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

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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. PRISMA 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 (RR: 1.56; 95% 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: 1.40; 95% CI 1.31 – 1.49) 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 small for gestational age was increased only after high uterine radiotherapy dosage.

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

Key words: cancer survivors; perinatal risk; premature delivery; postpartum haemorrhage; low birth weight; congenital abnormalities

Introduction

Around 5% of all cancers are diagnosed before the age of 40 [1], and survival rates after cancer in children and young adults are relatively high with approximately 80% being alive five 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 as compared to 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 labor 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 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]. Due to the low prevalence of both cancer in children and young adults and of some pregnancy and labor complications, evaluation of these data benefits from large number of subjects being involved, giving increased statistical power. To synthesize the available data across studies, we performed a systematic review and meta-analysis.

Methods

This review and meta-analysis was registered in PROSPERO (CRD42017078007) and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 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). Briefly, we searched for articles reporting on any perinatal outcomes (maternal and fetal/neonatal) in survivors of any cancer until the age of 40. The search was limited to the following criteria: reported between 1990 – September 2018; published in English. All titles and abstracts were reviewed to select potentially eligible studies by two independent reviewers (ALFvdK and TWK). Full text papers were retrieved to assess fulfillment 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 papers 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 finding evidence and appraising the evidence based on methodology and validity. The standardized checklist for cohort studies consists of eleven questions within three parts: "Are the results of the study valid" (Section A, focusing on bias and confounding), "What are the results" (Section B, on strength and precision), and "Will the results help locally" (Section C, on generalizability). . This assessment was performed by three independent authors (ALFvdK, TWK, RAA) and disagreements were discussed and resolved among them.

Outcome measures that were included were: low birth weight (<2500g), 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

85 defined by the authors of included studies, including placenta praevia, placental abruption and other
86 bleeding), postpartum haemorrhage, and congenital abnormalities.

87 For all outcomes, incidence or prevalence numbers were extracted for both the cancer survivor
88 group and the control group. In addition, incidence or prevalence numbers from survivors treated with
89 abdominal radiotherapy were extracted, or 'any radiotherapy' if no more details were available.
90 Heterogeneity between the eligible studies was assessed using the I^2 statistic, with $I^2 > 80\%$ indicating
91 high variation between included studies, I^2 between 50% and 80% indicating moderate variation, and I^2
92 <50% indicating sufficient similarity between the studies to ensure that pooling was valid. When
93 heterogeneity was considerable (i.e., $I^2 \geq 50\%$ and $p<0.05$), pooled estimates based on the random
94 effects model were presented. Otherwise, pooled fixed effects were presented. Meta-analysis was only
95 performed if more than two studies were available for the meta-analysis. Funnel plots were created to
96 evaluate the possibility of publication bias. This type of graph are useful tools in meta-analyses and plots
97 each study's study precision on the y-axis and study result on the x-axis. In this way, studies with high
98 precision are plotted near the average and studies with lower precision are spread evenly on its side in a
99 funnel-shaped manner. Asymmetry of the resulting scatterplot can be a result of publication bias or
100 other study heterogeneity and warrants further investigation of its cause. Summary measures of
101 Relative Risk (RR) and 95% confidence intervals (95% CI) were obtained using standard meta-analysis in
102 the R package meta [20, 21].

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 3 other publications were identified from cross-reference checking. The remaining 50 studies were included for CASP scoring, in which ≥9 out 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 of age [10, 22-27, 30, 35] and the remaining five studies included survivors diagnosed with cancer between 0-40 years of age [12-14, 18, 36]. Five studies reported on the risks after a specific cancer diagnosis: cervical cancer [22, 27], Hodgkin lymphoma [30] or breast cancer [10, 23].

Outcomes

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 to 6,070,504 controls. The relative risk 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) (Figure 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 a relative risk of 2.27 (95% CI 1.34 – 3.82) (Figure 6A) [9, 30, 31, 36]. Four studies only reported ratios but not 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).

Low birth weight

Twelve studies of those reporting on prematurity also reported the incidence of low birth weight (<2.500g), comparing in total 19,073 cancer survivors to 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 to controls (RR 1.47 (95% CI 1.24 – 1.73). Due to the high heterogeneity (I^2 = 82%, p <0.01), the random effects model was employed (Figure 2B). The funnel plot did not reveal publication bias (supplementary Figure, online only). Low birth weight after high-risk treatment was reported in 6 studies [8, 9, 13, 25, 31, 35], but only 2 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).

Small for gestational age

Six studies (comparing in total 12,236 cancer survivors to 5,887,753 controls) reported on the outcome of small for gestational age, defined as a weight less than the 10^{th} 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 significant different for cancer survivors compared to controls (RR 0.99 (95% CI 0.81 – 1.22) in the random effects model. There was high heterogeneity amongst the studies (I^2 = 89%, p <0.01) (Figure 2C). The funnel plot did not reveal any significant publication bias (supplementary Figure, online only). Two studies reported on the risk on small for gestational age 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).

Spontaneous vaginal delivery

There were five studies that reported on the incidence of spontaneous vaginal deliveries, in total reporting on 3,497 cancer survivors and 24,370 controls [12, 13, 23, 24, 28]. In the random effect model, cancer survivors were equally likely to have a spontaneous vaginal delivery: relative risk was 0.95 (95% CI 0.84 – 1.07) (Figure 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].

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 relative risk of an assisted vaginal delivery was 1.10 (95% CI 1.02 – 1.18) (Figure 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 sub study with 6 survivors [28], and one study reported no increased risk after treatment with (any) radiotherapy [13] (Appendix C, online only).

Emergency caesarean section

Five studies with in total 5,471 survivors and 45,593 controls reported the incidence of emergency caesarean sections in their cohorts [9, 12, 13, 27, 28]. The relative risk was 1.22 (95% CI 1.15 – 1.30) (Figure 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).

Elective caesarean section

An elective caesarean section occurred more often in cancer survivors than in controls. Five studies reported on 6,786 survivors and 42,089 controls [8, 9, 12, 13, 27]. The relative risk 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 employed (Figure 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).

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 defined it as occurrence of placental abruption, placenta previa, or other excessive bleeding during labor and delivery [25]. In contrast, Rad et

al[14] and Van der Kooi et al[12] based their outcome on 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 to 1,759,869 controls. The relative risk 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) (Figure 4A). The funnel plot did not suggest publication bias (supplementary Figure, online only). None of the studies reported on the risk in a high-risk survivor population, e.g., after abdominal radiotherapy.

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 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) (Figure 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 papers [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 6 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 to survivors not treated with any radiotherapy [9] (Appendix C, online only).

222

223 **Congenital abnormalities**

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

Discussion

Principal findings

This systematic review and meta-analysis summarizes the evidence for risks in perinatal outcomes in female cancer survivors. Outcome measures investigated were low birth weight, preterm birth, 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 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 decidualization could interfere with normal placentation and trophoblast invasion. In addition, impairment of uterine vasculature leading to impaired fetal-placental blood flow may cause fetal 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 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 (40%) 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 pro-active management of women treated for cancer, specifically following 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 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 twelve 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.

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 summarized literature. A choice on relatively frequently evaluated outcomes was made, perinatal risks such as cardiomyopathy following 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 as a result of differences in types of diagnoses throughout the studies. Due to the varied designs of the observational studies and lack of individual patient data, systematic adjustment for confounders was not possible, so an over or underestimation of the relative risks 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, 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

306 fertility was not impaired, may become pregnant as a result of improving fertility preservation
307 techniques such as vitrification of oocytes and ovarian tissue cryopreservation [47-49]. Possible effects
308 of these fertility treatments have not been taken into account in these analyses, but the increase in
309 number of pregnancies in this at-risk population underline the importance of surveillance and
310 supervision of these pregnancies and deliveries.

Conclusions

This meta-analyses 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 health care providers.

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Figure legends:

Figure 1 PRISMA flowchart showing selection of studies.

Figure 2 Pooled relative risk (RR) of premature delivery (<37 weeks of gestation; A), low birth weight (<2,500 gram; B) and small for gestational age (<10^{th} percentile; C) of cancer survivors as compared to controls.

Figure 3 Pooled relative risk (RR) of mode of delivery of cancer survivors as compared to controls.

Figure 4 Pooled relative risk (RR) of antepartum (A) and postpartum haemorrhage (B) of cancer survivors as compared to controls.

Figure 5 Pooled relative risk (RR) of congenital abnormalities of cancer survivors as compared to controls.

Figure 6 Pooled relative risk (RR) of premature delivery and congenital abnormalities after treatment with radiotherapy (A and B, respectively) of cancer survivors as compared to controls.

Appendix D Funnel plots of assessed outcomes. Outer dashed lines indicate the triangular region within which 95% of studies are expected to lie in the absence of biases and heterogeneity. Vertical dotted lines depict the estimate of the random effects model and vertical dashed lines depict the estimate of the fixed effects model. RT = radiotherapy