

Cancer Induced by Cancer Treatment

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Much of the recently improved survival and disease-free survival for several types of cancer is due to the use of a variety of chemotherapeutic drugs, as well as aggressive radiotherapy. It has been known for some time that both of these modes of cytotoxic therapy also have a high carcinogenic potential. With prolonged survival and actual cures after cytotoxic therapy, the opportunity to observe long-term complications such as treatment-induced malignancies has increased dramatically.¹ Study of this phenomenon is important for several reasons. First, with use of cytotoxic agents earlier in malignancy and for nonmalignant conditions, quantification of risk of these malignancies becomes essential in making risk-benefit decisions about therapy. In addition, those at high risk of a second primary make ideal populations for intervention efforts. This would include primary prevention, such as avoidance of other carcinogenic exposures or application of chemopreventive measures, and secondary prevention, such as institution of intensive efforts at screening for early disease or premalignant lesions. Finally, and most importantly for the topic of this symposium, study of these populations provides an unparalleled opportunity to study basic mechanisms of carcinogenesis in humans. It is unprecedented for large groups of humans to be purposefully exposed to well-documented doses of known carcinogens and then to be closely followed for medical endpoints. The fact that this is often done after randomization of study subjects is even more extraordinary. Because of the opportunities afforded by these studies, they are being conducted in a variety of centers throughout the world. For purposes of this presentation, I will be focusing primarily on results from studies from the "Late Effects Study Group" at the National Cancer Institute. (Current investigators include J. Boice, R. Curtis, M. Fraser, J.F. Fraumeni, Jr., R. Hoover, R. Kleinerman, L. Travis, and M. Tucker.)

DESCRIPTION OF RISKS

Leukemia

The most well-studied secondary malignancy is that which occurs the most rapidly after cytotoxic therapy, acute nonlymphocytic leukemia (ANLL). In studies we have conducted, the relative risk of ANLL after

radiotherapy for cancer has ranged from close to 1.0 after treatment for childhood tumors² to 2-fold among cervical cancer patients,³ uterine corpus cancer patients (Curtis R, unpublished data), and breast cancer patients receiving regional radiotherapy,⁴ up to 11-fold for Hodgkin's disease patients (Table 1).⁵ However, the overwhelming risk factor for secondary leukemia is treatment with chemotherapy—specifically alkylating agents (Table 2). Here the range in relative risk of leukemia is from 5-fold after treatment of childhood tumors² to 8-fold for adjuvant treatment of breast cancer patients⁴ to 100-fold after high-dose alkylating agent treatment of Hodgkin's disease⁵ and ovarian cancer.⁶ In general, these therapy-related leukemias do not arise until 2 years after exposure, and the risk peaks 4–9 years after cessation of therapy and declines thereafter. In every instance presented here there was evidence of dose-response for both radiation and alkylating agent treatments.

Solid Tumors

Excess risk of solid tumors does not become apparent in these populations until about 10 years after therapy. Thus, we are only now beginning to identify these risks and, thus far, the groups that can be evaluated have been treated with radiotherapy, with little long-term follow-up data yet available for chemotherapy. Children receiving high-dose radiotherapy have a dose-related 6- to 40-fold increase in risk of osteosarcoma⁷ and a 15-fold increase in the risk of thyroid cancer.⁸ However, most of our emerging knowledge of solid tumor risks comes from long-term follow-up studies of Hodgkin's Disease. The actuarial risk of malignancy at 15 years of follow-up in one such study was 18% with 13% attributable to solid tumors.⁵ The distribution of sites that are excessive include lung, stomach, breast, melanoma, bone and soft-tissue sarcomas (Table 3). The risk of solid tumors was higher after adjuvant chemotherapy than after radiotherapy alone but the differences were not significant. Although adequate data on risks associated with chemotherapy have yet to be accumulated, there is a well-established excess bladder cancer risk associated with high-dose cyclophosphamide therapy⁹ and an excess endometrial cancer risk associated with either estrogen¹⁰ or tamoxiphen¹¹ treatment of breast cancer.

While focusing on hazards, not all of the information on risks is bad. As I mentioned, the data with respect to leukemia risks are virtually

TABLE 1. Acute Nonlymphocytic Leukemia (ANLL) After Radiotherapy

First primary	No. of all cases of ANLL	Relative risk
Cervix ³	133	2.0
Endometrium	118	1.9
Breast ⁴	35	2.1
Hodgkin's disease ⁵	3	11.0

TABLE 2. A

First primary
Breast ⁴
Childhood cancers ²
Hodgkin's disease ⁵
Ovary ⁶

restricted to drug data based on srx doxorubicin² and the risk reported, indicated the antir the antimetabolit risk. For exampl trial of colorecta 14 cases of cance 18 "expected" o were ANLL. Bec gestational troph also some long- women, that hav a six-center follo for 8 years or lo (Trapido E, unpr of actual protec cancer treatmen moxiphen, 61 t breast cancer du number of wom

TABLE 3

Secondary pr
All solid
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Stomach
Melanom
Bone
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Breast
Colon
Other

TABLE 2. Acute Nonlymphocytic Leukemia (ANLL) After Treatment With Alkylating Agents

First primary	No. of all cases of ANLL	Relative risk
Breast ⁴	48	10
Childhood cancers ²	19	27
Hodgkin's disease ⁵	26	130
Ovary ⁶	12	171

restricted to drugs with alkylating activity. There are some preliminary data based on small numbers that implicate the anti-tumor antibiotic doxorubicin² and similar data, worrisome because of the magnitude of the risk reported, for epipodophyllotoxins.¹² However, no data have yet indicted the antimetabolites or the vinca alkaloids. Indeed, the data for the antimetabolites are extensive and have revealed no excess leukemia risk. For example, in a long-term follow-up of a randomized clinical trial of colorectal cancers treated with 5 fluoro 2'doxyuridine (FUdR), 14 cases of cancer were observed in the treated patients compared with 18 "expected" on the basis of population rates.¹³ None of the cases were ANLL. Because of the early use of antimetabolites in treatment of gestational trophoblastic disease and the cures that resulted, there are also some long-term survivor data, albeit still on limited numbers of women, that have as yet not revealed any solid tumor excess either. In a six-center follow-up study of 1,600 such women, among these followed for 8 years or longer, 14 cancers developed compared with 13 expected (Trapido E, unpublished data). Finally, there is some recent evidence of actual protection against a second primary tumor associated with cancer treatment. In a recent meta-analysis of four clinical trials of tamoxifen, 61 tamoxifen-treated women developed a contralateral breast cancer during follow-up compared with 115 among a comparable number of women given placebo.¹¹

TABLE 3. Second Primary Solid Tumors After Hodgkin's Disease⁵

Secondary primary site	No. of cases	Relative risk
All solid tumors	46	3
Lung	14	2
Stomach	4	10
Melanoma	4	9
Bone	2	31
Connective tissue	2	15
Breast	3	2
Colon	4	1
Other	13	1

Summary

There is a dose-related risk of ANLL associated with both radiation and alkylating agent therapy of malignancy and perhaps a risk with some of the more recently introduced chemotherapy agents. Because of the relatively rapid onset of this complication and its poor prognosis, clinical trials, particularly those with 10-year follow-up, generally include this risk in their overall risk-benefit evaluation. On the other hand, secondary solid tumors arise later, have the potential for a much greater impact in terms of cumulative percentage of patients affected, and are typically not assessed in the usual time frame of clinical trials. The cumulative percent of Hodgkin's disease patients developing a second primary by 15 years of follow-up is around 20% and gives every indication of continuing to rise as follow-up is extended. To date, solid tumor excesses have been firmly linked to radiotherapy. With the exception of cyclophosphamide-induced bladder cancer and endometrial cancer associated with hormonal therapies, little information is available yet on risks associated with chemotherapy in the absence of radiotherapy. If chemotherapy turns out to mimic radiation effects in other organs as it does in the bone marrow, then its scope of organ exposure in the body could result in even higher risks than those seen with extensive radiation. Assessment of this aspect of risk of treatment-related cancers is undoubtedly a high priority in this general area of research.

INSIGHTS INTO MECHANISMS OF CARCINOGENESIS

From the standpoint of etiology and prevention, perhaps the most important aspect of this phenomenon of treatment-induced cancer is the opportunity provided to study mechanisms of carcinogenesis in humans. Insights into these mechanisms can come simply from detailed observations of various exposure and demographic determinants of the cancer risks, and, somewhat more elegantly, from the addition of biochemical and molecular components to these formal epidemiologic studies.

Exposure and Demographic Determinants

With respect to opportunities to learn about mechanisms simply from data obtained from records or questionnaires, four examples are illustrative of these opportunities.

(1). *Dose-response.* For radiation-induced leukemia, the risks noted are in themselves an anomalous finding. In previous studies of radiation-induced leukemia in A-bomb survivors and medically irradiated populations, a well worked-out dose-response curve has been modeled and became the accepted description for a variety of purposes.¹⁴ However, the risks observed in patients treated with radium for benign gynecologic

conditions¹⁵ and medical therapy for cancers (unpublished data) are modeled (Fig. 1). Although the risk may be attributable to this possibility is expected. Understar valuable insights in leukemogens in gen
(2). *Carcinogenic* nancies have uncovered between specific drugs. We have been able to therapeutic dose for the leukemogen than cyc high doses employed involved in adjuvant reason for this disparity substantially aid in carcinogenesis.

(3). *Interaction* involves treatment with

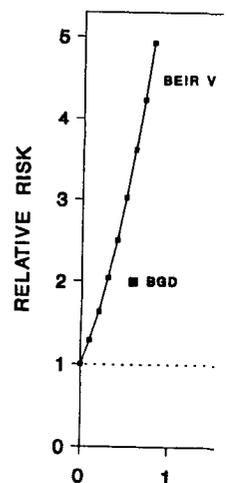


FIG. 1. Expected relative risk according to the model described on the Biological Effects of Radiation studies of women treated with radium receiving radiotherapy for cancer.

conditions¹⁵ and much more dramatically in those treated with radiotherapy for cancers of the cervix,³ breast,⁴ and endometrium (Curtis R, unpublished data) are substantially lower than that expected by this model (Fig. 1). Although some of the difference of observed to expected risk may be attributable to cell-killing at high radiation doses, adjustment for this possibility results in risks which are still substantially less than expected. Understanding the reasons for this discrepancy could yield valuable insights into mechanisms of dose-response relationships for leukemogens in general.

(2). *Carcinogenic potency.* Studies of chemotherapy-related malignancies have uncovered substantial differences in carcinogenic risks between specific drugs of the same class that have equal therapeutic efficacy. We have been able to demonstrate in two separate contexts that therapeutic dose for therapeutic dose, melphalan is a much more potent leukemogen than cyclophosphamide. This is true both at the relatively high doses employed for ovarian cancer treatment¹⁶ and at the low doses involved in adjuvant therapy for breast cancer.⁴ Identification of the reason for this disparity in cytotoxic versus carcinogenic potency could substantially aid in our efforts to understand the mechanisms of chemical carcinogenesis.

(3). *Interaction of carcinogens.* Because cytotoxic therapy often involves treatment with more than one carcinogen, there are some cir-

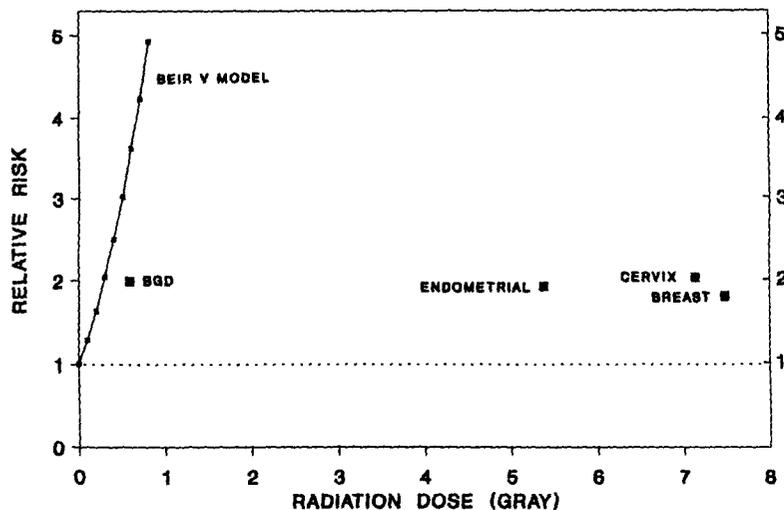


FIG. 1. Expected relative risks of leukemia by radiation dose to the active bone marrow according to the model developed by the National Academy of Sciences (NAS) Committee on the Biological Effects of Ionizing Radiation V (BEIR V),¹⁴ and those actually observed in studies of women treated with radium for benign gynecologic disease (BGD),¹⁵ and those receiving radiotherapy for cervical,³ breast,⁴ and endometrial (Curtis R, unpublished data) cancer.

cumstances that allow an assessment of the joint effects of these exposures. Table 4 illustrates two different mechanisms of joint effects. The risk of ANLL after breast cancer is related to radiotherapy (RR = 2) and to alkylating agent chemotherapy (RR = 10).⁴ The risk in those exposed to both agents (RR = 17) is consistent with a multiplicative effect. The implication of this is that both exposures must share at least some common pathways of carcinogenesis. In the other example, one study has related the risk of bone sarcoma after treatment for childhood cancer to radiation (high dose RR = 37) and alkylating agent chemotherapy (high dose RR = 9).⁷ However, in this instance the risk among those exposed to high doses of both treatments (RR = 59) was not multiplicative, but much more consistent with an additive model, implying independent mechanisms of carcinogenesis. In these examples, the number of subjects for certain categories are quite limited and the findings need replication before acceptance, but indicate the insights possible from this approach.

(4). *Host factors.* Characteristics of the exposed subjects may also modify the risks associated with cancer treatment. Perhaps the most graphic example of this is the relationship of radiation-induced breast cancer risk to age at exposure among patients treated for Hodgkin's disease. Table 5 combines data from the large series of patients from Stanford University¹⁷ with previously unpublished data from the Surveillance, Epidemiology, and End Results (SEER) Program of NCI-sponsored population-based cancer registries. The risk of breast cancer is over 35-fold for women irradiated under age 20. This risk drops with increasing age-at-exposure until there is no detectable excess risk for those exposed after age 40, even though the exposure is to over 40 Gy of ionizing radiation. This age effect, consistent with data on A-bomb survivors and some other medically irradiated groups, should be an important clue to breast carcinogenesis in general. The solution to this

TABLE 4. Relative Risks of Two Second Primary Cancers According to Treatment of the First Primary With Radiation and/or Alkylating Agents

	Radiation therapy	Alkylating agents	
		No	Yes
ANLL after breast cancer ⁴	No	1.0	10
	Yes	2.4	17.4
		Alkylator dose	
Bone sarcoma after childhood cancer ⁷	Radiation dose	None	High
	None	1.0	8.5
	≥1,000 rad	37.4	59.2

TABLE 5. Breast Cancer

Age at treatment
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20-39 yr
≥40 yr

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TABLE 6. Biochem

TABLE 5. Breast Cancer After Treatment for Hodgkin's Disease by Age at Such Treatment

Age at treatment	Observed	Relative risk	95% C.I.
<20 yr	10	35.7	17.1-65.7
20-39 yr	25	3.7	2.4-5.5
≥40 yr	16	1.3	0.7-2.1

clue could have profound implications for prevention of this most common of malignancies in women.

Biochemical and Molecular Studies

If there are important leads to mechanisms of carcinogenesis from simply evaluating the exposure and demographic determinants of risk in these patient groups, what is the potential for the addition of clinical and laboratory measurements to give us even better insights? In this era of rapid advances in interdisciplinary studies, this is truly an area of research that offers almost unlimited possibilities for understanding multiple aspects of carcinogenesis in humans. Table 6 gives a number of examples of the types of laboratory tools used in these studies and organizes them into groups. The groupings are obviously arbitrary and any one tool could actually be relevant to any of the groups. For example, DNA adducts are not only a measure of relevant exposure but differences between individuals are undoubtedly partially the result of host factors, and the consequences of these interactions can be specific forms of genetic damage. However, this is a useful scheme for organizing a discussion of these types of studies.

Measurement of exposure. A number of possibilities exist for pursuing which aspects of exposure to carcinogens are responsible for their carcinogenic action. Several *in vitro* and *in vivo* measures have been developed to test substances for their potential for and level of carcinogenic

TABLE 6. Biochemical and Molecular Studies of Treatment-Induced Cancer

Yes	Measurement of exposure
10	"Activity" of agent
17.4	Adduct formation
dose	Host susceptibility
High	Differential toxicity
8.5	DNA repair
59.2	P450 metabolic polymorphisms
	Genetic damage
	Cytogenetics
	Sister chromatid exchange
	Mutational spectra

activity.¹⁸ Relating these measures to actual human carcinogenicity data for these same substances should define which of these assays are most relevant and thus imply which mechanistic pathways are involved. A number of other studies are focused on whether the amount of an activated carcinogen that actually ends up attached to DNA (adducts) may be a more relevant biological dosimeter than the dose of the carcinogen to which the patient was exposed. Research in this area is attempting to link these measures to the therapeutic effectiveness of various chemotherapeutic agents, as well as their toxicity.^{19,20}

Host susceptibility. Various parameters of host susceptibility have been pursued for sometime for their role in secondary malignancies, which even at the high risks noted here are still relatively rare events. A number of attempts have been made to relate susceptibility to acute bone marrow toxicity with susceptibility to secondary leukemia among Hodgkin's disease patients. Although no correlation has been noted with lymphocyte count during chemotherapy or other measures of white-cell toxicity,²¹ a marked relationship of toxicity to the erythrocytic series with subsequent ANLL was observed in one study (Table 7).²² Both the increase in mean corpuscular volume of erythrocytes (MCV) and the maximum MCV attained during chemotherapy were substantially greater in patients who subsequently developed a secondary leukemia compared with survivors who did not.

Another aspect of host susceptibility that can be assessed in this context is DNA repair. A number of general and specific parameters associated with repair mechanisms are possible to measure and could shed some light on interindividual susceptibility. In one provocative study, levels of O⁶-alkylguanine alkyltransferase (AGT) were measured in the peripheral blood lymphocytes of patients with treatment-related ANLL, *de novo* ANLL, and controls.²³ AGT is a DNA repair protein that is responsible for repair of alkylation damage at the O⁶ position of guanine resulting from exposure to alkylating agents. In this study, the levels in controls and patients with *de novo* ANLL were similar, while those in patients with treatment-related ANLL were only 60% of the control values.

TABLE 7. Mean Corpuscular Volume of Erythrocytes (MCV) During Cytotoxic Therapy and Secondary Leukemia (SL)

	Maximum MCV (FI)	Maximum MCV increase (FI)
Patients without SL	99.8 ± 14.7	16.2 ± 8.4
Patients with SL	112.6 ± 7.1	30.1 ± 7.4

Adapted from DeGramont.²²

An aspect of host susceptibility in a variety of areas of cancer polymorphisms in activation of secondary cancers malignancies. For example, the enzyme responsible for the repair of DNA damage has been taken to evaluate the relationship for this enzyme to the development of leukemias and bladder cancer.

Genetic damage. Finally, as markers of exposure to radiation, events leading from chromosome breaks have been used include global chromosome changes of sister chromatid exchange monitored in lymphocytes. A test developed for measurement of chromosome development of a certain type of chromosome exposures, or indeed specific chromosome malignancy. Although many studies will undoubtedly offer more information on cancers. Meanwhile, several studies in the area of cytogenetics with treatment-related radiation syndrome, 61 displayed these, chromosomes 5 and 12, and interstitial deletions on chromosome 11 in the region of 5q23 to 5q31. The same region is known to be important for hematopoietic growth factors.

In the late effects program, genetic evaluations of survivors of secondary malignancies. In particular, lymphocytes for the presence of chromosome changes at these locations, inversions, and translocations who received from 1 Gy to 10 Gy of bone marrow during treatment with such cytogenetic changes. In those among A-bomb survivors, there is a difference in leukemia risk between these two populations (Figs. 1 and 2). If these cytogenetic changes are related to the dose, dose rate, bone marrow dose, and other factors, the dominant factors of these major risk

An aspect of host susceptibility that is generating much enthusiasm in a variety of areas of carcinogenesis is the role of various P450 metabolic polymorphisms in activation and deactivation of carcinogens. Studies of secondary cancers might provide a powerful model for such investigations. For example, with the recent identification of P450 2B1 as the enzyme responsible for metabolism of cyclophosphamide, steps could be taken to evaluate the relevance of polymorphisms of the gene encoding for this enzyme to the development of cyclophosphamide-induced leukemias and bladder cancers.

Genetic damage. Finally, measures of genetic damage can be used either as markers of exposure or actual intermediate end points on the cascade of events leading from exposure to a malignancy. Measures that have been used include global measures of DNA damage, such as frequency of sister chromatid exchange and nonspecific aberrations that can be monitored in lymphocytes. Recently, considerable enthusiasm has developed for measurement of mutations that may be specific for the development of a certain type of tumor, specific for certain carcinogenic exposures, or indeed specific for a certain exposure causing a particular malignancy. Although much of this work is currently developmental, it will undoubtedly offer major advantages for future studies of secondary cancers. Meanwhile, several provocative observations have been made in the area of cytogenetics. In a study by Le Beau *et al.*²⁴ of 63 patients with treatment-related nonlymphocytic leukemia and myelodysplastic syndrome, 61 displayed a clonal chromosomal abnormality. In 55 of these, chromosomes 5 and/or 7 were involved. Fully 17 of these involved interstitial deletions on the long arm of chromosome 5, specifically in the region of 5q23 to 5q32. This is particularly provocative since this same region is known to contain genes for encoding of a number of hematopoietic growth factors.

In the late effects program at the NCI we have incorporated cytogenetic evaluations of survivors into a number of our studies of secondary malignancies. In particular, we have assayed peripheral blood lymphocytes for the presence of stable chromosomal aberrations (*i.e.*, translocations, inversions, and deleted segments) in cervical cancer survivors who received from 1 Gy to over 10 Gy of radiation to their active bone marrow during treatment for their malignancy.²⁵ The percentage of cells with such cytogenetic changes in cervical cancer patients compared with those among A-bomb survivors mirrors almost exactly the marked difference in leukemia risk by radiation dose previously noted between these two populations (Fig. 2). Thus, it appears as though we can use these cytogenetic changes as surrogates for leukemia in our pursuit of the dose, dose rate, bone marrow cellular dynamics and other determinants of these major risk differences.

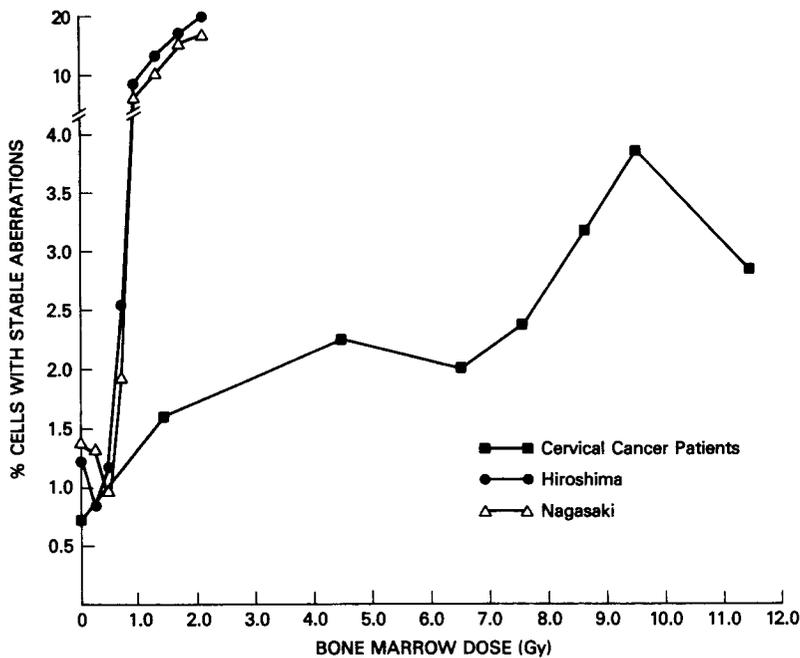


FIG. 2. Mean percentage of cells bearing stable chromosome aberrations according to total radiation dose to the active bone marrow for cervical cancer patients and for atomic bomb survivors, by city. (Reprinted from Kleinerman *et al.*²⁵)

I have touched on only a few of the laboratory tools that have been and are being developed which could be used in patients undergoing cancer treatments and that could yield major insights into generalizable, basic mechanisms of carcinogenesis in humans. Indeed, perhaps many of these tools could be used early on in their development in such populations. The high doses of known carcinogens, the high cancer risks, and the control over other parameters that are associated with these studies could provide the opportunity to assess whether these tools might be useful in more subtle and less controlled human population studies of environmental and genetic determinants of cancer.

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