Trade-offs in cancer and reproduction

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TABLE OF CONTENTS

Introduction
Why are malignant diseases of breast and reproductive tissues so common?
What risks for fertility and the offspring?
What options for fertility conservation?
References

Introduction

Until recently, specialists in cancer and fertility appeared to have little in common, except for occasional exchanges of information, somewhat resembling the situation between friendly trading countries. Oncologists and haematologists were mainly preoccupied with preventing patients from succumbing to dread diseases, while reproductive specialists were concerned principally with couples who were healthy apart from problems of infertility. Now, after two decades of revolutionary advances, practitioners are at last realising the benefits of— and the need for—closer cooperation and interaction. In basic science, for instance, molecular endocrinology has provided insights for oncology, and vice versa, and from this dialogue new therapeutic strategies have emerged that are in turn informed by reproductive epidemiology. On occasion, the successful treatment of cancer in young patients causes infertility and hypogonadism, and indeed presents a challenge for reproductive technology (Meirow and Schenker, 1996). This symposium comprises an unusual and valuable collection of reports from the border territories of oncology, haematology and reproductive medicine. In addition to updating knowledge, it illustrates a welcome drift towards more holistic management and multidisciplinary research in cancer. No two readers ever take away exactly the same impressions, but perusal of these reports left the present author considering three issues.

Why are malignant diseases of breast and reproductive tissues so common?

It is strange that any hormone required for generating new life—such as oestrogen—should also be a risk factor for a life-threatening disease. This paradox is borne out by the fact that breast cancer rates are lowered by oophorectomy, which becomes clearer in the light of life history theory. According to the theory of antagonistic pleiotropy, increasing vulnerability to disease with age, including susceptibility to women’s cancers, is due to constitutional trade-offs between the beneficial actions and potential harms of normal physiological factors, including hormonal mechanisms (Williams, 1966). During evolution, genes promoting health and fertility at young ages were selected irrespective of whether they had any adverse effects later in life. And genes, or genetic polymorphisms, that did not produce harmful effects until after the reproductive lifespan had ended (i.e. postmenopause) have no countervailing selective force undermining reproductive success and tending to eliminate them from the population. Thus, we are trapped by the brutal phenomenon of ageing, and there may always be a price to pay for offsetting some undesirable effects. No example is clearer or of greater importance for contemporary women’s health than the balance between the necessary and beneficial effects of oestrogen and the tendency of this hormone to promote disease.

Cancers of the reproductive system, particularly the breast, are at epidemic frequencies in Western countries today. Lifetime risks hover around 1 in 10, although mortality rates are gradually falling in some places. The duration of exposure to unopposed oestrogen during the follicular phase of the menstrual cycle is widely thought to predispose to disease. Balen (2001) points out that this is consistent with the higher incidence of endometrial (but apparently not ovarian) carcinoma in patients with polycystic ovarian syndrome (PCOS). Unfortunately, research to identify any genetic basis has not made as much progress with PCOS as it has with reproductive cancers.

The problem is far broader than a specific disease, however common. Whereas our hominoid ancestors were serially pregnant and lactated almost continuously after puberty, modern contraceptive practices have tended to reinforce the monthly rhythm of oestrogen secretion and ovulation. Menstrual cyclicity from puberty to menopause looks like an artefact of civilization, and the risks of childbearing and delivery are being partly replaced by new hazards (Eaton et al., 1994; Gosden et al., 1999). Perhaps a safer and more physiological state for the reproductive system will be found for women who choose to have fewer children and start later.
Genetics and epidemiology have demonstrated many contributory factors, although attention still focuses on the mechanisms of oestrogen action, and timid hopes remain that selective oestrogen receptor modulators (SERMs) might deliver the advantages of hormone replacement therapy without risk. We had assumed that oestrogen was the demon-princess, but progesterone can no longer be regarded as its benign sister. Progesterone has a protective role on the endometrium and it too may carry some responsibility for breast disease, with many implications for steroid contraception and replacement therapy.

Besides the potential hazard of cyclical bombardment of breast and endometrial tissues with steroids, ovulation may itself be a risk factor for ovarian cancer. It is not clear whether polypeptide hormones make any direct contribution to disease although, in animals, elevated gonadotrophin concentrations can promote ovarian tumours whereas inhibin seems to suppress them. At a time when thousands of women are undergoing hyperstimulation using exogenous gonadotrophins, the question of safety is repeatedly asked. So far, the reassuring, but still tentative, conclusion is that there are no excess risks of ovarian cancer after assisted reproduction.

Cancer presents a special dilemma if it is diagnosed during pregnancy because of the strained balance of interests between the mother and her child-to-be. Fortunately rare (0.1%), its frequency is bound to rise if women continue delaying maternity until late reproductive years. In the case of malignant melanoma, the high risk of involving the placenta and fetus presents a challenge for patient management. It has been concluded (Weisz et al., 2001) that pregnancy hormones have little, if any, impact on breast cancer progression, and so abortion seems to be an unnecessary precaution. Most concern has focused on alkylating agents, because they are potentially mutagenic, but in other disorders of folate metabolism by methotrexate treatment and other dangers exist. The first trimester of pregnancy is the most critical for teratogenesis, but cancer treatment could compromise the more slowly developing nervous system. One clear message emerging from these chapters is the need for multidisciplinary cooperation between centres so that enough statistical power can be obtained for prospective studies of physical and cognitive development.

What risks for fertility and the offspring?

The benefits of chemotherapy and radiotherapy come at a price and, in young people, this can include infertility. It has been noted (Howell and Shalet, 2001) that iatrogenic gonadal damage has been lessened by the introduction of hybrid formulations with a lower alkylating agent content, but there is no sign that the problem is disappearing. Furthermore, the return of menses does not necessarily signal the absence of ovarian harm and the prospect of a full span of reproductive life. A man may take greater assurance if spermatogenesis returns soon after completing cancer treatment, but what of the individual who later relapses and did not bank semen because first-round treatment was not expected to completely sterilize him? He may have to undergo high-dose sterilizing treatment before sperm production resumes, and loses his chance of storing gametes. This example does not imply that every man should avail himself of the technology, because every case brings a unique set of medical and social circumstances and personal priorities.

Others (Lass et al., 2001) urge that semen cryopreservation should always be offered to 'young' men unless they have completed their family. From a British perspective, they argue that the costs should be borne by the state as part of the package of cancer treatment, even though only a minority of patients (<10%) ever use their cryopreserved semen. A few patients cannot produce a satisfactory specimen until after starting cytotoxic treatment, but it would be ill-advised to use it until the risks of aneuploidy and/or new mutations have been fully tested. We are hampered because knowledge of biology and toxicology lags behind that of reproductive technology.

Arnon et al. (2001) point out that epidemiology has not revealed any excess of birth defects from former cancer patients (Arnon et al., 2001). This pleasing finding is surprising in view of animal studies which have shown increased pregnancy losses and malformations in the offspring after treatment with radiation and alkylating agents (Trasar and Doerksen, 1999; Meirov et al., 2001). We should bear in mind that most of the patients who were studied recovered fertility spontaneously and conceived naturally. The advent of powerful assisted reproduction technology (ART), such as intracytoplasmic sperm injection (ICSI), now extend the chance of genetic parenthood to others who were irreversibly sterilized, and the increased hazard and lack of natural selection of gametes multiplies the genetic risks for their offspring.

What options for fertility conservation?

A succession of breakthroughs in ART has revolutionized options for patients (Figures 1 and 2). Men can bank semen for intrauterine insemination (IUI) and, if spermatozoa are aspirated from the gonad or epididymis, the method of last resort—donor insemination—is avoided. Women can undergo ART to cryopreserve embryos, and oocyte banking is now on trial for those without male partners. This optimistic outlook needs to be qualified by the relatively low success rates and the unsuitability of these procedures for children. Being invasive, complex and costly, ART also adds to the stress of cancer treatment, and there may not be time for an IVF cycle before chemotherapy should begin. For all these reasons, other strategies for fertility conservation are being sought.

Howell and Shalet (2001) review evidence for the moderating effects of gonadotrophin-releasing hormone (GnRH) analogues on gonadotoxicity, concluding that these drugs appear more promising in animal studies than clinical experience. There may be new options around the corner, judging from recent experimental studies showing an anti-apoptotic effect of small lipid molecules on the ovarian follicle population (Morita et al., 2000). Preserving germ cells in vivo is attractive in theory because of the convenience of drug delivery and avoidance of invasive procedures. The question remains, however, whether it is safer to remove the cells from the zone of genetic harm.

Gonadal tissue cryopreservation followed by autotransplantation provides a safeguard, and has the merit of being potentially suitable for children. Ovarian transplantation has been practised in animals for over a century, and encouraging studies in monkeys and humans are now appearing in print. One of the protagonists of this approach (Oktay, 2001), suggests that, in addition to emergency use for cancer patients, women with a family history of ovarian malignancy might elect to bank ovarian tissue to
safeguard health and provide insurance for future motherhood at
the same time. Follicle culture might be safer for the would-be
mother, but this technology is difficult and unlikely to be available
in the near future.

The complex architecture of the seminiferous epithelium seems
to preclude a parallel strategy in the male, but Hovatta reviews a
radical approach developed in Philadelphia (Hovatta, 2001).
Isolated spermatogonial stem cells can restore sperm production
and even fertility after orthotopic transfer to chemically or
genetically sterilized host animals. It might be imagined that some
men (and boys) could store their own stem cells for autotrans-
plantation in a way which is analogous to practice with bone
marrow. The goal is to restore natural fertility, but if this is too
ambitious, it should be possible to use cryopreserved tissue as a
subcutaneous graft to generate enough spermatozoa for an ICSI
procedure long after a testicular biopsy was obtained prepubertally.

These technologies address a matter of quality of life that most
of us take for granted—the ability to become a genetic parent.
Notwithstanding ethical debates about the extension of these
technologies to other scenarios, they should be welcomed as a
contribution to the ongoing conquest of cancer and its side effects.
As some of these procedures evolve to become standard, demands
on clinical decision-makers will rise, but the more options
available to their patients, the more they can benefit.

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