph plots each study's precision against its result. In this way, studies with high precision are plotted near the average, and studies with lower precision are spread to the side in a funnel-shaped manner. Asymmetry of the resulting scatterplot can be a result of publication bias or other study heterogeneity and warrants further investigation. Summary measures of RR and 95% confidence intervals (95% CIs) were obtained using standard meta-analysis in the R package meta [20,21].

3. Results

After exclusion of duplicates, the search yielded 2,922 citations. After screening of titles, 239 remained of which 192 could be excluded based on abstract or full-text, while three other publications were identified from cross-reference checking. The remaining 50 studies were included for CASP scoring, in which ≥9 of 11 points were required for inclusion in the meta-analysis. Studies reporting on cohorts from the same region were examined for overlapping data, and in these cases, the oldest reports were excluded. A total of 22 studies were included for the meta-analysis [6,8–14,18,22–34]. The list of included and excluded studies and their assigned CASP scores can be found in Appendix B (online only).

All 22 included studies were retrospective cohort studies. Most studies (n = 15), especially the most recently reported, had obtained data by population registry linkage. One study was based on medical records [24], and six studies were based on questionnaire data [6,22,27,31–33].

While all studies included survivors of cancer, age at diagnosis varied. Eight studies had included only survivors of childhood cancer [8,9,28,29,31–34], the largest cohorts being the CCSS and the BCCSS, confined to survivors diagnosed before the age of 21 and 15 years, respectively [6,9]. Eight studies included adults until the age of approximately 40 years [10,22–27,30,35], and the remaining five studies included survivors diagnosed with cancer between 0 and 40 years [12–14,18,36]. Five studies reported on the risks after a specific cancer diagnosis: cervical cancer [22,27], Hodgkin's lymphoma [30] or breast cancer [10,23].

3.1. Outcomes

3.1.1. Prematurity

Fourteen studies reported the incidence of prematurity (gestational age less than 37 weeks) [8–13,22–27,30,31] For this outcome, in total, 17,495 cancer survivors were compared with 6,070,504 controls. The RR in the random effects model of a preterm delivery for cancer survivors was 1.56 (95% CI 1.37–1.77), with moderate to high heterogeneity ($I^2 = 82\%$, $p < 0.01$) (Fig. 2A). The funnel plot did not suggest publication bias (Supplementary Figure, online only). Prematurity in high-risk groups, e.g., after radiotherapy or (if available) after abdominal radiotherapy, was reported in eight of these studies. The random effects meta-analysis of the four studies which also provided incidence data showed an RR of 2.27 (95% CI 1.34–3.82) (Fig. 6A) [9,30,31,36]. Four studies reported only ratios but not the exact number, of which two showed similar effect sizes [8,35], one did not find an increased risk [13] and one found an increased risk in those treated with radiotherapy only but not in survivors treated with radiotherapy in combination with chemotherapy [25] (Appendix C, online only).

3.2. Low birth weight

Twelve of the studies reporting on prematurity also reported the incidence of low birth weight (<2.500 g), comparing in total 19,073 cancer survivors with 6,099,456 controls [8–13,22,24–27,31]. Meta-analysis showed a significantly higher risk of having a baby with a low birth weight in cancer survivors when compared with controls (RR 1.47; 95% CI 1.24–1.73). Owing to the high heterogeneity ($I^2 = 86\%$, $p < 0.01$), the random effects model was used (Fig. 2B). The funnel plot did not reveal publication bias (Supplementary Figure, online only). Low birth weight after high-risk treatment was reported in six studies [8,9,13,25,31,35], but only two studies reported incidence numbers, which prohibited meta-analysis (Appendix C, online only). RR ranged from 1.38 (95% CI 1.03–1.85) after any radiotherapy versus controls [8] to 2.31 (95% CI 1.50–3.55) after abdominal radiotherapy in comparison to survivors not treated with radiotherapy [9] (Appendix C, online only).

3.3. Small for gestational age

Six studies (comparing in total 12,236 cancer survivors with 5,887,753 controls) reported on the outcome of being small for gestational age, defined as a weight less than the 10th percentile for that gestational age in the reference population [8,10–12,31,36]. The risk of having a small-for-gestational-age baby was not statistically significantly different for cancer survivors compared with controls (RR 0.99; 95% CI 0.81–1.22) in the random effects model. There was high heterogeneity among the studies ($I^2 = 89\%$, $p < 0.01$) (Fig. 2C). The funnel plot did not reveal any significant publication bias (Supplementary Figure, online only). Two studies reported on the risk on being small for gestational age

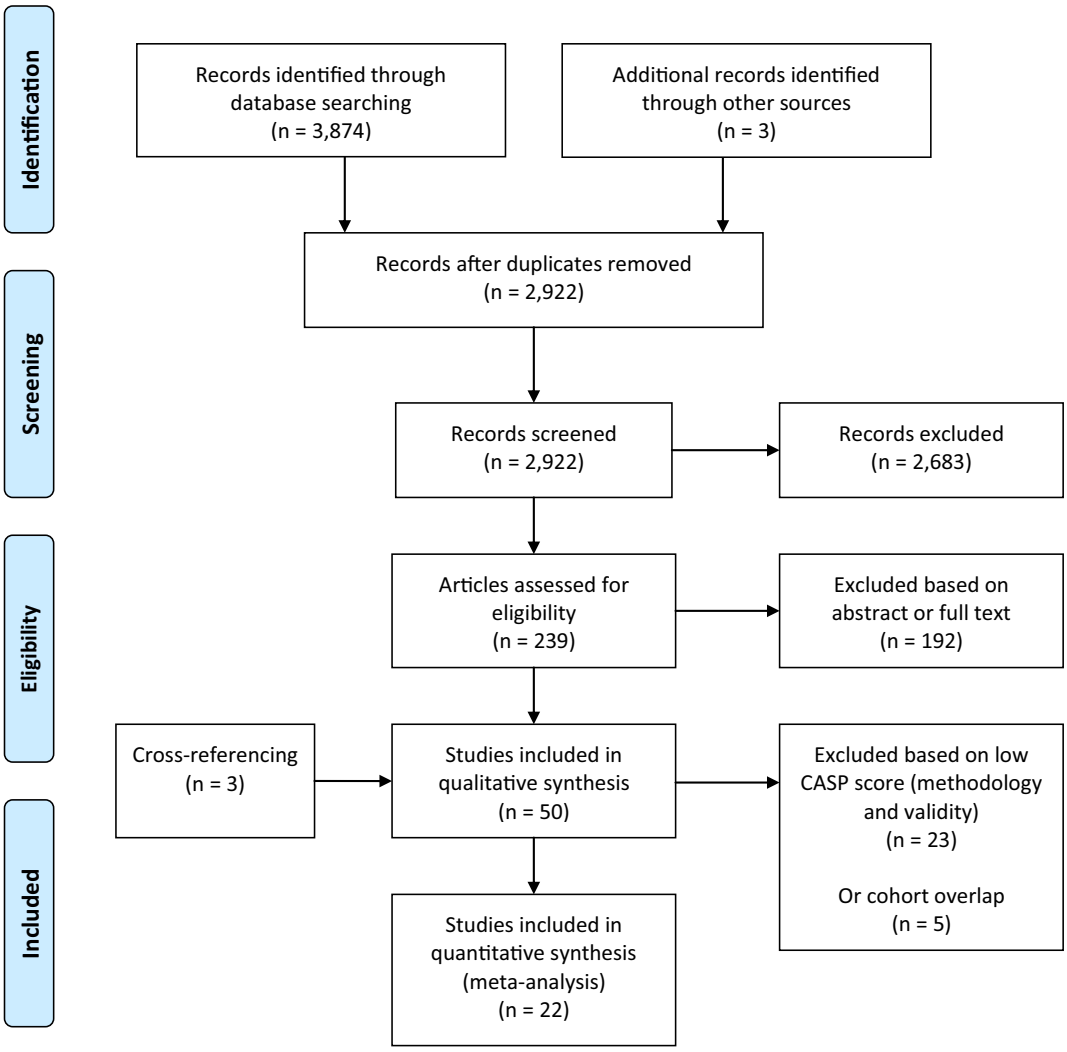


Fig. 1. PRISMA flowchart showing selection of studies. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

after radiotherapy: one did not detect any increased risk after radiotherapy alone or in combination with chemotherapy [35] and the other found an increased odds ratio (4.0, 95% CI 1.6–9.8) after a radiation dose of >500cGy to the uterus but no significant effect at lower doses [31] (Appendix C, online only).

3.4. Spontaneous vaginal delivery

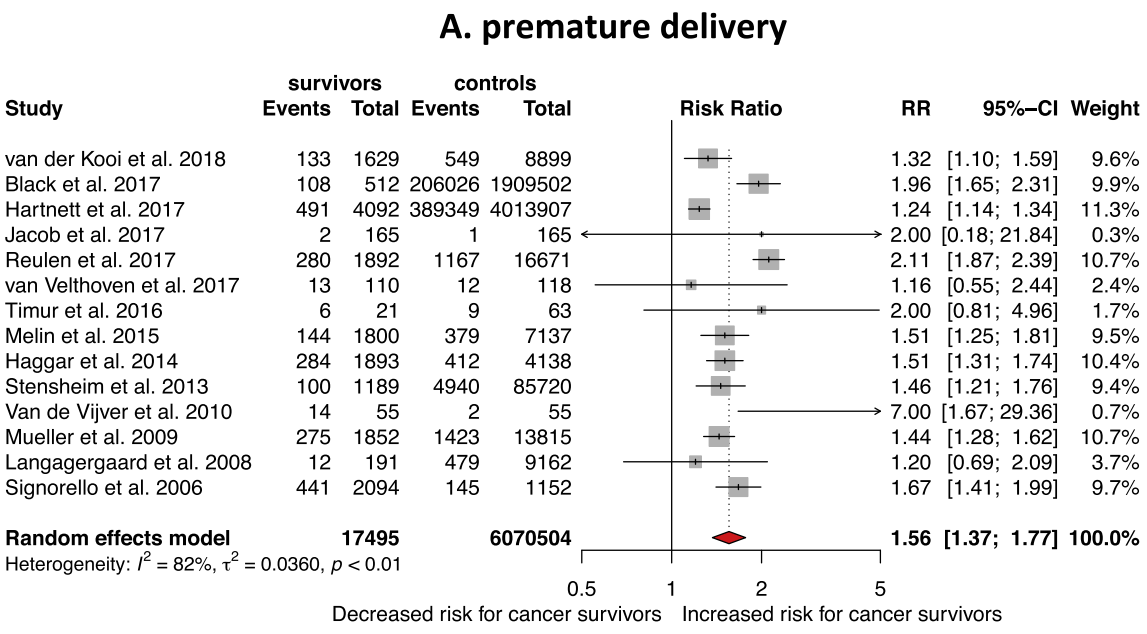
There were five studies that reported on the incidence of spontaneous vaginal deliveries, in total reporting on 3497 cancer survivors and 24,370 controls [12,13,23,24,28]. In the random effects model, cancer survivors were equally likely to have a spontaneous vaginal delivery: RR was 0.95 (95% CI 0.84–1.07) (Fig. 3A). Heterogeneity was high ($I^2 = 82\%$, $p < 0.01$), and the funnel plot showed a deviation, a study of breast cancer survivors, which showed that breast cancer survivors were more likely to have a spontaneous vaginal delivery (Supplementary Figure, online only) [23].

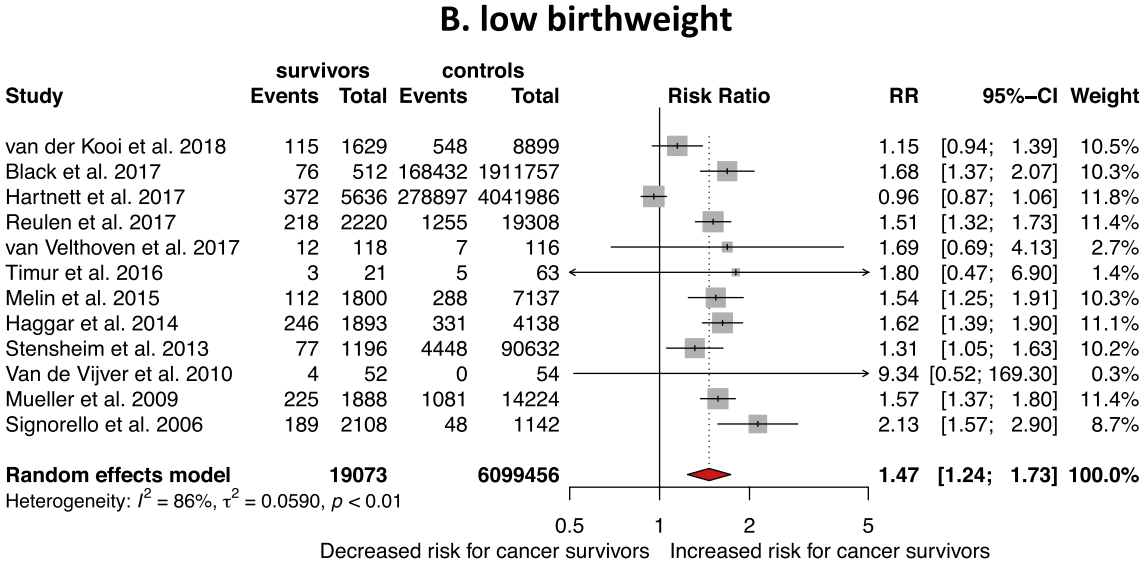
3.5. Assisted vaginal delivery

Six studies reported the incidence of assisted vaginal deliveries, in 10,710 survivors and 1,771,131 controls [12–14,23,27,28]. The RR of an assisted vaginal delivery was 1.10 (95% CI 1.02–1.18) (Fig. 3B). Heterogeneity was low to moderate ($I^2 = 49\%$, $p = 0.08$), and the funnel plot showed a deviation with overrepresentation of studies on the left side of the plot, presenting small studies not showing a significant increase in the risk (Supplementary Figure, online only). The risk of assisted vaginal delivery after abdominal radiation was only assessed in one substudy with six survivors [28], and one study reported no increased risk after treatment with (any) radiotherapy [13] (Appendix C, online only).

3.6. Emergency caesarean section

Five studies with, in total, 5471 survivors and 45,593 controls reported the incidence of emergency caesarean





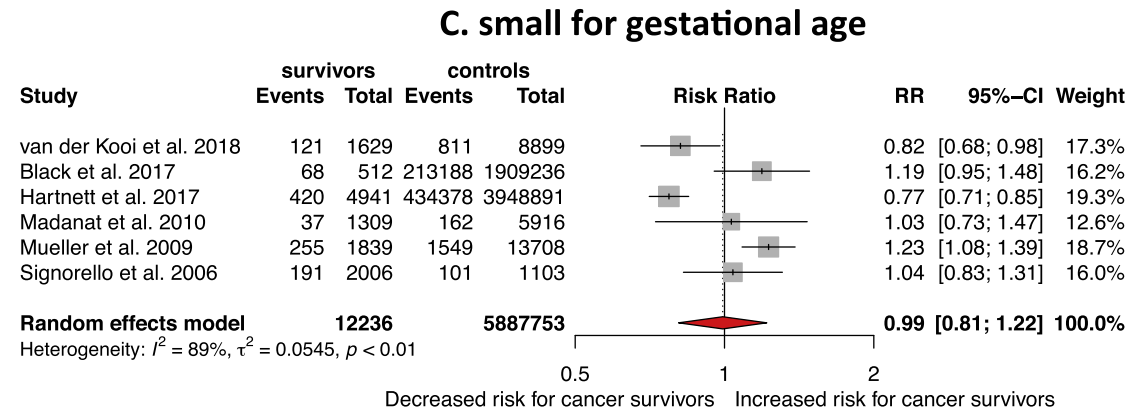


Fig. 2. Pooled relative risk (RR) of premature delivery (<37 weeks of gestation; A), low birth weight (<2500 g; B) and being small for gestational age (<10th percentile; C) of cancer survivors compared with controls. CI, confidence interval.

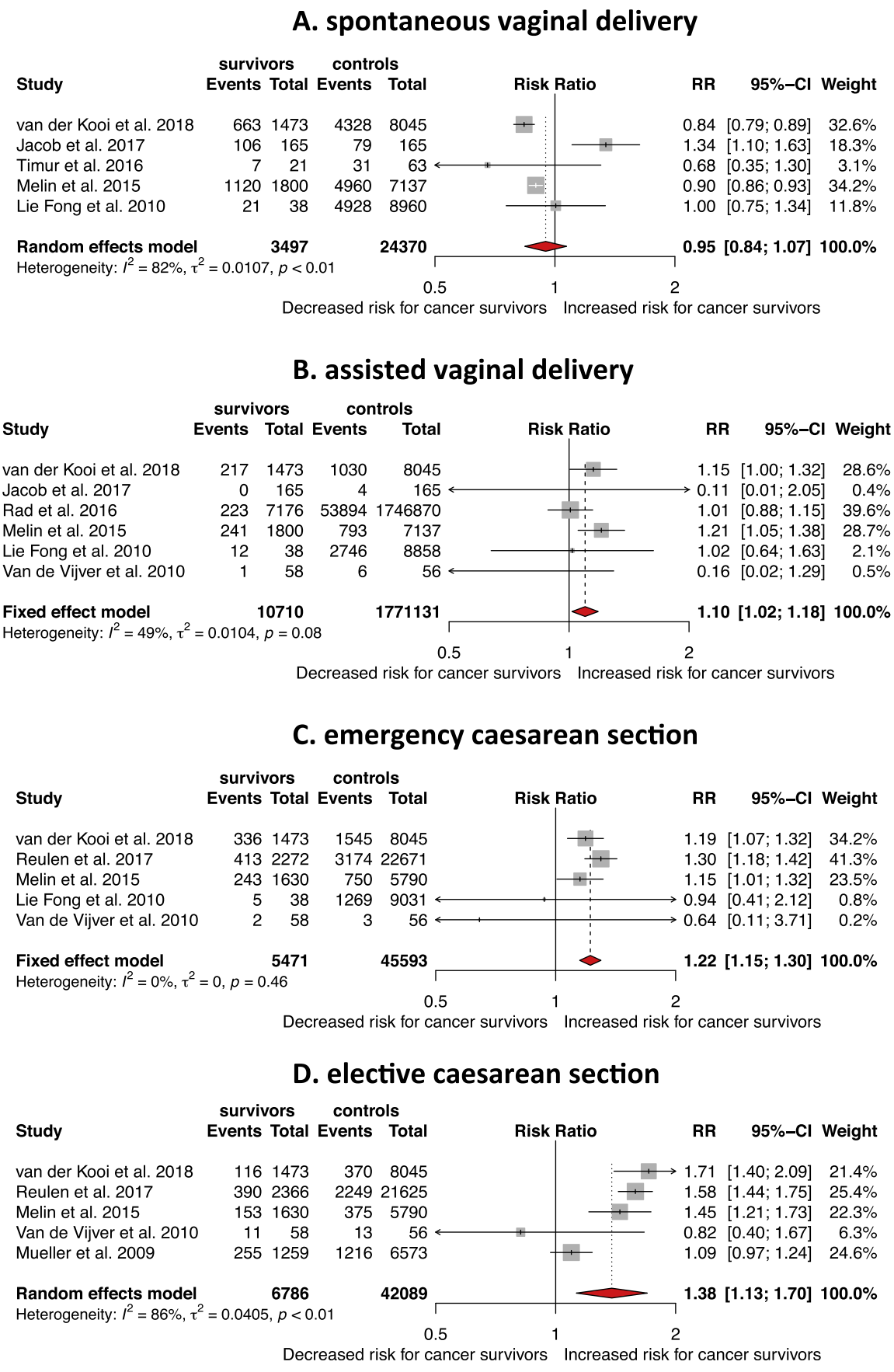


Fig. 3. Pooled relative risk (RR) of spontanuous vaginal delivery (A), assisted vaginal delivery (B), emergency caesarean section (C) and elective caesarean section (D) of cancer survivors compared with controls. CI, confidence interval.

sections in their cohorts [9,12,13,27,28]. The RR was 1.22 (95% CI 1.15–1.30) (Fig. 3C). There was no heterogeneity (I^2 = 0%, p = 0.46), and the funnel plot did not suggest publication bias (Supplementary Figure, online only). The two studies that reported on the risk on an emergency caesarean section after radiotherapy [13] or abdominal radiotherapy [9] showed no increased risk (Appendix C, online only).

3.7. Elective caesarean section

An elective caesarean section occurred more often in cancer survivors than in controls. Five studies reported on 6786 survivors and 42,089 controls [8,9,12,13,27]. The RR of elective caesarean section was 1.38 (95% CI 1.13–1.70). Heterogeneity was high (I^2 = 86%, p < 0.01); therefore, the random effects model was used (Fig. 3D). The funnel plot suggested no significant publication bias (Supplementary Figure, online only). The risk in survivors treated with radiotherapy to the abdomen was only reported in the BCCSS cohort, showing an increased risk of 1.46 (1.07–1.99). The risk from any radiotherapy was reported to be not elevated in two other studies [8,13] (Appendix C, online only).

3.8. Antepartum haemorrhage

Three studies reported the incidence of antepartum haemorrhage [12,14,25]. The definition of antepartum haemorrhage varied between the studies. Hagger *et al.* [25] defined it as occurrence of placental abruption, placenta praevia or other excessive bleeding during labour and delivery. In contrast, Rad *et al.* [14] and Van der Kooi *et al.* [12] based their outcome on the International Classification of Diseases (ICD) 10, where 'antepartum haemorrhage' does not include placenta praevia or abruptio placentae, as those outcomes were separately reported.

For this outcome, in total 10,505 cancer survivors were compared with 1,759,869 controls. The RR of antepartum haemorrhage for cancer survivors was not significant with an RR of 1.06 (95% CI 0.88–1.29), while there was no heterogeneity of this RR (I^2 = 0%, p = 0.86) (Fig. 4A). The funnel plot did not suggest publication bias

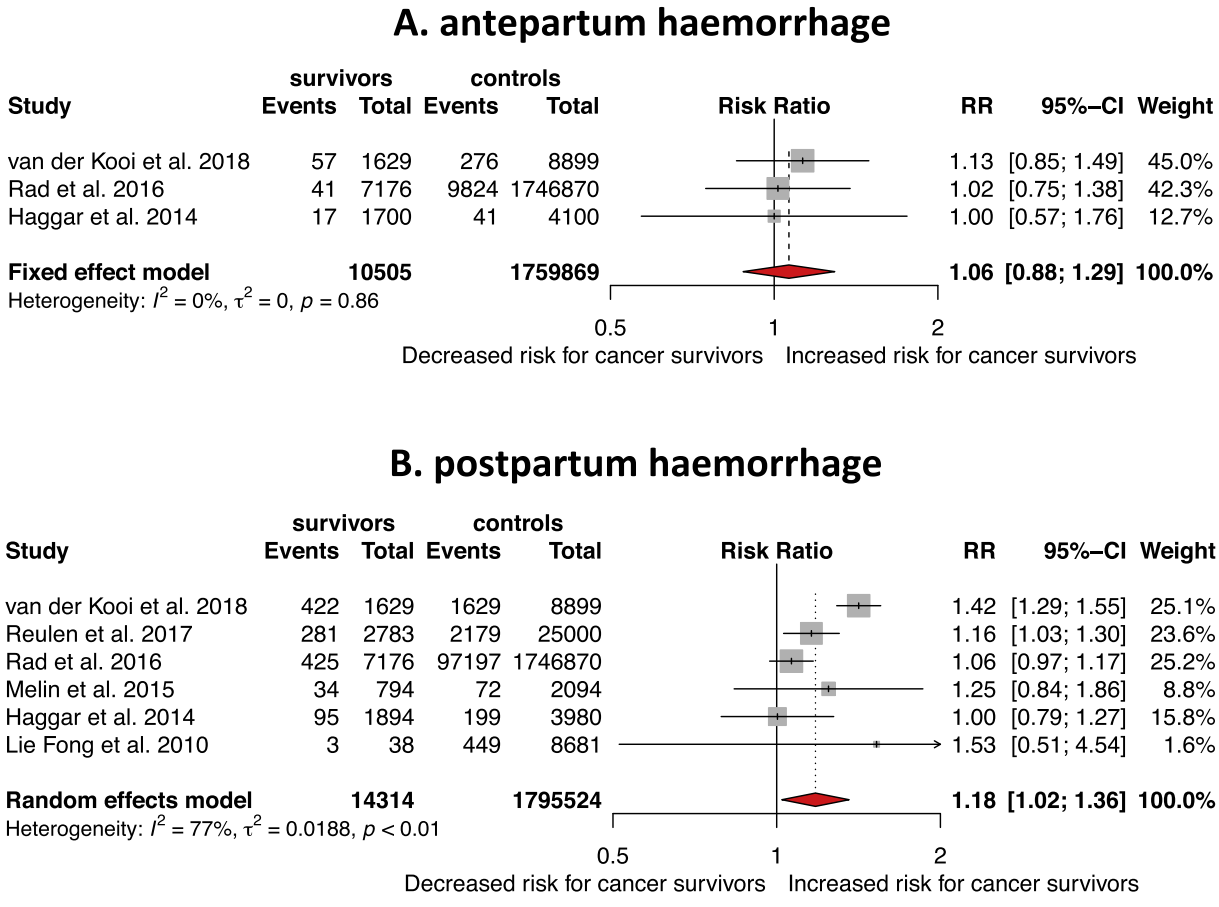


Fig. 4. Pooled relative risk (RR) of antepartum (A) and postpartum haemorrhage (B) of cancer survivors compared with controls. CI, confidence interval.

(Supplementary Figure, online only). None of the studies reported on the risk in a high-risk survivor population, e.g., after abdominal radiotherapy.

3.9. Postpartum haemorrhage

Postpartum haemorrhage was reported in six studies [9,12–14,25,28]. Three studies [9,12,14] based postpartum haemorrhage on O72 of the ICD 10 which defines postpartum haemorrhage as blood loss >500 mL after vaginal delivery or >1000 mL after caesarean delivery. In contrast, Melin *et al.* [13] and Lie Fong *et al.* [28] defined postpartum haemorrhage as >1000 mL while Hagger *et al.* [25] defined it as >500 mL.

The incidence of postpartum haemorrhage was compared between in total 14,314 cancer survivors and 1,795,524 controls. Cancer survivors were at increased risk of postpartum haemorrhage (RR: 1.18; 95% CI 1.02–1.36) (Fig. 4B). Heterogeneity across studies was substantial (I^2 = 77%, p < 0.01); therefore, the random effects model is presented; the funnel plot did not suggest publication bias (Supplementary Figure, online only). Adjustment for parity and maternal age had reduced the effect sizes in some of the original articles [9,13]. Postpartum haemorrhage after (abdominal) radiotherapy was reported in three studies; in one, it is described not to have an increased risk but without numerical data [13]; therefore, a meta-analysis was not feasible. One small study found an increased risk in the subgroup of six abdominally radiated survivors [28], and one analysis from the BCCSS found no increased risk after adjustment for confounding (RR 1.33; 95% CI 0.84–1.07) compared with survivors not treated with any radiotherapy [9] (Appendix C, online only).

3.10. Congenital abnormalities

Twelve studies reported the prevalence of congenital abnormalities in a total cohort of 23,099 cancer survivors and 254,264 controls [8,12,18,24–26,28–30,32–34]. The definition of congenital abnormalities ranged from 'coded as ICD diagnoses (ICD8 740–760)' to 'presence of any malformation'. All reported anomalies are pooled in this meta-analysis. The resulting pooled RR of congenital abnormalities appears to be higher in the cancer survivor group, with an RR of 1.10 (95% CI 1.02–2.20) (Fig. 5). There was moderate observed heterogeneity (I^2 = 45%, p = 0.05), and the funnel plot did not suggest publication bias (Supplementary Figure, online only). Five studies also reported incidence numbers of congenital abnormalities after high-risk radiation [18,28–30,32,33]. The fixed effect model showed a non-significant RR of 1.15 (95% CI 0.76–1.75) in keeping with the statistically non-significant reported risks or odds ratios in all the source articles (Appendix C, online only).

4. Discussion

4.1. Principal findings

This systematic review and meta-analysis summarises the evidence for risks in perinatal outcomes in female cancer survivors. Outcome measures investigated were low birth weight, preterm birth, being small for gestational age, mode of delivery, antepartum haemorrhage, postpartum haemorrhage and congenital abnormalities. Offspring of cancer survivors are at increased risk of prematurity and a low birth weight but do not face an

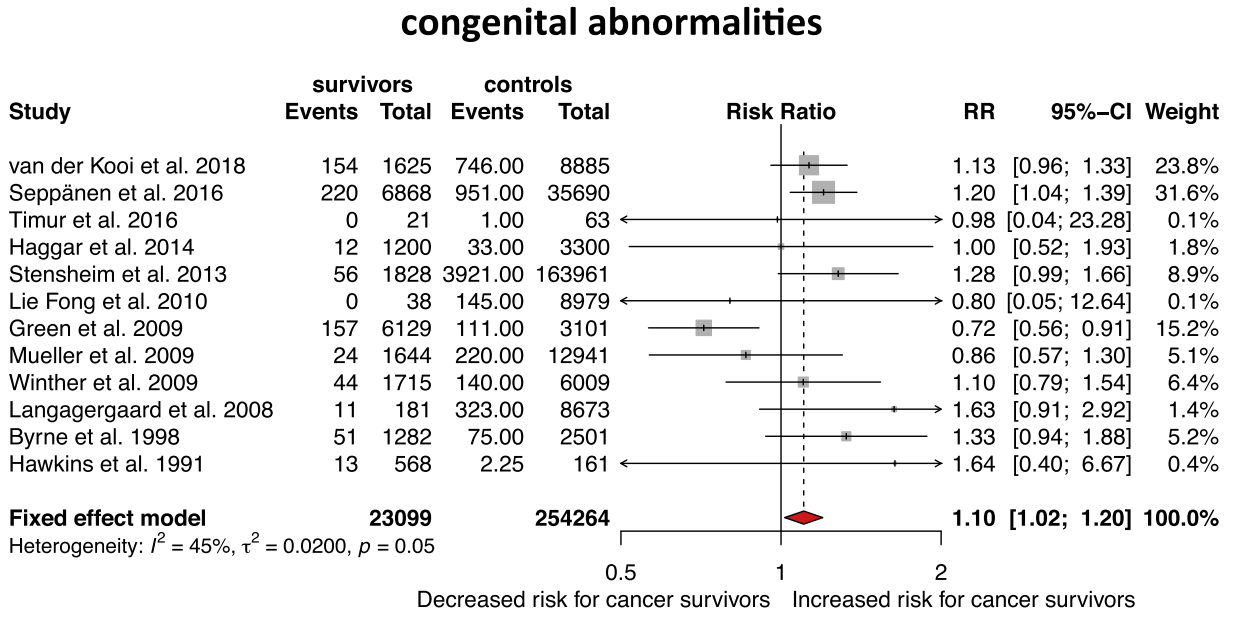


Fig. 5. Pooled relative risk (RR) of congenital abnormalities of cancer survivors compared with controls. CI, confidence interval.

increased risk of being small for gestational age. Cancer survivors are at increased risk of elective and emergency caesarean section as well as assisted vaginal delivery and postpartum but not antepartum haemorrhage.

Cancer treatment protocols can include chemotherapy and radiotherapy. Irradiation of the abdomen can damage the uterine vasculature and the muscular development of the uterus [39]. Endometrial function, possibly partly due to impaired blood supply, has also been postulated to be defective. Impairment of decidualisation could interfere with normal placentation and trophoblast invasion. In addition, impairment of uterine vasculature leading to impaired foetal placental blood flow may cause foetal growth restriction, and reduced uterine elasticity and volume could lead to preterm delivery or postpartum haemorrhage [39,40]. Smaller uterine volumes can also be the result of hormonal deficiency as a consequence of ovarian failure [40].

Although the risks of a premature birth and low birth weight were increased, the pooled estimates showed no evidence for increased risks of offspring being small for gestational age. Despite this reassurance, future research on very premature deliveries, such as before 32 weeks of gestation instead of the 37 weeks of gestation that is now most often evaluated, may be of value. Very premature birth may be of a greater consequence for future health and well-being [41], even if the offspring is not small for gestational age. One study reported the risk of being small for gestational age to be increased only after a high radiation dose [31]. The effect of radiation dose to the uterus has not been sufficiently examined to review, but it is likely that a distinction between higher and lower dosages of radiotherapy will reveal an increased risk currently obscured by pooling all dosages.

There was a markedly increased risk (38%) in elective caesarean section, although one study showed that this risk may have reduced in more recent years [12]. There was also an increased risk of an emergency caesarean section (by 22%) and the need for assistance during a vaginal delivery (by 10%). These increased risks may be the reflection of an increased awareness and proactive management of women treated for cancer, specifically, after treatment with abdominal radiotherapy. This analysis showed an increased risk of postpartum haemorrhage, indicating that a proactive approach to prevention may be warranted.

The meta-analysis indicates an increased risk of congenital abnormality. Congenital abnormalities could be a result of germ cell mutagenicity cause by chemotherapy or irradiation of the ovarian follicle pool. Most

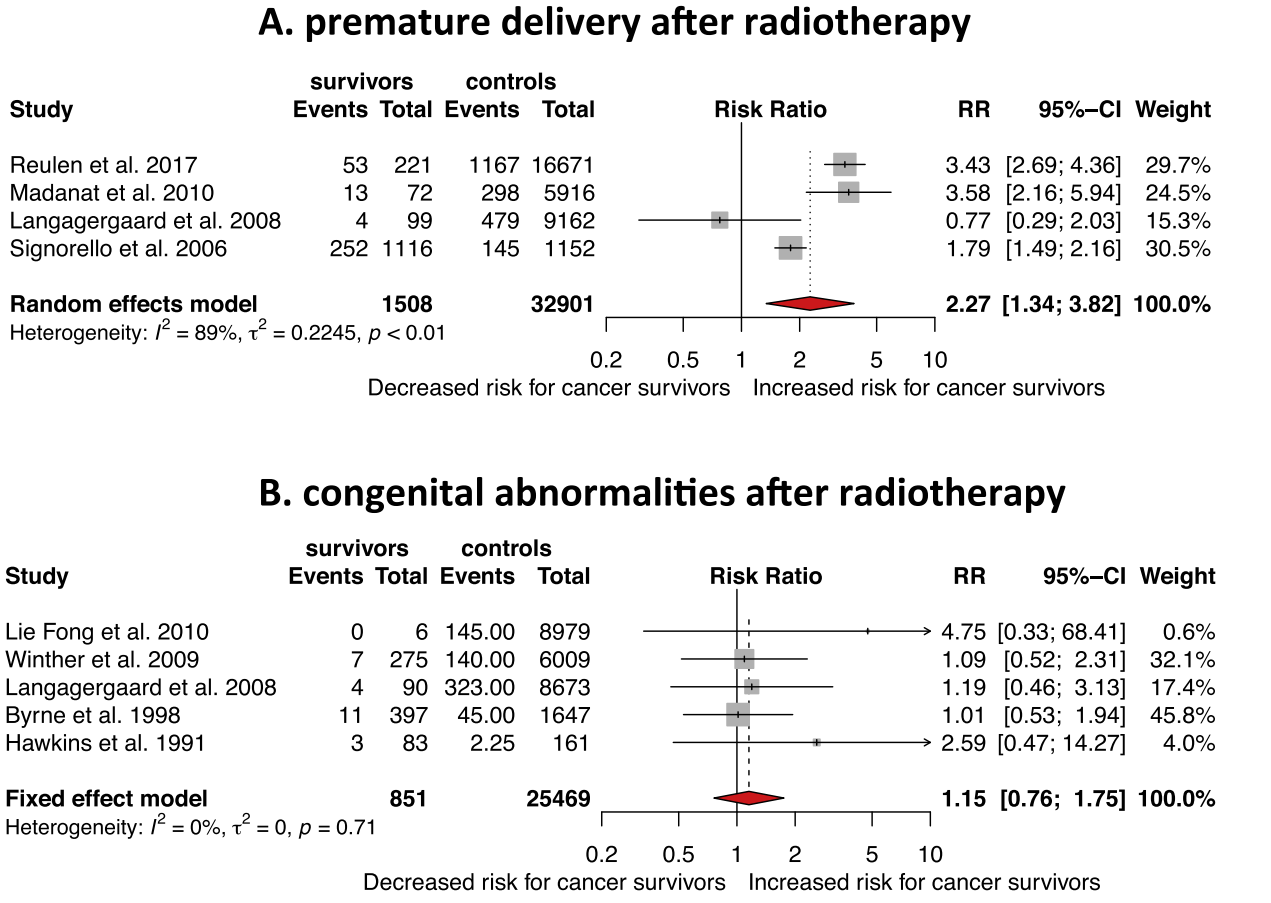


Fig. 6. Pooled relative risk (RR) of premature delivery and congenital abnormalities after treatment with radiotherapy (A and B, respectively) of cancer survivors compared with controls. CI, confidence interval.

evidence on radiation and chemical induced mutations is based on germ cells of mice [42]. In humans, however, long-term follow-up studies of the offspring of Japanese atomic bomb survivors did not indicate an increased risk of congenital abnormalities as a result of parental radiation exposure [43,44]. The apparent increased risk of congenital abnormalities is likely to be an example of Simpson's paradox, a statistical phenomenon in which certain effects observed in different groups or cohorts disappear or reverse when the groups are combined. In such cases, there is often an unidentified confounding variable introduced either by the recruitment of subjects, by the analysis for studies forming the pool, or by the analysis of pooled results [37,38]. In the case of congenital abnormalities, the definition varies greatly—with large fluctuations in prevalence rates ranging from 1.4% [8] to 9.5% [12]. In the separate studies, only one of the 12 studies reporting on congenital abnormalities reported a higher prevalence in cancer survivors [18]. In that study, the unadjusted prevalence ratio was 1.21 (95% CI 1.03–1.40), but after adjustment for maternal age at birth of child, parity, sex of child and birth decade of child, the adjusted prevalence ratio was 1.07 (95% CI 0.91–1.25). This study accounted for 31.6% of weight in the meta-analysis. The apparent increased effect is, therefore, likely to be biased (or paradoxical), introduced by a heterogeneous definition of congenital abnormalities resulting in large variation in prevalence rates and the absence of adjustment for possible confounders such as maternal age or genetic predisposition/hereditary disease.

4.2. Strengths and limitations

This systematic review offers an inclusive overview of relevant publications and meta-analyses of eleven outcomes, which facilitate the interpretation of the summarised literature. A choice of relatively frequently evaluated outcomes was made: perinatal risks such as cardiomyopathy after treatment with anthracyclines [45], pregnancy-induced hypertension [9,46], diabetes mellitus or gravidarum [8,9,25] and others were, therefore, beyond the scope of this report. The main limitation is the heterogeneity within the meta-analyses, possibly a result of differences in the diagnostic criteria between the studies. Owing to the varied designs of the observational studies and lack of individual patient data, systematic adjustment for confounders was not possible, so an overestimation or underestimation of the RRs could have occurred. For congenital abnormalities, this is especially striking with a possible example of the Simpson's paradox as a result. In addition, there was no uniformity in sub-analysis of potential high-risk groups, such as women who had received radiotherapy to a field that included the uterus. Some studies reported risks after any radiotherapy, some after only radiotherapy and some after certain fields of radiotherapy. Nonetheless, these subgroups can be used as an approximation of high-risk treatment groups, and conclusions can be drawn where the observed risks are consistent.

The increasing numbers of cancer survivors as a result of better treatment protocols, and the increasing possibilities for fertility preservation, will in the future allow more survivors to consider a pregnancy. In the near future, more survivors who otherwise would not have had the possibility of reproduction, who are likely to have been exposed to higher doses of chemotherapy and radiotherapy than those whose fertility was not impaired, may become pregnant as a result of improving fertility preservation techniques such as vitrification of oocytes and ovarian tissue cryopreservation [47–49]. Possible effects of these fertility treatments have not been taken into account in these analyses, but the increase in number of pregnancies in this at-risk population underline the importance of surveillance and supervision of these pregnancies and deliveries.Fig. 1.

5. Conclusions

This meta-analysis confirms that survivors of cancer are at increased risk of postpartum haemorrhage, especially, after abdominal radiotherapy, and of increased rates of elective and emergency caesarean section. In addition, offspring of cancer survivors are at increased risk of prematurity and a low birth weight but not for being small for gestational age. Our results show a likely Simpson's paradox regarding the risk of congenital abnormalities, with the true effect being no increased risk. The magnitude of the perinatal risks warrants a proactive approach from healthcare providers.

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Conflict of interest statement

The authors have declared no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2019.01.104.

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