SECOND CANCERS IN SURVIVORS OF CHILDHOOD CANCER

Smita Bhatia and Charles Sklar‡*

More than 70% of children diagnosed with cancer can now be expected to be long-term survivors. However, the consequences of 'cure' might be considerable for the survivors of cancer: 60–70% of young adults who have survived childhood cancer will develop at least one medical disability as a result of their cancer or, more commonly, as a result of their therapy. Of these, the most devastating is a second cancer.

A second cancer is defined as a histologically distinct cancer that develops after the first cancer. In total, 95,000 of the ~1.2 million new cancers diagnosed every year in the United States are second cancers. Second cancers therefore account for ~6–10% of all cancer diagnoses, and are the fourth or fifth most common cancer in the United States[1]. Several studies following large cohorts of childhood cancer survivors have reported a 3–6-fold increased risk of a second cancer, when compared with the background incidence of cancer in the general population, and this risk continues to increase as the cohort ages (FIG. 1). Abnormalities of the endocrine and central nervous systems are far more common among childhood cancer survivors[2], but second cancers are associated with greater morbidity and mortality. Recent research indicates that the risk determinants of second cancers are multifactorial (FIG. 2); second cancers are more likely to develop in survivors who were diagnosed with cancer at a younger age, following exposure to high-dose radiation therapy and certain chemotherapeutic agents, and in those with a known genetic predisposition to cancer[3–13]. Although we have begun to understand some of the causes of second cancers, we still have much to learn about the nature of the interaction between the treatments given for the initial cancer, genetic susceptibility to cancer, medical complications and an individual's lifestyle choices in the genesis of subsequent new cancers.

Second cancers after cancer in adulthood

What is the burden of second cancers following primary cancers in adulthood? Several large epidemiological studies have tried to answer this question. For example, 470,000 cancer patients registered between 1953 and 1991 in Finland[14], and followed for the development of a second cancer, revealed that, overall, the cohort was not at an increased risk of developing a second cancer, when compared with the risk of cancer in an age- and gender-matched healthy population. However, patients who were less than 50 years of age at diagnosis of their primary cancer were at a 1.7-fold increased risk of developing a second cancer. Another cohort of 633,964 cancer patients diagnosed between 1958 and 1996 in Sweden, and followed for the development of subsequent cancers, revealed a modestly increased risk (less than twofold), when compared with the general population[15]. A third cohort of 250,000 patients followed for the development of a second cancer in the United States showed that cancer patients had a 1.3-fold increased risk of developing a second cancer, when compared with the general population[16]. However, when we look at second cancers following a first cancer in childhood or adolescence, a clearer and somewhat different picture emerges.

Second cancers after cancer in early life

Follow-up of a Nordic cohort of 30,880 patients, diagnosed with their first cancer at 21 years of age or less between 1943 and 1987, resulted in the identification of 247 second cancers[17]. The estimated cumulative incidence of second cancers in this cohort was 3.5% at 25 years, and the cohort was at a 3.6-fold increased risk of developing a second cancer when compared with an age- and gender-matched healthy population. In a recent report, a retrospective cohort of 13,581

**City of Hope National Medical Center, Duarte, California 91010, USA.*
‡Memorial Sloan-Kettering Cancer Center, New York, New York 10021, USA.
Correspondence to C.S.
e-mail: sklarc@mskcc.org
DOI: 10.1038/nrc722

Summary

- Survivors of childhood cancer are at a 3–6-fold increased risk of developing a second cancer, compared with the general population. Although second cancers are a comparatively rare complication in cancer survivors, they are associated with significant morbidity and mortality.
- For most second cancers, the risk decreases with increasing age of diagnosis of the first cancer; female gender is also associated with an increased risk of second cancers.
- Radiation therapy increases the risk of several second cancers in a dose-dependent manner. Most second cancers associated with radiotherapy occur in or near the area that was irradiated, and most have a long latency.
- Certain chemotherapeutic agents, particularly alkylating agents and topoisomerase II inhibitors, increase the risk of developing a second cancer. In some cases, specific genetic changes caused by these agents explain the increased risk of particular second cancers.
- Emerging risk factors for second cancers include familial cancer syndromes, gene–environment interactions, lifestyle choices and other medical complications associated with treatment for the primary cancer.
- By understanding the factors that increase risk of second cancers, we might be able to implement strategies to prevent them. For example, individuals known to be at increased risk of therapy-induced cancers can be treated with modified regimens that reduce this risk.

under- 21-year-olds diagnosed with common cancers in the United States between 1970 and 1986, and surviving at least five years, were followed for the development of second cancers. The estimated cumulative incidence of second cancers was 3.2% at 20 years. Overall, the cohort was at a 6.4-fold increased risk of developing a second cancer. However, only 1.9 excess malignancies occurred per 1,000 years of patient follow-up so, even though the incidence of a second cancer is greater in those whose first cancer occurred in early life, the annual excess risk of second cancers in this group is still very small[3].

Second cancers following a primary childhood cancer can be of two main types — acute leukaemias and myelodysplastic syndromes, or solid non-haematopoietic tumours. Certain second cancers have been reported more commonly after particular first cancers[3]; these associations between first and second cancers are summarized in TABLE 1. The latency between diagnosis and treatment of the primary cancer and the development of a secondary leukaemia is generally short, whereas non-haematopoietic malignancies seem to have a longer latency, and the risk continues to rise for two or more decades[4] (FIG. 3; TABLE 1).

Known risk factors for second cancers

Although acute lymphoblastic leukaemia (ALL) and central nervous system tumours are the most common types of childhood cancer[18], neither type is among the most common primary cancers in children who go on to develop a second cancer. A review of the literature on second cancers following childhood cancer reveals that hereditary retinoblastoma, soft-tissue sarcomas and Hodgkin's disease are the most common first cancers associated with the development of second cancers, and are considerably over-represented among patients with second cancers relative to their incidence in the general population[3,5]. It has, therefore, become clear that certain types of primary cancer are associated with higher risks of specific second cancers. For subjects with hereditary retinoblastoma, this is due to an interaction between a genetic predisposition to develop cancer and specific cancer therapies (for example, radiation; see below). However, for individuals with Hodgkin's disease and soft-tissue sarcomas, it is not yet clear whether the primary diagnosis is an independent risk factor for the development of second cancer, or whether the specific therapy required to treat the primary cancer is the main contributor (in addition to other host-related factors, as discussed below) to the development of second cancer.

Host-related risk factors

Age at diagnosis and treatment of primary cancer. Younger age at diagnosis is associated with an increased risk of second cancers[3,6–10], with the exception of secondary MYELODYSPLASIA and acute myeloid leukaemia (AML), in which the risk increases with older age at diagnosis and treatment of the primary cancer[19,20]. The association of younger age at diagnosis of the primary cancer with an increased risk of a second cancer is seen primarily among radiation-associated second cancers (see below). The reasons for these age effects might be related to one or more of the following: increased susceptibility of the underlying tissue to the mutagenic effect of therapy at a younger age; the higher rate of cell proliferation during the early stages of development; genetic susceptibility; or a longer period of follow-up of the childhood cancer survivor cohort, which allows second cancers with typically long latencies to emerge. Conversely, the association of secondary myelodysplasia and leukaemia with older age at treatment could possibly be related to the greater susceptibility of the haematopoietic stem cells

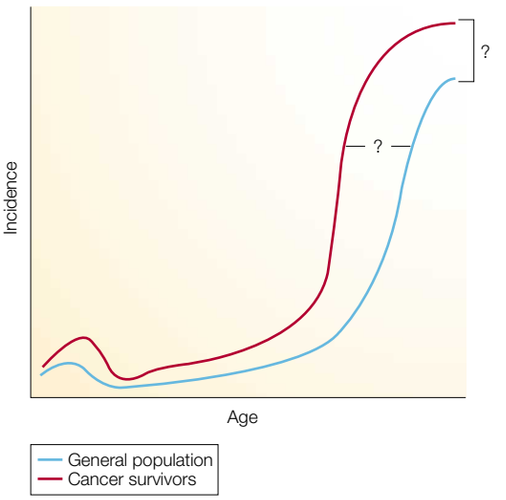

Figure 1 | **Cancer incidence in childhood cancer survivors.** This schematic representation compares cancer incidence in the general population with the incidence of second cancers in survivors of childhood cancer, as a function of age. We have substantial data on the risk of second cancers in the first 10–20 years after diagnosis of the initial cancer, whereas the magnitude of the risk with advancing age remains largely unknown.

MYELODYSPLASIA
A syndrome that is characterized by ineffective haematopoiesis. Morphological abnormalities occur in at least one, and often several, types of haematopoietic cell, particularly erythrocytes. Secondary myelodysplasia is characterized by progression to acute myeloid leukaemia after a variable length of time.

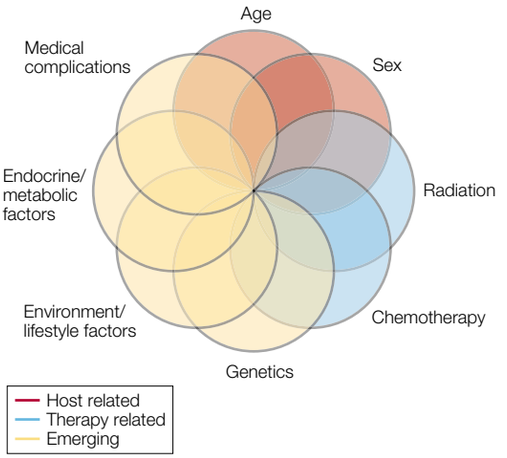

Figure 2 | **Risk factors for subsequent cancers.** This schematic illustrates the difficulties that are involved in unravelling interactions between risk factors.

among older subjects to the mutagenic effects of chemotherapy and/or radiation therapy, possibly because of a background accumulation of premalignant mutations from environmental exposures.

Gender. Female sex is associated with an increased risk of second primary cancers. This effect is due primarily to the excess number of secondary breast cancers and, to some extent, to the increased occurrence of thyroid cancer in female survivors[4]. Among adults, several studies indicate that, for a given dose of radiation, women are more susceptible to carcinogenesis than men. Possible mechanisms that underlie this increased susceptibility are greater activity of CYTOCHROME P450 enzymes, enhanced formation of DNA ADDUCTS and *TP53* mutations, and the effects of hormones, particularly oestrogens, on tumour promotion[21].

Therapy-related risk factors

Radiation. Ionizing radiation can cause most types of cancer, but different organs vary in their susceptibility. The risk is highest when the exposure occurs at a younger age[4,6–13] — possibly because younger children have a larger number of dividing stem cells, although there are no data to support this idea. The cancer risk increases as the total dose of radiation increases[22–32] and there seems to be a long latency period, probably due to the time required for sufficient mutations to accumulate[33]. Most radiation-associated second cancers develop within the radiation field (TABLE 2).

Radiation-associated bone tumours and sarcomas show all the characteristics of radiation-associated second cancers: there is a clear relationship with radiation dose and the second cancers develop within the radiation field, typically after a latency period of ten years. The radiation-associated bone tumours and sarcomas can be aggressive and respond poorly to therapy[23,25].

Another radiation-associated tumour is breast cancer, which has been increasingly reported among patients receiving radiation for Hodgkin's disease[3,4,26,27]. The latency is typically between 15 and 20 years from primary diagnosis, and the risk is highest among patients diagnosed at a younger age, decreasing to that of the general population for patients receiving radiation for their primary cancer after the age of 30 years. Again, the risk seems to increase with radiation dose and the tumours typically develop within or at the edge of the radiation field[4,26].

Patients receiving radiation to the neck region are at an increased risk of developing thyroid cancers[25,30,31]. Radiation therapy and younger age at treatment have been identified as risk factors for the development of secondary thyroid cancers[25]. Thyroid cancer has also been reported among patients receiving radiation to the craniospinal axis for ALL and brain tumours[3,6].

Brain tumours have been reported following cranial radiation for histologically distinct brain tumours or for prophylaxis or treatment of central nervous system

Table 1 | **Second cancers and their relationship with primary cancers**

Second cancers	Primary cancers	Latency (median in years)	Risk factors	References
Brain tumours	ALL; brain tumours; HD	9–10	Radiation; younger age	3,4,6,103
MDS/AML	ALL; HD; bone tumours	3–5	Topoisomerase II inhibitors; alkylating agents	4,6,103, 104
Breast cancer	HD; bone tumours; soft-tissue sarcomas; ALL; brain tumours; Wilms' tumours; NHL	15–20	Radiation; female gender	3,4,22
Thyroid cancer	ALL; HD; neuroblastoma; soft-tissue sarcomas; bone tumours; NHL	13–15	Radiation; younger age; female gender	3,4,6,103
Bone tumours	Retinoblastoma (heritable); other bone tumours; Ewing's sarcoma; soft-tissue sarcomas; ALL	9–10	Radiation; alkylating agents; removal of the spleen	6,11,23,103
Soft-tissue sarcomas	Retinoblastoma (heritable); soft-tissue sarcomas; HD; Wilms' tumours; bone tumours; ALL	10–11	Radiation; younger age; anthracyclines	3,11,12, 22,23,103

ALL, acute lymphocytic leukaemia; AML, acute myelogenous leukaemia; HD, Hodgkin's disease; MDS, myelodysplasia; NHL, non-Hodgkin's lymphoma.

CYTOCHROME P450
A family of enzymes, most abundant in the hepatic endoplasmic reticulum, that are responsible for the metabolism of various chemicals, including carcinogens.

DNA ADDUCT
A DNA adduct forms as a result of DNA binding to a genotoxic chemical. It reflects exposure to specific carcinogens, and is a marker of cumulative unrepaired DNA damage.

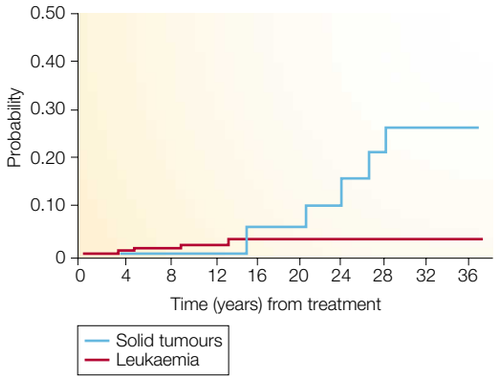

Figure 3 | **Second cancers in survivors of Hodgkin's disease.** Cumulative probability of secondary leukaemia and solid tumours among survivors of Hodgkin's disease in childhood, showing the longer latency (but higher incidence) for solid tumours compared with leukaemia. Reproduced with permission from REF. 4 © (1996) Massachusetts Medical Society.

disease among patients with ALL[3,6,32]. Patients identified to be at greatest risk were those receiving radiation before the age of six years.

Finally, patients receiving radiotherapy for retinoblastoma are at an increased risk of developing leukaemias and osteosarcoma. Interestingly, the incidence of second cancers among patients with retinoblastoma is primarily restricted to patients with hereditary retinoblastoma; very few cases are seen among patients with sporadic retinoblastoma[11]. This illustrates the potential of a germline *RB* mutation to interact with radiation and increase the incidence of secondary cancer.

Chemotherapeutic agents. Secondary myelodysplasia and AML have been associated with certain chemotherapeutic agents, such as ALKYLATING AGENTS[4,5] and TOPOISOMERASE II INHIBITORS (epipodophyllotoxins and anthracyclines)[34] (TABLE 3). Exposure to alkylating agents has also been shown to increase the risk of bone[25] and bladder cancers[35]. The incidence of therapy-related leukaemia associated with alkylating agents varies greatly among studies, depending on the intensity of the therapeutic schedule, the cohort size and the primary diagnosis. Increasing doses of alkylating agents and older age at exposure have been identified as risk factors[19,20,36–40]. The incidence, which is typically less than 5%, peaks between four and six years after exposure, with a plateau after 10–15 years. Different alkylating agents are not equally leukaemogenic: melphalan and mechlorethamine are more potent leukaemogens than cyclophosphamide[38,39].

Alkylating agents kill cancer cells by transferring alkyl groups to cellular molecules, and alkylation of DNA is the main cause of cell killing. The most significant site of alkylation in DNA in terms of cytotoxicity is probably the formation of a covalent bond between the drug and the ^{7}N group of guanine in DNA, although the ^{6}O-alkylguanine position is also favoured. Alkylation results in inaccurate base pairing during replication, and single- and double-strand breaks in the double helix as the alkylated bases are repaired[41,42]. The toxicity of alkylating agents is correlated with the formation of interstrand DNA crosslinks, which probably interfere with the orderly segregation of chromosomes at anaphase, leading to the loss of genetic material in some cells. This damage probably occurs throughout the genome, but loss of putative tumour-suppressor genes on chromosomes 5 or 7 seems to provide a selective advantage[43]. However, these genes have not yet been identified.

There is a wide variation in the estimates of risk of leukaemia associated with topoisomerase II ihibitors, which reflects small sample size, differences in susceptibility among different patient populations, varying schedules of drug administration and different cumulative doses[34,44–48]. A series of studies from St Jude Children's Research Hopsital have shown that the risk of secondary leukaemia associated with epipodophyllotoxins is related to the intensity of the dosing schedule, but not to the total dose of epipodophylotoxins[44]. The overall cumulative risk of secondary leukaemia was 3.8%, but within the subgroups of patients who received epipodophyllotoxins (etoposide (VP-16) or teniposide (VM-26)) twice weekly or weekly, the cumulative risks were 12.3% and 12.4%, respectively. Of the remaining subgroups — including patients who received epipodophyllotoxins every two weeks, did not receive epipodophyllotoxins, or received them only after their primary cancer had gone into remission — the cumulative risk was 1.6%. Smith *et al.* have similarly shown a lack of dose–response relationship for exposure to epipodophyllotoxins[34]. Less intensive use of these agents (for example, administration every two weeks) might allow sufficient time for DNA to be repaired, so that relatively high doses can be given without appreciably increasing the risk of AML. However, there are no data to support this idea.

DNA topoisomerase II catalyses the relaxation of supercoiled DNA by covalently binding, and transiently cleaving and re-ligating, both strands of the DNA helix. DNA topoisomerase II inhibitors stabilize the enzyme–DNA covalent intermediate, decrease the religation rate and have the net effect of increasing cleavage by topoisomerase II. This damages the DNA, and cells with irreparable DNA damage die by apoptosis[48]. But if the drug-induced DNA damage is insufficient to kill the cells and, instead, the damage is repaired, translocations form[49–53]. Most of the translocations disrupt a breakpoint cluster region between exons 5 and 11 of the *MLL* gene at chromosome band 11q23, and fuse *MLL* with a partner gene[54–58]. A large comprehensive study of chromosomal abnormalities among patients with therapy-related leukaemia indicates that translocations to 11q23 predominated following therapy with epipodophyllotoxins, whereas patients with translocations to 21q22, inv(16), t(15;17) and t(9;22) had, most often, received anthracyclines[59]. The generation of balanced translocations by topoisomerase II inhibitors is probably due to the generation of double-strand breaks that then predispose to non-homologous recombination. The reason why specific translocations are generated remains the subject of speculation. It is possible that these translocations confer a growth or survival advantage on myeloid cells but this remains to be proven.

ALKYLATING AGENTS
An important group of anticancer drugs that exert their cytotoxic effect through the alkylation of DNA, resulting in inhibition of DNA replication and transcription. Examples include mechlorethamine, cyclophosphamide, melphalan, busulphan and cisplatin.

TOPOISOMERASE II INHIBITORS
Topoisomerase II inhibitors block the unwinding of supercoiled DNA during DNA cleavage by forming a complex between the enzyme and DNA. Those that are used as chemotherapeutic agents include epipodophyllotoxins, anthracyclines, acridine, anthracenedione and doxorubicin.

Table 2 | **Characteristics of selected radiation-associated second cancers**

Second cancer	Primary cancer	Cohort size	Cumulative probability	Relative risk*	Risk factors	References
Bone tumours	Childhood cancer	9,170	2.8% (20 years)	133	Radiation therapy (+ve dose–response relationship); alkylating agents (+ve dose–response relationship)	25
	Childhood cancer	13,175	0.9% (20 years – overall) 7.2% (hereditary retinoblastoma) 5.4% (Ewing's sarcoma) 2.4% (other bone tumours)	NA	Radiotherapy (+ve dose–response relationship); alkylating agents (+ve dose–response) relationship)	23
Breast cancer	HD	885	NA	136 (<15 years at diagnosis)	Radiation therapy Age <30 years at irradiation	26
	HD	483	28% (30 years)	75	Radiation therapy Age between 10 and 16 years at irradiation	4
	Childhood cancer	13,851	NA	16	Radiation therapy	3
	HD	5,925	NA	14	Radiation therapy	27
	HD	257	1.7% (25 years)	20	Radiation therapy	28
	HD	3,869	NA	61 (<16 years at diagnosis)	Age <16 years at diagnosis	29
Thyroid cancer	Childhood cancer	4,096	NA	NA	Radiation therapy (+ve dose–response relationship)	30
	Childhood cancer	9,170	NA	53	Radiation therapy (+ve dose–response relationship); younger age at irradiation	25
	HD	1,791	NA	18	Radiation therapy	31
Brain tumours	ALL	9,720	NA	22	Younger age (<6 years) at irradiation to central nervous system axis	6
	ALL	5,006	1.0% (15 years)	19	Radiation therapy (+ve dose–response relationship); younger age at irradiation	32
	Childhood cancer	13,581	NA	9.9	Younger age at irradiation to the central nervous system axis	3

ALL, acute lymphoblastic leukaemia; HD, Hodgkin's disease; NA, information not available. *Relative risk is the ratio of risk in an exposed group to the risk in an unexposed group.

Traditionally, the alkylating agent cisplatin has not been regarded as a carcinogenic agent, but secondary myelodysplasia and AML can develop among patients receiving cisplatin-based therapy. Two epidemiological studies have addressed the question of cisplatin as a carcinogenic agent: one indicated that the combination of cisplatin and the topoisomerase II inhibitor doxorubicin is leukaemogenic in humans, whereas the other implicated etoposide rather than cisplatin. Formal epidemiological studies of large cohorts of patients treated with cisplatin are now needed to resolve this question[60].

DNA repair is necessary to maintain genomic integrity, and defects in DNA repair and its regulation increase susceptibility to cancer, so we might expect that individuals with defects in DNA repair would be particularly susceptible to therapy-induced cancers. In one study, 15 out of 16 patients (94%) with therapy-related leukaemia had microsatellite instability[61], which indicates that patients with therapy-related leukaemia might have an inherited defect in a mismatch repair gene, leading to accelerated DNA instability in other oncogenes or tumour-suppressor genes occurring as a consequence of treatment of a primary malignancy. Another study reported microsatellite instability in 5–7 loci in the secondary tumours of all nine paediatric patients studied[62]. This hypothesis for why only a small percentage of those receiving chemotherapy for leukaemia go on to develop a second cancer awaits confirmation, but could offer a potential means of screening patients at increased risk of developing second cancers.

Emerging risk factors

Gene–environment interactions. Interactions between the gene and environment are defined as the interaction between genetic susceptibility and environmental exposures, resulting in a greater risk for the development of cancer than could be attributed to either risk factor alone. These same gene–environment interactions have an impact on the risk of developing second cancers, as exemplified by the extremely high incidence of secondary sarcomas among subjects with hereditary retinoblastoma who are treated with external radiotherapy[11].

Table 3 | **Features of chemotherapy-induced haematopoietic cancers**

Property	Alkylating agents	Epipodophyllotoxins	References
Median latency	4–6 years (range, 1–20 years)	1–3 years (range, 0.5–4.5 years)	4,6,20,105
Presentation	Myelodysplasia	Abrupt, no pre-leukaemia	105,106
Cytogenetic translocations	Loss of genetic material, often from chromosomes 5 and 7	Balanced abnormalities (often include 11q23)	106
Age	Typically older patients	Younger patients	106
Cumulative probability (%)	0.8–2.8	3.8–18.4	4,36–38, 44–46
Outcome	Poor	Poor	4,19,105,106

Patients with a family history of early-onset cancers have been shown to be at an increased risk for developing a second cancer. In one study, 159 three-year survivors of childhood soft-tissue sarcoma and their relatives were surveyed to determine the frequency of second malignant neoplasms in patients and cancer in their relatives[12]. A highly significant excess of cancer was observed in the relatives of cancer survivors who developed a second cancer. The tumour types that occurr in excess in close relatives were also observed as second cancers in patients (that is, cancers of the breast, bone, joint or soft tissue), which indicates that the risk of second cancers is associated with a familial predisposition.

In another study, members of families with Li–Fraumeni syndrome — a hereditary susceptibility to several cancers that is usually caused by mutation of the *TP53* tumour-suppressor gene — were reported to be at increased risk of multiple subsequent cancers compared with the general population[63]. The highest risk was observed among survivors of childhood cancer. Moreover, the excess risk was mainly for cancers that are characteristic of Li–Fraumeni syndrome. It therefore seems that germ-line mutations in tumour-suppressor genes, as occur in Li–Fraumeni syndrome, might interact with therapeutic exposures to result in an increased risk of second cancers.

Mutational analysis of the *ATM* gene — which is mutated in individuals with a recessive hereditary cancer syndrome, ATAXIA TELANGIECTASIA (AT) — has been carried out in cohorts of patients with radiation-associated second cancers. *ATM* encodes a protein kinase that is involved in regulation of the G1/S cell-cycle checkpoint. Following ionizing radiation, ATM phosphorylates p53 to result in its stabilization. *In vitro* studies have shown that cells from AT patients and *ATM* heterozygotes have an increased sensitivity to ionizing radiation, and there is epidemiological evidence that heterozygotes are at an increased risk of radiation-induced breast cancer[64]. The studies conducted so far have failed to support the hypothesis that AT carriers account for a significant fraction of radiation-induced second cancers[65,66], although there is some evidence that missense mutations in *ATM* are more common in primary breast cancer cases selected for family history and young age at diagnosis[67].

ATAXIA TELANGIECTASIA
An autosomal recessive genetic disorder that is characterized by cerebellar ataxia, oculocutaneous telangiectasia and immunodeficiency.

Another example shows how underlying genetic characteristics can interact with chemotherapy to increase the risk of certain second cancers. The enzyme thiopurine *S*-methyltransferase (TPMT) catalyses the inactivation, by *S*-methylation, of thiopurines, including 6-mercaptopurine and 6-thioguanine. Approximately 10% of the population carries a polymorphism in the gene for TPMT that leads to an inactive enzyme, and about 1 in 300 individuals inherit two copies of this polymorphism, so they accumulate thiopurines. There is emerging evidence that this increases the risk of second cancers, including brain tumours and AML[68,69].

Several other genetic polymorphisms of enzymes that are capable of metabolic activation or detoxification of anticancer drugs have been examined for their involvement in the development of therapy-related leukaemia or myelodysplasia[70–78]. The quinone metabolites that are generated as a result of metabolism of epipodophyllotoxins are carcinogenic, probably owing to the generation of DNA adducts, which enhance chromosomal breakage and recombination. These carcinogenic quinone metabolites are reduced to catechol by NAD(P)H:quinone oxidoreductase (NQO1). There is evidence that an *NQO1* polymorphism (homozygosity for serine at codon 187) resulting in loss of function of the enzyme is significantly associated with the genetic risk of therapy-related acute leukaemia and myelodysplasia[70]. Glutathione *S*-transferases detoxify potentially mutagenic and toxic DNA-reactive electrophiles, including metabolites of several chemotherapeutic agents. Functional polymorphisms exist in at least three genes that encode GSTs — *GSTM1*, *GSTT1* and *GSTP1* — which result in a functional decrease in the activity of the enzymes, so increasing the carcinogenic potential of the substrate. For example, Allan *et al.* have reported that inheritance of at least one Val allele at *GSTP1* codon 105 confers a significantly increased risk of developing therapy-related leukaemia after chemotherapy, but not after radiotherapy[77]. The cytochrome P450 CYP3A metabolizes epipodophyllotoxins and other chemotherapeutic agents. CYP3A metabolism generates epipodophyllotoxin quinone metabolites, which could damage DNA. Individuals with the CYP3A4-W genotype might be at increased risk of treatment-related leukaemia, by increasing the production of reactive intermediates that might damage DNA[72].

Environmental and lifestyle factors. Environmental risk factors have been most frequently studied in survivors of adult cancers, and the exposures most commonly examined include tobacco and alcohol[79–89]. Tobacco use is strongly associated with respiratory and upper digestive tract cancers, but has also been linked to cancers of the uterine cervix, pancreas, bladder, and kidney[90]. Smoking also seems to increase the risk of at least one radiation-associated second cancer: survivors of Hodgkin's disease are at an increased risk of lung cancer, and the excess risk of lung cancer in Hodgkin's disease survivors treated with radiation

Box 1 | Endocrine and metabolic consequences of cancer therapy

Endocrine and metabolic complications are the most prevalent late effects observed in survivors of childhood cancer. These sequelae occur more commonly following therapy for Hodgkin's disease and brain tumours, and in survivors of stem-cell transplantation. The most frequently diagnosed endocrine and metabolic disorders include:

- *Primary hypothyroidism.* The main risk factor is radiation (10 Gy or more) to the neck area. It is more common in females and can develop as soon as six months or as late as 25 or more years after treatment.
- *Primary ovarian failure and premature menopause.* Risk factors include irradiation to the pelvis, treatment with high doses of alkylating agents (for example, cyclophosphamide, busulphan) and older age at treatment.
- *Growth hormone deficiency.* This is seen primarily in survivors treated with higher doses (>18 Gy) of irradiation to the region of the hypothalamus and pituitary (for example, whole-brain irradiation for acute leukaemia or various brain tumours). Growth hormone deficiency usually develops within the first five years after high-dose irradiation (>30 Gy), whereas it can take ten or more years to develop following lower doses (18–24 Gy) of irradiation.
- *Obesity.* Exposure to glucocorticoids and radiation to the brain are established risk factors. Obesity might be more prevalent in females treated at a younger age.
- *Early onset of puberty.* This is observed most often in young girls (<four years) treated with whole-brain irradiation.

therapy is related to the radiation dose received. However, smokers experience a significantly greater risk attributable to radiotherapy than non-smokers. Alcohol consumption has been shown to be a risk factor for oral, oesophageal and liver cancers, when they occurr as second cancers[91–93].

Medical complications and therapy for them. The impact of medical complications on subsequent cancer risk in cancer survivors has received little attention. For various reasons, it is reasonable to assume that the endocrine and metabolic sequelae of cancer therapy (BOX 1) might contribute to overall cancer risk in these survivors. First, many human cancers are modulated by the endocrine system. Examples include the role of oestrogen in the development of breast cancer[94,95], the androgen dependence of many prostate cancers[96], and the association between high circulating concentrations of the growth-hormone-dependent growth factor insulin-like growth factor 1 (IGF1) and a heightened risk for the common cancers of adulthood (for example, breast, prostate, colon, and lung cancers)[97]. Second, endocrine disorders are the most prevalent late complications observed in survivors of childhood cancer; some 20–50% of survivors followed into adulthood will develop an endocrinopathy[2]. So, a substantial percentage of survivors will experience alterations of their hormonal system and many will require long-term hormone therapy.

Some of these endocrine and metabolic disturbances, such as obesity and early menarche, both of which are seen following whole-brain irradiation[98,99], are established risk factors for future cancer risk[100,101]. For others, potential interactions might exist between the endocrine complication and/or the therapy for the complication and other risk factors for second cancers. For example, loss of ovarian function is nearly universal following total body irradiation as preparation for stem-cell transplantation of leukaemia patients[102]. Most of the young women who undergo this treatment will require oestrogen replacement to optimize their physical and psychosexual health, but we understand very little about the interplay between long-term hormone-replacement therapy and breast irradiation on the lifetime risk of breast cancer in these individuals. The challenge of future research will be to identify and quantify the contribution of these endocrinological factors on cancer risk, both to understand the underlying mechanisms and to learn ways to minimize the risks of second cancers.

Implications and future directions

Survivors of childhood cancer are at a 3–6-fold increased risk of developing a second primary cancer when compared with the general population. A potential limitation of the cohort studies used to derive these figures is the inability to follow all patients completely. The reported incidence could be an underestimate, because of incomplete reporting, or it could be artificially inflated because patients who develop complications are likely to be followed up more completely. However, as similar estimates have been reported from several large studies, the reported incidence does seem to reflect a fairly accurate representation of the true incidence.

Now that we have established this increased risk, high priority needs to be given to characterizing and preventing second cancers because they are associated with high levels of morbidity and mortality. Patients and health-care providers must be aware of risk factors for second cancers so that surveillance is focused and early prevention strategies can be implemented. PRIMARY PREVENTION strategies are now being implemented to tailor the therapy of the primary cancer for patients considered at high risk of developing a second cancer. An example of primary prevention is the use of gender-specific therapy for patients with Hodgkin's disease: to reduce the risk of radiation-associated breast cancer, adolescent girls with Hodgkin's disease now receive a chemotherapy-based regimen; radiation therapy to the chest area is reserved primarily for those patients with disease that is considered to be at high risk of local relapse. Other primary prevention strategies include identification of patients who are heterozygous for *TPMT* or other drug-metabolizing enzymes before initiation of therapy for the primary cancer; therapy can then be modified accordingly, to reduce the risk of developing a second cancer. SECONDARY PREVENTION strategies that are being considered include programmes to educate clinicians and survivors about the risk of second cancers, and about measures that can be taken to decrease the morbidity associated with second cancers, including adopting healthy lifestyle choices such as giving up smoking. Other approaches include periodic and aggressive screening for breast, lung and

PRIMARY PREVENTION
Prevention of disease by altering susceptibility or reducing exposure for susceptible individuals.

SECONDARY PREVENTION
The early detection and treatment of disease.

cervical cancers, chemoprevention for specific cancers, and avoidance of unnecessary exposure to sunlight, especially among patients who have received radiation[28]. By understanding the risk factors for second cancers, and taking measures to avoid them, we might be able to decrease the incidence of the most devastating consequences of surviving cancer, while maintaining the high cure rates in this population.

1. Neugut, A. I., Meadows, A. T. & Robinson, E. (eds). *Multiple Primary Cancers 1999* 3–10 (Lippincott Williams & Wilkins, Philadelphia, 1999).
2. Sklar, C. A. Overview of the effects of cancer therapies: the nature, scale, and breadth of the problem. *Acta Paediatr.* **433** (Suppl.), 1–4 (1999).
3. Neglia, J. P. *et al*. Second malignant neoplasms in five-year survivors of childhood cancer: childhood cancer survivor study. *J. Natl Cancer Inst.* **93**, 618–629 (2001).
In a large cohort of five-year survivors of childhood cancer, the authors describe the incidence of second cancers, characterize the second cancers and describe the risk factors associated with their development.
4. Bhatia, S. *et al.* Breast cancer and other second neoplasms after childhood Hodgkin's disease. *N. Engl. J. Med.* **334**, 745–751 (1996).
The authors describe the incidence and risk factors associated with the development of second primary breast cancer and other second cancers in a large multinational cohort of childhood Hodgkin's disease survivors followed for an extended period of time.
5. Meadows, A. T. Risk factors for second malignant neoplasms: report from the Late Effects Study Group. *Bull. Cancer* **75**, 125–130 (1988).
6. Neglia, J. P. *et al*. Second neoplasms after acute lymphoblastic leukaemia in childhood. *N. Engl. J. Med.* **325**, 1330–1336 (1991).
7. Boice, J. D. Jr, Land, C. E. & Preston, D. L. in *Cancer Epidemiology and Prevention* (eds Schottenfeld, D. & Fraumeni, J. F. Jr) 319–354 (Oxford Univ. Press, New York, 1996).
8. Preston, D. *et al*. Cancer incidence in atomic bomb survivors. III. Leukaemia, lymphoma, and multiple myeloma, 1950–1987. *Radiat. Res.* **137**, S68–S97 (1994).
9. Thompson, D. E. *et al.* Cancer incidence in atomic bomb survivors. II: solid tumours, 1958–1987. *Radiat. Res.* 137, S17–S67 (1994).
10. Ron, E. *et al*. Radiation-induced skin carcinomas of the head and neck. *Radiat. Res.* **125**, 318–325 (1991).
11. Wong, F. L. *et al.* Cancer incidence after retinoblastoma. Radiation dose and sarcoma risk. *J. Am. Med. Assoc.* **278**, 1262–1267 (1997).
In a large cohort of patients with retinoblastoma, diagnosed between 1914 and 1984, the authors describe the incidence and risk factors of second cancers and show that genetic predisposition has a substantial impact on the risk of subsequent cancers, which is further increased by radiation therapy.
12. Strong, L. C., Stine, M. & Norsted, T. L. Cancer in survivors of childhood soft tissue sarcoma and their relatives. *J. Natl Cancer Inst.* **79**, 1213–1220 (1987).
13. Land, C. E. *et al.* Incidence of salivary gland tumours among atomic bomb survivors, 1950–1987. Evaluation of radiation-related risk factors. *Radiat. Res.* **146**, 28–36 (1996).
14. Sankila, R., Pukkala, E. & Teppo, L. Risk of subsequent malignant neoplasms among 470,000 cancer patients in Finland, 1953–1991. *Int. J. Cancer* **60**, 464–470 (1995).
15. Dong, C. & Hemminki, K. Second primary neoplasms in 633,964 cancer patients in Sweden, 1958–1996. *Int. J. Cancer* **93**, 155–161 (2001).
16. Curtis, R. E., Boice, J. D. Jr, Kleinerman, R. A., Flannery, J. T. & Fraumeni, J. F. Jr. Summary: multiple primary cancers in Connecticut, 1935–1982. *Natl Cancer Inst. Monogr.* **68**, 219–242 (1985).
17. Olsen, J. H. *et al.* Second malignant neoplasms after cancer in childhood or adolescence. Nordic Society of Paediatric Haematology and Oncology Association of the Nordic Cancer Registries. *Br. Med. J.* **307**, 1030–1036 (1993).
18. Reis, L. A. G. *et al.* (eds). SEER Cancer Statistics Review, 1973–1998, National Cancer Institute. (National Cancer Institute, Bethesda, Maryland, 2001).
19. Bhatia, S. *et al.* Malignant neoplasms following bone marrow transplantation. *Blood* **87**, 3633–3639 (1996).
20. Darrington, D. L. *et al.* Incidence and characterization of secondary myelodysplastic syndrome and acute myelogenous leukaemia following high-dose chemoradiotherapy and autologous stem cell transplantation for lymphoid malignancies. *J. Clin. Oncol.* **12**, 2527–2534 (1994).
21. Zang, E. A. & Wynder, E. L. Differences in lung cancer risk between men and women: examination of the evidence. *J. Natl Cancer Inst.* **88**, 183–192 (1996).
22. Breslow, N. E. *et al.* Second malignant neoplasms following treatment of Wilm's tumour: a report from the National Wilms' Tumour Study Group. *J. Clin. Oncol.* **13**, 1851–1859 (1995).
23. Hawkins, M. M. *et al.* Radiotherapy, alkylating agents, and risk of bone cancer after childhood cancer. *J. Natl Cancer Inst.* **88**, 270–278 (1996).
In a large population-based cohort study, the authors report a low incidence of bone tumours among three-year survivors of childhood cancer, except following hereditary retinoblastoma, Ewing's sarcoma and other malignant bone tumours. They show the dose–response relationship of the second primary bone tumours with increasing doses of radiation, and the association of second primary bone tumours with alkylating agents.
24. Garwicz, S. *et al.* Second malignant neoplasms after cancer in childhood and adolescence: a population-based case–control study in the 5 Nordic countries. The Nordic Society for Pediatric Hematology and Oncology. The Association of the Nordic Cancer Registries. *Int. J. Cancer* **88**, 672–678 (2000).
The authors carried out a nested case–control study within a Nordic cohort of 25,120 patients to assess the risk factors associated with the development of second primary cancers following a first primary cancer in childhood. Radiation therapy was the most important treatment-related risk factor identified.
25. Tucker, M. A., D'Angio, G. J., Boice, J. D. Jr *et al.* Bone sarcomas linked to radiotherapy and chemotherapy in children. *N. Engl. J. Med.* **317**, 588–593 (1987).
26. Hancock, S. L., Tucker, M. A. & Hoppe, R. T. Breast cancer after treatment of Hodgkin's disease. *J. Natl Cancer Inst.* **85**, 25–31 (1993).
27. Metayer, C. *et al.* Second cancers among long-term survivors of Hodgkin's disease diagnosed in childhood and adolescence. *J. Clin. Oncol.* **18**, 2435–2443 (2000).
28. Kaste, S. C. *et al.* Breast masses in women treated for childhood cancer: incidence and screening guidelines. *Cancer* **82**, 784–792 (1998).
29. Travis, L. B., Curtis, R. E. & Boice, J. D. Jr. Late effects of treatment for childhood Hodgkin's disease. *N. Engl. J. Med.* **334**, 745–751 (1996).
30. De Vathaire, F. *et al.* Thyroid carcinomas after irradiation for a first cancer during childhood. *Arch. Intern. Med.* **159**, 2713–2719 (1999).
31. Sklar, C. *et al.* Abnormalities of the thyroid in survivors of Hodgkin's disease: data from the Childhood Cancer Survivor Study. *J. Clin. Endocrinol. Metab.* **85**, 3227–3232 (2000).
32. Loning, L. *et al.* Secondary neoplasms subsequent to Berlin–Frankfurt–Munster therapy of acute lymphoblastic leukaemia in childhood: significantly lower risk without cranial radiotherapy. *Blood* **95**, 2770–2775 (2000).
The authors followed a large cohort of patients treated for ALL in childhood on Berlin-Frankfurt–Munster (BFM) therapeutic protocols, and showed that the incidence of second cancers is relatively low, except among patients receiving cranial irradiation.
33. de Vathaire, F. *et al.* Second malignant neoplasms after a first cancer in childhood: temporal pattern of risk according to type of treatment. *Br. J. Cancer* **[vol?]**1884–1893 (1999).
34. Smith, M. A. *et al.* Secondary leukaemia or myelodysplastic syndrome after treatment with epipodophyllotoxins. *J. Clin. Oncol.* **17**, 569–577 (1999).
The Cancer Therapy Evaluation Program of the National Cancer Institute has developed a monitoring plan to describe the incidence of secondary leukaemia after epipodophyllotoxin treatment and the relationship between epipodophyllotoxin cumulative dose and risk of secondary leukaemia. The study failed to show a dose–response relationship between epipodophylltoxins and therapy-related leukaemia.
35. Pedersen-Bjergaardd, J. *et al.* Carcinoma of the urinary bladder after treatment with cyclophosphamide for non-Hodgkin's lymphoma. *N. Engl. J. Med.* **[Au: VOL??]** 1028–1032 (1988).
36. Wolden, S. L., Lamborn, K. R., Cleary, S. F., Tate, D. J. & Donaldson, S. S. Second cancers following pediatric Hodgkin's disease. *J. Clin. Oncol.* **16**, 536–544 (1998).
37. Sankila, R. *et al.* Risk of subsequent malignant neoplasms among 1,641 Hodgkin's disease patients diagnosed in childhood and adolescence: a population-based cohort study in the five Nordic countries — Association of the Nordic Cancer Registries and the Nordic Society of Pediatric Hematology and Oncology. *J. Clin. Oncol.* **14**, 1442–1446 (1996).
38. Schellong, G. *et al.* Low risk of secondary leukaemia after chemotherapy without mechlorethamine in childhood Hodgkin's disease: German–Austrian Pediatric Hodgkin's Disease Group. *J. Clin. Oncol.* **15**, 2247–2253 (1997).
39. Greene, M. H. *et al.* Melphalan may be a more potent leukaemogen than cyclophosphamide. *Ann. Intern. Med.* **105**, 36–67 (1986).
40. Tucker, M. A. *et al.* Leukaemia after therapy with alkylating agents for childhood cancer. *J. Natl Cancer Inst*. **78**, 459–464 (1987).
41. Chabner, B. A. & Myers, C. E. in *Principles and Practice of Oncology* 2nd edn (eds DeVita **[Au: initials?]**, Hellman, S. & Rosenberg, S. A.) 349–395 (J. B. Lippincott, Philadelphia, 1989).
42. Tew, K. D., Clovin, M. & Chabner, B. A. in *Cancer Chemotherapy and Biotherapy: Principles and Practice* Vol. 1 (eds Chabner, B. A. & Longo, D. L.) 297–232 (Lippincott-Raven Publishers, New York (1996).
43. Karp, J. E. & Smith, M. A. The molecular pathogenesis of treatment-induced (secondary) leukemias: foundations for treatment and prevention. *Semin. Oncol.* **24**, 103–113 (1997).
44. Pui, C.-H. *et al.* Acute myeloid leukaemia in children treated with epipodophyllotoxins for acute lymphocytic leukaemia. *N. Engl. J. Med.* **325**, 1682–1687 (1991).
Pui *et al.* assessed the risk of therapy-related AML among children with ALL treated with epipodophyllotoxins, and showed that the risk of epipodophyllotoxin-related leukaemia depended largely on the schedule of drug administration.
45. Winick, N. J. *et al.* Secondary acute myeloid leukaemia in children with acute lymphoblastic leukaemia treated with etoposide. *J. Clin. Oncol.* **11**, 209–217 (1993).
46. Sugita, K. *et al.* High frequency of etoposide (VP-16)-related secondary leukaemia in children with non-Hodgkin's lymphoma. *Am. J. Pediatr. Hematol. Oncol.* **15**, 99–104 (1993).
47. Hawkins, M. M. *et al.* Epipodophyllotoxins, alkylating agents, and radiation and risk of secondary leukaemia after childhood cancer. *Br. Med. J.* **304**, 951–958 (1992).
The authors investigated the incidence and aetiology of secondary leukaemia after childhood cancer in a cohort of 16,422 patients diagnosed and treated in the United Kingdom, and showed that epipodophyllotoxins acting alone or together with alkylating agents or radiation seem to be involved in secondary leukaemia after childhood.
48. Corbett, A. H. & Osheroff, N. When good enzymes go bad: conversion of topoisomerase II to a cellular toxin by antineoplastic drugs. *Chem. Res. Toxicol.* **6**, 585–597 (1993).
49. Felix, C. A. Secondary leukaemias induced by topoisomerase targeted drugs. *Biochim. Biophys. Acta* **1400**, 233–235 (1998).
50. Atlas, M. *et al.* Cloning and sequence analysis of four t(9;11) therapy-related leukaemia breakpoints. *Leukaemia* **12**, 1895–1902 (1998).
51. Megonigal, M. D. *et al.* Detection of leukaemia-associated MLL-GAS7 translocation early during chemotherapy with DNA topoisomerase II inhibitors. *Proc. Natl Acad. Sci. USA* **97**, 2814–2819 (2000).
52. Lovett, B. D. *et al.* Etoposide metabolites enhance DNA topoisomerase II cleavage near leukaemia-associated MLL translocation breakpoints. *Biochemistry* **40**, 1159–1170 (2001).

53. Super, H. J. G. *et al.* Rearrangements of the *MLL* gene in therapy-related acute myeloid leukaemia in patients previously treated with agents targeting DNA topoisomerase II. *Blood* **82**, 3705–3711 (1993).
54. Felix, C. A. *et al.* Chromosome band 11q23 translocation breakpoints are DNA topoisomerase II cleavage sites. *Cancer Res.* **55**, 4287–4292 (1995).
55. Bower, M. *et al.* Human trithorax gene rearrangements in therapy-related acute leukaemia after etoposide treatment. *Leukaemia* **8**, 226–229 (1994).
56. Felix, C. A. *et al.* Common region of *ALL-1* gene disrupted in epipodophyllotoxin-related secondary acute myeloid leukaemia. *Cancer Res.* **53**, 2954–2956 (1993).
57. Broeker, P. L. S. *et al.* Distribution of 11q23 breakpoints within the MLL breakpoint cluster region in *de novo* acute leukaemia and therapy-related acute myeloid leukaemia: correlation with scaffold attachment regions and topoisomerase II consensus binding sites. *Blood* **87**, 1912–1922 (1996).
58. Hunger, S. P. *et al.* HRX involvement in *de novo* and secondary leukaemias with diverse chromosome 11q23 abnormalities. *Blood* **81**, 3197–3203 (1993).
59. Andersen, M. K., Johansson, B., Larsen, S. O. & Pedersen-Bjergaard, J. Chromosomal abnormalities in secondary MDS and AML. Relationship to drugs and radiation with specific emphasis on the balanced rearrangements. *Haematologica* **83**, 483–488 (1998).
60. Jeha, S., Jaffe, N. & Robertson, R. Secondary acute nonlymphoblastic leukaemia in two children following treatment with a *cis*-diamminechloroplatinum-II-based regimen for osteosarcoma. *Med. Pediatr. Oncol.* **20**, 71–74 (1992).
61. Ben-Yehuda, D. *et al.* Microsatellite instability and p53 mutations in therapy-related leukaemia suggest a mutator phenotype. *Blood* **88**, 4296–4303 (1996).
62. Gafanovich, A. *et al*. Microsatellite instability and p53 mutations in pediatric secondary malignant neoplasms. *Cancer* **85**, 504–510 (1999).
63. Hisada, M. *et al.* Multiple primary cancers in families with Li–Fraumeni syndrome. *J. Natl Cancer Inst.* **90**, 606–611 (1998).
64. Swift, M., Morrell, D., Massey, R. B. & Chase, C. L. Incidence of cancer in 161 families affected by ataxia-telangiectasia. *N. Engl. J. Med.* **325**, 1831–1836 (1991).
65. Nichols, K. E. *et al.* Heterozygous germline ATM mutations do not contribute to radiation-associated malignancies after Hodgkin's disease. *J. Clin. Oncol.* **17**, 1259 (1999).
66. Shafman, T. D. *et al.* Prevalence of germline truncating mutations in ATM in women with a second breast cancer after radiation therapy for a contalateral tumour. *Genes Chromosomes Cancer* **27**, 124–129 (2000).
67. Teraoka, S. N. *et al.* Increased frequency of ATM mutations in breast carcinoma patients with early onset disease and positive family history. *Cancer* **92**, 479–487 (2001).
68. Relling, M. V. *et al.* High incidence of secondary brain tumours after radiotherapy and antimetabolites. *Lancet* **354**, 34–39 (1999).
The authors assessed the clinical, biological and pharmacokinetic features among children with ALL receiving cranial radiotherapy, and showed that underlying genetic characteristics and treatment variables might be associated with an increased risk of radiation-associated brain tumours.
69. Relling, M. V. *et al.* Etoposide and antimetabolite pharmacology in patients who develop secondary acute myeloid leukaemia. *Leukaemia* **12**, 346–352 (1998).
The authors assessed the pharmacological characteristics of patients who developed epipodophyllotoxin-related AML after ALL, and showed that patients with lower thiopurine methyltransferase activity were more likely to develop secondary AML in this setting.
70. Naoe, T. *et al.* Analysis of genetic polymorphism in NQO1, GST-M1, GST-T1, and CYP3A4 in 469 Japanese patients with therapy-related leukaemia/myelodysplastic syndrome and *de novo* acute myeloid leukaemia. *Clin. Cancer Res.* **6**, 4091–4095 (2000).
71. Chen, H. *et al.* Increased risk for myelodysplastic syndromes in individuals with glutathione transferase θ1 (GSTT1) gene defect. *Lancet* **347**, 295–297 (1996).
72. Felix, C. A. *et al.* Association of CYP3A4 genotype with treatment-related leukaemia. *Proc. Natl Acad. Sci. USA* **95**, 13176–13181 (1998).
The authors showed that individuals with the CYP3A4-W genotype might be at increased risk for treatment-related leukaemia and that epipodophyllotoxin metabolism by CYP3A4 might contribute to the secondary leukaemia by increasing production of potentially DNA-damaging reactive intermediates.
73. Hayes, J. D. & Pulford, D. J. The glutathione *S*-transferase supergene family: regulation of GST and the contribution of the isoenzymes to cancer chemoprotection and drug resistance. *Crit. Rev. Biochem. Mol. Biol.* **30**, 445–600 (1995).
74. Smith, G., Stanley, L. A., Sim, E., Strange, R. C. & Wolf, C. R. Metabolic polymorphisms and cancer susceptibility. *Cancer Surv.* **25**, 27–65 (1995).
75. Raunio, H. *et al.* Diagnosis of polymorphisms in carcinogen activating and inactivating enzymes and cancer susceptibility. *Gene* **159**, 113–121 (1995).
76. Wrighton, S. & Stevens, J. The human hepatic cytochromes P450 involved in drug metabolism. *Crit. Rev. Toxicol.* **22**, 1–21 (1992).
77. Allan, J. M. *et al.* Polymorphism in glutathione *S*-transferase P1 is associated with susceptibility to chemotherapy-induced leukaemia. *Proc. Natl Acad. Sci. USA* **98**, 11592–11597 (2001).
The authors assessed polymorphisms in glutathione *S*-transferases and sought to identify an association with therapy-related leukaemia. They showed that inheritance of at least one Val allele at GSTP1 codon 105 confers a significantly increased risk of developing therapy-related leukaemia after cytotoxic chemotherapy.
78. Woo, M. H. *et al.* Glutathione *S*-transferase genotypes in children who develop treatment-related acute myeloid malignancies. *Leukaemia* **14**, 226–231 (2000).
79. Van Leeuwen, F. E. *et al.* Roles of radiotherapy and smoking in lung cancer following Hodgkin's disease. *J. Natl Cancer Inst.* **87**, 1530–1537 (1995).
This study investigated the effects of radiation dose, chemotherapy and smoking on the risk of lung cancer following treatment of Hodgkin's disease. The authors showed that the excess risk of lung cancer in patients with Hodgkin's disease who were treated with radiotherapy is related to the radiation dose received by the affected area of the lung. Moreover, smokers experience a significantly greater risk attributable to radiotherapy than non-smokers.
80. Boivin, J. F. Smoking, treatment for Hodgkin's disease, and subsequent lung cancer. *J. Natl Cancer Inst.* **87**, 1502–1503 (1995).
81. Tucker, M. A. *et al.* Second primary cancers related to smoking and treatment of small-cell lung cancer. *J. Natl Cancer Inst.* **89**, 1782–1788 (1997).
82. Inskip, P. D. & Boice, J. D. Jr. Radiotherapy-induced cancer among women who smoke. *Cancer* **73**, 1541–1543 (1994).
83. Neugut, A. I. *et al.* Increased risk of lung cancer after breast cancer radiation therapy in cigarette smokers. *Cancer* **73**, 1615–1620 (1994).
84. Jensen, O. M., Paine, S. L., McMichal, A. J. & Ewertz, M. in *Cancer Epidemiology and Prevention* 2nd edn (eds Schottenfeld, D. & Fraumeni, J. F.) 290–318 (Oxford, Oxford Univ. Press, 1996).
85. Rothman, K. & Keller, A. Z. The effect of joint exposure to alcohol and tobacco on risk of cancers of the mouth and pharynx. *J. Chronic Dis.* **25**, 711–716 (1972).
86. Flanders, W. D. & Rothman, K. J. Interaction of alcohol and tobacco in laryngeal cancer. *Am. J. Epidemiol.* **115**, 371–379 (1982).
87. LaVecchia, C. & Negri, E. The role of alcohol in esophageal cancer in nonsmokers, and the role of tobacco in nondrinkers. *Int. J. Cancer* **43**, 784–785 (1989).
88. van Leeuwen, F. E. *et al.* Roles of radiotherapy and smoking in lung cancer following Hodgkin's disease. *J. Natl Cancer Inst.* **87**, 1530–1537 (1995).
89. Perera, F. P. Environment and cancer: who are susceptible? *Science* **278**, 1068–1073 (1997).
90. Baron, J. A. & Rohan, T. E. in *Cancer Epidemiology and Prevention* 2nd edn (eds Schottenfeld, D. & Fraumeni, J. F.) 269–289 (Oxford, Oxford Univ. Press, 1996).
91. Rothman, K. & Keller, A. Z. The effect of joint exposure to alcohol and tobacco on risk of cancers of the mouth and pharynx. *J. Chronic Dis.* **25**, 711–716 (1972).
92. Flanders, W. D. & Rothman, K. J. Interaction of alcohol and tobacco in laryngeal cancer. *Am. J. Epidemiol.* **115**, 371–379 (1982).
93. LaVecchia, C. & Negri, E. The role of alcohol in esophageal cancer in nonsmokers, and the role of tobacco in nondrinkers. *Int. J. Cancer* **43**, 784–785 (1989).
94. Thomas, H. V., Reeves, G. K. & Key, T. J. Endogenous oestrogen and postmenopausal breast cancer: a quantitative review. *Cancer Causes Control* **8**, 922–928 (1997).
95. Pike, M. C., Spicer, D. V., Dahmoush, L. & Press, M. F. Oestrogens, progesterone, normal breast cell proliferation, and breast cancer risk. *Epidemiol. Rev.* **15**, 17–35 (1993).
96. Bosland, M. C. The role of steroid hormones in prostate carcinogenesis. *J. Natl Cancer Inst. Monogr.* **27**, 39–66 (2000).
97. Yu, H. & Rohan, T. Role of the insulin-like growth factor family in cancer development and progression. *J. Natl Cancer Inst.* **92**, 1472–1489 (2000).
98. Sklar, C. A. Growth and neuroendocrine dysfunction following therapy for childhood cancer. *Pediatr. Clin. N. Am.* **44**, 489–503 (1997).
99. Sklar, C. A. *et al.* Changes in body mass index and prevalence of overweight in survivors of childhood acute lymphoblastic leukaemia: role of cranial irradiation. *Med. Pediatr. Oncol.* **35**, 91–95 (2000).
100. Tavani, A. *et al.* Risk factors for breast cancer in women under 40 years. *Eur. J. Cancer* **35**, 1361–1367 (1999).
101. Willett, W. C., Dietz, W. H. & Colditz, G. A. Guidelines for healthy weight. *N. Engl. J. Med.* **341**, 427–434 (1999).
102. Sklar, C., Boulad, F., Small, T. & Kernan, N. Endocrine complications of pediatric stem cell transplantation. *Front. Biosci.* **6**, G17–G22 (2001).
103. Bhatia, S., Sather, H. N., Trigg, M., Gaynon, P. & Robison, L. L. Low incidence of second neoplasms following childhood ALL: follow–up of the Children's Cancer Group Cohort. Presented at the American Society of Hematology Meeting, San Francisco, California, 2000.
104. Bhatia, S., Krailo, M., Robison, L. L. & Meyers, P. Secondary myelodysplasia among survivors of osteosarcoma. Presented at the American society of Clinical Oncology Meeting, San Francisco, California, 2001.
105. Krishnan, A. *et al.* Predictors of therapy-related leukaemia and myelodysplasia following autologous transplantation for lymphoma: an assessment of risk factors. *Blood* **95**, 1588–1593 (2000).
106. Bhatia, S., Davies, S. M. & Robison, L. L. in *Multiple Primary Cancers* (eds Neugut, A. I., Meadows, A. T. & Robinson, E.) 257–275 (Lippincott Williams & Wilkins, Philadelphia, 1999).

Online links

DATABASES

The following terms in this article are linked online to:

CancerNet: http://cancernet.nci.nih.gov/
acute lymphoblastic leukaemia | acute myeloid leukaemia | bladder cancers | bone tumours | breast cancers | colon cancer | Hodgkin's disease | kidney cancer | liver cancer | oesophageal cancer | oral cancer | pancreatic cancer | prostate cancer | retinoblastoma | soft-tissue carcinomas | uterine cervical cancer

LocusLink: http://www.ncbi.nlm.nih.gov/LocusLink/
ATM | CYP3A | *GSTM1* | *GSTP1* | *GSTT1* | IGF1 | *MLL* | NQO1 | *TP53*

Medscape DrugInfo: http://promini.medscape.com/drugdb/search.asp
cisplatin | doxorubicin | etoposide | mechlorethamine | melphalan | teniposide

OMIM: http://www.ncbi.nlm.nih.gov/Omim/
Li–Fraumeni syndrome

Access to this interactive links box is free online.