Risks of adverse obstetric outcomes among female survivors of adolescent and young adult cancer in England (TYACSS): a population-based, retrospective cohort study

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See Comment page 953

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Summary

Background There are limited data on the risks of obstetric complications among survivors of adolescent and young adult cancer with most previous studies only reporting risks for all types of cancers combined. The aim of this study was to quantify deficits in birth rates and risks of obstetric complications for female survivors of 17 specific types of adolescent and young adult cancer.

Methods The Teenage and Young Adult Cancer Survivor Study (TYACSS)—a retrospective, population-based cohort of 200 945 5-year survivors of cancer diagnosed at age 15–39 years from England and Wales—was linked to the English Hospital Episode Statistics (HES) database from April 1, 1997, to March 31, 2022. The cohort included 17 different types of adolescent and young adult cancers. We ascertained 27 specific obstetric complications through HES among 96 947 women in the TYACSS cohort. Observed and expected numbers for births and obstetric complications were compared between the study cohort and the general population of England to identify survivors of adolescent and young adult cancer at a heighted risk of birth deficits and obstetric complications relative to the general population.

Findings Between April 1, 1997, and March 31, 2022, 21 437 births were observed among 13 886 female survivors of adolescent and young adult cancer from England, which was lower than expected (observed-to-expected ratio: 0·68, 95% CI 0·67–0·69). Other survivors of genitourinary, cervical, and breast cancer had under 50% of expected births. Focusing on more common (observed ≥100) obstetric complications that were at least moderately in excess (observed-to-expected ratio ≥1·25), survivors of cervical cancer were at risk of malpresentation of fetus, obstructed labour, amniotic fluid and membranes disorders, premature rupture of membranes, preterm birth, placental disorders including placenta praevia, and antepartum haemorrhage. Survivors of leukaemia were at risk of preterm delivery, obstructed labour, postpartum haemorrhage, and retained placenta. Survivors of all other specific cancers had no more than two obstetric complications that exceeded an observed-to-expected ratio of 1·25 or greater.

Interpretation Survivors of cervical cancer and leukaemia are at risk of several serious obstetric complications; therefore, any pregnancy should be considered high-risk and would benefit from obstetrician-led antenatal care. Despite observing deficits in birth rates across all 17 different types of adolescent and young adult cancer, we provide reassurance for almost all survivors of adolescent and young adult cancer concerning their risk of almost all obstetric complications. Our results provide evidence for the development of clinical guidelines relating to counselling and surveillance of obstetrical risk for female survivors of adolescent and young adult cancer.

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Introduction

The survival of adolescents and young adults (ie, aged 15–39 years) diagnosed with cancer has increased over the past four decades, with current 5-year survival rates exceeding 80%.[1] This increase has resulted in an expanding population of survivors of adolescent and young adult cancer at risk of long-term complications following treatment. Fertility and obstetric complications are concerns for many young female survivors of cancer.[2] Birth rates in female survivors of cancer are 30–40% lower than those in women without a history of cancer.[3–5] However, most of the evidence estimating birth deficits originates from studies of childhood survivors of cancer. Cancer treatment given in childhood could affect reproductive organs differently than treatment given during reproductive ages. Therefore, it is important to investigate birth rates of survivors of adolescent and young adult cancer separately.

Apart from fertility, previous cancer treatment could also affect pregnancy and labour among women who manage to conceive. Treatment of childhood cancer involving pelvic and abdominal irradiation, primarily for Wilms' tumour, has been associated with obstetric complications, particularly preterm birth and low birthweight offspring.[2]

Research in context

Evidence before this study

Fertility and obstetric complications are concerns for many young female survivors of cancer. Treatment of childhood cancer involving pelvic and abdominal irradiation—primarily for Wilms' tumour—has been associated with obstetric complications, particularly preterm birth and low birthweight infants. However, the risks of obstetric complications for survivors of adolescent and young adult (diagnosed age 15–39 years) cancer are less well characterised than that for survivors of childhood cancer (diagnosed 0–14 years). Some studies have suggested that survivors of adolescent and young adult cancer are also at risk of preterm birth and low birthweight infants, but to our knowledge, no study has ascertained the risks of a wide spectrum of obstetric complications by specific types of cancer. We searched PubMed for relevant articles relating to observational studies published up to Nov 1, 2023, using the search terms (pregnancy outcome) OR (obstetric complication) OR (birth rate) AND (cancer survivors), with no language restrictions. A more focused search using each specific adolescent and young adult cancer as keywords (eg, breast cancer) was also done. Additionally, we examined the bibliographies of selected references.

Added value of this study

This study, to our knowledge, is the largest ever cohort study to comprehensively investigate obstetric outcomes among female survivors of adolescent and young adult cancer. We characterise the risk of 27 different obstetric complications among women who survived one of 17 different specific types of adolescent and young adult cancer diagnosed between age 15 and 39 years. We report that survivors of cervical cancer are at risk for a whole spectrum of serious pregnancy and labour complications, including malpresentation of fetus, obstructed labour, disorders of the amniotic fluid and membranes, premature rupture of membranes, preterm birth, placental disorders including placenta praevia, and antepartum haemorrhage. Survivors of leukaemia are at risk of preterm delivery, obstructed labour, postpartum haemorrhage, and retained placenta. However, survivors of all other specific cancers had no more than two obstetric complications that exceeded an observed-to-expected ratio of 1·25.

Implications of all the available evidence

We provide important evidence to inform the development of clinical guidelines for the management of pregnancies among women with a history of adolescent and young adult cancer, particularly for survivors of cervical cancer and leukaemia, because current formal guidelines are absent. However, our results also provide reassurance for other female survivors of adolescent and young adult cancers concerning their risk of almost all obstetric complications.

However, the risks of obstetric complications for survivors of adolescent and young adult cancer are less well characterised than the risks for survivors of childhood cancer.[6–12] Some studies have suggested that survivors of adolescent and young adult cancer are also at risk of preterm birth and low birthweight offspring,[2,7,8,11–14] but to our knowledge, no study has ascertained the risks of a wide spectrum of obstetric complications by specific types of adolescent and young adult cancer.

In this largest ever study of nearly 100 000 women who survived a cancer diagnosed at age 15–39 years, we included more than four times the number of births compared with the next largest comparable study.[12] This dataset allowed us to investigate among survivors of each specific type of cancer a wide spectrum of obstetric complications that have not been previously explored. The principal aims of this study were to investigate among female survivors of adolescent and young adult cancer the observed birth rate versus that expected from the general population, and to identify and quantify any excess risks of specific obstetric complications by specific cancer type.

Methods

Study design and participants

The Teenage and Young Adult Cancer Survivor Study (TYACSS) is a large-scale, retrospective, population-based cohort study of 200 945 5-year survivors of cancer diagnosed at age 15–39 years between 1971–2006 in England and Wales. The cohort was based on cancer registrations obtained through the Office for National Statistics (ONS) and the Welsh Cancer Registry and electronically linked by National Health Service-England (NHS-England) to National Death Registration. When the TYACSS cohort was established, the most accurate and complete source of cancer ascertainment for England and Wales was the ONS. All cancer registrations in England are sent to ONS centrally. The Welsh Cancer Intelligence and Surveillance Unit (WCIU) have responsibility for the sub-cohort of cancers registered in Wales that is also sent to ONS. Using these two sources rather than contacting individual cancer registration sources independently ensured efficient utilisation of resources and that the ascertainment of cancers was as complete as possible for England and Wales. Ethical approval was obtained via the National Research Ethics Service (21/LO/0133) and legal approval to process identifiable data without explicit patient consent being required from the Confidentiality Advisory Group (21/CAG/0078).

For the current study, birth and obstetric outcomes data for England were obtained through linking of the TYACSS cohort with Hospital Episode Statistics (HES) for England. HES is an electronic database warehouse managed by NHS-England that captures data relating to delivered patient care in England, including maternity services, which are recorded in the Maternity Services

Data Set of HES.[15] The purpose of HES is to ensure hospitals are reimbursed for delivered care, hence a high accuracy is essential, but it can be used for research purposes. HES has existed in various forms since the late 1980s, but 1997–98 was the first financial year in which a dataset was captured that offers a high level of data quality. Completely private hospitals do not submit data to HES and private maternity care, although available, is very rarely used. To our knowledge, information on sensitivity, specificity, and positive predicted value associated with maternity-related ICD-10 codes is not available. However, the HES Maternity Services Data Set captures most English births and has been shown to be of high quality.[16]

Procedures

All individuals diagnosed with a first primary malignant neoplasm, intracranial or intraspinal CNS tumour, or bladder tumour of any behaviour (malignant, benign, in situ, or uncertain) based on the International Classification of Diseases for Oncology, third edition (ICD-O-3) morphology and topography, were eligible for inclusion in the TYACSS cohort, except for individuals with non-melanoma skin cancer.[17] These first primary neoplasms were then grouped into 17 main cancer groups based on a specific classification scheme for adolescent and young adult tumours.[18] The group other genitourinary cancers included all genitourinary cancers not already classified as cervical, ovarian, bladder, or kidney cancer. Individuals had to have survived at least 5 years from their primary cancer diagnosis to be included in the study cohort. Individuals in the TYACSS cohort, including 96 947 female survivors of adolescent and young adult cancer (appendix p 1), were linked to HES admission records from April 1, 1997, to March 31, 2022. The key identifiers for the linkage were: unique NHS number, date of birth, and postcode. Both the TYACSS and HES are population based, thereby minimising potential selection bias. The size of the cohort was determined by the number of eligible female survivors of adolescent and young adult cancer in England and Wales and hence this national population-based cohort provides the maximum amount of statistical power that is practically achievable in this setting. A birth was recorded when an individual had at least one HES maternity episode that related to care provided as part of a delivery by a consultant at an NHS hospital. A birth was defined as any live birth or stillbirth delivered after at least 24 weeks of gestation. Births that occurred before a cancer diagnosis or in the first 9 months following a cancer diagnosis were excluded. Obstetric complications were defined as any complication associated with a delivery admission that was recorded in the HES diagnosis field using the ICD-10 chapter O. Obstetric complications were subdivided into the following categories: (1) oedema, proteinuria, and hypertensive disorder in pregnancy, childbirth, and the puerperium (ICD10: O10–O16); (2) other maternal disorders predominantly related to pregnancy (ICD10: O20–O29); (3) maternal care related to the foetus and amniotic cavity and possible delivery problems (ICD10: O30–O48); (4) complications of labour and delivery (ICD10: O60–O75); and (5) complications predominantly related to the puerperium (ICD10: O85–O92). Obstetric complications were examined for first-time and subsequent births. Although we ascertained stillbirths in our cohort, we decided not to report risks by cancer type due to the rarity and sensitivity of this data item, thus avoiding any potential risk of disclosure of individual identities. Data on parity was based on the number of births per individual and its order as recorded in HES. A social deprivation score, divided into deciles based on the Index of Multiple Deprivation (IMD) ranking (rank 1 most deprived to rank 10 least deprived) as recorded in HES, was used in multivariable analyses.

See Online for appendix

Outcomes

The primary study objective was to identify survivors of specific types of cancer at heighted risk of (1) potential deficits in births and (2) obstetric complications by comparing the observed number of births affected to the expected number based on general population rates.

Statistical analysis

To evaluate potential deficits in births, we compared the observed number of births in the TYACSS cohort against the expected number of births based on English national general population birth rates. Person-years were accrued until the first occurrence of death, leaving the NHS (ie, embarkation), study end date (March 31, 2022), or until survivors were age 50 years. Tabulated data relating to the number of births recorded in HES for the general population of England, by financial years (1997–2021) and maternal age (age 20–24, 25–29, 30–34, 35–39, 40–44, or 45–49 years), were obtained from NHS Maternity Statistics.[19] These number of births were then divided by the female mid-year general population size of England for each corresponding year and maternal age stratum. The expected number of births was estimated by multiplying the estimated birth rate in the general population within each year and maternal age stratum by the person-years in each corresponding stratum in the TYACSS cohort and then summing across the strata. Absolute excess risks were calculated as the observed minus expected number of births divided by the person-years and then multiplied by 10 000. This measure provides the deficit in number of births compared with the general population, indirectly standardised for maternal age and year. An additional sensitivity analysis only including births that occurred after 5 years from cancer diagnosis was performed to explore any potential bias, because the original analysis included all births after 9 months from the original cancer diagnosis.

For obstetric complications, standardised incidence ratios (SIRs) were calculated as the observed over expected number of births affected by the relevant complication. The expected number was calculated by multiplying the number of births within the TYACSS cohort by the proportion of births affected within each year and maternal age stratum (5-year bands) in the overall HES population for England.[19] Only SIRs for complications that were relatively common (observed ≥100 for all cancer types combined; appendix p 2), at least moderately increased (SIR ≥1·25), and statistically significantly in excess were described.

To explore the effect of potential confounding by parity and social deprivation, we undertook an internal multivariable analysis using a log-binomial regression model with a population-averaged generalised estimating equation modification to account for correlations between births to the same individual. Using melanoma survivors as the reference category, relative risks were calculated with adjustment made for maternal age, HES year, parity (one, two, or three or more births), and social deprivation index. The rationale for selecting melanoma survivors as the reference group was based on the largest number of births being in this group. Multiple pregnancies were excluded (n=486) from this internal analysis because they were so few. Information on social deprivation index was missing for 105 (0·5%) of the 21 547 births contributing to this multivariable analysis. In our multivariable analyses we used a complete case approach to deal with missing data.

To ascertain whether there was any variation in the risk of obstetric outcomes by year of cancer diagnosis, we conducted a sensitivity analysis comparing SIRs of survivors diagnosed between 1971 and 1994 with SIRs of survivors diagnosed between 1995 and 2006.

The criterion for statistical significance was a two-sided p value less than 0·05. Stata (version 17.0) was used for all analyses.

Role of the funding source

The funders had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between April 1, 1997, and March 31, 2022, 21 437 births were observed in HES among 13 886 English female survivors of adolescent and young adult cancer during the 1 140 023 person-years of follow-up (median 11·9 years [IQR 7·7–15·7]; figure; appendix p 3). The observed-to-expected ratio for births in survivors was 0·68 (95% CI 0·67–0·69). Survivors of most types of cancer had fewer observed births than expected in the general population, except for survivors of bladder cancer (0·89, 0·78–1·01) and lung cancer (0·84, 0·70–1·01). Survivors of other genitourinary cancers (other than cervix, ovary, bladder or kidney) had the greatest birth deficit (0·35, 0·29–0·43), followed by cervical cancer (0·42, 0·40–0·44), breast cancer (0·49, 0·47–0·52), and leukaemia (0·53, 0·49–0·58). When including births that occurred after 5 years from cancer diagnosis, no appreciable differences in the observed-to-expected ratio were observed compared with our original analysis (ie, 9 months from diagnosis; appendix p 4). When evaluating the observed-to-expected ratio of births by year of cancer diagnosis, consistent increases in birth rates in women diagnosed more recently were seen for cervical cancer, ovarian cancer, Hodgkin lymphoma, and CNS tumours (appendix p 5), with no clear pattern of change seen in other diagnoses (appendix p 6). Particularly among women treated for cervical cancer there was a substantial increase in the birth rate (appendix p 5). In terms of absolute deficits in births, survivors of leukaemia had the largest deficit, followed by survivors of cervical cancer, survivors of other genitourinary tumours, and survivors of CNS tumours; appendix p 3).

For analyses relating to obstetric complications, 22 033 births among 14 051 female survivors were available (including Welsh individuals who gave birth in an English hospital; table 1). Survivors of cancer of the kidney, bladder, ovary, and CNS were at increased risks of having pre-existing hypertension that further complicated their pregnancy. Overall, survivors were not more likely to develop gestational hypertension compared with the general population, except for survivors of kidney cancer and ovary cancer (table 1).

Survivors of bladder cancer and cervical cancer were at excess risk of malpresentation of the foetus during labour compared with women in the general population (table 2). Survivors of cervical cancer were also at

	Observed	Expected	Observed-to-expected ratio (95% CI)	p value
Melanoma	5009	5289	0·95 (0·92–0·97)	<0·0001
Hodgkin lymphoma	2852	3626	0·79 (0·76–0·82)	<0·0001
Breast	2274	4598	0·49 (0·47–0·52)	<0·0001
Thyroid	2081	2408	0·86 (0·83–0·90)	<0·0001
CNS tumour	1957	3057	0·64 (0·61–0·67)	<0·0001
Cervical	1935	4649	0·42 (0·40–0·44)	<0·0001
Non-Hodgkin lymphoma	910	1258	0·72 (0·68–0·77)	<0·0001
Ovarian	817	1358	0·60 (0·56–0·64)	<0·0001
Soft-tissue sarcoma	768	994	0·77 (0·72–0·83)	<0·0001
Leukaemia	527	996	0·53 (0·49–0·58)	<0·0001
Gastrointestinal	490	776	0·63 (0·58–0·69)	<0·0001
Head and neck	465	551	0·84 (0·77–0·92)	<0·0001
Bone	419	536	0·78 (0·71–0·86)	<0·0001
Other	370	508	0·73 (0·66–0·81)	<0·0001
Bladder	224	252	0·89 (0·78–1·01)	0·080
Lung	115	137	0·84 (0·70–1·01)	0·060
Kidney	112	163	0·69 (0·57–0·83)	<0·0001
Other genitourinary	112	317	0·35 (0·29–0·43)	<0·0001
Overall	**21 437**	**31 471**	**0·68 (0·67–0·69)**	**<0·0001**

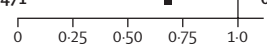

Figure: **Observed-to-expected ratio of births and corresponding 95% CI recorded in Hospital Episode Statistics by cancer type among female survivors of cancer from England**

	Total individuals (n)	Total births (n)	Pre-existing hypertension complicating pregnancy (ICD10: O10)		Gestational oedema and proteinuria without hypertension (ICD10: O12)		Gestational hypertension (ICD10: O13)		Pre-eclampsia (ICD10: O14)		Unspecified maternal hypertension (ICD10: O16)		Infections of genitourinary tract in pregnancy (ICD10: O23)		Diabetes arising in pregnancy (ICD10: O24)	
			Observed (%)	SIR (95% CI)	Observed (%)	SIR (95% CI)	Observed (%)	SIR (95% CI)	Observed (%)	SIR (95% CI)	Observed (%)	SIR (95% CI)	Observed (%)	SIR (95% CI)	Observed (%)	SIR (95% CI)
All survivors	14051	22033	123 (0·6%)	1·16 (0·97–1·38)	105 (0·5%)	1·16 (0·95–1·40)	503 (2·3%)	1·00 (0·92–1·10)	433 (2·0%)	1·03 (0·94–1·14)	380 (1·7%)	0·98 (0·88–1·08)	141 (0·6%)	0·95 (0·80–1·12)	670 (3·0%)	0·83 (0·77–0·90)
Melanoma	3242	5141	14 (0·3%)	0·56 (0·33–0·94)	22 (0·4%)	1·05 (0·69–1·59)	108 (2·1%)	0·93 (0·77–1·12)	92 (1·8%)	0·94 (0·77–1·16)	39 (1·7%)	0·88 (0·64–1·21)	31 (0·6%)	0·90 (0·63–1·28)	103 (2·0%)	0·54 (0·45–0·66)
Hodgkin lymphoma	1765	2929	11 (0·4%)	0·89 (0·49–1·61)	13 (0·4%)	1·09 (0·63–1·88)	66 (2·3%)	1·01 (0·80–1·29)	68 (2·3%)	1·24 (0·98–1·58)	23 (1·2%)	0·64 (0·43–0·97)	10 (0·3%)	0·49 (0·27–0·92)	108 (3·7%)	1·05 (0·87–1·26)
Breast	1693	2299	11 (0·5%)	0·78 (0·43–1·41)	8 (0·3%)	0·81 (0·40–1·62)	55 (2·4%)	1·00 (0·77–1·30)	51 (2·2%)	1·12 (0·85–1·47)	89 (1·7%)	0·98 (0·79–1·20)	12 (0·5%)	0·80 (0·45–1·40)	72 (3·1%)	0·83 (0·66–1·04)
Thyroid	1326	2146	15 (0·7%)	1·44 (0·87–2·38)	11 (0·5%)	1·25 (0·69–2·25)	52 (2·4%)	1·06 (0·81–1·40)	46 (2·1%)	1·13 (0·84–1·50)	42 (2·0%)	1·16 (0·86–1·57)	13 (0·6%)	0·90 (0·52–1·55)	75 (3·5%)	0·92 (0·74–1·16)
CNS tumour	1372	2074	19 (0·9%)	2·01 (1·28–3·15)	13 (0·6%)	1·52 (0·88–2·61)	52 (2·5%)	1·11 (0·84–1·45)	35 (1·7%)	0·89 (0·64–1·24)	41 (1·4%)	0·82 (0·61–1·12)	19 (0·9%)	1·34 (0·86–2·11)	81 (3·9%)	1·09 (0·88–1·36)
Cervical	1282	1972	8 (0·4%)	0·82 (0·41–1·64)	9 (0·5%)	1·10 (0·57–2·11)	28 (1·4%)	0·63 (0·43–0·91)	28 (1·4%)	0·75 (0·52–1·09)	16 (1·7%)	0·98 (0·60–1·61)	15 (0·8%)	1·16 (0·70–1·92)	45 (2·3%)	0·66 (0·49–0·88)
Non-Hodgkin lymphoma	567	937	6 (0·6%)	1·42 (0·64–3·15)	5 (0·5%)	1·32 (0·55–3·18)	25 (2·7%)	1·20 (0·81–1·78)	15 (1·6%)	0·85 (0·51–1·41)	41 (1·9%)	1·09 (0·80–1·48)	6 (0·6%)	0·94 (0·42–2·09)	22 (2·3%)	0·65 (0·43–0·99)
Ovarian	516	830	13 (1·6%)	3·64 (2·12–6·28)	3 (0·4%)	0·88 (0·28–2·73)	29 (3·5%)	1·57 (1·09–2·26)	21 (2·5%)	1·35 (0·88–2·07)	7 (1·4%)	0·80 (0·38–1·68)	7 (0·8%)	1·22 (0·58–2·55)	29 (3·5%)	1·06 (0·74–1·53)
Soft-tissue sarcoma	469	788	3 (0·4%)	0·84 (0·27–2·61)	3 (0·4%)	0·92 (0·30–2·85)	12 (1·5%)	0·68 (0·39–1·20)	14 (1·8%)	0·94 (0·56–1·59)	21 (2·7%)	1·53 (1·00–2·35)	6 (0·8%)	1·11 (0·50–2·47)	28 (3·6%)	1·00 (0·69–1·45)
Leukaemia	334	548	<3	0·42 (0·06–3·01)	<3	0·91 (0·23–3·64)	19 (3·5%)	1·54 (0·98–2·42)	16 (2·9%)	1·54 (0·94–2·51)	8 (1·5%)	0·88 (0·44–1·76)	4 (0·7%)	1·06 (0·40–2·82)	23 (4·2%)	1·10 (0·73–1·65)
Gastrointestinal	313	502	<3	0·40 (0·06–2·86)	4 (0·8%)	1·96 (0·74–5·22)	11 (2·2%)	0·97 (0·54–1·75)	8 (1·6%)	0·83 (0·42–1·67)	16 (1·9%)	1·10 (0·68–1·80)	4 (0·8%)	1·17 (0·44–3·13)	20 (4·0%)	1·02 (0·66–1·58)
Head and neck	299	478	<3	0·89 (0·22–3·56)	3 (0·6%)	1·52 (0·49–4·72)	13 (2·7%)	1·19 (0·69–2·05)	7 (1·5%)	0·77 (0·37–1·62)	5 (2·2%)	1·21 (0·50–2·90)	4 (0·8%)	1·22 (0·46–3·25)	14 (2·9%)	0·77 (0·46–1·31)
Bone	248	433	4 (0·9%)	2·10 (0·79–5·58)	4 (0·9%)	2·28 (0·86–6·08)	9 (2·1%)	0·93 (0·48–1·78)	10 (2·3%)	1·22 (0·66–2·27)	<3	0·98 (0·24–3·90)	5 (1·2%)	1·66 (0·69–3·99)	15 (3·5%)	0·89 (0·54–1·48)
Other	242	379	3 (0·8%)	1·63 (0·52–5·04)	3 (0·8%)	1·86 (0·60–5·76)	10 (2·6%)	1·12 (0·60–2·08)	9 (2·4%)	1·24 (0·65–2·38)	6 (1·3%)	0·74 (0·33–1·64)	<3	0·38 (0·05–2·73)	14 (3·7%)	1·06 (0·63–1·78)
Bladder	143	231	5 (2·2%)	4·26 (1·77–10·24)	<3	NA	5 (2·2%)	0·95 (0·39–2·27)	5 (2·2%)	1·13 (0·47–2·71)	8 (2·1%)	1·19 (0·59–2·38)	<3	0·63 (0·09–4·45)	9 (3·9%)	1·09 (0·57–2·10)
Lung	79	118	<3	NA	<3	NA	<3	0·37 (0·05–2·65)	<3	0·44 (0·06–3·15)	9 (2·1%)	1·24 (0·65–2·38)	<3	2·53 (0·63–10·12)	5 (4·2%)	1·07 (0·44–2·56)
Kidney	83	114	5 (4·4%)	8·76 (3·64–21·03)	<3	2·08 (0·29–14·78)	7 (6·1%)	2·71 (1·29–5·68)	5 (4·4%)	2·30 (0·96–5·52)	<3	0·97 (0·24–3·89)	<3	NA	<3	0·51 (0·13–2·06)
Other genitourinary	78	114	<3	3·79 (0·95–15·15)	<3	2·00 (0·28–14·21)	<3	0·37 (0·05–2·66)	<3	0·92 (0·23–3·69)	5 (4·4%)	2·38 (0·99–5·71)	<3	1·33 (0·19–9·43)	5 (4·4%)	1·32 (0·55–3·17)

Analysis includes Welsh individuals who gave birth in an English hospital. SIRs were considered moderately increased if 1·25 or higher. To prevent potential identification of individuals, any table cell counts with an observed number of less than three were reported as <3. NA indicates that the numbers observed were too few to be able to calculate SIR and corresponding 95% CIs. The other category includes unspecified malignant neoplasms, NEC; other specified neoplasms, NEC; extragonadal germ-cell tumours; carcinoma of other and ill-defined sites, NEC; skin carcinomas; paraganglioma and glomus tumours; adrenocortical carcinoma; other paediatric and embryonal tumours, NEC; and neuroblastoma. The other genitourinary category includes corpus uteri, vulva, other and unspecified female genital organs, uterus unspecified, Wilms' tumour, renal pelvis, uterine adnexa (other than ovary), placenta, other and unspecified urinary organs, and ureter. NEC=not elsewhere classified. SIR=standardised incidence ratio.

Table 1: **SIR of developing oedema, proteinuria, hypertensive disorder, or maternal disorders predominantly related to pregnancy during pregnancy, childbirth, and puerperium, in survivors by cancer type**

	Malpresentation of fetus (ICD10: O32)		Polyhydramnios (ICD10: O40)		Other disorders of amniotic fluid and membranes (ICD10: O41)		Premature rupture of membranes (ICD10: O42)		Placental disorders (ICD10: O43)		Placenta praevia (ICD10: O44)		Antepartum haemorrhage (ICD10: O46)	
	Observed (%)	SIR (95% CI)	Observed (%)	SIR (95% CI)	Observed (%)	SIR (95% CI)	Observed (%)	SIR (95% CI)	Observed (%)	SIR (95% CI)	Observed (%)	SIR (95% CI)	Observed (%)	SIR (95% CI)
All survivors	1316 (6·0%)	1·09 (1·03–1·15)	191 (0·9%)	1·06 (0·92–1·22)	343 (1·6%)	1·13 (1·01–1·25)	1861 (8·4%)	1·05 (1·01–1·10)	251 (1·1%)	1·02 (0·90–1·16)	186 (0·8%)	1·02 (0·88–1·17)	300 (1·4%)	1·03 (0·92–1·15)
Melanoma	305 (5·9%)	1·08 (0·96–1·21)	50 (1·0%)	1·18 (0·90–1·56)	74 (1·4%)	1·05 (0·83–1·31)	437 (8·5%)	1·05 (0·96–1·16)	68 (1·3%)	1·19 (0·94–1·51)	34 (0·7%)	0·79 (0·56–1·10)	65 (1·3%)	0·96 (0·75–1·22)
Hodgkin lymphoma	167 (5·7%)	1·07 (0·92–1·25)	22 (0·8%)	0·93 (0·61–1·42)	41 (1·4%)	1·00 (0·73–1·35)	229 (7·8%)	0·97 (0·85–1·10)	27 (0·9%)	0·82 (0·56–1·19)	13 (0·4%)	0·60 (0·35–1·03)	28 (1·0%)	0·72 (0·50–1·04)
Breast	130 (5·7%)	0·98 (0·82–1·16)	16 (0·7%)	0·83 (0·51–1·36)	34 (1·5%)	1·09 (0·78–1·53)	178 (7·7%)	1·00 (0·87–1·16)	22 (1·0%)	0·87 (0·58–1·33)	23 (1·0%)	0·98 (0·65–1·48)	28 (1·2%)	0·92 (0·64–1·34)
Thyroid	118 (5·5%)	1·00 (0·83–1·20)	25 (1·2%)	1·38 (0·94–2·05)	22 (1·0%)	0·74 (0·49–1·12)	167 (7·8%)	0·96 (0·83–1·12)	17 (0·8%)	0·71 (0·44–1·14)	22 (1·0%)	1·24 (0·81–1·88)	28 (1·3%)	0·98 (0·67–1·41)
CNS tumour	119 (5·7%)	1·06 (0·88–1·27)	21 (1·0%)	1·25 (0·82–1·92)	23 (1·1%)	0·80 (0·53–1·20)	167 (8·1%)	1·01 (0·86–1·17)	17 (0·8%)	0·73 (0·45–1·17)	13 (0·6%)	0·78 (0·46–1·35)	24 (1·2%)	0·87 (0·58–1·30)
Cervical	141 (7·2%)	1·31 (1·11–1·54)	12 (0·6%)	0·79 (0·45–1·39)	66 (3·3%)	2·49 (1·96–3·18)	242 (12·3%)	1·57 (1·38–1·78)	33 (1·7%)	1·53 (1·09–2·15)	27 (1·4%)	1·60 (1·09–2·33)	37 (1·9%)	1·45 (1·05–2·00)
Non-Hodgkin lymphoma	57 (6·1%)	1·14 (0·88–1·47)	10 (1·1%)	1·32 (0·71–2·45)	14 (1·5%)	1·08 (0·64–1·82)	62 (6·6%)	0·81 (0·63–1·04)	11 (1·2%)	1·05 (0·58–1·90)	12 (1·3%)	1·64 (0·93–2·88)	19 (2·0%)	1·53 (0·98–2·40)
Ovarian	44 (5·3%)	1·00 (0·75–1·35)	<3	0·32 (0·08–1·27)	17 (2·0%)	1·47 (0·91–2·36)	76 (9·2%)	1·15 (0·92–1·44)	5 (0·6%)	0·54 (0·22–1·29)	10 (1·2%)	1·58 (0·85–2·94)	14 (1·7%)	1·30 (0·77–2·19)
Soft-tissue sarcoma	42 (5·3%)	0·99 (0·73–1·34)	6 (0·8%)	0·95 (0·43–2·11)	12 (1·5%)	1·09 (0·62–1·93)	66 (8·4%)	1·05 (0·82–1·33)	11 (1·4%)	1·24 (0·69–2·25)	5 (0·6%)	0·80 (0·33–1·93)	9 (1·1%)	0·86 (0·45–1·66)
Leukaemia	36 (6·6%)	1·21 (0·87–1·68)	3 (0·5%)	0·62 (0·20–1·93)	11 (2·0%)	1·39 (0·77–2·51)	49 (8·9%)	1·07 (0·81–1·42)	7 (1·3%)	1·12 (0·54–2·36)	5 (0·9%)	1·24 (0·52–2·99)	6 (1·1%)	0·79 (0·36–1·76)
Gastrointestinal	33 (6·6%)	1·19 (0·85–1·68)	8 (1·6%)	1·83 (0·91–3·66)	7 (1·4%)	0·99 (0·47–2·08)	45 (9·0%)	1·08 (0·81–1·45)	7 (1·4%)	1·25 (0·60–2·63)	5 (1·0%)	1·21 (0·50–2·91)	8 (1·6%)	1·17 (0·59–2·34)
Head and neck	28 (5·9%)	1·06 (0·73–1·53)	5 (1·0%)	1·23 (0·51–2·95)	5 (1·0%)	0·74 (0·31–1·78)	42 (8·8%)	1·09 (0·80–1·47)	4 (0·8%)	0·73 (0·28–1·95)	<3	0·52 (0·13–2·08)	11 (2·3%)	1·69 (0·94–3·06)
Bone	28 (6·5%)	1·19 (0·82–1·73)	3 (0·7%)	0·79 (0·26–2·45)	6 (1·4%)	0·97 (0·44–2·16)	33 (7·6%)	0·91 (0·65–1·28)	8 (1·8%)	1·62 (0·81–3·23)	4 (0·9%)	1·25 (0·47–3·33)	4 (0·9%)	0·68 (0·25–1·80)
Other	29 (7·7%)	1·38 (0·96–1·99)	5 (1·3%)	1·66 (0·69–3·99)	5 (1·3%)	0·93 (0·39–2·25)	21 (5·5%)	0·73 (0·48–1·12)	6 (1·6%)	1·40 (0·63–3·11)	5 (1·3%)	1·55 (0·65–3·72)	6 (1·6%)	1·19 (0·53–2·64)
Bladder	21 (9·1%)	1·65 (1·08–2·54)	<3	1·09 (0·27–4·36)	<3	0·63 (0·16–2·50)	22 (9·5%)	1·23 (0·81–1·87)	4 (1·7%)	1·53 (0·57–4·08)	<3	0·51 (0·07–3·59)	5 (2·2%)	1·66 (0·69–3·99)
Lung	7 (5·9%)	1·07 (0·51–2·24)	<3	NA	<3	1·23 (0·31–4·93)	8 (6·8%)	0·82 (0·41–1·63)	<3	NA	<3	2·00 (0·50–7·98)	<3	1·26 (0·32–5·05)
Kidney	8 (7·0%)	1·30 (0·65–2·60)	<3	1·15 (0·16–8·18)	<3	0·64 (0·09–4·54)	7 (6·1%)	0·78 (0·37–1·64)	<3	1·59 (0·40–6·37)	<3	3·06 (0·99–9·48)	<3	0·69 (0·10–4·92)
Other genitourinary	3 (2·6%)	0·48 (0·15–1·49)	<3	NA	<3	0·66 (0·09–4·65)	10 (8·8%)	1·17 (0·63–2·17)	<3	1·59 (0·40–6·36)	<3	NA	5 (4·4%)	3·26 (1·36–7·84)

Analysis includes Welsh individuals who gave birth in an English hospital. SIRs were considered moderately increased if 1·25 or higher. To prevent potential identification of individuals, any table cell counts with an observed number of less than three were reported as <3. NA indicates that the numbers observed were too few to be able to calculate SIR and corresponding 95% CIs. The other category includes unspecified malignant neoplasms, NEC; other specified neoplasms, NEC; extragonadal germ-cell tumours; carcinoma of other and ill-defined sites, NEC; skin carcinomas; paraganglioma and glomus tumours; adrenocortical carcinoma; other paediatric and embryonal tumours, NEC; and neuroblastoma. The other genitourinary category includes corpus uteri, vulva, other and unspecified female genital organs, uterus, unspecified, Wilms' tumour, renal pelvis, uterine adnexa (other than ovary), placenta, other and unspecified urinary organs, and ureter. NEC=not elsewhere classified. SIR=standardised incidence ratio.

Table 2: **SIR of developing obstetric complications related to the foetus, amniotic cavity, and possible delivery problems during pregnancy, childbirth, and puerperium, by cancer type**

increased risk of disorders of the amniotic fluid and membranes, premature rupture of membranes, placental disorders including placenta praevia, and antepartum haemorrhage compared with women in the general population. The risk of antepartum haemorrhage was also elevated among survivors of other genitourinary cancers (table 2).

Survivors of several specific cancers were at risk of preterm labour and delivery, including survivors of cervical cancer, leukaemia, other cancers (mostly unspecified malignant neoplasms), gastrointestinal cancer, non-Hodgkin lymphoma, and CNS tumours (table 3). Survivors of breast cancer were the only survivors at excess risk of unsuccessful induction of labour. Obstructed labour due to malposition and malpresentation of fetus was more likely than expected among survivors of cervical cancer and leukaemia (table 3). Survivors of leukaemia and melanoma were at increased risk of retained placenta and membranes without haemorrhage. Although rare, survivors of breast cancer were at increased risk of intrapartum haemorrhage (table 4). Survivors of leukaemia had an elevated risk of postpartum haemorrhage. Survivors of gastrointestinal and thyroid cancer showed increased risk of puerperal infection except sepsis (table 4).

Patterns of relative risks based on the multivariable analysis were generally consistent with the univariable analysis indicating that the results from the SIR analysis are robust to potential confounding from parity and social deprivation (appendix pp 7–11). Sensitivity analyses for obstetric outcomes by year of cancer diagnoses did not reveal any differences except for survivors of cervical cancer diagnosed more recently (ie, 1995 or later) being at higher risk of placental disorders and premature delivery than those diagnosed before 1995 (appendix p 12). Survivors of other cancers diagnosed before 1995 were at higher risk of premature delivery than those diagnosed after 1995.

Discussion

This is, to our knowledge, by far the largest study to comprehensively investigate birth rates and obstetric complications in female survivors of adolescent and young adult cancer and to report accurate risk estimates of a wide spectrum of obstetric outcomes among specific types of cancer. Overall, survivors had 68% of births expected in the general population. Survivors of other genitourinary cancers (other than cervix, ovary, bladder, or kidney), cervical cancer, and breast cancer had under 50% of expected births of expected, and survivors of leukaemia had 53% of expected births. We report here that survivors of cervical cancer are at risk of a spectrum of obstetric complications, including malpresentation of foetus, obstructed labour, amniotic fluid and membranes disorders, premature rupture of membranes, preterm birth, placental disorders including placenta praevia, and antepartum haemorrhage. To our knowledge, only the risks of preterm birth and premature rupture of membranes have been reported before in smaller scale studies,[2,6,7,20–22] but not the risks of the other obstetric complications discussed in this study. Survivors of leukaemia were at risk of preterm delivery, obstructed labour, postpartum haemorrhage, and retained placenta and membranes. Survivors of all other specific cancers had no more than two obstetric complications that exceeded an observed-to-expected ratio of 1·25 or more, providing reassurance for almost all survivors of adolescent and young adult cancer concerning their risks in pregnancy.

Survivors of cervical cancer had one of the lowest birth rates of all survivors of cancer, and those who gave birth were at a higher risk relative to the general population of a whole range of obstetric complications. Evaluation of obstetric complications among survivors of cervical cancer has only recently been possible because historical treatment (ie, before 1990)—including hysterectomy or pelvic radiation, or both—for cervical cancer would have typically rendered a woman infertile. This development is supported by our findings that the observed-to-expected ratio for births increased substantially over time, from less than 20% around 1985 to 50% in women diagnosed in 2006. Currently, 53% of patients diagnosed with cervical cancer have surgery (including local resection by conisation for early disease), 40% have radiotherapy, and 33% have chemotherapy as initial care.[23] More advanced fertility-sparing surgery for early stage or localised cervical cancer using radical trachelectomy could preserve the fertility of young women with cancer, but carries a high risk of cervical incompetence or scarring or stenosis of the cervix, which in all likelihood increases the risk of obstetric complications, particularly preterm labour.[24,25] These increased risks of adverse obstetric outcomes suggest that survivors of cervical cancer require a high-risk pregnancy care plan that requires close monitoring and assessment with input from an obstetric multidisciplinary team. Our results provide evidence for the potential development of guidelines for the management of pregnancies in survivors of cervical cancer to complement existing guidelines on the management of cervical cancer[26] and a benchmark against which the obstetric risks of future cancer treatment can be compared.

Survivors of leukaemia were also at risk of several obstetric complications. Treatment for leukaemia could necessitate a haematopoietic stem-cell transplant (HSCT) involving total body irradiation as conditioning treatment, and although infertility is common, a natural pregnancy or a pregnancy through assisted reproductive technology is still possible. However, we show in this Article that there are risks to such pregnancies, including the risk of preterm delivery, obstructed labour, postpartum haemorrhage, and retained placenta and membrane. Although the exact biological mechanism needs clarification, previous exposure of the uterus to

	Prolonged pregnancy (ICD10: 048)		Preterm labour and delivery (ICD10: 060)		Unsuccessful induction of labour (ICD10: 061)		Abnormalities of forces of labour (ICD10: 062)		Long labour (ICD10: 063)		Obstructed labour due to malposition and malpresentation of fetus (ICD10: 064)	
	Observed (%)	SIR (95% CI)	Observed (%)	SIR (95%CI)	Observed (%)	SIR (95%CI)	Observed (%)	SIR (95%CI)	Observed (%)	SIR (95%CI)	Observed (%)	SIR (95%CI)
All survivors	1546 (7·0%)	0·99 (0·95–1·04)	1446 (6·6%)	1·25 (1·19–1·31)	249 (1·1%)	1·09 (0·96–1·23)	628 (2·9%)	0·94 (0·87–1·02)	2343 (10·6%)	1·02 (0·98–1·06)	566 (2·6%)	1·12 (1·03–1·22)
Melanoma	376 (7·3%)	1·04 (0·94–1·15)	242 (4·7%)	0·89 (0·79–1·01)	47 (0·9%)	0·88 (0·66–1·17)	158 (3·1%)	1·01 (0·87–1·18)	568 (11·0%)	1·06 (0·97–1·15)	140 (2·7%)	1·18 (1·00–1·39)
Hodgkin lymphoma	238 (8·1%)	1·14 (1·00–1·29)	163 (5·6%)	1·07 (0·92–1·25)	33 (1·1%)	1·14 (0·81–1·60)	95 (3·2%)	1·04 (0·85–1·28)	352 (12·0%)	1·15 (1·03–1·27)	59 (2·0%)	0·91 (0·70–1·17)
Breast	174 (7·6%)	1·09 (0·94–1·27)	134 (5·8%)	1·07 (0·91–1·27)	43 (1·9%)	1·63 (1·21–2·20)	54 (2·3%)	0·83 (0·64–1·09)	270 (11·7%)	1·17 (1·03–1·31)	62 (2·7%)	1·13 (0·88–1·45)
Thyroid	157 (7·3%)	1·04 (0·89–1·21)	126 (5·9%)	1·11 (0·94–1·33)	21 (1·0%)	0·94 (0·61–1·45)	66 (3·1%)	1·00 (0·78–1·27)	193 (9·0%)	0·87 (0·75–1·00)	56 (2·6%)	1·14 (0·88–1·49)
CNS tumour	130 (6·3%)	0·88 (0·74–1·05)	140 (6·8%)	1·29 (1·10–1·53)	20 (1·0%)	0·94 (0·61–1·46)	62 (3·0%)	0·97 (0·76–1·25)	190 (9·2%)	0·88 (0·76–1·01)	42 (2·0%)	0·89 (0·66–1·20)
Cervical	89 (4·5%)	0·63 (0·52–0·78)	282 (14·3%)	2·74 (2·44–3·08)	26 (1·3%)	1·26 (0·86–1·85)	53 (2·7%)	0·92 (0·70–1·20)	231 (11·7%)	1·11 (0·98–1·27)	81 (4·1%)	1·72 (1·38–2·13)
Non-Hodgkin lymphoma	76 (8·1%)	1·14 (0·91–1·43)	65 (6·9%)	1·32 (1·04–1·69)	14 (1·5%)	1·48 (0·88–2·50)	20 (2·1%)	0·70 (0·45–1·08)	94 (10·0%)	0·96 (0·78–1·17)	24 (2·6%)	1·12 (0·75–1·67)
Ovarian	58 (7·0%)	0·98 (0·76–1·27)	50 (6·0%)	1·16 (0·88–1·53)	11 (1·3%)	1·31 (0·73–2·37)	17 (2·0%)	0·69 (0·43–1·10)	88 (10·6%)	1·00 (0·81–1·24)	16 (1·9%)	0·84 (0·52–1·38)
Soft-tissue sarcoma	58 (7·4%)	1·04 (0·81–1·35)	47 (6·0%)	1·14 (0·86–1·52)	4 (0·5%)	0·50 (0·19–1·33)	18 (2·3%)	0·75 (0·47–1·19)	88 (11·2%)	1·07 (0·86–1·31)	9 (1·1%)	0·50 (0·26–0·96)
Leukaemia	40 (7·3%)	1·03 (0·76–1·41)	43 (7·8%)	1·50 (1·11–2·02)	10 (1·8%)	1·84 (0·99–3·41)	19 (3·5%)	1·07 (0·68–1·68)	60 (10·9%)	1·06 (0·82–1·36)	19 (3·5%)	1·65 (1·05–2·58)
Gastrointestinal	31 (6·2%)	0·88 (0·62–1·25)	37 (7·4%)	1·38 (1·00–1·90)	4 (0·8%)	0·77 (0·29–2·05)	12 (2·4%)	0·77 (0·43–1·35)	46 (9·2%)	0·90 (0·67–1·20)	16 (3·2%)	1·42 (0·87–2·32)
Head and neck	29 (6·1%)	0·87 (0·60–1·25)	27 (5·6%)	1·08 (0·74–1·57)	4 (0·8%)	0·81 (0·31–2·17)	11 (2·3%)	0·74 (0·41–1·33)	46 (9·6%)	0·93 (0·69–1·24)	15 (3·1%)	1·43 (0·86–2·38)
Bone	30 (6·9%)	0·98 (0·69–1·41)	25 (5·8%)	1·10 (0·74–1·62)	<3	0·46 (0·12–1·85)	16 (3·7%)	1·14 (0·70–1·86)	39 (9·0%)	0·87 (0·64–1·19)	10 (2·3%)	1·06 (0·57–1·97)
Other	26 (6·9%)	0·98 (0·67–1·44)	29 (7·7%)	1·47 (1·02–2·12)	<3	0·50 (0·13–2·00)	12 (3·2%)	1·07 (0·61–1·88)	27 (7·1%)	0·69 (0·47–1·01)	5 (1·3%)	0·59 (0·25–1·43)
Bladder	11 (4·8%)	0·68 (0·38–1·23)	18 (7·8%)	1·46 (0·92–2·32)	3 (1·3%)	1·22 (0·39–3·79)	7 (3·0%)	1·05 (0·50–2·19)	23 (10·0%)	0·97 (0·64–1·45)	4 (1·7%)	0·76 (0·28–2·02)
Lung	8 (6·8%)	0·97 (0·49–1·94)	4 (3·4%)	0·64 (0·24–1·71)	<3	0·81 (0·11–5·72)	<3	0·54 (0·13–2·14)	11 (9·3%)	0·89 (0·49–1·60)	<3	0·36 (0·05–2·57)
Kidney	9 (7·9%)	1·12 (0·58–2·15)	8 (7·0%)	1·33 (0·67–2·66)	3 (2·6%)	2·44 (0·79–7·56)	4 (3·5%)	1·21 (0·46–3·23)	9 (7·9%)	0·76 (0·39–1·46)	3 (2·6%)	1·09 (0·35–3·39)
Other genitourinary	6 (5·3%)	0·74 (0·33–1·65)	6 (5·3%)	1·03 (0·46–2·29)	<3	0·87 (0·12–6·18)	<3	0·59 (0·15–2·36)	8 (7·0%)	0·68 (0·34–1·37)	4 (3·5%)	1·52 (0·57–4·04)

Analysis includes Welsh individuals who gave birth in an English hospital. SIRs were considered moderately increased if 1·25 or higher. To prevent potential identification of individuals, any table cell counts with an observed number of less than three were reported as <3. The other category includes unspecified malignant neoplasms, NEC; other specified neoplasms, NEC; extragonadal germ-cell tumours; carcinoma of other and ill-defined sites, NEC; skin carcinomas; paraganglioma and glomus tumours; adrenocortical carcinoma; other paediatric and embryonal tumours, NEC; and neuroblastoma. The other genitourinary category includes corpus uteri, vulva, other and unspecified female genital organs, uterus unspecified, Wilms' tumour, renal pelvis, uterine adnexa (other than ovary), placenta, other and unspecified urinary organs, and ureter. NEC=not elsewhere classified. SIR=standardised incidence ratio.

Table 3: **SIR of developing obstetric complications of labour and delivery during pregnancy, childbirth, and puerperium, by cancer type**

	Intrapartum haemorrhage (ICD10: O67)		Fetal stress (ICD10: O68)		Umbilical cord complications (ICD10: O69)		Perineal laceration (ICD10: O70)		Postpartum haemorrhage (ICD10:O72)		Retained placenta and membranes without haemorrhage (ICD10: O73)		Puerperal infections (except sepsis)* (ICD10: O86)	
	Observed (%)	SIR (95% CI)	Observed (%)	SIR (95% CI)	Observed (%)	SIR (95% CI)	Observed (%)	SIR (95% CI)	Observed (%)	SIR (95% CI)	Observed (%)	SIR (95% CI)	Observed (%)	SIR (95% CI)
All survivors	120 (0·5%)	1·04 (0·87–1·24)	4701 (21·3%)	0·99 (0·96–1·01)	570 (2·6%)	1·04 (0·96–1·13)	7661 (34·8%)	0·96 (0·94–0·98)	2375 (10·8%)	1·04 (1·00–1·08)	241 (1·1%)	1·09 (0·96–1·24)	177 (0·8%)	1·03 (0·88–1·19)
Melanoma	23 (0·4%)	0·85 (0·56–1·27)	1109 (21·6%)	1·00 (0·94–1·06)	157 (3·1%)	1·24 (1·06–1·46)	1951 (37·9%)	1·05 (1·00–1·10)	548 (10·7%)	1·02 (0·94–1·11)	69 (1·3%)	1·33 (1·05–1·68)	24 (0·5%)	0·60 (0·40–0·90)
Hodgkin lymphoma	16 (0·5%)	1·09 (0·67–1·78)	657 (22·4%)	1·03 (0·95–1·11)	73 (2·5%)	1·00 (0·80–1·26)	1085 (37·0%)	1·01 (0·95–1·07)	297 (10·1%)	0·97 (0·86–1·08)	28 (1·0%)	0·99 (0·69–1·44)	21 (0·7%)	0·89 (0·58–1·37)
Breast	21 (0·9%)	1·57 (1·03–2·41)	540 (23·5%)	1·10 (1·01–1·20)	68 (3·0%)	1·14 (0·90–1·45)	752 (32·7%)	0·95 (0·88–1·02)	254 (11·0%)	1·11 (0·98–1·25)	29 (1·3%)	1·16 (0·81–1·67)	25 (1·1%)	1·43 (0·97–2·12)
Thyroid	13 (0·6%)	1·17 (0·68–2·02)	445 (20·7%)	0·96 (0·87–1·05)	42 (2·0%)	0·80 (0·59–1·08)	773 (36·0%)	0·99 (0·93–1·07)	208 (9·7%)	0·91 (0·79–1·04)	27 (1·3%)	1·27 (0·87–1·85)	28 (1·3%)	1·66 (1·14–2·40)
CNS tumour	7 (0·3%)	0·66 (0·31–1·37)	428 (20·6%)	0·95 (0·86–1·05)	51 (2·5%)	0·97 (0·74–1·28)	712 (34·3%)	0·95 (0·88–1·02)	224 (10·8%)	1·04 (0·91–1·18)	12 (0·6%)	0·58 (0·33–1·03)	20 (1·0%)	1·21 (0·78–1·88)
Cervical	14 (0·7%)	1·32 (0·78–2·23)	401 (20·3%)	0·95 (0·86–1·05)	50 (2·5%)	1·00 (0·76–1·32)	541 (27·4%)	0·76 (0·70–0·83)	192 (9·7%)	0·98 (0·85–1·12)	24 (1·2%)	1·17 (0·78–1·74)	14 (0·7%)	0·95 (0·56–1·60)
Non-Hodgkin lymphoma	4 (0·4%)	0·85 (0·32–2·25)	206 (22·0%)	1·01 (0·88–1·16)	27 (2·9%)	1·20 (0·83–1·76)	308 (32·9%)	0·90 (0·80–1·01)	118 (12·6%)	1·20 (1·00–1·44)	5 (0·5%)	0·55 (0·23–1·31)	8 (0·9%)	1·09 (0·55–2·18)
Ovarian	<3	0·47 (0·12–1·86)	179 (21·6%)	1·00 (0·86–1·16)	17 (2·0%)	0·81 (0·50–1·31)	314 (37·8%)	1·04 (0·93–1·16)	95 (11·4%)	1·14 (0·93–1·40)	9 (1·1%)	1·09 (0·57–2·10)	4 (0·5%)	0·61 (0·23–1·64)
Soft-tissue sarcoma	3 (0·4%)	0·74 (0·24–2·29)	161 (20·4%)	0·95 (0·81–1·10)	24 (3·0%)	1·22 (0·82–1·82)	277 (35·2%)	0·97 (0·86–1·09)	84 (10·7%)	1·03 (0·84–1·28)	9 (1·1%)	1·15 (0·60–2·21)	7 (0·9%)	1·12 (0·54–2·36)
Leukaemia	<3	0·37 (0·05–2·65)	119 (21·7%)	0·98 (0·82–1·17)	15 (2·7%)	1·14 (0·69–1·89)	189 (34·5%)	0·93 (0·81–1·07)	76 (13·9%)	1·25 (1·00–1·56)	10 (1·8%)	1·97 (1·06–3·66)	6 (1·1%)	1·30 (0·59–2·90)
Gastrointestinal	3 (0·6%)	1·17 (0·38–3·62)	102 (20·3%)	0·93 (0·77–1·13)	7 (1·4%)	0·60 (0·28–1·25)	172 (34·3%)	0·94 (0·81–1·09)	60 (12·0%)	1·10 (0·85–1·41)	6 (1·2%)	1·23 (0·55–2·73)	8 (1·6%)	2·00 (1·00–4·00)
Head and neck	4 (0·8%)	1·62 (0·61–4·31)	100 (20·9%)	0·96 (0·79–1·17)	10 (2·1%)	0·82 (0·44–1·53)	161 (33·7%)	0·93 (0·79–1·08)	51 (10·7%)	1·00 (0·76–1·32)	<3	0·43 (0·11–1·72)	<3	0·51 (0·13–2·05)
Bone	3 (0·7%)	1·41 (0·46–4·38)	85 (19·6%)	0·89 (0·72–1·10)	10 (2·3%)	0·97 (0·52–1·80)	136 (31·4%)	0·85 (0·72–1·01)	55 (12·7%)	1·14 (0·88–1·49)	5 (1·2%)	1·24 (0·52–2·98)	4 (0·9%)	1·12 (0·42–3·00)
Other	<3	0·48 (0·07–3·38)	69 (18·2%)	0·86 (0·68–1·08)	7 (1·8%)	0·67 (0·32–1·40)	98 (25·9%)	0·73 (0·60–0·89)	49 (12·9%)	1·31 (0·99–1·73)	<3	NA	<3	0·32 (0·05–2·30)
Bladder	<3	0·80 (0·11–5·65)	43 (18·6%)	0·88 (0·65–1·18)	6 (2·6%)	1·01 (0·45–2·25)	72 (31·2%)	0·88 (0·70–1·10)	23 (10·0%)	1·00 (0·66–1·50)	<3	0·83 (0·21–3·32)	<3	1·11 (0·28–4·45)
Lung	<3	3·27 (0·82–13·07)	22 (18·6%)	0·86 (0·56–1·30)	<3	0·72 (0·18–2·87)	50 (42·4%)	1·16 (0·88–1·54)	13 (11·0%)	1·01 (0·59–1·74)	<3	1·69 (0·42–6·74)	<3	1·08 (0·15–7·66)
Kidney	<3	1·60 (0·22–11·33)	17 (14·9%)	0·70 (0·44–1·13)	4 (3·5%)	1·39 (0·52–3·71)	36 (31·6%)	0·89 (0·64–1·23)	12 (10·5%)	1·07 (0·61–1·88)	<3	NA	<3	2·36 (0·59–9·45)
Other genitourinary	<3	1·70 (0·24–12·06)	18 (15·8%)	0·74 (0·47–1·17)	<3	NA	34 (29·8%)	0·84 (0·60–1·18)	16 (14·0%)	1·43 (0·88–2·33)	<3	1·69 (0·42–6·75)	<3	..

Analysis includes Welsh individuals who gave birth in an English hospital. SIRs were considered moderately increased if 1·25 or higher. To prevent potential identification of individuals, any table cell counts with an observed number of less than three were reported as <3. NA indicates that the numbers observed were too few to be able to calculate SIR and corresponding 95% CIs. The other category includes unspecified malignant neoplasms, NEC; other specified neoplasms, NEC; extragonadal germ-cell tumours; carcinoma of other and ill-defined sites, NEC; skin carcinomas; paraganglioma and glomus tumours; adrenocortical carcinoma; other paediatric and embryonal tumours, NEC; and neuroblastoma. The other genitourinary category includes corpus uteri, vulva, other and unspecified female genital organs, uterus, unspecified, Wilms' tumour, renal pelvis, uterine adnexa (other than ovary), placenta, other and unspecified urinary organs, and ureter. NEC=not elsewhere classified. SIR=standardised incidence ratio. *Complications predominantly related to the puerperium.

Table 4: **SIR of developing obstetric complications related to labour and delivery during pregnancy, childbirth, and puerperium**

total body irradiation given as conditioning treatment as part of a HSCT might cause fibrosis or affect muscular or vascular functioning of the uterus analogous to that observed in survivors of childhood cancer treated with abdominal radiotherapy.

In our study, survivors of breast cancer were at risk of unsuccessful induction of labour and intrapartum haemorrhage, but not more likely to have preterm labour and birth. This finding is inconsistent with findings from a meta-analysis published in 2021,[27] in which a summary odds ratio of 1·45 (95% CI 1·11–1·88) of preterm birth was reported. Our study excluded any births that occurred in the first 9 months after cancer diagnosis, which would have typically included cancer treatment. However, when including those births in a sensitivity analysis, the SIR for preterm birth (data not shown) was consistent with the risk reported previously.[27] Consistent with this finding, Black and colleagues[28] reported in a population-based registry study that the risks of preterm birth was only increased in the first 2 years following diagnosis and no longer after 5 years. These observations suggest that the increased of risk of preterm birth might only be present among pregnant women undergoing or shortly after breast cancer treatment, but not in subsequent years following treatment. Risks of other obstetric complications evaluated in the meta-analysis, including pre-eclampsia and post-partum haemorrhage, were generally concordant with our findings in that no excess risk was observed. However, the risks of unsuccessful induction of labour and intrapartum haemorrhage have, to our knowledge, not been reported before although the exact mechanism for these increased risks is uncertain.

Our study found that survivors of kidney cancer had an increased risk of gestational hypertension, but not pre-eclampsia. Although we do not have treatment details available for the TYACSS cohort, unilateral nephrectomy might be implicated in the increased risk of gestational hypertension. In support of this hypothesis, unilateral nephrectomy in kidney donors has been associated with gestational hypertension in some studies, although not all.[29] Likewise, previous abdominal and pelvic radiation exposing one or both kidneys could increase the risk of gestational hypertension. For example, in the British Childhood Cancer Survivor Study,[5] survivors of Wilms' tumour treated with pelvic and abdominal radiotherapy were at a greater than three-times risk of developing hypertension during pregnancy compared to those treated without abdominal radiotherapy.[5] Survivors of ovarian cancer were also at risk of gestational hypertension and pre-existing hypertension complicating pregnancy, but no other obstetric complications. There is evidence that survivors of ovarian germ-cell tumours are at risk of hypertension not only during pregnancy[30]—possibly related to cancer treatment with long-term platinum-based chemotherapy—and would thus also be important to monitor during a future pregnancy.

Previous studies among survivors of adolescent and young adult cancer generally reported similar findings in relation to observed-versus-expected number of birth rates with a 2021 meta-analysis[27] reporting an overall likelihood of giving birth of 0·65 (95% CI 0·55–0·77) among all female cancer survivors compared with the general population, which is very similar to the observed-to-expected ratio we report in our Article. Survivors of cervical cancer had the lowest probability of a birth in the meta-analysis (RR 0·33, 95% CI 0·31–0·35); although we reported a slightly more optimistic figure. This finding might be due to our study including more recently diagnosed women (ie, up to 2006), and thus including more survivors of cervical cancer who were offered fertility-sparing surgery.

Potential limitations of our study include, firstly, the absence of detailed information on cancer therapy, such as cumulative doses of radiotherapy or chemotherapy for all individuals in the cohort. However, with nearly 100 000 female survivors of cancer in the TYACSS cohort, collecting details of cancer treatments on such a large-scale is currently not feasible. However, in the UK, comprehensive treatment details are being recorded for individuals treated from 2013 through the Systemic Anti-cancer Therapy Dataset[31] and from 2009 through the National Radiotherapy Dataset.[32] Furthermore, we are planning to undertake a study in the foreseeable future to investigate the risks of obstetric complications by detailed treatment modalities. Secondly, our results indicate that adolescent and young adult survivors are generally not more likely to develop almost all obstetric complications than expected from the general population, except for survivors of cervical cancer and leukaemia. Previous studies have reported increased risks for other cancer types; however, this inconsistency could be due to our data relating to 5-year survivors of adolescent and young adult cancer only. Inevitably, post-5-year survivors would typically be healthier than individuals who do not survive to 5 years, which means that our results might not necessarily be generalisable to individuals who have not survived 5 years. Moreover, another reason for this inconsistency could relate to our study being population-based, thereby largely avoiding selection bias. Non-population-based studies could have suffered from selection bias because these would probably include cancer survivors who attended treatment centres or were on long-term clinical follow-up; such survivors are inherently more likely to be at risk of health conditions that could contribute to obstetric complications. Thirdly, births that occurred before April 1, 1997, were not captured; however, because the purpose of our study was to provide evidence applicable to survivors who are currently planning a pregnancy or are pregnant, we believe this should not be of major concern. Another limitation of our study is that we could not provide cancer specific risk estimates of adverse obstetric outcomes by factors such as age at diagnosis and follow-up time due

to insufficient numbers of affected pregnancies for most outcomes, even when focusing only on significant results with a SIR of at least 1·25. Finally, our analyses should be considered exploratory due to the large number of statistical tests performed, hence any findings should be interpreted with caution and supported by further studies. Although we found some significant SIRs of less than 1·00, these are probably due to the multiple comparisons issue rather than a true protective effect of previous cancer on adverse obstetric outcomes.

Focusing on obstetric complications that were relatively common, at least moderately in excess (observed-to-expected ratio ≥1·25), and statistically significantly in excess provides broad reassurance for survivors of most adolescent and young adult cancers. Only survivors of cervical cancer and leukaemia had such excess risk for more than two specific complications from among the 27 complications investigated. Our results provide an evidence base for providing reassurance to survivors of almost all specific cancers in relation to almost all obstetric complications. To our knowledge, clinical guidelines specifically for the management of pregnancy and birth amongst adolescent and young adult cancer survivors do not currently exist and thereby it is not possible to assess the implications of previous cancer treatment during adolescence and young adulthood in an evidence-based way. General population guidelines for preterm labour and birth, such as those from the National Institute for Health and Care Excellence, do not explicitly provide recommendations for management of pregnancy in women with a history of cancer.[33] The NHS England Saving Babies' Lives care bundle for reducing perinatal mortality[34] recognises that women with a history of trachelectomy for cervical cancer are at high risk for preterm birth and recommend referral to a preterm-prevention clinic for further risk assessment. However, comprehensive guidelines for managing other obstetric outcomes in cervical cancer survivors are, to our knowledge, non-existent. Guidelines relating to counselling and surveillance of obstetrical risk for female childhood cancer survivors have been reported,[35] but no equivalent guidelines exist for cancer survivors diagnosed beyond age 25 years; our results provide evidence for the development of such clinical guidelines. For the 27 specific obstetric complications with at least 100 observed events, the tabulated excess risks were provided for 17 specific types of adolescent and young adult cancer. Such risk stratification provides an evidence base for survivors, health-care professionals, and the development of clinical guidelines.

Contributors

RCR and MMH contributed to study design and concept. CS, RCR, and MMH contributed to the statistical analysis. CS, RCR, and MMH contributed to the initial drafting of the manuscript. RCR, MMH, DLW, and GR contributed to data collection and curation. CS, RCR, MMH, EJH, AP, KAB, MG, RAA, and WHBW contributed to interpretation of data and critical revision of the manuscript. All authors approved the final version of the manuscript for publication. All authors had full access to all the data in the study and had final responsibility for the decision to submit the manuscript.

Declaration of interests

RAA reports grants from Ferring Pharmaceuticals, UK Research and Innovation, and Children with Cancer UK, outside the submitted work. All other authors declare no competing interests.

Data sharing

Further aggregated data relating to this study might be available upon reasonable request. Individual patient data are not accessible, but special permission could be granted to accredited researchers through an honorary contract at the University of Birmingham and with explicit permission from all data providers involved (Office of National Statistics, Welsh Cancer Registry, and NHS England). Data can only be used for the purposes as stated in the original study protocol (available upon request via corresponding author) that was approved by the National Ethics Research Committee and the Confidentiality Advisory Group.

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