Pregnancy outcome and offspring after childhood cancer

Data show no evidence of mutagenesis of the germ cells

About two thirds of patients treated for childhood cancer in Britain survive at least five years, and over 90% of these survivors are probably cured.¹ Some survivors become infertile as a result of treatment, but many go on to have children.² Adverse outcomes of pregnancy or impaired health of the children might in theory be related to constitutional genetic abnormalities in survivors associated with their cancer or to germ cell mutagenesis from radiotherapy or cytotoxic drugs. Treatment may also result in dysfunction of reproductive organs adversely affecting pregnancy outcomes or offspring. Adverse outcomes include increased risks of miscarriage, stillbirth, low birth weight, congenital malformation, cancer, and early death.

Survivors of cancer occurring in childhood or early adult life form one of the largest groups of people exposed to high doses of mutagenic agents before reproducing. Radiation dosimetry and cytotoxic drug doses are obtainable from detailed clinical records (although the retention of such records in the future is under threat in Britain).³ Assessment of a possible relation between treatments for cancer and adverse reproductive outcomes is important to families and clinicians—but it also provides valuable data on possible associations between exposure to mutagens and germ cell mutagenesis in the wider community.

Only three large cohort studies of offspring of survivors of childhood cancer have been published, but together these account for nearly 4000 offspring.⁴⁻⁶ In the more numerous small (<200 offspring) cohort studies, no malignant neoplasm has been observed in the offspring.⁷ Cancers were diagnosed in offspring within each of the three large cohorts. However, when inherited retinoblastomas and a family with Sipple's syndrome were excluded there were only seven cases. About five cancers would have been expected by chance. Only one of the seven survivors to whom these children were born had received treatment that might have been mutagenic to germ cells. Some of the seven parent/offspring pairs of malignant neoplasms seemed consistent with the Li-Fraumeni familial cancer syndrome.⁸ Even the relatively large numbers of offspring available from these three cohorts do not provide data from which an increase in the risk of the generality of childhood cancers could be detected with confidence.

Serious congenital malformations, another indicator of a possible germ cell mutagenic effect of treatment, are important because they occur more commonly than malignant neoplasms in young children—so fewer offspring and a shorter follow up will achieve a study of comparable statistical power. The large studies reported so far have found no evidence of an increased risk of congenital malformations associated with cancer treatment that was potentially mutagenic to germ cells.^{6,9-11} Again, however, larger numbers would be needed to rule out an association.^{9,10}

The most extensive data on the effects of irradiation on germ cells come from survivors of the atomic bombing of Hiroshima and Nagasaki. These studies found no evidence that increased exposure to gonadal irradiation was associated with either an increased risk of pregnancies ending in stillbirth or an increased risk of neonatal mortality, congenital malformations, or cancers in the offspring.^{12,13}

Radiotherapy to the abdomen of girls increases the risk

of subsequent pregnancies ending in miscarriage, and their offspring are at an increased risk of having a low birth weight and of perinatal death.^{14,15} The underlying mechanism is uncertain, but it seems unlikely to be due to germ cell mutagenesis. The more likely explanations are an impaired vascular supply affecting placental and inelasticity of the uterus due to radiation fibrosis.^{14,16} A long term risk of serious cardiac disease has been found among patients treated with anthracyclines.¹⁷ Concerns have been expressed regarding a possible increased risk of cardiac problems during pregnancy after such treatments, but no satisfactory data are available to address this question.

Apart from the small groups of survivors identified above, most pregnancies and offspring of survivors do not seem to be at an increased risk of adverse outcomes. Vigilance should be maintained, in particular to identify any newly introduced elements of treatment that may have unforeseen long term adverse effects.

Two research areas should be given priority. Firstly, original data from previous cohort studies of offspring should be pooled and analysed to obtain more precise estimates of the heritability of different types of childhood cancer and to clarify the extent to which treatment may adversely affect the outcomes of pregnancy and the health of offspring of survivors. Secondly, further studies are required as most of the survivors included in previous studies were treated according to regimens used before the era of modern chemotherapy. Two large studies, one recently begun in the United States and the other in advanced planning in Britain, should provide information on the risks and aetiology of long term adverse outcomes from 25 000 and 14 000 former patients, who survived at least five years after diagnosis of childhood or adolescent cancer.

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