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Review

Childhood and adult cancers: Contrasts and commonalities

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ABSTRACT

Tumours occurring in children differ considerably from those occurring at older ages but exhibit common features. Those occurring in the teenage/young adult (TYA) years represent a transitional mixture of child and adult tumours and pose a considerable challenge for optimal clinical management and service provision. Nevertheless the fundamental processes of malignant change, arising from genetic/epigenetic interaction with environmental exposures, seem to operate across all ages and the entire tumour spectrum. We focus here on the ways in which genotype (and epigenetic modification), growth processes (particularly in utero), and exposure to ionising radiation (in conjunction with genetic susceptibility) affect cancer risk from childhood to adulthood, whether as a primary occurrence, or a second primary tumour following earlier primary occurrence and treatment.

Contents

1. Introduction: childhood cancer origins, management and outcome

Childhood cancers are a rare and heterogeneous disease group. They comprise the haematopoietic tumours (leukaemia/lymphoma), about 40%, central nervous system (CNS) tumours, about 25%, and other solid tumours, about 35%. All three groups differ in underlying pathology, behaviour and treatment outcome compared to the much more commonly occurring tumours of middle and old age. The contrast is especially marked for non-CNS solid tumours. In children, these are predominantly embryonal tumours of early life and a few specific types of sarcomas and germ-cell tumours, whereas in adults carcinomas are the most common type [1]. The spectra of sarcomas and germ-cell tumours are also quite different in the two age-groups [2,3]. Nevertheless, the fundamental processes of malignant change (namely accumulation of clonal mutations in a progenitor cell line with the potential for self-renewal) are likely to be a common feature.

Few people have direct knowledge and experience of tumours occurring at young ages. General practitioners in the UK may only encounter the conditions once or twice in a professional lifetime, amidst the welter of other childhood illnesses about which they are consulted. Hospital services for children with cancer are procured in the NHS through Specialised Commissioning. Outcome of specialist care for childhood cancer, whether delivered in a Principal Treatment centre (PTC) or in conjunction with a Paediatric Oncology Shared Care Unit (POSCU), has improved considerably over the last 50 years, from a time when most children with the

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disease died rapidly to the present, when the 5 year survival rate is approximately 80%. This is considerably higher than the average for a person developing cancer (of the same or different type) at older ages in the UK. There are however important complications of the treatments and a lingering price to pay in the survivors, of whom there are now estimated to be about 35,000 in the UK and 350,000 in the USA, or about 1/1000 of the general adult population. This is against a background risk of developing a childhood cancer by age 15 years of about 1 in 500 compared with the lifetime risk of an adult cancer at 1 in 3 or higher.

The UK National Registry of Childhood Tumours (NRCT) is regarded as among the best specialist registries in the world. It has a long history of completeness of recording. The UK data suggest that tumours in childhood are increasing secularly as part of a worldwide phenomenon. Nevertheless, UK rates remain amongst the lowest in the world (Fig. 1) [4–6].

2. Causes: contrasts and commonalities

The causes of childhood cancer are not well understood, though of those candidate exposures (genetic or environmental) which are emerging, several are probably also linked to the separate development of other different cancers at older ages. Moreover, the treatments that are effective against childhood cancers may also give rise to subsequent primary tumours (SPTs) in the ageing childhood cancer survivors, and study of these SPTs informs general knowledge of cancer causes. We review here some of the features common to childhood and older age cancers, namely genetic and host constitutional factors, the influence of intrauterine growth patterns, exposure to ionising radiation, and the consequences of chemotherapy/radiotherapy (and surgical) treatments for an initial childhood primary tumour. Infection contact is a further plausible candidate influence on childhood cancer risk, particularly for the leukaemias but, in contrast to the proven role of certain infections in a proportion of adult cancers, the involvement of infection in childhood cancer risk remains a hypothesis, and as such it is not further discussed here [7–9].

3. Genotype: interaction with medical and environmental exposures

Constitutional genotype affects cancer risk and response to treatment in both childhood and adulthood. The rare childhood eye tumour retinoblastoma (2% of all childhood cancers), which occurs in both heritable and somatic forms, has formed a paradigm for understanding carcinogenic processes in children and adults. The retinoblastoma gene *RB1* was the first tumour suppressor gene (appearing dominant at the pedigree level, recessive at the cellular level) to be identified, following Knudson's investigations [10]. The retinoblastoma gene product, pRb, is intimately involved in control of the cell cycle. Whether inactivation of both copies of the gene is sufficient for a child to develop retinoblastoma, or whether other gene mutations or epigenetic alterations are also necessary, is currently disputed [10,11]. What is clear is that germline mutations in *RB1* not only confer a highly penetrant risk of retinoblastoma, but they also affect risk of a wide variety of tumours occurring from late childhood through to middle-age onwards, because of increased sensitivity to further DNA damaging mutations in tissues outside the eye. Germline *RB1* mutations affect the risk of melanoma, bladder, lung cancer and other malignancies, perhaps through sensitising the progenitor cells concerned to UV radiation and carcinogens present in tobacco smoke and from other sources [12]. Whether treatments with irradiation and chemotherapy for primary (heritable) retinoblastoma separately affect SPT risk, particularly within the radiation field (head and neck), is not precisely quantified, but these treatments seem likely to interact with each other as well as with the *RB1* genotype [13].

Other genes important in control of the cell cycle and response to DNA damage are also known to affect adult cancer risk. For instance, rare genetic variants of the Ataxia Telangiectasia Mutated (ATM) gene appear to increase the risk of breast cancer following irradiation for medical purposes [14]. In addition to the well defined associations between *BRCA* gene mutations and risk of a number of adult cancers [15], biallelic mutations in *BRCA2* (which is also a Fanconi anaemia gene) affect childhood cancer risk (or may be otherwise prenatally fatal) [16,17]. Congenital malformation/tumour suppressor gene mutation syndromes are also estimated to be associated with about 5% of the total occurrence of childhood cancer, and may further be associated with the earlier rather than later occurrence of any SPT within the childhood years [18]. As gene mutations associated with tissue growth, development, cell death and malformation are conceptually associated with the general notion of the cellular/tissue processes underlying malignant change, it is not surprising that empirical evidence of these kinds of relationships has been observed.

4. Growth and cancer risk

Intrauterine growth does seem to be closely wedded to the occurrence of many childhood and adult cancers [19–22]. The measure that is widely available of intrauterine growth is birthweight, which is intimately related to gestational age. Numerous studies have suggested associations of being bigger at birth with childhood cancer risks, and recent studies have suggested that risk is in fact associated with increased or accelerated intrauterine growth, across the entirely normal birthweight range. The factors related to general size of the foetus, or growth of specific organs, e.g. head circumference and childhood brain tumour risk, seem to be implicated [23,24]. Achieved height may also be associated with childhood cancer risk [25,26], as may mature adult height and adult cancer risk [27], indicating further associations with postnatal growth. Bone tumour risk associated with the adolescent growth spurt (but not with intrauterine growth) may be another example of the influence of different growth factors affecting risk in specific ways [28]. Perhaps uniquely, risk of certain childhood tumours may be specifically decreased in association with enhanced foetal growth, for instance hepatic tumours [29].

Twin babies, weighing on average about 1000 g less at birth each than a comparable singleton birth, have been found to experience a consistently reduced childhood cancer risk, and perhaps a reduced risk in the teenage/young adult (TYA) years, though total lifetime risk of cancer in twins (dominated by the adult age experience) is probably the same as for babies born as singletons [30]. It is unlikely that treatment for subfertility modifies this reduction of risk that twins experience [31]. Low average birthweight may be the unifying explanation for reduced childhood cancer risk, although twins experience unusual intrauterine exposure levels, e.g. to oestrogens which both promote growth and may modify the risk of certain cancers. Testis cancer illustrates the complexity of potential explanatory mechanisms [32]. Twin babies appear to be at greater risk of testis cancer, perhaps because of oestrogen exposure in utero, though on average testis cancer is also associated with lower birthweight, which twin babies exhibit. Unravelling the potentially competing mechanisms underlying growth and cancer risk is proving a complex task.

5. Ionising radiation exposures

Exposure to ionising radiation is now clearly demonstrated to be a cause of childhood, TYA, and older age cancers. Increased