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Commentary

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There has been a dramatic improvement in the survival rate for children and adolescents diagnosed with cancer, confirmed by data from both the United Kingdom [1] and the United States [2]. This success has resulted in the maturation of a population of successfully treated children and adolescents into adults, estimated to be one in 900 persons between the ages of 15 and 44 years in the year 2000 [3]. These individuals have concerns regarding several issues, including their fertility and the health of their offspring.

In their Update, Thomson and her colleagues have concisely reviewed the potential effects of chemotherapy and radiation therapy on gonadal function, indicating that specific exposures may produce sub-fertility or infertility. Many survivors of childhood and adolescent cancer are sub-fertile. A large study (The Five-Center Study) of survivors, most of whom were treated with surgery only (51.6%, 636/1232) or surgery plus radiation therapy (33.8%, 417/1232) between 1945 and 1975, revealed an adjusted relative fertility of survivors of 0.85 (95% confidence interval (CI) 0.78–0.92), compared with that of their siblings. The adjusted relative fertility of male survivors (0.76, 95% CI 0.68–0.86) was slightly lower than that of females (0.93, 95% CI 0.83–1.04). The lowest relative fertility rates were demonstrated in male survivors who had been treated with alkylating agents, with or without infradiaphragmatic irradiation [4].

Ovarian or pelvic irradiation and/or treatment with alkylating agents may also damage female fertility and pregnancy outcome [5]. Some of these patients were excluded from the fertility analysis in the Five-Center Study because one entry requirement was that there was no evidence of sterility prior to their first marriage. In addition, only married women were included in the analysis of female fertility. Future analyses based on the Childhood Cancer Survivor Study [6] cohort will provide additional insight into the relative impact of various chemotherapeutic agents and gonadal or uterine irradiation [7,8] on the fertility of survivors.

Infertility may be the result of damage, such as azoospermia or amenorrhea that is expressed immediately. Shortened reproductive lifespan, as the result of premature menopause, has a more subtle effect on fertility. Women diagnosed with cancer after 12 years of age are significantly more likely to be menopausal during the interval 21–30 years of age than their healthy sibling controls (relative risk (RR) 2.32, 95% CI 1.63–3.29). Women treated for Hodgkin's disease had a significantly increased risk of early (premature) menopause compared with their siblings (RR 3.35, 95% CI 2.06–5.47), a risk that increased if treatment included both radiation therapy below the diaphragm and use of an alkylating agent (RR 9.57, 95% CI 4.93–18.69) [9].

Pregnancy outcome after treatment during childhood and adolescence for cancer has been studied by several groups. There was a deficit of males in the offspring of male survivors in the Childhood Cancer Survivor Study cohort, and an increased risk of low birthweight offspring among those of the female survivors who had received pelvic irradiation [10]. There is no evidence that there is an increased risk of cancer [11,12] or genetic disease [13] among the offspring of childhood cancer survivors, so long as the survivor has no evidence of a cancer predisposition syndrome, such as familial retinoblastoma or neurofibromatosis type I.

Most of the research on pregnancy outcome following treatment for childhood cancer has been descriptive and, in general, reassuring. As a result, there is increasing interest in interventional research, with the goal of preventing or circumventing the effects of chemotherapy and/or radiation therapy on gonadal reproductive function. The availability of accepted techniques for fertility preservation differs for boys and girls. Thompson and her colleagues provide a thorough review of the currently available methods for fertility preservation. Sperm banking is a well-recognised preservation tech-

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nique but its usefulness is limited, first, by the requirement that the patient be sexually mature and mentally competent and, second, that the start of anti-cancer treatment has to be delayed until a sufficient number of adequate semen samples have been obtained. Ovarian transposition or heterotransplantation of ovarian cortical strips may be useful for fertility preservation if the planned treatment involves pelvic irradiation [14]. There are insufficient data regarding the efficacy of this technique for fertility preservation when the patient is also treated with gonadotoxic chemotherapeutic agents, such as nitrogen mustard, chlorambucil, cyclophosphamide and/or procarbazine.

Other interventions require the harvesting of gonadal tissue or immature germ cells using an operative procedure, and, at present, must be considered experimental in paediatric cancer patients. These procedures are not without risk, both with respect to the future fertility of the patient, should the treatment not prove to be sterilising, and with respect to patient morbidity and mortality, as anaesthetic deaths, although extremely uncommon, do occur.

The ethical issues that attend the harvesting of germ cells, the use of *in vitro* fertilisation techniques, the possibility of harvesting malignant cells with the germ cells, the potential for continued transmission of germ line mutations in cancer predisposition genes and the potential mutagenicity of germ cell harvest, manipulation and storage are of particular concern [15–17]. At present, there are inadequate data regarding the risk of cancer in children who are the product of *in vitro* fertilisation techniques that utilise germ cells from subjects without a personal history of childhood cancer. All these issues argue strongly for the conduct of fertility-preservation research only in the context of well controlled clinical trials that are carefully reviewed and monitored by Institutional Review Boards and conducted by investigators who are free of conflict of interest, particularly potential financial gain. These trials will require prolonged follow-up to determine the excess risk, if any, for the occurrence of cancer or other diseases in the offspring.

Survival rates for children and adolescents with cancer will continue to improve, with the use of more selective and more aggressive therapies. The use of more aggressive therapies may increase the size of the population at risk for gonadal reproductive failure. These young men and women will want to know if they will be fertile, if their children will have a greater risk of developing cancer, and, if sterilisation is likely, what alternatives there are for having genetically related offspring. The continued and systematic evaluation of offspring of childhood cancer survivors, and the investigation of alternative methods for conception will provide scientifically valid answers to these important questions.

References

1. Capocaccia R, Gatta G, Magnani C, Stiller C, Coebergh J-W, eds. Childhood Cancer Survival in Europe 1978–1992: the EUROCARE Study [special issue]. *Eur J Cancer* 2001, **37**, 671–816.
2. Ries LAG, Smith, MA, Gurney, J.G. *et al*., eds. *Cancer Incidence and Survival among Children and Adolescents: United States SEER Program 1975–1995*. SEER Program. NIH Publication Number 99–4649. Bethesda, MD, National Cancer Institute, 1999.
3. Bleyer WA. The impact of childhood cancer on the United States and the world. *Ca Cancer J Clin* 1990, **40**, 355–367.
4. Byrne J, Mulvihill JJ, Myers MH, *et al*. Effects of treatment on fertility in long-term survivors of childhood or adolescent cancer. *N Engl J Med* 1987, **317**, 1315–1321.
5. Green DM. Fertility and pregnancy outcome after treatment for cancer in childhood or adolescence. *Oncologist* 1997, **2**, 171–179.
6. Robison LL, Mertens AC, Boice JD, *et al*. The Childhood Cancer Survivor Study. Methodology and cohort characteristics. *Med Pediatr Oncol* 2002, **38**, 229–239.
7. Critchley HOD, Wallace WHB, Shalet SM, Mamtora H, Higginson J, Anderson DC. Abdominal irradiation in childhood: the potential for pregnancy. *Br J Obstet Gynecol* 1992, **99**, 392–394.
8. Sanders JE, Hawley J, Levy W, *et al*. Pregnancies following high-dose cyclophosphamide with or without high-dose busulfan or total-body irradiation and bone marrow transplantation. *Blood* 1996, **87**, 3045–3052.
9. Byrne J, Fears TR, Gail MH, *et al*. Early menopause in long-term survivors of cancer during adolescence. *A:m J Obstet Gynecol* 1992, **166**, 788–793.
10. Green DM, Whitton J, Stovall M, *et al*. Pregnancy outcome after treatment for cancer during childhood or adolescence. A report from the Childhood Cancer Survivor Study (CCSS). *Med Pediatr Oncol* **33**, 1999, 146 (abstr).
11. Mulvihill JJ, Myers MH, Connelly RR, *et al*. Cancer in offspring of long-term survivors of childhood and adolescent cancer. *Lancet* 1987, **ii**, 813–817.
12. Hawkins MM, Draper GJ, Smith RA. Cancer among 1,348 offspring of survivors of childhood cancer. *Int J Cancer* 1989, **43**, 975–978.
13. Byrne J, Rasmussen SA, Steinhorn SC, *et al*. Genetic disease of offspring of long-term survivors of childhood and adolescent cancer. *Am J Hum Genet* 1998, **62**, 45–52.
14. Oktay K, Economos K, Kan M, Rucinski J, Veeck L, Rosenwaks Z. Endocrine function and oocyte retrieval after autologous transplantation of ovarian cortical strips to the forearm. *JAMA* 2001, **286**, 1490–1493.
15. Grundy R, Gosden RG, Hewitt M, *et al*. Fertility preservation for children treated for cancer (1): scientific advances and research dilemmas. *Arch Dis Child* 2001, **84**, 355–359.
16. Grundy R, Larcher V, Gosden RG, *et al*. Fertility preservation for children treated for cancer (2): ethics of consent for gamete storage and experimentation. *Arch Dis Child* 2001, **84**, 355–359.
17. Wallace WHB, Walker DA. Conference consensus statement: ethical and research dilemmas for fertility preservation in children treated for cancer. *Human Fertil* 2001, **4**, 69–76.