CHAPTER 20

Age and susceptibility

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PART 2
CHAPTER 20

Introduction

There is abundant experimental evidence from studies in animals, especially rats and mice, that susceptibility to certain chemical carcinogens is higher, and sometimes much higher, during prenatal and early postnatal life than in adulthood. There is also an extensive epidemiological literature on the differential effects of a wide variety of carcinogens in humans at different stages of life, including various forms of radiation, carcinogenic infectious agents, and chemicals and chemical mixtures. This chapter summarizes the literature that documents this high susceptibility of the fetus, infant, and child to many potentially carcinogenic exposures.

Studies in experimental animals

Most experimental studies of carcinogenesis during prenatal life and infancy have been conducted with chemical agents. Experimental evidence for susceptibility in utero and during infancy to chemical carcinogens and, to a lesser extent, to various sources of ionizing radiation has been summarized in reviews and symposium proceedings (Tomatis and Mohr, 1973; Rice, 1979; Napalkov et al., 1989; Rice, 2004).

At least in experimental animals, greater susceptibility to chemical carcinogens in utero and during early postnatal life is usually manifested as a higher incidence of the same kinds of tumours that occur in exposed adults, with a shorter latency period from the time of exposure to the carcinogen until the appearance of the tumour. In bioassays for carcinogenicity in adult rodents, the incidence and multiplicity of tumours increase and the latency period decreases with increasing dose. Thus, the predominant results of early-life exposure are what would be expected from a higher effective dose to the fetus or infant than that experienced by the mother.

However, in some cases the tumours that result from prenatal or perinatal exposures are different from those that occur in exposed adults. Tumours induced prenatally become manifest only during adult life in rats and mice, except in certain genetically modified strains, because in these species the interval between birth and sexual maturity is only a few weeks. Therefore, the types of tumours that occur during childhood in humans, including various embryonal solid tumours, are observed as tumours of adult life in conventional rodents. An example is the development of nephroblastomas – embryonal kidney tumours that correspond to Wilms tumour in humans – in the adult rat after perinatal exposure to a chemical carcinogen. Such tumours do not develop in rats exposed to the same carcinogen during adult life (Diwan and Rice, 1995).

Chemical carcinogens that reach the fetus via the maternal circulation must have crossed the placenta, and consequently are generally referred to as transplacental carcinogens. All but a few known transplacental carcinogens are organic compounds that act principally or entirely by a genotoxic mode of action. Factors that contribute to fetal susceptibility to these agents include maternal, placental, and fetal metabolism, the immature state of fetal DNA repair capability, the high rate of cell division during prenatal development, and the rapidly changing patterns of gene expression in fetal target tissues, which may render the genetic material of fetal cells highly accessible to carcinogens.

Different organs and tissues are not equally susceptible to transplacental carcinogens: in experimental animals, some fetal organs, notably the developing nervous system, are exceptionally susceptible to a wide range of agents. Although differences between mother and fetus in absorption and distribution of a carcinogen may well exist and may contribute to greater apparent effects of an administered dose in the offspring, these differences are likely to be less important than certain other physiological differences between mother and fetus, including differences in metabolic competence and in DNA repair capacity.

Most chemicals that have a genotoxic mode of action must be biotransformed to chemically reactive metabolites to initiate carcinogenicity. The requisite enzymes are often expressed in fetal tissues only late in gestation, and then at low levels of activity; thus, only small amounts of reactive metabolites are generated in fetal tissues. Metabolites of maternal or placental origin may contribute to carcinogenic effects in utero, but when the reactive metabolites formed in maternal tissues are too unstable to circulate in the maternal bloodstream, cross the placenta, and reach the fetus, a carcinogenic chemical may have no transplacental carcinogenic activity or may only cause a low incidence of tumours near the end of gestation, in offspring that were exposed transplacentally. This pattern can be seen in the transplacental carcinogenicity of single doses of *N*-nitrosodimethylamine (NDMA) in rats (Alexandrov, 1968). In both the fetus and the pregnant female rat, the target organ for single doses of NDMA is the kidney, but a much lower incidence of tumours is observed in the offspring. For many other compounds whose reactive metabolites are longer-lived in vivo, the maternal contribution of reactive metabolites to fetal tissue burden may be substantial, and the resulting susceptibility of the fetus may be greater than that of the mother.

Short-chain alkylnitrosourea compounds are chemically highly reactive and are extremely potent, direct-acting transplacental carcinogens. In rats, a single exposure to one of these short-lived agents can cause a high incidence and multiplicity of tumours of the nervous system in the offspring of females treated during the second half of gestation (Ivankovic and Druckrey, 1968). These substances are direct-acting, and the simplest members of this chemical class, especially *N*-ethyl-*N*-nitrosourea (ENU), have been used to probe changing susceptibility to carcinogenesis during prenatal life due to factors other than carcinogen metabolism. Tumours are induced in offspring exposed once transplacentally to ENU, beginning at approximately 12 days of gestation in the rat, when organogenesis starts. Tumour multiplicity rises to a maximum in offspring exposed at approximately 21 days of gestation, a few days before birth. The susceptibility of the fetus relative to that of adult rats is measured as the incidence and multiplicity of tumours that develop in offspring after birth, compared with the incidence and multiplicity of the same types of tumours in their directly exposed mothers. By that measure, the susceptibility of the rat fetus to induction of brain tumours by ENU during the final week of gestation is approximately 50 times that of the mother.

Transplacental carcinogenesis studies with ENU in non-human primates, although far less extensive than studies in rats, also indicate that the susceptibility of the fetus is greater than that of the mother. Tumours have been induced in the offspring of rhesus and patas monkeys exposed to ENU during the first trimester of pregnancy (Rice et al., 1989).

Ionizing radiation, both from external sources and from internalized radionuclides, is capable of producing mutations, mainly by large-scale gene deletions, as well as gross chromosomal damage, and thus is similar in its effects to direct-acting genotoxic chemical carcinogens, because there is no metabolic biotransformation of the agent (IARC, 2012e). There are many examples of carcinogenesis by different forms of ionizing radiation, in experimental animals and in humans and at all ages, from prenatal life to adulthood. Solar and ultraviolet radiation also are carcinogens that directly damage DNA, but they are less penetrating than the more highly energetic forms of ionizing radiation (e.g. X-rays), and thus exert their carcinogenic effects primarily on the skin,

causing distinctive mutations in DNA (Agar et al., 2004; IARC, 2012e).

Results from experiments with genetically engineered transgenic and knockout mice, especially double knockouts, provide information about the significance of individual genes and gene combinations in susceptibility to and pathogenesis of specific tumours, including embryonal neurogenic tumours of childhood such as medulloblastoma (reviewed in Rice, 2004), and offer some insight into why embryonal tumours appear relatively later in life in mice than in humans.

For example, the gene *PTCH1*, the human homologue of the *Drosophila* segment polarity gene *patched*, is a tumour suppressor gene associated with nevoid basal cell carcinoma syndrome. Patients with this syndrome are predisposed to develop primitive neuroectodermal tumours of the central nervous system, including medulloblastomas, and mutations in *PTCH1* have been identified in a subset of sporadic primitive neuroectodermal tumours. Genetically engineered knockout mice with only a single normal allele of *Ptc1*, the mouse homologue of *PTCH1*, develop medulloblastoma-like cerebellar tumours (7–14% incidence). Neonatal exposure of these *Ptc1+/−* mice to 3 Gy X-radiation increased this incidence to 50%, but irradiation in adulthood had no effect on medulloblastoma incidence (Pazzaglia et al., 2002).

Dramatically, 95% of *Ptc1+/−* mice that had also been genetically engineered to remove both alleles of the tumour suppressor gene *p53* developed medulloblastomas, and did so very early in life, at younger than 12 weeks (Wetmore et al., 2001). This combination of inactivating gene mutations is not seen in conventional mice exposed to transplacental carcinogens, presumably because the probability of such a combination of events without concomitant lethal genetic damage is immeasurably low.

Although the importance of specific genetic events, including mutations and chromosomal alterations, in the genesis of cancers is clear, evidence is accumulating that many carcinogens also cause intracellular changes that may contribute to the carcinogenic process but do not involve carcinogen-induced alterations in genetic sequences. These changes, which may occur several cell generations after exposure to the carcinogen, are termed epigenetic and can be caused by ionizing radiation, chemicals, and ultraviolet light. They include genomic instability, a reduced ability to replicate the genotype faithfully (Barcellos-Hoff, 2005), and various other effects (IARC, 2012e). It is not yet clear how epigenetic events in carcinogenesis may vary with age at time of exposure to the carcinogen.

Epidemiological findings in humans

The consequences of environmental exposures to chemicals and radiation during childhood for the risk of cancer later in life have been reviewed (Carpenter and Bushkin-Bedient, 2013). In patients who receive anticancer therapies, the exposures are much more intense, and consequently the risk of cancer is higher.

Anticancer therapy

Non-surgical therapy for cancer in childhood and adolescence – by ionizing radiation, combination chemotherapy, or both – has become increasingly effective and in many cases is curative, but it imposes a long-term risk of second cancers in survivors. The most intense exposure of children to ionizing radiation and to genotoxic chemicals most commonly occurs in the context of anticancer therapy. Carcinogenic effects resulting from early-life exposures are most clearly seen among the long-term survivors of childhood cancers who were successfully treated with high doses of radiation and/or chemotherapy. The examples given here and in the next section are representative rather than comprehensive.

The risk of acute myeloid leukaemia, non-Hodgkin lymphoma, and solid cancers of the breast, thyroid, bone, central nervous system, colorectum, and stomach increased significantly in survivors of Hodgkin lymphoma diagnosed before age 16 years and successfully treated with radiation, chemotherapy with alkylating agents, or both. Breast cancer occurred only in women who had received X-radiation alone or chemotherapy and X-radiation combined to treat Hodgkin lymphoma. Breast cancers developed usually within the radiation field, and the risk of breast cancer was 75 times as great as that in the general population. Second cancers occurred at increased rates in patients originally treated with chemotherapy alone, X-radiation alone, or chemotherapy and X-radiation combined, but at different sites; breast cancers occurred only in patients who had received X-radiation with or without chemotherapy, and leukaemia was observed only in patients who had received chemotherapy (Bhatia et al., 1996). In survivors of childhood cancers overall, the risk of gastrointestinal second cancers increased

significantly with abdominal radiation and after high-dose chemotherapy with procarbazine and platinum drugs (Henderson et al., 2012a).

Radiation from nuclear weapons and nuclear reactor accidents

There is a statistically significant excess risk of solid cancers in people who were exposed to ionizing radiation from the atomic bombs in Japan either in utero or during early childhood (age < 6 years). Cancers developed in both children and adults (age 12–55 years at the time of diagnosis) and included leukaemia and a variety of solid tumours (Preston et al., 2008; IARC, 2012e). Cancers of the thyroid are notable in this cohort in the context of an exceptional susceptibility to develop cancer during early life, because they occurred almost exclusively in survivors who were younger than 14 years at the time of the bombings.

Short-lived radionuclides of iodine, especially iodine-131, were released into the atmosphere in enormous quantities during the accident with the Chernobyl Nuclear Power Plant in Ukraine, in 1986. Children in Ukraine and in neighbouring countries who were exposed to this radiation at an early age developed papillary adenocarcinoma of the thyroid later in childhood, beginning only a few years after the event (Bennett et al., 2006; IARC, 2012e). Thyroid cancer has also been observed in children from highly contaminated areas who were in utero at the time of the accident (Hatch et al., 2009). Children exposed to radioisotopes of iodine from the Chernobyl accident were at much higher risk of thyroid cancer than adults who were similarly exposed.

Medical radiation

People who were exposed to diagnostic X-rays in utero and in childhood during the 1950s are at increased risk of cancer, as documented in the Oxford Survey of Childhood Cancers (Wakeford and Little, 2003). However, a more recent meta-analysis (Schulze-Rath et al., 2008) of studies published after 1990 did not find any association between in utero exposure to medical radiation and the risk of childhood cancer, probably because in utero diagnostic doses for single-film X-rays are now substantially lower than those that were used previously and that formed the database for earlier reports of increased cancer risk.

Computed tomography (CT) diagnostic scans, for which much higher doses of radiation are used than for single-film X-rays, have come into common use for diagnostic procedures in both adults and children. CT scans have recently been reported to increase the risk of leukaemia and brain tumours in a dose-dependent fashion in patients who received their first scan when younger than 22 years (Pearce et al., 2012).

Therapeutic X-radiation of the head and neck during childhood for non-neoplastic conditions, most commonly to treat fungal infections of the scalp, caused a statistically significant increase in the incidence of intracranial meningiomas and nerve sheath tumours and a smaller increase in the incidence of brain tumours (Ron et al., 1988; Sadetzki et al., 2005). Thyroid carcinoma also occurred in irradiated children, who were much more sensitive to X-ray-induced thyroid cancer than were adults (Ron et al., 1995; IARC, 2012e). The risk of thyroid cancer

in survivors of various childhood cancers who had received radiotherapy for their first malignancy increased linearly with radiation dose to the thyroid up to 20 Gy; the relative risk peaked at 14.6-fold (Bhatti et al., 2010).

Therapeutic anti-tumour X-radiation to the chest during childhood or adolescence for Hodgkin lymphoma, and to a lesser extent for non-Hodgkin lymphoma, Wilms tumour, leukaemia, bone cancer, neuroblastoma, and soft tissue sarcoma, greatly increased the risk of breast cancer in female survivors, who tended to develop the second malignancy at a comparatively early age, during young adulthood (Henderson et al., 2010). Secondary sarcomas are associated in a dose-dependent fashion with radiation therapy for childhood tumours; radiation exposure was the most important factor for development of secondary sarcomas in survivors of childhood cancer (Henderson et al., 2012b).

Solar radiation

Solar radiation and sunburn during childhood are significant risk factors for malignant melanoma of the skin. Duration of residence in Australia – and the associated exposure to intense solar radiation – is associated with the risk of developing malignant melanoma, and childhood is an especially vulnerable life stage (Holman and Armstrong, 1984). A history of sunburn, especially during childhood, is also correlated with the risk of cutaneous melanoma. A study in England concluded that the strongest association with elevated melanoma risk was for sunburn that occurred in children aged 8–12 years (Elwood et al., 1990).

Chemicals and chemical mixtures other than cytotoxic anti-tumour agents

Diethylstilbestrol (DES) is a synthetic non-steroidal estrogen that was administered to pregnant women during the 1950s and 1960s in an effort to maintain high-risk pregnancies. Although DES is rarely used now, it has been estimated that 5–10 million women in the USA were treated with DES during pregnancy or were exposed to the drug in utero (Giusti et al., 1995).

Female offspring of women treated with DES developed an unusual cancer of the vagina and cervix, clear cell adenocarcinoma, which became clinically evident during adolescence and early adulthood (Herbst et al., 1971). DES caused breast cancer and is positively associated with the risk of endometrial cancer in women who were exposed while pregnant. In addition, a positive association has been observed between prenatal exposure to DES and squamous cell carcinoma of the cervix in female offspring and cancer of the testis in male offspring (IARC, 2012d). DES is the only chemical carcinogen known to have caused cancer in humans by transplacental exposure.

The mechanism of action of DES as a carcinogen is complex. DES is a potent estrogen, and some of its effects are mediated, at least in large part, by estrogen receptor alpha. DES can also undergo oxidative metabolism. In fetal mouse tissues, it causes aneuploidy, chromosomal breaks, and other chromosomal aberrations; it binds covalently to DNA and thus probably acts in part through a DNA-reactive genotoxic mechanism. In mice, neonatal exposure to DES also causes persistent changes in gene expression in target tissues (Newbold et al., 2006).

These changes were found in specific genes (*Fos* and *Ltf* [lactoferrin]) and persisted even after cessation of treatment. Interestingly, changes in gene expression were associated with epigenetic alterations: specifically, the genes that were differentially expressed in animals treated with DES also exhibited abnormal DNA methylation (Newbold et al., 2000, 2006). These findings, although limited in genome coverage, strongly suggest that exposure to DES may have a significant and long-term effect on gene expression through epigenetic mechanisms. More recent studies that used microarray-based transcriptome analysis in both rats and mice identified DES-induced changes in expression of a wide range of genes (Hsu et al., 2009; Warita et al., 2010; Lee et al., 2011). Whether these changes are caused by epigenetic deregulation has not been tested.

Another interesting feature of exposure to DES is its potential impact on cancer incidence in subsequent generations. In addition to an increased cancer susceptibility associated with epigenetic changes in parents treated with DES, an epigenetic mechanism may operate in subsequent generations of mice (the second generation) (Newbold et al., 2006). These findings further support the notion that DES-induced carcinogenesis may operate in part through an epigenetic mechanism, although studies extending to the third generation are needed to establish a true transgenerational epigenetic inheritance.

Parental cigarette smoking causes hepatoblastoma, an embryonal tumour of the liver, in children. The effects of prenatal and postnatal exposures to parental cigarette smoke cannot be evaluated separately, although the weight of evidence favours the greater importance of prenatal exposures. Also, a positive association has been observed between parental smoking and risk of childhood leukaemia (particularly acute lymphoblastic leukaemia) (IARC, 2012c).

A plethora of experimental studies indicate that chemical components in tobacco smoke induce a wide range of genetic changes (Hainaut and Pfeifer, 2001; Pfeifer et al., 2002; Wistuba et al., 2002; Lea et al., 2007). More recent studies also implicate epigenetic events in human cancer associated with tobacco exposure (Herceg, 2007; Lin et al., 2010; Huang et al., 2011).

In a study of the methylome in cord blood of newborns in connection with maternal smoking during pregnancy, differential DNA methylation changes in a specific set of genes were associated with tobacco exposure (Joubert et al., 2012). A genome-wide methylomics approach and measurement of cotinine (a validated and objective biomarker of smoking) were used to identify methylation alterations in newborn cord blood samples from a mother–child cohort in relation to maternal smoking. Maternal smoking during pregnancy influenced methylation changes in specific genes. *CYP1A1* and *AHRR*, which encode proteins involved in the detoxification of chemicals in tobacco smoke, were among the differentially methylated genes (Joubert et al., 2012), suggesting a potential epigenetic mechanism involved in adverse effects associated with in utero exposure to tobacco smoke.

Various forms of inorganic arsenic have been collectively classified as *carcinogenic to humans* (Group 1). These compounds cause cancer of

the skin, bladder, and lung, and possibly of the liver and kidney, in exposed humans. Arsenic compounds have been notoriously difficult to evaluate in conventional animal bioassays for carcinogenicity. However, during the past decade sodium arsenite has been shown in several studies to be a transplacental carcinogen for the lung, liver, ovary, and adrenal cortex in mice (Waalkes et al., 2007; IARC, 2012a; see also Chapter 3, by Waalkes). Sodium arsenite is unique in this respect among inorganic carcinogens.

Also, recent epidemiological studies indicate that early-life exposure of humans to inorganic arsenic, most commonly in drinking-water but also in contaminated food products (Yorifuji et al., 2011), can lead to liver cancer during childhood (Liaw et al., 2008), to lung cancer in young adulthood (Smith et al., 2006), and to kidney cancer decades later (Yuan et al., 2010).

The possible transplacental effects of other inorganic Group 1 agents, such as nickel, cadmium, and chromium(VI), in animals or humans have not been well established.

Infectious agents

The factors that underlie the high susceptibility to oncogenic infectious agents during early life are different from those that govern susceptibility to chemical carcinogens and radiation. Lack of immunity to the agents in infants and immature immune responses to infection in infancy and during childhood are major contributors to susceptibility to these agents early in life, in common with the well-known susceptibility of children to other, non-oncogenic infections.

Several oncogenic infectious agents readily establish persistent

infections in young children, setting in motion pathogenic processes that may lead to overt cancer development during childhood. Examples are Epstein–Barr virus (EBV) and hepatitis B virus (HBV). Other oncogenic pathogens, including Kaposi sarcoma-associated herpesvirus (KSHV), the bacterium *Helicobacter pylori*, and the bladder fluke *Schistosoma haematobium*, establish primary infection during childhood, but the resulting cancers appear after the paediatric age (> 18 years) and may require cofactors, especially immunosuppression. Suppression of the immune response may result either from co-infection with a second agent, generally the malarial parasite *Plasmodium falciparum* or human immunodeficiency virus type 1 (HIV-1), or by iatrogenic immunosuppression before and after organ or tissue transplantation.

EBV is a ubiquitous oncogenic gamma herpesvirus that infects and persists for life in more than 90% of the adult population worldwide. Children in certain regions of Africa become infected with EBV early in life, and nearly all have seroconverted by age 3 years, whereas in affluent countries primary infection is often delayed until adolescence (Biggar et al., 1978a, b). Primary EBV infection in early childhood, unlike that in adolescence, is usually asymptomatic (Chan et al., 2001).

EBV coexists for a lifetime in most human hosts without causing overt disease, but viral replication can be reactivated in several ways, including malaria infection, specifically *P. falciparum* malaria. Children living in areas endemic for malaria, notably in tropical regions of sub-Saharan Africa, have an elevated EBV viral load and a diminished EBV-specific immunosurveillance at

ages 5–9 years. As a result of this combined infection, they are at high risk of developing endemic Burkitt lymphoma (eBL) during that period (IARC, 2012b). eBL is a high-grade B-cell lymphoma characterized by the consistent presence of EBV (zur Hausen et al., 1970) and is the most common paediatric cancer in sub-Saharan Africa (Greenwood et al., 1970). The determining factors that bring about eBL are, as far as is now known, the malaria parasite *P. falciparum* and EBV.

HBV readily infects young children by percutaneous and permucosal exposure to infected blood and other body fluids. The infection causes chronic active hepatitis that leads to a high incidence of hepatocellular carcinoma (HCC) in young children in Asian and African countries where the prevalence of HBV infection is high. Perinatal transmission from HBV surface antigen-positive mothers to their newborn babies, or transmission from one child to another, is a major source of HBV infection in many areas of the world (WHO, 2001). In utero transmission is relatively rare. Most (80–90%) of infected infants and 30–50% of children infected at ages 1–4 years develop a chronic infection, and about 25% of those who become chronically infected during childhood develop either cirrhosis or HCC. HCC can become clinically evident in chronically HBV-infected children during – or even before – adolescence (IARC, 2012b).

KSHV is transmitted primarily by saliva; in geographical areas where the virus is highly prevalent, infection occurs during childhood, and the peak age of acquisition is generally 6–10 years (Whitby et al., 2000; Dedicoat et al., 2004; Malope et al., 2007). KSHV infection is necessary

but not sufficient to cause Kaposi sarcoma or other cancers in the absence of severe immunosuppression, for example by co-infection with HIV-1 (IARC, 2012b).

The bacterium *H. pylori* typically establishes infection of the human stomach during childhood, and untreated infections may persist for life (Malaty and Graham, 1994; Goodman et al., 1996; Brown, 2000). The infection evolves to cause chronic atrophic gastritis, a pre-neoplastic condition that leads to development of gastric adenocarcinoma and gastric mucosa-associated lymphoid tissue lymphoma later in life (IARC, 2012b).

Infestation with the bladder fluke *S. haematobium* causes squamous cell carcinoma of the bladder as a result of chronic inflammation. The parasite has a complex life-cycle that includes an infective cercaria form present in freshwater bodies in sub-Saharan Africa, the Nile valley in Egypt and Sudan, and the Arabian Peninsula. Infections are percutaneous and result from direct contact with contaminated water. Maintenance of transmission of the infection depends on contamination of fresh water with excreta containing schistosome eggs, the presence of snails as intermediate hosts, and human contact with contaminated water (Jordan and Webbe, 1993). Children start to accumulate worms as soon as they are old enough to have contact with water, and they may be continuously reinfected and remain infected throughout their lives (IARC, 2012b). The incidence of schistosome-related bladder cancer in Africa peaks at ages 40–49 years, whereas infection with *S. haematobium* begins as early as age 6 months and usually peaks at ages 5–15 years (Mostafa et al., 1999).

Children whose mothers are infected with HIV-1 can be infected during gestation and at birth, and during infancy by nursing (IARC, 2012b). In the absence of any intervention, transmission of HIV-1 in utero and during birth is estimated to occur in approximately 25% of infants born to HIV-1-positive women (Connor et al., 1994). The risk of mother-to-child transmission increases steadily towards the late stages of pregnancy; almost 80% of new HIV-1 infections occur during the period from 36 weeks of pregnancy to delivery (Kourtis et al., 2006).

In summary, infants and children are exceptionally susceptible to many carcinogenic infectious agents. Some infections can result in the onset of malignancy within the first decade of life. In children, HBV infection causes HCC, and EBV accompanied by *P. falciparum* malaria infection results in eBL. Infections with KSHV, *H. pylori*, and *S. haematobium* typically occur within the first few years of life but result in development of cancer – Kaposi sarcoma, gastric adenocarcinoma and gastric mucosa-associated lymphoid tissue lymphoma, and bladder carcinoma, respectively – decades later. On a global scale, in terms of the numbers of children exposed and the numbers of cancer cases that result, oncogenic infectious agents pose the greatest cancer risks during childhood.

Summary

Treatment of childhood cancers with high doses of ionizing radiation and combinations of cytotoxic drugs, many of which are *carcinogenic to humans* (Group 1), has been very successful in recent years, but survivors are at high risk of second cancers, including acute myeloid leukaemia, non-Hodgkin lymphoma, and solid cancers of the breast, thyroid, bone, central nervous system, colorectum, and stomach. Certain tissues are extremely radiosensitive during childhood and adolescence, including the thyroid and the female breast. Cancers of these and other tissues occur at increased frequency not only among survivors of childhood cancer but also in individuals exposed as children and adolescents to diagnostic X-rays (including CT scans) and to ionizing radiation from nuclear weapons and nuclear reactor accidents.

Other high-dosage circumstances early in life that pose increased cancer risks include transplacental exposure to the non-steroidal estrogen DES, which causes distinctive carcinomas of the reproductive tract in female offspring of women treated with DES during pregnancy. Intense and repeated exposures to solar radiation during childhood, including sunburn, predispose to development of cutaneous malignant melanoma. Evidence is beginning to accumulate that exposure to inorganic arsenic in utero and during childhood can cause cancer of the liver during childhood and of the lung or kidney decades later.

The consequences of exposures to lower doses or concentrations of other carcinogens during prenatal and early postnatal life have been more difficult to establish (Carpenter and Bushkin-Bedient, 2013). Parental cigarette smoking can cause hepatoblastoma in children, an extreme case of the danger of second-hand tobacco smoke. Possible environmental causes of other embryonal tumours of childhood continue to be investigate.

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