Adverse reproductive effects of treatment for cancer in childhood and adolescence

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Introduction

Modern treatments for cancer include high doses of ionising radiation and combinations of high-dose systemic chemotherapy. Although these curative therapies have the potential to produce germ-cell mutations leading to genetic disease in the next generation, there is still little understanding of the genetic consequences of such treatments. To date, no environmental exposure has been proven to cause new heritable disease in human beings [1].

Childhood cancer is a success story of modern medicine in which effective treatments have been identified for previously untreatable disease. With the lifesaving advances in treatment introduced after 1970, using combinations of multiagent chemotherapy, surgery and radiotherapy, the overall 5-year survival after cancer has reached 81% for children and 87% for adolescents and young adults [2]. The continuing rise in survival rates for young cancer patients, and the ability for survivors to have children of their own, have highlighted the importance of evaluating the impact of cancer therapy on fertility, pregnancy and health of the growing number of children of cancer survivors.

Cancer survivors offer one of the largest groups of people exposed to high doses of potent mutagens before reproductive age [3], and the timing and dose of their exposure to radiotherapy and mutagenic chemotherapy are accurately documented in their medical records [4]. Their curative radiation and chemotherapy treatments can result in non-sterilising gonadal exposures that offer a special opportunity for studying possible genetic changes that are inherited by their children.

Preconception cancer treatment in cancer survivors might cause trans-generational germ cell mutations and, if so, these mutations might lead to adverse pregnancy outcomes or a clinically recognisable disease in the offspring. Some of these outcomes, however, may have been familial rather than the result of a new mutation, and others might be the result of radiation-induced somatic mutations. This paper gives an overview of the evidence for trans-generational effects including untoward outcomes of pregnancies such as spontaneous abortions and stillbirths, and health problems in the offspring, the main emphasis being laid on cancer in the next generation.

Concern of survivors

Infertility is not the only issue in deciding whether to have children after cancer. Several studies have indicated that childhood cancer survivors worry about the possible health and social risks of having children [5–12]. Women have unrealistically high anxiety about pregnancy causing cancer recurrence and both male and female survivors worry about whether their children would be healthy and whether they might pass on a genetic risk or predisposition for cancer. Survivors also worry about being a future burden on their child because of their own physical health problems, the possibility of their cancer recurring later in life, and living to see their children grow up. Despite these worries, parenthood is important to survivors of cancer with typically three-quarters of young adults who are yet childless expressing a wish for future offspring and the distress that infertility brings.

Infertility

Cancer therapy may cause a spectrum of damage to the reproductive tract. Women treated with radiation affecting ovarian function are at high risk of acute ovarian failure and premature menopause, but also surgical removal of reproductive organs, hypothalamic–pituitary radiation and high-dose chemotherapy with alkylating agents might lead to infertility [13–16]. A successful pregnancy will require not only an intact hypothalamic–pituitary–ovarian axis and an adequate ovarian follicle reserve but also a normally functioning uterus; i.e. a uterine cavity that is not only receptive to implantation but, in addition, able

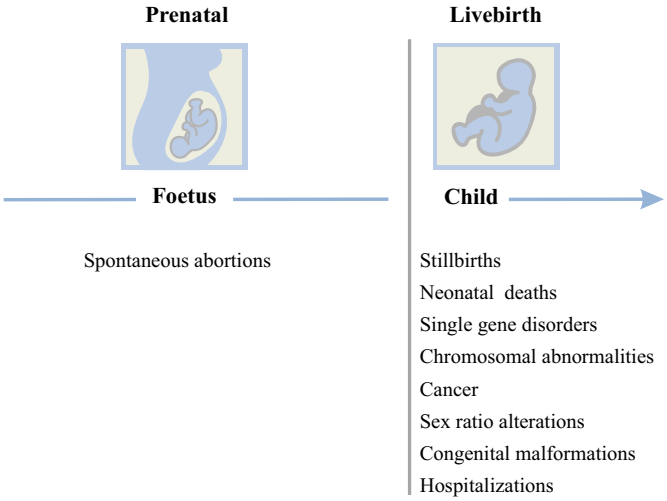

Fig. 1. Markers of potential damage to germ cells.

to accommodate normal growth of the developing foetus to term. Pelvic radiation may affect reproductive function by impairing uterine growth and development and blood flow [17], whereas chemotherapy does not appear to have any significant lasting adverse effect on uterine function. The majority of female cancer survivors, however, will have normal reproductive function and would be expected to have a successful pregnancy [14]. In males, both cytotoxic chemotherapy and radiotherapy might lead to testicular damage resulting in hormone insufficiency and sterility and, as in females, hypothalamic–pituitary radiation might lead to hypogonadotrophic hypogonadism [15,18].

Infertility remains one of the most common life-altering treatment effects experienced by long-term childhood cancer survivors [10]. Compared with siblings, female cancer survivors included in the Childhood Cancer Survivor Study (CCSS) [19] were less likely to become pregnant (relative risk of ever becoming pregnant 0.81; CI 0.73–0.90) [20], and reduced live birth rates of 0.50–0.70 compared to sisters [21] or to expected numbers of live births based on rates in the general population [22] have been reported both from the CCSS and the British Childhood Cancer Survivor Study (BCCSS) [23], with the highest deficits in live births in the British study for those treated with abdominal or brain radiotherapy. The relative probability of parenthood following young-age cancer was significantly reduced by 50% for both male and female survivors in a Finnish study; but among those who were able to have a child, the ability to have a second child was only slightly reduced compared to siblings [24]. The psychosocial literature confirms the strong desire to have children after cancer and the distress that infertility brings [11]. Thus biological limitations on fertility are probably the major cause of decreased birth rates in young cancer survivors, although concerns about the health of offspring, or difficulty finding a partner in some subgroups of survivors [5,25–27] might be another reason why survivors produce fewer offspring than the general population. For childhood and young adulthood cancer survivors who maintain fertility, there are major concerns about their ability to have full-term pregnancies and normal children.

Indicators of genetic disease

A pioneering study of the pregnancies and offspring of childhood cancer survivors was carried out by Li and colleagues [28] in 1979. No evidence of an excess of untoward outcomes of pregnancy or problems among offspring of survivors was found, but larger studies were requested to satisfactorily address the question of possible germ cell mutation.

The earliest studies of trans-generational effects among offspring of childhood cancer survivors have been summarised by Mulvihill and Byrne in 1992, Green in 2004, and Nagarajan and Robison in 2005 [29–31]. These studies considered outcomes with a high genetic component such as chromosomal abnormalities, single gene disorders and congenital malformations, but spontaneous abortions, cancer, stillbirths and sex ratio alterations have also been used as measures of genetic disease in the next generation (Fig. 1).

An early large interview study from 1998 by Byrne and colleagues [32], who studied the risk of genetic disease (defined as a cytogenetic syndrome, a single-gene disorder, or one of 15 simple malformations)

in 2,198 offspring of 1,092 cancer survivors and 4,544 offspring of 2,032 siblings of survivors, deserves to be mentioned. The rates of genetic defects in offspring of survivors and of sibling controls were not significantly different (3.4% versus 3.1%), and there was no association of the risk of sporadic genetic disease in children with the treatment status of the parent; i.e., exposure to potentially mutagenic therapy versus non-mutagenic therapy.

Cancer in offspring

Cancer treatments have the potential to cause germline mutations that are feared to increase the risk of cancer in the offspring of former cancer patients. Far from all cancers, however, are due to trans-generational germ-cell mutations related to treatment of surviving parents. The existence of a number of inherited cancer-predisposing germline mutations has been documented over the years. The list of well-defined familial cancer syndromes is steadily growing and the malignancies arising in this context involve a large variety of organ systems and affect individuals of all ages [33]. Today, more than 600 single-gene traits associated with specific neoplasms have been identified in clinical and epidemiological studies [34,35]. Most of these family syndromes are autosomal dominant disorders such as neurofibromatosis 1 and 2, von Hippel–Lindau disease, Li–Fraumeni syndrome, and retinoblastoma. Although cancer predisposition syndromes presenting in childhood and adolescence in general are regarded as rare, familial cancer syndromes have to be taken into consideration, when evaluating the risk of treatment-induced cancer in offspring of cancer survivors.

In the first population-based cohort study of cancer risk in offspring of paediatric cancer patients, Sankila and colleagues [36] examined the risk of cancer in 5,847 offspring of 14,652 survivors diagnosed under the age of 20 in a Nordic setting. A standardised incidence ratio (SIR) of 2.6 (1.9–3.5) was reported based on 44 observed cases. To assess the risk of sporadic cancer, Sankila and co-investigators excluded 20 offspring with hereditary retinoblastoma and other familial syndromes and two offspring with treatment-related tumours, resulting in a SIR of only 1.3 (0.8–2.0). The age at diagnosis of the cancer survivor appeared predictive, with the risk for cancer other than retinoblastoma among the offspring limited to children of survivors whose cancers were diagnosed when they were less than 10 years of age (SIR 3.9).

Virtually all earlier studies [28,37–45] have not reported any increased cancer risk in offspring of childhood cancer survivors, in the absence of known cancer predisposition syndromes (overview given in Nagarajan and Robison 2005 [30]). Table 1 gives an overview of the current evidence of pregnancy complications and health risks in offspring including cancer. The largest population-based study to date, from Finland, increasing the sample size of the previous Nordic study by adding to the study cohort offspring of cancer survivors diagnosed in early adulthood (age <35), reported similar findings when the risk of cancer among 9,877 children born after their parent's cancer diagnosis was compared with population expectations [78]. This study reported no increased risk of sporadic cancer among the children of survivors of non-hereditary cancer; i.e., a 70% significantly increased risk of cancer in the offspring disappeared after removing those with hereditary cancer syndromes (SIR 1.0; 0.7–1.4). Besides the inclusion of young adults, access to siblings as a second comparison group distinguished this most recent study from prior investigations. The risk among the offspring of survivors with non-hereditary cancer was also similar to that for the offspring of their healthy siblings.

Other health risks in offspring

No indication of genetic disease was found in the vast majority of the larger studies of adverse health outcomes in the offspring of childhood and adolescent cancer survivors using several markers of potential damage to germ cells (Table 1). Although most of the studies did not report an excess risk of congenital malformations, conflicting results have recently been published on the risk of congenital malformations in offspring of male survivors; i.e., while a US study found no increased risk [54], two recently published studies reported an increased risk in offspring of Norwegian male cancer patients aged 15–35 years at diagnosis and in offspring of Danish and Swedish male cancer patients diagnosed at any age [72,76] (Table 1). Only limited treatment data, however, was available for the cancer survivors in the two studies reporting an increased risk of congenital malformations [72,76], which made it difficult to tie their results to any specific treatment exposure [80].

These generally very reassuring findings are in accordance with the results of decades of interdisciplinary studies of offspring of atomic bomb survivors [61] and previous studies of childhood cancer survivors. Especially it is notable that no excess risk was found in any of the studies including outcomes being purely genetic diseases such as chromosomal

Table 1
Pregnancy complications and health risk in offspring of cancer survivors – review of current evidence

Adverse outcomes	Current evidence	References
Pregnancy complications		
Foetal death (spontaneous abortions and stillbirths[a])	Excess risk in female childhood cancer survivors if treated with high radiation doses to the uterus	[21,22,46–48]
Preterm birth and foetal growth restriction (manifested as small-for-gestational-age and low birth weight infants)	Excess risk in female childhood cancer survivors if treated with high radiation doses to the uterus	[21,22,46,49–53]
Neonatal deaths	Excess risk in female childhood cancer survivors if treated with high radiation doses to the uterus. (related to preterm birth)	[46,47]
Health risk in offspring		
Sex ratio alterations	No indications of sex ratio alterations	[3,21,32,49,54–59]
Single-gene disorders	No excess risk	[32,60]
Chromosomal abnormalities	No excess risk	[32,60–62]
Congenital malformations	Most studies reported no excess risk. Conflicting results, however, have recently been published on the risk of congenital malformations in offspring of male survivors	[3,32,37–40,44,46,49–51,54,60,63–77]
Cancer	No excess risk, in the absence of known cancer predisposition syndromes	[28,36–45,78]
Hospitalisations	No risk of untoward disorders measured as hospitalisation for diseases in childhood, except for neoplasms, which was anticipated based on the known association with cancer syndromes	[79]

[a] Note that definitions of stillbirth and abortion differ between countries; for instance, stillbirths in weeks 20–27 in the USA would be classified as spontaneous abortions in Denmark.

abnormalities and Mendelian disorders [32,60–62]. Thus, evidence to support that irradiation of human germ cells or chemotherapy results in genetic damage to the offspring is still lacking.

Pregnancy complications

Li was also prominent in the identification of the now well-established problem of increased spontaneous abortion, low birth weight, and increased perinatal mortality in offspring associated with abdominal irradiation of girls [71,81]. Germ cell mutation is generally considered to be an unlikely explanation of this spectrum of untoward outcomes [3].

Severe sequelae of cancer treatment seem to include the inability to bear children. The results of the population-based studies and other large epidemiological studies on pregnancy outcomes published within the last decade (Table 1) strongly indicate that high radiation doses to the uterus of female childhood cancer survivors, especially to the uterus of young girls in the premenarchal age, increase the risk of foetal death (either spontaneous abortions or stillbirths) as well as the risk of preterm birth and foetal growth restriction manifested as small-for-gestational-age and low birth weight infants. Several of the studies which included flank radiation doses or organ doses showed that the risk of these adverse outcomes were increased in a manner directly related to radiation dose to the flank or uterus [47,50,51,53].

Importantly, several studies evaluating the prevalence of pregnancy complications among partners of male survivors of childhood cancer collectively found no effect of childhood cancer treatment on the ability of male survivors to contribute to a successful pregnancy [82]; that is, evidence of an excess risk

of adverse pregnancy outcomes including spontaneous and induced abortion, stillbirth, premature delivery, low birth weight infant, or neonatal death was not reported in the vast majority of large well-conducted studies [22,47,51,55]. Based on these studies, any large risk among partners of male survivors can be excluded. The finding that partners of male survivors have no apparent excess risk for problem pregnancies, which was observed already in the very first studies from the 1980s [65,71,81], further supported the observations regarding the impact of uterine irradiation on pregnancy outcome in female survivors.

Chemotherapy did not appear to be associated with adverse pregnancy outcomes in most previous studies, including those which were able to include detailed information on drugs and doses and especially mutagenic alkylating agents [21,47,53].

Discussion

The presence of treatment-induced germ-line mutations is feared to increase the risk of cancer in the offspring of cancers survivors but already the earliest studies reported that most cancers in the offspring could be attributed to a known familial cancer syndrome. This has later been confirmed in large population-based studies [36,78]. Today cancer is not regarded as a plausible treatment-induced genetic disease.

Combining the results of three large population-based cohort studies assessing cancer risk in first-degree relatives of Nordic childhood cancer patients (offspring, siblings and parents) [36,83,84] gave us a powerful means of assessing cancer risk in close relatives of childhood cancer patients, allowed us to evaluate the possible role of both dominant [36,83] and recessive familial cancer syndromes of importance to the population [84], including hitherto unknown syndromes (if any), and finally to estimate the proportion of childhood cancer that can be explained by hereditary factors. These studies [36,83,84] did not show any features that suggested hitherto unknown genetic cancer syndromes of population importance or evidence that recessive conditions might contribute to cancers not explained by syndromes [84]. The risk for cancer in close relatives of children with a genetically inherited cancer syndrome was generally increased only when they were of a similar age to the index patient at the time of diagnosis. Further, an apparent absence of association between cancers in childhood and cancers in adulthood was observed both in the sibling and in the parent study. The aggregated results of these three Nordic studies indicate that less than 5% of childhood cancer can be explained by hereditary factors. Apart from rare cancer syndromes, paediatric cancer is not *per se* an indicator of familial cancer risk.

Although large pedigrees were not constructed in any of these studies, we have no reason to believe that our failure to identify new cancer syndromes was due to low statistical power or bias. Cancer-predisposing syndromes, however, might be undetected by linkage among cancer registries, because of the limited primary sources of the registries and the restricted range of variables collected, and the rarity of such syndromes [85]. However, the clinical details of affected families available within the cancer registries, such as topography and morphology (site and histology), might show cancer combinations highly indicative of known hereditary cancer syndromes as seen in all three studies [36,83,84]. Several clinical features indicate a possible underlying predisposition to cancer such as a tumour at an atypical age or site, or a very rare or unusual tumour type, especially if associated with birth defects, a single-gene disorder, or with other rare diseases such as chromosomal aberration [34,86,87]. Another strong indication is a first-degree relative with any of the features mentioned above or two first-degree relatives with any cancer. Several of these features can only be touched on in register-based studies, and others cannot be addressed at all. A final diagnosis of a hereditary syndrome cannot be reached without other information. This task would be most successful when patients are seen for a comprehensive evaluation, including physical examination, imaging, extended pedigree collection, and genetic laboratory testing. Such tasks are not now feasible in a record-linkage study, but could happen in the future with close collaboration between clinicians and epidemiologists.

The serious adverse pregnancy outcomes such as foetal death and growth restriction are in all likelihood related to structural (somatic) damage imparted to the immature uterus that restricted foetal growth and development, although radiation-induced germinal mutations from ovarian exposure or decreased hypothalamic–pituitary–ovarian function from cranial radiotherapy could not be ruled out.

No or little convincing effect on these outcomes resulting from an indirect hormonal effect of radiation, however, was apparent for radiation exposure to the pituitary gland either when the outcome was spontaneous abortion [21,22,48], stillbirth [47] or preterm delivery or a low birth weight infant [52,53]. Furthermore, the fact that doses to the ovary at levels that allowed for future fertility were not found to increase

either the risk for preterm birth and foetal growth restriction [53], or stillbirth and neonatal death [47] in studies which included accurate estimations of ovarian doses did not suggest radiation-induced oocyte damage as the explanation.

The reassuring results of the studies of cancer survivors and their offspring might be due to what Brent called 'biological filtration'; that is, a phenomenon where the mammalian organism can eliminate serious chromosome abnormalities or lethal mutations before conception or early in pregnancy and, therefore, results in surviving offspring that have normal or background incidence of birth defects or genetic disease [88]. The mutated germ cells of the survivor might not mature, the mature eggs or sperm may have a decreased capacity to be fertilised or to fertilise, or the abnormal zygotes or foetuses may elude detection because they may be eliminated during pre-implantation or early organogenesis by natural biological processes such as early embryonic loss.

Another explanation for the reassuring results reported in the vast majority of the studies is that the agents and doses to which these survivors have been exposed do not induce transmissible mutations in human spermatogonial stem cells or resting oocytes at a frequency high enough to be detected over the background of spontaneous mutations. Yet another possibility is lack of sufficient power (due to inadequate study size) or failure in measuring the appropriate outcome in studies assessing heritable disease phenotypes in exposed survivors [1]; that is, certain outcomes such as Mendelian disorders might be very difficult to identify and the interpretation of these rare disorders complex, and very early abortions might be underreported both in studies that rely on recalled abortion data [89] and in register-based studies – or not even noticed by the woman herself [90].

Conclusion

Mutagenic cancer therapy seems not to be associated with genetic defects in the children of cancer survivors. This seems to be true for all types of disease outcome with a genetic component. With the exception of well-known familial cancers, the risk of cancer in offspring of cancer survivors is very low or non-existing. High radiation doses to the uterus of young girls, however, are linked to serious adverse pregnancy outcomes including foetal death, preterm birth and neonatal death, related in all likelihood to structural damage imparted to the immature uterus that restricted foetal growth and development.

Clinical implications

These findings should prove useful when counselling cancer survivors who wish and are able to have children of their own. The results of the offspring studies imply that fear that their offspring might develop cancer is no reason for the survivors of sporadic cancer not to have children, and efforts to screen for cancer in the offspring of survivors of non-hereditary cancer in childhood and adolescence are not warranted. Although the absence of clear evidence for curative cancer treatments to be related to genetic disease in children is reassuring, the increased risk of foetal death and growth restriction during pregnancy in female survivors who received high-dose pelvic and abdominal radiotherapy at young age suggests the need for counselling and special monitoring of those who are able to become pregnant.

Conflict of interest statement

The authors have no conflict of interest to declare.

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