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EXTENDED ABSTRACTS

American Statistical Association Conference on Radiation and Health

Howard Johnson Plaza Resort, Deerfield Beach, Florida, June 23–26, 2002

The 15th ASA Conference on Radiation and Health, held June 23–26, 2002 in Deerfield Beach, FL, offered a unique forum for radiation researchers from a variety of disciplines to present and discuss recent findings and current issues related to the effects of radiation exposures on human health. The Conference also furnished investigators the opportunity to learn about new approaches to problems within their disciplines.

The focus of the 2002 conference was current issues in radiation and health with sessions on:

1. lung cancer related to residential radon exposures and cancer risk from plutonium exposure;
2. novel efforts at low doses such as the bystander effect, i.e. the response of neighboring cells not directly irradiated;
3. diagnostic medical radiation, which is the primary source of U.S. population exposure from man-made radiation;
4. sensitive subpopulations and novel approaches to characterize genetic predisposition to radiogenic cancers; and
5. exposure and cancer risks in medical radiation workers, plus a recent finding that work-required X-ray examinations account for the bulk of radiation exposure in a cohort of nuclear workers.

The Conference also included a timely and provocative banquet presentation on ''Nuclear and Radiological Terrorism.'' The 15th biannual conference on Radiation and Health proved to be as stimulating and informative as in previous years. The participants enthusiastically look forward to the 16th conference to be held in 2004!

Susan Preston-Martin, Co-Chair
James M. Smith, Co-Chair

RESIDENTIAL RADON AND ALPHA EMITTERS

Jerome Puskin, Chair

The Risk of Cancer from Exposure to Plutonium

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The risk of cancer from exposure to plutonium has been evaluated in experimental animal studies and in epidemiological studies of workers involved in the production of nuclear weapons. The BEIR IV Committee (*1*) and, more recently, NCRP 131 (*2*) have reviewed these data.

Experimental studies in dogs and rats, supplemented by autopsy studies in humans, have contributed greatly to our understanding of health risks from plutonium. Findings from these studies indicate that inhalation is the route of exposure of greatest concern, and that exposures to intact skin or to the gastrointestinal tract are of considerably less concern. These studies have demonstrated that doses to the lung, skeleton and liver (the most highly exposed organs of the body) depend not only on the amount of deposited plutonium and time since intake but also on the size of the inhaled particles, solubility and other physicochemical characteristics of the plutonium. Life-span studies in dogs and rats exposed to various forms of plutonium have clearly demonstrated excess risks of cancers of the lung, liver and bone with little evidence of excess risks of other cancers. Animal experiments have also informed us regarding comparative risks of different types of radiation exposure such as plutonium compared to radon or high-LET compared to low-LET radiation.

In contrast to the experimental studies, epidemiological studies of plutonium-exposed workers at Rocky Flats, Los Alamos, and Hanford in the United States (*2*) and the Sellafield plant in the United Kingdom (*3*) have provided little evidence of excess cancer risk, probably because the numbers of exposed workers and the doses were too low to yield adequate statistical power. Because of limitations in direct epidemiological data, quantitative estimates of risks from exposure to plutonium have been obtained either from studies of persons exposed to other α-particle-emitting radionuclides or by applying a radiation weighting factor to estimates obtained from Japanese A-bomb survivors exposed to low-LET radiation. For example, the BEIR IV Committee (*1*) based its lung cancer risk estimate on studies of underground miners exposed to radon and radon progeny, its liver cancer risk estimate for Thorotrast from human data, and its bone cancer risk estimate on a Bayesian analysis data for exposure of human to radium and of animals to transuranics and radium. NCRP (*2*), in a more recent evaluation, continued to support the BEIR IV recommendations.

With the opening up of the former Soviet Union, data from an epidemiological study of about 20,000 workers at the Mayak nuclear facility in Ozyorsk, Russian Federation have become available. The Mayak worker cohort was initially established by Dr. Nina Koshurnikova of the Southern Urals Biophysics Institute (SUBI) and is now the focus of collaborative research between Russian scientists and scientists at several organizations in the United States, Europe and Japan. Doses from both external sources and plutonium are much larger for Mayak workers than for plutonium workers in other countries, especially for workers who began employment in the period 1948–1958. Among about 5700 workers in the radiochemical and plutonium plants who were monitored for plutonium, the average body burden was 1.9 kBq (52 nCi). Over 1000 workers had body burdens that exceeded 1.5 kBq (40 nCi), a level that has served as a guideline for the maximum permissible burden in many countries, and about 260 workers had burdens that exceeded 7.4 kBq (200 nCi). Average doses to the lung, liver and bone surfaces among the 5700 monitored workers were 0.26, 0.29 and 1.8 Gy, respectively. By contrast, the highest body burden reported in U.S. workers was 3.2 kBq (*4*), and the average lung dose among 4600 Sellafield workers monitored for plutonium was about 0.01 Gy (*3*).

Risks of lung, bone and liver cancers have been clearly linked with plutonium exposure in Mayak workers. Lung cancer risks have been studied by several investigators, most recently by Kreisheimer *et al.* (*5*), who evaluated the risk of lung cancer as a function of external dose and internal dose from plutonium among males who either were monitored for plutonium or worked only in the reactor plant, where there was little potential for plutonium exposure. A statistically significant association was demonstrated for internal dose and suggested for external dose, and both associations were consistent with linear dose dependencies. For dose from plutonium, the excess relative risk (ERR) per Sv at age 60 (with a radiation weighting factor of 20 for particles) was estimated to be 0.6 (95% CI: 0.4–1.0). For external dose, the ERR per Sv at age 60 was estimated to be 0.2 (95% CI: 0.04–0.7). Bone and liver cancers have also been studied. In analyses by Koshurnikova *et al.* (*6*) and Gilbert *et al.* (*7*), relative risks in the highest plutonium exposure category (estimated body burden 7.4+ kBq) were estimated to be 7.9 (95% CI: 1.6–32) for bone cancer and 17 (95%CI: 8.0–36) for liver cancer. Further analyses evaluating the dose–response relationship for lung, liver and bone cancers are under way, and they incorporate recent improvements in plutonium dosimetry. Results of these analyses will be presented.

A limitation of the Mayak worker study is that a systematic bioassay program based on measurements of plutonium in large urine samples did not begin until about 1970. As a result, only about 40% of workers with potential for plutonium exposure have the data needed to estimate body burdens and doses. In addition, estimated doses from plutonium are subject to many sources of uncertainty, including imprecision in urine measurements, uncertainties in the time and form of plutonium exposure that in most cases occurred many years before measurements were taken, uncertainties in the biokinetic models and parameter values that are used to estimate deposition and clearance of plutonium in the human body, and the fact that these models can only approximate the behavior of plutonium in any given individual. Nevertheless, the Mayak worker cohort is a unique resource for future estimation of cancer risks from exposure to plutonium, and it is important to continue to follow these workers and also to continue efforts that are now under way to improve both external and internal dose estimates. However, it is also important to consider other approaches for evaluating risks from plutonium exposure and to check the consistency of estimates derived from different types of data.

Acknowledgments. I would like to acknowledge the contribution of several collaborators in the Mayak worker studies, including N. A. Koshurnikova, N. S. Shilnikova and M. Sokolnikov of the Southern Urals Biophysics Institute; D. L. Preston of the Radiation Effects Research Foundation; and E. Ron of the National Cancer Institute.

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Residential Radon and Lung Cancer in a High Radon Area of Gansu Province, China

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Although studies of underground miners demonstrate convincingly that exposure to radioactive radon gas and its decay products increases the risk of lung cancer (*1*), direct demonstration of excess risks from residential radon is needed to confirm the risk for residential exposures and to affirm extrapolations from the miner data. To date, some case–control studies of residential radon find no risk with indoor radon exposure, while others are consistent with increasing risk with increasing indoor exposure. Meta-analyses report statistically significant excess risk from radon exposure.

Residential studies are hampered by low radon exposure, resulting in small risks, and uncertainties from imprecise reconstruction of historical exposures due to residential mobility and missing data (*2–5*). To address these limitations, we conducted a case–control study in an area of China where indoor radon concentrations are high and residential mobility is low (*6*).

Materials and Methods

The study was conducted in Pingliang and Qingyang, two rural prefectures in Gansu Province, China, where most residents live or have lived in underground dwellings, and where radon levels are high. Case subjects included all individuals between ages 30 and 75 years who were diagnosed with lung cancer between January 1994 and April 1998 at prefecture and county hospitals, anti-tuberculosis stations, or hospitals in large nearby cities. Based on clinical/radiological symptoms or pathological evidence and a review by an expert panel, we identified a total of 938 cases. Of those, 43 cases were not located, 6 cases were outside the age range and 3 cases moved from the area, leaving 886 cases (656 males, 230 females). Diagnoses of lung cancer were based on clinical/radiological criteria for 533 cases (60%) and pathological evidence for 353 cases (40%). Among the clinical/radiologically identified cases, 414 (78%) died prior to the end of the study period.

We randomly selected 1,968 controls from 1990 census lists and frequency-matched on age in 1995 to cases in 5-year age groups, within categories of sex and prefecture. The number of controls was based on twice the expected number of lung cancers. Among controls, 6 refused to be interviewed, 23 moved from the area, 62 were not located, 73 died before 1994, 4 became cases, and 35 were not interviewed for other reasons. The study enrolled 1,310 male and 455 female controls.

Questionnaires were administered by trained interviewers and included questions on smoking habits, occupational, residential and medical histories, and other factors. Next of kin, usually the spouse, provided information for 481 (54%) cases and 71 (4.0%) controls.

We defined reference age as age at diagnosis for a case and age at interview for a control and designated 5–30 years prior to the reference age as the time-relevant exposure period for lung cancer risk. Interviewers placed two 1-year α-particle track detectors, one in the living area and one in the sleeping area, in the current house and in all former houses within the study area occupied by the subject within the exposure window. For cases and controls, 87.5% and 94.6% had measurements within the exposure window, respectively, based on 1.9 and 1.6 mean eligible residences per subject.

We computed time-weighted average radon concentration within the exposure window in becquerels per cubic meter (Bq/m^3), using years resident as weights. Two control subjects were excluded due to extreme values (1,554 and 1,676 Bq/m^3) that were more than 40% greater than the next largest value. We imputed values for gaps in residential history from missing measurements or less than 2 years occupancy using mean radon for control houses within house type and prefecture (*7*). Alternative approaches, which adjust for imputation variance, were similar due to high coverage of the exposure window.

We computed odds ratios (ORs), adjusted for age, sex, prefecture, tobacco use, and, where appropriate, other factors using unconditional logistic regression (8). We calculated 95% Wald confidence intervals (CI) for category-specific ORs. We also fitted a linear model, $OR(x) = 1 + \beta x$, where x was mean radon level and β was the excess OR (EOR) per Bq/m^3, and derived likelihood-based CIs for estimates of β.

We initiated a substudy to assess variation in radon within and between rooms, between dwellings, and over time to provide data to adjust for exposure uncertainty. We placed six 1-year α-particle track detectors in each room (two at the front, middle and back) of 55 houses in three consecutive years, starting July 1996. A total of 1,654 detectors were placed in one to five rooms in each house (mean 2.3 rooms/house).

Three important sources of error in radon exposure assessment were (1) measurement error of the detector, (2) use of contemporary measurements to estimate radon throughout the house and in prior years, and (3) missing radon values. Detector error was relatively small and was ignored. Estimation of radon induces classical error, while missing data induced Berkson error. For the error adjustment, we restricted data to subjects with 70% or greater coverage of the exposure window, thus minimizing Berkson error, so that classical error predominated. Based on a multiplicative error structure, we estimated the geometric standard deviation (GSD) for the error as 1.5 and used Monte Carlo methods to adjust the observed exposure–response relationship for this uncertainty.

Results

There were 768 cases (563 males and 205 females) and 1,659 controls (1,232 males and 427 females) with radon measurements and data on the primary adjustment factors. Most men smoked (92.3%), while most women did not (10.4%). Consistent with other studies in China, the OR for ever-smokers compared to never-smokers was low, OR = 1.69 (1.2, 2.4), and was similar for males and females, although it increased to 4.26 (2.4,7.4) for those who smoked 40 years or more or 20 cigarettes per day. Based on preliminary analysis, we adjusted ORs for socioeconomic factors, smoking rate, age, sex and prefecture.

Radon concentrations for the 3,188 measured houses were approximately log-normally distributed, with arithmetic mean (AM) 222.9 Bq/m^3, geometric mean (GM) 176.2 Bq/m^3, and GSD 2.08.

Mean concentrations for cases and controls were 230.4 and 222.2 Bq/m^3, respectively, with 81.6% of cases and 76.3% of controls at or above 150 Bq/m^3. ORs increased significantly with increasing concentration. Relative to <100 Bq/m^3, ORs and 95% confidence intervals for categories 100–149, 150–199, 200–249, 250–299 and 300+ Bq/m^3 were 1.00 (0.7,1.5), 1.42 (1.0, 2.0), 1.36 (1.0, 1.9), 1.28 (0.8, 1.9) and 1.58 (1.1, 2.3). The estimated EOR at 100 Bq/m^3 was 0.19 (95% CI: 0.05, 0.47).

Coverage of the exposure window ranged from 8% to 100%, with 76.7% (71.6% for cases and 79.1% for controls) mean coverage. Subjects with 70% or greater coverage (463 cases and 1,143 controls with 98.1% coverage), 90% or greater coverage (398 cases and 1,069 controls with 99.8% coverage), or 100% coverage (366 cases and 1,045 controls) had EORs at 100 Bq/m^3 of 0.22 (95% CI: 0.06, 0.54), 0.26 (95% CI: 0.08, 0.66), and 0.31 (95% CI: 0.10, 0.81), respectively.

Results were similar when data were restricted to histologically confirmed cases or were restricted to subject respondents, as opposed to surrogates. In addition, there was no significant variation in radon effects by age, sex, smoking status, previous diagnosis of pulmonary tubercu-

losis, indoor smokiness, or amount of coal use. There was heterogeneity in the EOR by type of house, with a significant trend in risk for those living in underground dwellings, but no trend for subjects living in standard above-ground dwellings or apartments. However, this heterogeneity disappeared with more detailed adjustment for smoking and with greater coverage of the exposure time window.

For subjects with 70% or greater coverage of the exposure window, the EORs at 100 Bq/m^3 adjusted for error GSDs of 1.25, 1.5 and 1.6 were 0.27 (95% CI: 0.03, 0.69), 0.32 (95% CI: 0.08, 1.37) and 0.59 (95% CI: 0.14, 2.73), respectively, in contrast to the unadjusted estimate 0.22 (95% CI: 0.06, 0.54). EOR estimates, as well as widths of the CIs, increased with the adjustments for exposure error.

Summary

Uncertainty in dosimetry can have an impact on estimates of radon effect. The estimated EOR increased after adjustment for our best estimate of exposure uncertainty by about 50%. This agrees with previous attempts at uncertainty adjustment of the EOR, which also increased estimates about 50–100% (*3, 5, 6*). In addition, three recent studies with enhanced exposure assessments found an increased risk of lung cancer (*2, 9, 10*), suggesting that radon risks may be higher than previously estimated.

In conclusion, radon concentrations in our study were high, exceeding most previous indoor studies, and the population was stable, suggesting improved accuracy in dosimetry. The overall EOR at 100 Bq/m^3 was 0.19 (0.05, 0.47). These results provide evidence that high levels of residential radon increased the risk of lung cancer and support findings from meta-analyses of indoor studies and from miners. In addition, our estimates suggest that the effects of residential radon may equal or exceed miner-based estimates, which are currently used for risk evaluation.

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A Combined Analysis of North American Case–Control Studies of Residential Radon and Lung Cancer: An Update

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Cellular mutagenesis studies, experimental research in several animal species, and epidemiological studies of underground miners have established radon as a human carcinogen (*1*). While results of miner studies are unambiguous in demonstrating an excess risk from radon exposure, airborne contaminants in mines, differences in breathing characteristics of miners and residents at home, and other differences in the environments of mines and homes are substantial. The miner studies provide no direct information on lung cancer risks from exposure to radon in females or children. Thus it is important to evaluate directly whether residential radon exposure is associated with lung cancer risk (*2*) and to confirm the extent to which exposure-related risks in mines and homes are comparable.

To date, 18 case–control studies of residential radon and lung cancer have been published, including seven studies in North America, nine in Europe, and two in China (Table 1). Studies involved from 161 to 1,449 cases, with most studies comprised of between 400 and 1,000 cases. Some of these studies reported a positive or weakly positive association between lung cancer risk and residential radon concentration, while others have reported results consistent with no association. To date, no case–control study has reported a statistically significant negative association.

In 1989, the U.S. Department of Energy (DOE) and the Commission of the European Communities (CEC) sponsored a workshop in Arlington, VA, that brought together investigators who had ongoing or planned studies of lung cancer and residential radon to establish a common working

TABLE 1
Case-Control Studies of Residential Radon and Lung Cancer

Region	No. of cases	No. of controls	Average radon concentration (Bq/m^3)	Reference
North American				
New Jersey (NJ)	480	442	29	(*14*)
Winnipeg (Winn)	738	738	141	(*8*)
Missouri-I (MO-I)	538	1,183	63	(*9*)
Missouri-II (MO-II)	512	553	55	(*10*)
Iowa (IA)	413	614	129[a]	(*11*)
Connecticut (CT)	963	949	33	(*13*)
Utah-South Idaho (UT-ID)	511	862	57	(*13*)
Europe				
Sweden (Stockholm)	198	379	133	(*17*)
Sweden (national)	969	2,054	96	(*18*)
South Finland	161	328	213	(*19*)
Finland (national)	863	1,166	102	(*20*)
South West England	960	3,126	55	(*21*)
Italy	387	406	94[a]	(*22*)
East Germany	1,053	1,667	75	(*23*)
West Germany	1,449	3,746	50	(*24*)
Sweden (non-smokers)	258	487	75	footnote 2
France	552	1,103	148	Pending
Czech Republic	206	824	519	Pending
China				
Shenyang	308	356	85[b]	(*25*)
Gansu	768	1,659	223	(*26*)

[a] Geometric mean household radon.
[b] Median household radon level.

framework for the pooling of radon data (*3*). Investigators recognized that the excess risk due to radon would likely be small, and that because the characterization of historical exposure to radon is problematic and subject to misclassification, large sample sizes would be required to demonstrate a significant excess risk, evaluate subtle patterns of variation in radon risk, and verify extrapolations of risk from miner-based exposure–response models. In 1991 and 1995, the DOE and CEC sponsored subsequent workshops in Arlington and Baltimore to continue the process of harmonizing design protocols to facilitate the eventual pooling of data (*4–6*). These meetings encouraged a collaborative environment among investigators and established a common set of variables and exposure assessment procedures that provided flexibility to the collaborating investigators to tailor study design to the unique aspects of their study populations.

Officials from Health Canada hosted a subsequent planning meeting in October 1995, including the principal investigators for all completed and ongoing North American case–control studies, invited scientists with expertise in radon risk assessment, and representatives from the U.S. DOE, the CEC, and the European pooling project. The common data format was developed by the principal investigators for the North American case–control studies at the working group meetings. After a subsequent planning meeting hosted by Health Canada in June 1997, the data available from the three completed North American case–control studies were included in a pilot analysis.[1]

The North American pooling project included investigators from the six primary North American case–control studies conducted in New Jersey (*7*), Winnipeg (*8*), Missouri-I (*9*), Missouri-II (*10*), Iowa (*11, 12*), and Connecticut/Utah-South Idaho (*13*). While the Connecticut/Utah-South Idaho study was designed as a single study with common features, we included subjects for Connecticut and Utah-South Idaho separately in the pooled analysis and present the results separately, effectively leading to seven studies in North America.

A final data format for the analysis included age, year of case and control ascertainment, source of information, sex, ethnicity, home sequence identifier, radon concentration in living areas and in basements, radon estimation method, proportion of time spent in the home, smoking, family income, and education. The values of some of these variables (such as education and income) were determined at the time of enrollment of the subjects; others (such as residential radon concentration) were determined on a year-by-year basis in each of the 50 years prior to enrollment. Not all information was available for all subjects and all studies; however, this format served as the basis for merging of data and developing the analytical file that served as the basis for the combined analysis.

The North American pooling examines data on residential radon exposure and lung cancer for 4,420 cases and 5,707 controls. This extensive database permits a more detailed examination of radon and lung cancer risk and its potential modifiers than has previously been possible. The specific goals of the analysis of pooled data from studies of indoor radon and lung cancer are as follows: (1) to test the null hypothesis that residential radon does not increase risk of lung cancer; (2) if there is evidence for excess risk, to evaluate the consistency of effects among the different studies; (3) to evaluate variations in the exposure–response relationship with other lung cancer risk factors; and (4) to compare risk estimates from the pooled residential data with extrapolations from miner-based risk models, where typical exposures were higher.

Characteristics of the subjects participating in the seven North American case–control studies that form the basis for the present combined analyses are given in Table 2. In all studies, cases were ascertained

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TABLE 2
Characteristics of North American Case–Control Studies of Residential Radon and Lung Cancer

Study	Source of subjects		Years of ascertainment	Matching	Histological diagnosis	Subject selection	
	Cases	Controls				Cases	Controls
NJ	1. Rapid reporting system with hospital pathology depts. 2. Hospital pathology records, state cancer registry, and certificate files	Controls matched for live cases and matching of controls to cases for deceased cases. 1. Live cases: driver license (<65 years); medicare files (65+) 2. Deceased cases: Death certificates	Cases: 1982–1984 Controls: 1982–1983	Respondent type (P); 1. Live (Direct): age and race (FM) 2. Deceased (Proxy); age, race, closest date of death (P)	Histological type relied on outside pathology reports.	480 Females = 48% of 994 interviewed, 37% of 1306 eligible No radon measurements were available for an additional 87 homes	442 Females = 44% of 995 interviewed, 30% of 1449 eligible
Winn	Manitoba Registry	Phone directory	Cases 1983–1990 Controls; 1983–1990	Age (P) Sex (P)	Histological confirmation relied on outside pathology reports	488 M 250 F 53% of 1400 eligible	488 M 250 F <54% of eligible
MO-I	Missouri Cancer Registry	Driver license (30–64 years) Medicare files (65–84 years)	Cases 1986–1991 Controls 1986–1991	Age (FM)	Precise histological confirmation by independent review of 76% of the cases	538 F 83% of 650 eligible completed phone questionnaire and had dosimetry from at least one home	1183 F 78% of the 1587 eligible completed phone questionnaire and had dosimetry from at least 1 home
MO-II	Missouri Cancer Registry	Driver license (30–64 years) Medicare files (65–84 years)	Cases 1993–1994 Controls 1993–1994	2-stage randomized recruitment procedure; Age, sex, smoking status (F)	Precise histological confirmation by independent review of over 80% of the cases	512 F 69% of 742 eligible cases completed questionnaires and had some dosimetry[a]	553 F 3886 initially eligible 75% of 730 targeted had both interview and some dosimetry[a]
IA	Iowa SEER Cancer Registry with 90% of subjects rapidly reported	Driver license (40–64 years) Medicare files (65–84 years)	Cases 1993–1996 Controls 1993–1996	Age (FM)	Precise histological confirmation by independent review of 96% of the cases	413 F 68% of 603 eligible completed questionnaires and had complete dosimetry	614 F 46% of 1337 eligible completed questionnaires and had complete dosimetry
CT	Cancer registries and medical record review	Random telephone screening	Cases 1989–1992 Controls 1990–1993	Randomized recruitment was used to identify cases and controls that were similar in age, sex and smoking status (FM)	Histological confirmation relied on outside pathology reports	527 M, 436, F 75% of 5,216 cases screened for eligibility 963 (79%) qualifying cases completed the study[a]	442 M, 507 F 83% of randomly selected households screened. 949% (62% of eligible controls completed the study[a]
UT-ID	Cancer registries and medical record review	Random telephone screening	Cases 1989–1992 Controls 1989–1992	Randomized recruitment was used to identify cases and controls that were similar in age, sex and smoking status (FM)	Histological confirmation relied on outside pathology reports	319 M, 192 F 81% of 1,388 cases screened for eligibility 511 (85%) of eligible cases completed the study[a]	587 M, 275 F 94% of randomized selected households screened for eligible controls <65. 91% of HCFA sample (>65) screened 862 completed the study[a], 85% of eligible RDD controls and 78% of eligible HCFA controls

Notes. F: Female-restricted study, M and F: Males and females included; FM: Frequency matching; P: Pairwise matching.
[a] Many subjects were excluded who did not pass smoking randomization and other study criteria.

TABLE 3
Radon Dosimetry in the North American Case–Control Studies of Residential Radon and Lung Cancer

Study	Duration and method	Residence inclusion criteria	Location of dosimeter placement	Exposure time window	Exposure time window (ETW) coverage	Method of imputing missing data
NJ	1 year ATD T, some short-term charcoal canister detectors and TLDs[a]	Last NJ residence of ± 10 years during the period 10–30 years prior to diagnosis or selection.	Living area (76%); basement (5%); 4 day charcoal canister (8%)[a]	5–30 years prior to diagnosis or selection	Only 1 residence monitored first phase of study; Median ETW residence time in years: 20 years (cases) and 21 years (controls); 82% cases and 79% controls resident >15 years	Median value of controls assigned for periods not residing in index home; apartments assigned 0.4 pCi/liter
Winn	1 year ATD G	All Winnipeg residence of ±1 year during index period	Bedroom and basement (reported separately)	5–30 and 5–15 years prior to interview	33% of eligible residences monitored; Mean years covered: 17 in 5–30 years ETW (68% of person-time); 8 in the 5–15 year ETW (80% of person-time)	Calibration to bedroom or basement monitored; if no measurement, average study value for all subjects
MO-I	1 year ATD T	All in-state index period residences	Bedroom and kitchen area	5–30 years prior to interview	Average coverage of 20 years; ETW coverage: living cases: 78.5%; deceased cases: 76%; controls: 78.8%	Stratum-specific mean (cases and controls assigned the respective group mean)
MO-II	20+ years RSM 1 year ATD	All in-state index period residences	Bedroom and kitchen (each other no differences for both method, but values by RSM significantly higher than that by ATD)	5–25 years prior to diagnosis for cases and interview for controls	Average coverage of 18.2 years in ETW; ETW coverage: 91% for cases and controls using at least one of the detectors; only 9% of pertinent years in need of imputation for missing radon values.	Annual means were used for imputation of missing values for both measure methods
IA	1 year ATD T RRD Outdoor ATD M	Current home only—inclusion criteria limited subjects to those subjects occupying the current home for at least the past 20 years.	Each level of home, bedrooms and work areas of home including outdoor regional radon concentrations. RRD results will be available in near future.	5–19 years prior to diagnosis for cases and interview for controls	100% coverage of exposure time window. All homes were measured. Median coverage 32 years.	No missing home radon measurements period over exposure time window. No imputation.
CT	1 year ADT T	All homes occupied for at least 1 year since age 25	Bedroom, another room on lowest living area and some basements depending on occupancy. A sample of homes measured every level.	Age 25 up to 5 years prior to diagnosis	Maximum window, age 25 up to 5 years before diagnosis/interview. Analysis window, 5–25 years prior to diagnosis/interview. Average coverage for eligible homes was 57% for the maximum window and 69% for the analysis window.	The percentage time coverage for the maximum window was 69% and 79% for the analysis window. Regression trees aided in providing stratum-specific control means for imputation.

(*Continued on page 789*)

TABLE 3
Continued

Study	Duration and method	Residence inclusion criteria	Location of dosimeter placement	Exposure time window	Exposure time window (ETW) coverage	Method of imputing missing data
UT/S. ID	1 year ATD T	All homes occupied for at least 1 year since age 25	Bedroom, another room on lowest living area and some basements depending on occupancy. A sample of homes measured every level.	Age 25 up to 5 years prior to diagnosis	Maximum window, age 25 up to 5 years before diagnosis/interview. Analysis window, 5–25 years prior to diagnosis/interview. 62% of homes in maximum window and 78% of homes in analysis window measured.	The percent time coverage for the maximum window was 73% and 82% for the analysis window. Regression trees aided in providing stratum specific control means for imputation.

Notes. Abbreviations: ATD T: α-particle track detector manufactured and read by Terradex Corporation; ATD G: Government office responsible for dosimeter provision; ATD M: α-particle track detector manufactured and read by the Minnesota Radon Project; CONC: Only radon concentration in the one monitored home considered; CUM: Exposures were cumulated over the ETW; ETW: Exposure time window; RRD: Glass-based Retrospective Reconstruction Detector; RSM: Glass-based Retrospective Surface Monitor; TWAC: Analysis was by time weighted (by residence time) averaging of measured concentrations; IMP: Results were analyzed with imputation of missing data as described.

[a] The remaining 13% of monitored homes had 2-week thermoluminescent detectors, from which regression analysis was used to estimate annual radon concentrations.

through state and provincial cancer registries and were confirmed histologically. New Jersey and Iowa identified cases through rigid reporting criteria based on hospital pathology records and death certificates as well as the state cancer registry (*7, 11, 12*). In the Missouri and Iowa studies, the registry-reported histological type was verified independently by microscopic examination of the tissues by experienced pathologists.

In three of the seven studies (Connecticut, Utah-South Idaho, and Winnipeg), controls were selected by random digit dialing (*8, 13*). Driver's license and health care financing records were used to identify controls in Iowa (*11*), Missouri-I (*9*) and Missouri-II (*10*), and New Jersey (*14*) and for those 65 and older in Utah-South Idaho. Death certificates were used as the source of controls for proxy-interviewed cases in New Jersey.

All studies matched controls to cases on the basis of age (±5 years) and sex (Iowa, Missouri-I, and New Jersey included only females). Race was used as a matching variable in New Jersey. Smoking status was used as a matching variable in Connecticut and Utah-South Idaho (based on smoking status 10 years prior to interview) and in Missouri-II. Frequency matching or randomized recruitment was used for control selection, except in New Jersey and Winnipeg, where pair matching was used.

All of the seven North American case–control studies used α-particle track detectors as the principal method to measure the concentration of radon progeny in indoor air (Table 3). Contemporaneous measurements were necessarily made in homes that the subjects had occupied or were currently occupying and were used as an indicator of historical radon concentrations in those homes. Detectors were placed in the living area and bedroom areas of the home in which subjects were expected to spend the majority of their time. Although investigators in the Iowa study also incorporated estimates of non-residential radon exposures (including both occupational and ambient exposures) into their overall radon exposure assessment, these non-residential exposures were not included in the combined analysis to maintain comparability with the radon dosimetry in the remaining six studies. Ignoring non-residential exposures will have some impact on the estimated lung cancer risk associated with residential radon exposures, although this effect is likely to be small (*15*).

In most studies, an attempt was made to monitor all in-state homes occupied for a period of at least 1 year within the exposure time window of interest. In Winnipeg, radon measurements were made in all homes occupied by study subjects within the Winnipeg metropolitan area. In New Jersey, only the last residence occupied for at least 10 years during the period 10–30 years prior to recruitment was monitored. A small number of measurements (8%) were made using charcoal canisters rather than track detectors in New Jersey. The Iowa study also measured only one home, but the participants were required to have occupied this home for at least 20 years.

Although some investigators monitored radon in homes occupied by study subjects as much as 50 years prior to recruitment (*8*), the combined analysis of the seven North American case-control studies of residential radon and lung cancer focuses on the exposure time window 5–30 years prior to the index date, the period identified by the National Research Council (*16*) as being most relevant for lung cancer risk. Restriction of radon exposure assessment to this period presumes that neither radon exposure within 5 years of lung cancer occurrence nor exposure 30 years or more prior to the index date contributes to lung cancer risk.

The final results of the combined analysis of the seven North American residential radon case–control studies are expected by the end of 2002. Additional information on residential radon lung cancer risks will be provided by an ongoing combined analysis of European case–control studies, to be followed by a planned combined analysis of both North American and European data, as well as studies from other parts of the world including China (Table 1). Subsequent reports on the European and global pooling of residential radon lung cancer studies will serve to further clarify the magnitude of the lung cancer risk associated with radon in homes.

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Discussion

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Drs. Gilbert, Lubin and Krewski are to be congratulated both on the excellence of their scientific work and on their fine oral presentations. The study presented by Dr. Gilbert makes use of the very high plutonium exposures received by workers in the former Soviet Union to characterize the cancer risks after exposure to plutonium. The studies presented by Drs. Lubin and Krewski provide substantial evidence of the carcinogenicity of exposure to radon at levels found environmentally, especially in homes. Intervention to reduce radon levels in houses and other buildings has been shown to be feasible for a moderate cost in most situations. Therefore, the accumulation of detailed quantitative evidence regarding the lung cancer risk associated with environmental radon exposure is an important step before appropriate cost-effectiveness analysis of various radon remediation programs can be carried out. The vast majority of radon-induced lung cancers occur in conjunction with exposure to other lung carcinogens, especially cigarette smoke but possibly also other indoor air pollutants, and the absolute risk of lung cancer after exposure to radon will depend on the level of risk caused by these other carcinogens. Therefore, care must be taken when using risk estimates derived in one population and applying them to another population with a different spectrum of risks from lung carcinogens other than radon.

NOVEL EFFECTS AT LOW DOSES

Amy Kronenberg, Chair

Bystander Effects May Dominate Domestic Radon Risks—But Current Risk Estimates are Probably Okay

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Radon risks derive from exposure of bronchio-epithelial cells to high-LET α particles. Alpha-particle exposure can result in bystander effects,

where irradiated cells emit signals resulting in damage to nearby unirradiated bystander cells. This can result in nonlinear dose–response relationships and inverse dose-rate effects. Domestic radon risk estimates are currently extrapolated from miner data that are for both higher doses and higher dose rates, so bystander effects on non-hit cells could play a large role in the estimate of risk that is extrapolated to estimate the risk in homes. We have therefore extended an earlier quantitative mechanistic model of bystander effects to include protracted exposure, with the aim of quantifying the significance of the bystander effect for very prolonged exposures.

A model of bystander effects after exposure to high-LET radiation, originally developed to analyze oncogenic transformation *in vitro* (*1*), has been extended to low dose rates (*2*). The model considers radiation response as a superposition of bystander and linear direct effects. It attributes bystander effects to a small subpopulation of hypersensitive cells, with the bystander contribution dominating the direct contribution at very low acute doses but saturating as the dose increases. Inverse dose-rate effects are attributed to replenishment of the hypersensitive subpopulation during prolonged irradiation. In this approach, therefore, bystander effects and the inverse dose-rate effect are manifestations of the same phenomenon.

The model was fitted to the data from miners exposed to radon for protracted periods (*3*); the results suggest that one directly hit target bronchio-epithelial cell can send bystander signals to about 50 neighboring target cells. The results suggest that, at low radon exposures, the risk could be dominated by bystander effects.

The analysis concludes that a naïve linear extrapolation of radon miner data to low doses, without accounting for dose rate, would result in an underestimation of domestic radon risks by about a factor of four, a value comparable to the empirical ''inverse dose-rate correction'' estimate applied in the recent BEIR VI report on radon risk estimation (*4*). We conclude that the BEIR VI radon risk estimates are probably not unreasonable, despite not explicitly incorporating bystander effects.

Bystander effects represent a plausible quantitative and mechanistic explanation of inverse dose-rate effects by high-LET radiation, resulting in nonlinear dose–response relationships, and a complex interplay between the effects of dose and exposure time. The considerations presented here provide a potential mechanistic underpinning for the empirical exposure-time correction factors applied in the recent BEIR VI for domestic radon risk estimation.

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Genome-Wide Transcriptional Responses at Low Doses: The Power of Microarray Technology

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Many of the physiological responses to ionizing radiation exposure, including apoptosis, cell cycle arrest, and DNA damage repair, are mediated in part by changes in gene transcription. Gene transcription is in turn regulated by the complex interplay of multiple signal transduction pathways, and it may vary with factors including genetic background and cell or tissue type. For example, in the transcriptional response associated with radiation-induced apoptosis, induction of some genes is limited to TP53 wild-type cells from tissue types with the ability to undergo rapid apoptosis after irradiation. In contrast, other genes are triggered after irradiation in cell lines undergoing rapid apoptosis regardless of TP53 status. From such examples, it is apparent that the pattern of stress gene response is cell type specific in both primary and transformed lines. With the advent of the genomic era, the number and diversity of genes found to be modulated in response to stress seems ever increasing. Modern techniques, including microarray analysis, can monitor changes in expression in large sets of genes, potentially even across the entire expressed genome in a single experiment. We have previously used microarray analysis to identify a set of genes regulated by exposure to high doses of ionizing radiation (*1*) and to explore the differential effects of various DNA-damaging stresses and treatment conditions.

Interest is increasing, however, in the direct measurement of effects of lower doses of ionizing radiation, and we have been able to demonstrate reproducible changes in gene expression at doses as low as 2 cGy (*2*). Using a quantitative single-probe hybridization method to accurately measure increases in mRNA levels relative to untreated cells, we have demonstrated a linear, no-threshold response for multiple stress genes in the human TP53 wild-type myeloid ML-1 line and in human peripheral blood lymphocytes (PBLs) irradiated *ex vivo.* We have also used cDNA microarray hybridization analysis to identify radiation-regulated genes that could potentially serve as informative biomarkers of radiation exposure. Initial studies identified several genes that were significantly upregulated in human PBLs between 24 and 72 h after *ex vivo* irradiation (*3*). Three of these genes, *DDB2*, *CDKN1A* (*CIP1/WAF1*) and *XPC*, were induced in a linear fashion between 0.2 and 2 Gy at 24 and 48 h after treatment, with less linearity at earlier or later times. Interestingly, these and other strongly radiation-responsive genes are regulated by TP53, indicating a major role for TP53 in mediating radiation-induced gene responses in PBLs (and probably other primary cells). These results support the use of peripheral blood cells as an accessible and sensitive indicator of radiation exposure and begin laying the foundation for expression profiles that may someday provide signatures for past radiation exposure. The ability to measure changes in expression of large numbers of genes after small exposures holds great promise for future studies of molecular signaling pathways, interindividual variations in response, and other important aspects of low-dose radiation exposure.

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Post-translational Modification of Proteins at Low Doses: A Layer of Regulation That May Impact the Concept of Risk

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Humans are frequently exposed to very low doses of ionizing radiation through either environmental or occupational exposures, diagnostic medical procedures or, infrequently, accidental exposures. Since exposure to a radiation dose below 10 cGy can adapt mammalian cells to subsequent radiation exposures (*1*), mammalian cells must recognize and respond to very low doses. Adaptation of undamaged cells may also occur through intercellular communication of stress signals from cells that are ''hit'' to cells that have not been hit (*2*). Induction of a stress response in undamaged cells might change the character of the radiation response for the entire cell population.

To date, it is not clear what changes in the irradiated cell induce responses at such low doses, nor is it clear what biochemical pathways induce low-dose responses. Large radiation doses ($\geq$1 Gy) have been known for some time to activate signaling pathways that induce cellular stress responses such as DNA transcription and repair, cell cycle progression delays, and cell death processes. More recently, a functional genomics approach has demonstrated that transcription of a number of genes is either induced or repressed by radiation doses between 1 and 10 cGy (*3*). Many of the genes activated in this low-dose range are downstream targets of the DNA damage response pathway. This pathway is induced by the ATM protein, which senses cell damage and subsequently activates the TP53 protein as a transcription factor. The involvement of this stress-responsive pathway at low radiation doses indicates that the cascade of protein phosphorylations known to be induced by the ATM protein occurs at or below the 1–10-cGy dose range at which transcription is observed.

We are characterizing the stress-responsive proteins of the cellular components of human skin (cultured immortal or primary fibroblasts, keratinocytes and melanocytes) and of an *ex vivo* irradiated human neonatal foreskin model. Our approach involves Western analysis of gel-separated proteins and immunofluorescence analysis of intact cells. Our primary focus is on post-translational modification of the proteins involved in the radiation-induced DNA damage response pathway. In our presentation, we addressed these questions: (1) What is the dose dependence for radiation-induced, post-translational modifications of stress response proteins? (2) Do all cells respond in a similar manner at the same radiation dose? (3) Do cells *in vivo* and in culture respond in a similar manner to the same radiation dose?

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The Contribution of Radiation-Induced Microenvironments to Neoplastic Progression

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High doses of ionizing radiation are carcinogenic in both humans and animals. Epidemiological data demonstrate an increased risk of breast cancer in women exposed to doses of 1 Gy or more as a result of atomic bomb, therapeutic or diagnostic radiation exposures. Radiation-induced DNA damage and misrepair leading to mutations are commonly thought to initiate carcinogenesis. We have found that radiation also elicits microenvironment remodeling that can promote malignant progression in both murine and human models of breast cancer (*1*).

In the murine mammary gland, radiation elicits a rapid and dynamic program of ECM remodeling that is mediated in part by the activation of Tgfb (*2*). Tgfb acts as an extracellular linchpin that is released by radiation and other oxidative stressors to orchestrate multicellular response to damage (*3*). Our recent studies indicate that Tgfb signaling is a key mediator of cell fate decisions after irradiation.

To determine the contribution of the irradiated tissue to the process of carcinogenesis, we created radiation chimeric mammary glands (*4*). Unirradiated mammary epithelial cells that harbor mutation in both alleles of the *Trp53* gene were transplanted to irradiated stroma. These cells are not tumorigenic if they are implanted subcutaneously in nude mice or in 3-week-old mammary fat pads. Small tumors formed in some mice when they were transplanted into adult fat pads (18%). But when the cells were transplanted to fat pads in syngenic mice irradiated with a total-body dose of 4 Gy, more than 75% formed tumors. The tumors were also significantly larger than those in sham-irradiated controls. Since hemi-body irradiation resulted in tumors only on the irradiated side, we concluded that this effect was due to the stromal microenvironment. These results indicate that radiation exposure affects non-epithelial components of a tissue that in turn promote the neoplastic behavior of ''initiated'' epithelial cells. We postulated that the ability of radiation to modulate tissue-level interactions is another class of carcinogenic action that may affect the frequency and features, such as growth rate as mentioned, of tumors that develop in the perturbed tissue.

Equally important is the demonstration that the sham-irradiated tissue microenvironment is effective in suppressing the malignant potential of such cells. It appears that exposure to high doses can corrupt this program such that susceptible (initiated) cells progress readily. Determining whether a dose threshold exists for the deleterious effect on cancer suppression in tissue is an important objective for future studies. It is possible that low to very low radiation exposures may elicit microenvironment changes that support the re-establishment of homeostasis and contribute to cancer suppression. If so, it is likely that it is a very narrow window that is affected not only by radiation dose and dose rate but also by tissue specificity and genetic factors.

To test whether ionizing radiation also affects the manner in which epithelial cells interact with the microenvironment, we used a three-dimensional human mammary cell culture model of acinar morphogenesis. Functional mammary epithelial cells grown under appropriate conditions organize by cell–cell and cell–ECM interactions into acini (i.e. hollow spheres) and ducts. We asked whether this morphogenetic event was affected in the daughters of irradiated cells. In these preliminary studies, single cells were irradiated (0.1–2 Gy) at the time of embedding in a reconstituted basement membrane-type matrix. Colonies arising from surviving cells display a reproducible irradiated phenotype consisting of disturbed intercellular adhesion, deranged extracellular adhesion molecules, and loss of gap junction proteins. The irradiated phenotype is consistent with malignant progression in that the colonies are both larger and morphologically disorganized. These data are surprising in that the phenotype is exhibited by the daughters of individually irradiated cells, suggesting that radiation induces a heritable derangement of pathways affecting cell adhesion, ECM interactions, epithelial polarity, and cell–cell communication (*5*).

Our studies suggest that either irradiated mouse tissue or human cells can exhibit an altered phenotype that persists for days to weeks. A key aspect of this phenotype is the loss of critical controls imposed by the microenvironment resulting in disrupted tissue integrity. These events may be involved in the carcinogenic action of ionizing radiation (*6*). At doses that have yet to be clearly defined, ionizing radiation causes a tissue response that disrupts cell interactions that previously suppressed abnormal behavior in susceptible cells. Studies of the mutagenic effect and the

alteration in cellular microenvironment have provided insight into carcinogenesis.

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Discussion: Novel Effects at Low Doses

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This session provided an overview of the state of the science associated with the cellular-molecular changes induced by low doses of ionizing radiation. The four presentations in the session were aimed at providing a brief review of the new techniques and biological responses that may be useful in risk assessment.

David Brenner

David Brenner presented a paper that he and Ray Sachs wrote entitled ''Bystander Effects May Dominate Domestic Radon Risks—But Current Risk Estimates are Probably Okay''. In his presentation, he discussed how the technology associated with the microbeam makes it feasible to conduct studies that were not possible in the past. With this equipment, it is now practical to deliver known numbers of α particles to defined cells and then to observe the response of the cells traversed by the α particles as well as the response of the cells that were not ''hit'' by the particles. Dr. Brenner reviewed the literature that demonstrates that cells do not have to be traversed by α particles to elicit a biological response. There are a large number of different biological responses, such as sister chromatid exchanges, apoptosis, micronucleus induction, oncogenic transformation, changes in gene expression, and altered cell growth, that have been detected in non-hit bystander cells.

Dr. Brenner reviewed the data indicating that the bystander effects are very important in cell transformation. In these studies, the cell transformation frequency is the same whether all the cells receive α-particle hits or only 1 in 10 cells is hit. These data further demonstrate that the cell transformation frequency increases as a function of the number of particles that individual cells receive, rather than as a function of total energy or dose delivered to the culture. Thus the important variable in this study is the number of traversals that individual cells receive.

Using these cellular and molecular data, Dr. Brenner suggested that, even though the mechanisms of action of bystander effects are not well understood, changes in the cellular end points could be used to develop a model of lung cancer risk from exposure to high-LET radiation. He applied his model to estimate lung cancer risk induced by exposure to domestic radon. In these exposures, the doses and numbers of cells hit are very low and the damage and the predicted risk would be related to bystander effects and not to the direct effects on traversed cells. His model required several assumptions to link the *in vitro* data to the data for risks for humans. One of these was that the bystander effects and the direct effects could be added. There was a concern about this assumption since it is well known that the type of mutations produced in directly hit cells are different from those produced in bystander cells. However, he was able to derive four biological parameters related to his assumptions, and he used the model to fit the radon data as a function of exposure level and time. The model fit the data well at low doses but underestimated the response at high doses and at longer times of exposure. It was suggested that the lack of fit at the higher doses was related to the bystander effect playing less of a role at high doses than the direct effect. This would help explain the inverse dose-rate effect observed after exposure to high total doses of radon. From these data, he estimated that the risk derived by the BEIR VI Committee, using an effectiveness factor of four for the inverse dose-rate effect, would be similar to his data using a more mechanistic bystander approach. The bottom line from his presentation was that ''we are unlikely to be currently underestimating domestic radon risks because of bystander effects.''

This talk represented a useful attempt to apply cellular and molecular data to risk assessment, and it illustrated some of the strengths and potential difficulties associated with making such extrapolations.

Sally Amundson

Dr. Amundson gave the next presentation, ''Genome-Wide Transcription Responses at Low Doses: The Power of Microarray Technology.'' This provided a good review of the information that is available on radiation-induced changes in gene expression. With this modern microarray technology, it is possible to rapidly determine the changes in gene expression for a very large number of genes.

Her discussion was a good example of using the scientific process to evaluate a new area of interest in radiation biology. She first compared the genes that were either up-regulated or down-regulated after high or low doses of radiation. The results indicated that there were unique responses in the cells as a function of the radiation dose. She then established dose responses, time responses and tissue-specific responses for radiation-induced changes in gene expression. These studies demonstrate that for some genes there are linear dose–response relationships that extend to very low radiation doses, 1–2 cGy. Next, she reviewed her studies that demonstrate that there are rather small differences between individuals in both background levels of gene expression and the radiation-induced responses. These observations are very important to establish the potential usefulness of changes in gene expression as a method for agent-specific profiling and make it possible to develop a gene expression profile for ionizing radiation.

After establishing the radiation-induced changes in gene expression at a high dose rate, she evaluated the influence of low-dose-rate exposure on gene expression. Some very interesting patterns of gene expression were observed as a function of dose rate. As would be expected, several genes decreased their level of gene expression as the dose rate decreased. On the other hand, there were genes identified that had the same level of altered gene expression regardless of the dose rate of the radiation exposure.

Finally, Dr. Amundson reported on studies that demonstrate that physiological changes, such as modifications in the cell cycle, were also linked to the changes in gene expression. Using cluster analysis, her studies demonstrate that many genes involved in the control of the cell cycle were down-regulated. These studies were expanded to evaluate a large number of cell lines (NCI-60) that had well-defined cell-killing responses.

These studies lay the groundwork for studies to determine the changes in gene expression that are responsible for other radiation-induced biological phenomena. For example, it may now possible to determine what genes are up- or down-regulated during the induction of biological re-

sponses such as the adaptive response or low-dose radiation hypersensitivity. The gene profiles of cells that are genomically unstable may be defined and provide clues about the mechanisms underlying this important process. This gene chip technology can be used to investigate the changes observed in gene expression during cell transformation induced in bystander cells and the gene expression changes induced by low radiation doses.

Raymond Warters

The presentation ''Post-translational Modification of Proteins at Low Doses of Ionizing Radiation'' by Raymond Warters extended the discussion beyond the genome to the next level of biological organization, the proteins produced. He discussed changes that were induced in post-translation proteins by very low doses of ionizing radiation. He indicated that many of the genes activated in the low-dose region are downstream targets of the DNA damage response pathways. He suggested that there are many different types of post-translational modifications, all of which can alter protein function. His discussion focused on phosphorylation using two primary protein targets. The first was phosphorylation of the histone H2AX using serine 139. This protein is phosphorylated in chromatin adjacent to DNA double-strand breaks and is involved in recruiting DNA repair proteins to the site, making it an important protein the radiation response. The other protein in his studies was TP53, which was phosphorylated at serine 15. Once activated by phosphorylation, the TP53 protein functions as a transcription factor.

Dr. Warters was able to construct dose–response relationships for the phosphorylation of these to proteins. He determined that there was an increase in phosphorylation for the H2AX protein down to a dose of about 10 cGy. For the TP53 protein, the changes in the phosphorylation could be detected after doses as low as 1 cGy. This was similar to the level of dose responsible for producing a single DNA double-strand break in each cell.

His studies also evaluated the role of different cell types in these responses. He used primary skin fibroblasts and was able to demonstrate that the epidermis had a much higher protein phosphorylation response than the dermis, and that there was a very robust response in cultured keratinocytes exposed to 2 Gy of radiation. These results provide a link between the phosphorylation seen in the primary skin cultures and a model tissue. Such studies provide support for the wide differences seen in responses to gene induction and protein modification as a function of cell type. This may provide an additional link between cell type and cancer induction.

These studies serve to remind us that, after we understand what genes are up- or down-regulated, we need to take the next step and determine the post-transcriptional changes in the proteins. Such changes will ultimately result in a modification of cell phenotype and function and therefore potentially alter risk for disease.

Mary Helen Barcellos-Hoff

Dr. Barcellos-Hoff's presentation was entitled ''The Contribution of Radiation-Induced Microenvironments to Neoplastic Progression.'' She began by reminding us that ''it takes a tissue to make a tumor'' and that all tissues have unique radiation sensitivity as well as responsiveness to tumor induction. It is well established that there are interactions between the cells (seeds) and the microenvironment (soil) in the production of disease, especially cancer. The fact that normal tissues suppress cancer makes it important to evaluate the cellular and tissue targets and the mechanisms of action for radiation-induced cancer, especially after exposure to low doses of ionizing radiation.

Her discussion of targets in the cell that recognize radiation-induced changes was very helpful. She described the role of the extracellular matrix, the neighboring cells, and the cell–cell contacts in the recognition and communication of radiation-induced damage. All of these factors play important roles in the regulation of the number and types of genes expressed in response to a variety of insults, including radiation.

Dr. Barcellos-Hoff reviewed the extensive research that she has conducted on the response of transforming growth factor beta (Tgfb) to radiation and the central role that it appears to play in signal transduction. Radiation is capable of activating latent Tgfb which may provide a mechanism for the cell to both detect the radiation and to initiate signal transduction processes that are ultimately involved in activation of radiation-responsive genes. Research in this area is important, since it demonstrates that Tgfb signaling in susceptible cells (e.g. cells initiated or mutated by previous events that may or may be related to radiation exposure) can generate persistent phenotype of increased malignant potential. This is often called epithelial to mesenchymal transition and is characterized by loss of cell–cell contact and communication and malignant behavior such as an increase in motility and invasion.

Her research to establish the role of the extracellular matrix in cancer induction has been important. She has demonstrated that radiation is capable of altering the extracellular matrix in a way that results in the growth of tumors from subsequent injection of normal cells. These radiation-induced alterations of the matrix are maintained for a rather long time after the exposure. Dr. Barcellos-Hoff demonstrated that the cells do not have to be exposed or exhibit mutations to result in a change from normal phenotypes to tumors.

Her research suggests that at low doses of ionizing radiation, the probability of a pathological outcome is suppressed by the microenvironment. As the dose increases, the microenvironment is perturbed, which alters cell–cell communication and microenvironment control and results in an increase in tumor frequency. As the dose increases further above this level, the probability of cancer decreases. This concept suggests that DNA breakage may not be the single most important event involved in radiation carcinogenesis. A radiation risk of 5–10% per sievert is small for environmental exposures and exposures associated with health protection. Such studies help remind us that radiation is in fact a rather poor carcinogen. Therefore, cancer risk and cancer rates after the exposures and doses of concern in most human experiences may not be increased.

Summary

The results of the research reported here require that we rethink the basic paradigms used to describe the interaction of radiation with cells and tissues. These findings suggest that the ''hit theory'' needs to be reevaluated since many nontraversed cells show biological responses. Such bystander effects would alter the target size and may dominate the risk after exposure to low doses of high-LET radiation. This makes it essential to determine whether bystander effects are detrimental or protective and result in an increase or decrease in radiation risk. Changes in gene expression are demonstrated after exposure to low levels of ionizing radiation. Research to determine the impact of such changes on radiation risk is essential. In addition to changes in gene expression, the definition of radiation-induced post-transcriptional modification of proteins is demonstrated to exist, and it plays an important role in determining the phenotype of cells. Such changes in phenotype are demonstrated to exist without alteration in the genotype.

Research is being conducted to characterize protective mechanisms involved in control processes associated with cell–cell, cell–tissue and cell–matrix communication. Such studies require that radiation biologists consider the role of alterations in non-DNA targets in the cancer process. This broader view considers the impact of control mechanisms at the whole tissue, organ and organism level and how these can modify the shapes of dose–response relationships for cancer risk.

The final challenge is to extend the observations made at the cellular and molecular levels to whole organisms. It is essential to connect these basic mechanistic studies with human epidemiological studies. With such a connection, molecular studies can have an impact our understanding of the responses after low-dose radiation exposure and help define the magnitude of the effects of such exposures on human health.

DIAGNOSTIC MEDICAL RADIATION EXPOSURES: WHAT CAN WE REALISTICALLY LEARN FROM EPIDEMIOLOGIC STUDIES?

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Overview

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Diagnostic medical radiation exposures are by far the largest man-made source of radiation exposure. In 1987, NCRP in its Report 93 estimated that the total per capita radiation dose in the United States from natural and man-made sources is about 360 mrem (3.6 mSv) per year (*1*) [300 mrem (3 mSv) are from natural sources and 60 mrem (0.6 mSv) are from man-made sources]. The contribution from diagnostic radiology studies is 39 mrem (0.39 mSv), and from nuclear medicine studies it is 14 mrem (0.14 mSv). Since 1980, the per capita contribution from radiology and nuclear medicine studies has probably doubled. This increase is due to the increased use of certain diagnostic tests such as cardiac catheterization to detect coronary artery disease and to the introduction of new technology such as spiral computed tomography (*2–5*). Doses from some interventional studies can reach levels at which deterministic effects are seen (*6*). Brenner *et al.* have recently estimated the number of radiation-induced cancers that might result from performing CT scans in children (*7–9*).

The purpose of this session was to review uncertainties in dose as well as uncertainties in risk to estimate prospectively the power of an epidemiological study to detect an effect from diagnostic medical radiation exposure. In addition, the logistics and practical obstacles that must be surmounted were reviewed.

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Dose—What We Have vs. What We Want

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The largest source of radiation dose to the public is from diagnostic medical radiation exposures. Although computed tomography (CT) is typically used for less than 5% of diagnostic X-ray examinations, in some countries it may contribute as much as 40% of the collective dose from diagnostic radiology (*1*). There is particular concern about the high doses that can be delivered in pediatric CT examinations, many of which have been performed without modification of the settings used for examinations of adult patients (*2*). Unlike conventional film images, which become too dark with overexposure, CT and other digital X-ray images are always viewable at an acceptable brightness level, even when the patient is significantly overexposed.

The dose to the patient produced in a CT examination depends upon a wide variety of CT scanner settings—voltage (kV), current (mA), exposure time, X-ray beam collimation and filtration, and the type of X-ray detector—and on characteristics of the patient such as size, shape and tissue composition. While a patient or referring physician may know only that a CT examination of a specific area of the body was performed, it is possible to obtain an accurate estimate of dose from more specific data that are stored with each image in the CT image storage archive.

In the United States, the Food and Drug Administration (FDA) requires all CT manufacturers to supply the user with dose values for standard CT settings (*3*). In addition, European regulations require that CT manufacturers provide an indication of the estimated patient dose on the operator console before the scanning X-ray beam is activated. Most manufacturers now supply this information to U.S. customers as well.

The dose value provided by the manufacturers, and the one most often quoted by those who make measurements of CT dose, is the computed tomography dose index (CTDI). More recently two modifications of CTDI, $CTDI_{100}$ and $CTDI_w$, have been defined by the International Electro-technical Commission (IEC) (*4*). It is in fact the $CTDI_w$ that is presented to the operator on the CT console. For certain fairly typical conditions of operation, the CTDI or $CTDI_w$ provides a reasonably good estimate of the multiple-scan average dose (MSAD) (*5*), the dose descriptor of most interest in estimating risks to patients from CT examinations.

One concern for those who wish to obtain accurate dose estimates for a patient population is that dose measurements are typically made with standard phantoms specified by the FDA. The standard phantoms are polymethyl methacrylate cylinders with 1-cm-diameter cylindrical holes drilled parallel to the axis, at least four located at 0, 90, 180 and 270°, and centered 1 cm below the phantom surface, and one additional hole located on the phantom axis. The head phantom is 16 cm in diameter and the body phantom is 32 cm in diameter. Both phantoms are at least 14 cm long. Of course, the abdomen cross sections of most patients are not circular in shape but are more closely approximated by ellipses or even rectangles.

CT scanners operated at the manufacturers' standard technique will deliver doses of approximately 40–60 mGy throughout the standard head phantom. The body phantom will receive doses of 20–40 mGy at the near-surface locations and 10–20 mGy on the axis (*6*). Actual doses to patients can vary significantly from measured and published values. For instance, an abdominal scan performed on a pediatric or small adult patient with standard adult settings may lead to a dose at least twice that delivered to a typical adult.

Furthermore, since these dose values do not take into account the total length of tissue scanned, it is difficult to make accurate estimates of doses to specific organs or to bone marrow. Those estimates require knowledge of another dose-related quantity, the dose-length product (DLP), usually given in mGy-cm. An estimate of the DLP, along with the $CTDI_w$, does appear on the operator console of many new scanners. Effective dose can be estimated from the DLP (*1*).

In summary, actual doses to patients for CT examinations may differ

from reported standard doses by an order of magnitude or more due to incomplete knowledge of the technique settings of the scanner and also due to variations in the size, shape and composition of the patient.

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Children's Exposure to Diagnostic Medical Radiation and Cancer Risk: An Epidemiologist's Perspective

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A 1956 report linking elevated risk of childhood cancer with prenatal abdominal diagnostic X-ray exposures of mothers was followed by numerous case–control epidemiological studies that generally confirmed increased risks of leukemia, and often other childhood malignancies, subsequent to prenatal diagnostic X-ray exposures (reviewed in ref. *1*). Intense debate about the likely causality of this association for more than 45 years has mirrored ongoing controversy about the carcinogenic risks linked with other low-dose or low-dose-rate exposure to ionizing radiation (*1–3*). The possible role of prenatal (and, to a lesser degree, preconception and postnatal) exposures to diagnostic X rays in the occurrence of childhood cancer has received extensive attention because the etiology of childhood malignancies is poorly understood, ionizing radiation at high doses is a proven carcinogen but the cancer rates at low doses are less well quantified, the fetus (and children in general) may be more susceptible to the carcinogenic effects of ionizing radiation than adults, and technical improvements or the use of alternate diagnostic modalities can significantly reduce fetal or postnatal exposure to diagnostic X rays.

Epidemiological Evidence Linking Childhood Cancer with Prenatal Radiation

The report of Stewart and coworkers linking elevated childhood cancer mortality in England and Wales with mothers' abdominal X-ray examinations during pregnancy was initially met with disbelief. The findings were taken more seriously when they were replicated 2 years later in an extended series and validated with radiological records (reviewed in ref. *4*). In a continuing expansion of the study, risk declined over time, from an original odds ratio (OR) of 1.91 described in 1958 to an OR of 1.39 reported in 1989 (the latter based on 15,276 case–control pairs), due to substantial reductions in the number of films per examination, the estimated fetal dose, and the use of pelvimetry. A similar elevated risk (OR = 1.47) was observed in a study in the northeastern United States, and the causality of the association was further supported by risk increases in subsequent case–control studies, including several with confirmatory radiological reports. One report described a dose–response effect for childhood cancer associated with the number of fetal X-ray exposures during the third trimester (*4*). While the increased risk estimates ranged from 20–70%, overall there was little evidence for heterogeneity among the studies. Meta-analysis calculated an overall excess of 1.38, similar to the risk of 1.39 from the large study of Stewart and coworkers (*4*), consistent with the large size and proportional contribution to the entirety of case–control data provided by the study in England and Wales. Recent Swedish and U.S. case–control studies have described lower risks, although the upper confidence limits of both are consistent with earlier risk estimates.

The risk of childhood cancer in relation to maternal abdominal diagnostic X rays has been evaluated among twins, since earlier data indicated a fivefold higher frequency of pelvimetry among twin compared to singleton births (*1, 2*). Results from studies of twins in the large population in England and Wales, which were subsequently confirmed in Swedish and the U.S. studies, showed elevated risks of childhood cancer in association with prenatal diagnostic X-ray exposures to be similar for twins and singletons. A detailed search has not yielded evidence of confounding.

Cohort studies, ranging from less than 200 to 39,166 exposed children, have followed up the offspring of mothers who underwent diagnostic X-ray tests during pregnancy and identified 1 to 23 children who developed cancer (*1*). In a meta-analysis of 6 of the most reliable cohort studies, Doll and Wakeford calculated an overall relative risk of 1.2, not differing significantly from 1.0, but nevertheless compatible with an excess relative risk of approximately 40% as reported in the case–control studies.

In time-trend studies of childhood leukemia associated with fetal exposures to diagnostic radiation, risks declined between 1947–1957 and 1958–1960 in the northeast U.S., between 1940–1956 and 1957–1969 in England and Wales, and between 1936–1959 and 1960–1967 in Sweden, perhaps reflecting reduced use of prenatal X-ray examinations after publication of the report of Stewart *et al.* (reviewed in ref. *1*). A recent U.S. case–control study of children diagnosed with leukemia during 1989–1993 showed a decline in the proportion of subjects undergoing pelvimetry over time. The proportion of childhood leukemia cases undergoing pelvimetry has declined from 10.2% for those born in 1980 or before to 2.4% for those born in 1982–1986 and dropped further to 1.3% for those born after 1986; similarly, the corresponding proportion of controls undergoing pelvimetry has decreased from 60% for those born in 1980 or before to 2.3% for those born in 1982–1986 to 1.8% for those born after 1986 (*4*).

Controversies on Causality of Prenatal Diagnostic Radiation and Childhood Cancer Risk

The causality of the relationship of fetal diagnostic X-ray exposure to subsequent cancer risk has long been debated (*1–3*). The major argument opposing a conclusion of causation is the lack of an excess of childhood cancer among the 1,263 Japanese children exposed *in utero* to the atomic bomb explosions and followed up to age 15. Of the subset of 753 Japanese children exposed to at least 10 mGy, only two developed cancer, a 6-year-old dying of hepatoblastoma and a 14-year-old diagnosed with Wilms' tumor. Some have argued that the small number of observed cancers, particularly the absence of childhood leukemias, is inconsistent with the results of Stewart *et al.*, since the estimated doses of the Japanese survivors were larger than the fetal exposures from pelvimetry. It is possible that some of the Japanese survivors who were *in utero* at the time of the bombings could have died from leukemia before 1950, when the study of the atomic bomb survivors began. While 0.43 childhood cancer deaths were expected based on Japanese national mortality rates, 5–14 deaths were expected based on the results of Stewart *et al.* Similarly, the excess absolute risk increase estimated from the two childhood cancer cases observed was 0.7% per gray (95% CI = −0.1%–2.6% per gray), substantially less than the estimated absolute risk increase of 6% per gray

derived from the study of Stewart and colleagues. Other aspects of the epidemiological and experimental literature described as inconsistent with causation included the excess risks observed for several categories of childhood cancer in addition to the leukemias, some inconsistencies within the twin studies, and the absence of increased leukemia induction after fetal irradiation in animal studies.

Cancer and Mortality Risks Linked with Newer Diagnostic Radiological Procedures

A growing number of large investigations have shown no association between ultrasound tests during pregnancy and risk of childhood leukemia. The lack of an association was consistently observed as the use of ultrasound testing rose dramatically; ultrasound examination is currently employed, often repeatedly, in substantially more than half of all pregnancies in the U.S.

The use of pediatric CT examinations has grown rapidly from the mid-1980s to the present, driven in part by technical improvements and the speed of examination made possible by the helical CT. The number of requests for CT scans in children rose 63% between 1991 and 1994, while abdominal and pelvic CT examinations increased approximately 100% from 1996 through 1999 (*5*). The use of helical CT in children reduces the need for sedation and improves the quality and precision of evaluation of the acute abdominal conditions, particularly in younger, sicker and uncooperative children. While CT examinations comprise a relatively small proportion of all diagnostic radiological examinations in children, the contribution to a child's cumulative radiation dose is substantial because of the notably higher lifetime risk per unit dose of radiation for children compared to adults. Using existing databases, Brenner and colleagues calculated age-dependent lifetime cancer mortality risks per unit dose and estimated increased lifetime risks for death from cancer of 0.18% from a CT scan of the abdomen and 0.07% from a CT scan of the head in a 1-year-old child (*5*). These risks were an order of magnitude higher than for adults receiving comparable doses.

Prospects and Problems for Future Research

While the value of additional epidemiological studies of cancer risks associated with prenatal diagnostic X-ray or ultrasound tests is unclear, it is important to quantify risks of childhood cancer in relation to CT scans. Populations that should be evaluated include children who are not chronically ill, those receiving unusually large numbers of CT scans, and those who may be unusually susceptible to radiation. Study methods should include detailed dosimetry in conjunction with validation of the numbers and types of examinations and potential confounding factors. Opportunities to evaluate cancer and other health effects in relation to CT scans may be possible in record linkage studies and the longitudinal lifetime cohort study of 100,000 children being planned by the National Institute of Child Health and Human Development, the Centers for Disease Control and Prevention, and the Environmental Protection Agency.

The current benefit of pediatric CT examinations strongly outweighs the small increase in lifetime cancer mortality. Nevertheless, technical improvements are urgently needed to reduce the radiation dose while maintaining high-quality visualization.

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Power Analysis of Epidemiological Studies of Radiation-Related Disease Risk when Dose Estimates are Based on a Complex Dosimetry System with an Application to the Hanford Thyroid Disease Study

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Several recent epidemiological studies have used a complex dosimetry to estimate radiation-related health effects of exposures to fallout or releases from nuclear plants. Two examples are the Utah Thyroid Cohort Study (*1, 2*) and the Hanford Thyroid Disease Study (Draft Report). In both, individual doses of radioactive iodine (^{131}I) to the thyroid gland were estimated decades after exposure. Increasingly, the approach to uncertainty in dose in such studies seems to be to develop a dosimetry system that gives not just one estimate of dose, but rather many replications (100 in the case of the Hanford study) of possible dose for each subject. Moreover, the estimates are not generated independently for each subject; instead, each run of the dosimetry system provides a new realization of possible dose for the entire study population, and the uncertainties in shared characteristics result in a complex correlation between the dose estimates from subject to subject.

Let us pretend that this type of dosimetry system has evolved to the state where we can regard, in a Bayesian framework, each replication of dose to be a sample from the distribution, $f(X_1,X_2,\ldots,X_N|\mathbf{W})$, for true dose, given the full set of input data, $\mathbf{W}$, for all N subjects in the study. Because many replications, r, are available, we can calculate for each subject i, the expected value of the unknown true dose, X_i, given the input data, W_i, available for the subject simply as the average of the ith subject's simulated X_i. We will call the expected value, $Z_i = E(X_i|W_i)$, the estimated dose for each subject. We assume that the data, W_i, are available for each subject (and the dosimetry system is in place) before the collection of outcome data, D_i, for each subject (for example, as in the Hanford study). Finally we assume that D_i is independent of W_i, given X_i (so that W_i consists of only ''surrogate'' variables).

In addition, let us adopt a simple model for the joint distribution of the true doses, X_i, around the expected true doses, Z_i, which incorporates both shared and unshared dosimetry errors. Suppose that we have

$$X_{ir} = \varepsilon_{SM,r}\varepsilon_{Mi,r}Z_i + \varepsilon_{SA,r} + \varepsilon_{ai}, \quad (1)$$

where X_{ir} is a sample from the true conditional distribution of X_i, $\varepsilon_{SM,r}$ is shared multiplicative error (shared over replication r by all subjects i), ε_{Mi}, is unshared multiplicative error, and $\varepsilon_{SA,r}$ and $\varepsilon_{Ai,r}$ are shared and unshared additive error, respectively. Assume that the ε are all independent with $E(\varepsilon_{SM}) = E(\varepsilon_{Mi}) = 1$ and $E(\varepsilon_{SA}) = E(\varepsilon_{Ai}) = 0$. (For notational convenience, we have dropped the subject r except when needed for clarity.)

We first consider the unshared multiplicative and additive terms in model (1). Note that if only the unshared additive error term, ε_{Ai}, is included in model (1), then this corresponds to an additive Berkson error model with independent errors (c.f. ref. *3*). A well-known property of the additive Berkson error model is that estimates from linear regression analysis are unbiased (in the unshared error case), as are the usual estimates of the standard errors of the regression parameters. This implies that the usual regression techniques for linear models (weighted or unweighted least-squares) that ignore the errors in Z_i will produce appropriate estimates and confidence intervals regarding the regression parameters relating D_i to true X_i. Addition of the unshared multiplicative term ε_{Mi} will mean that linear regression estimates will remain unbiased, but that the

variance structure changes (generally so that larger values of Z_i are associated with more variable outcomes D_i).

The variance of the estimate, $\hat{b}$, of a (possibly weighted) linear regression parameter can, under this model, be written as

$$\mathrm{Var}(\hat{b}) = \mathrm{Var}\{E(\hat{b}\,|\,\varepsilon_{Sm}, \varepsilon_{SA})\} + E\{\mathrm{Var}(\hat{b}\,|\,\varepsilon_{Sm}, \varepsilon_{SA})\},$$

which can be further approximated if b is small as

$$\cong b^2\sigma^2_{SM} + \frac{\mathrm{Var}(D)}{N\,\mathrm{Var}(Z)}. \quad (2)$$

This expression implies that under the null hypothesis that $b = 0$, the expectation (over the shared error components) of the naïve estimate of the variance of $\hat{b}$ is equal to the true variance. However, if $|b| > 0$, the naïve variance estimate (3.4) is in fact biased downward by the amount $b^2\ \sigma^2_S$ compared with the true variance. From that, we may conclude the following:

1. Ignoring shared error in the dosimetry system does not affect the asymptotic size of the test of the null hypothesis that $b = 0$.
2. However, sample sizes or the power of a test calculated under a specific alternative hypothesis, $|b| > 0$, will, if they ignore shared dosimetry error, be incorrect. Power will be overstated or, equivalently, the necessary sample size will be understated.
3. Confidence intervals will also be affected. Ignoring shared dosimetry error while constructing confidence intervals will result in confidence intervals that are too narrow.

However, it is the upper bounds of $|b|$, and not the lower bounds, that are most affected; in particular, a confidence interval ignoring dosimetry error that does not overlap 0 will not overlap 0 once the shared errors in the dosimetry are properly handled. That follows because the validity of a test of the value $b = 0$ does not depend on shared dosimetry error, because the variance estimate of $\hat{b}$ under the null hypothesis is correct.

We now consider the application of this model to the 100 replications of exposure provided by the Hanford Environmental Dose Reconstruction (HEDR) system used by the HTDS, we restrict ourselves to those 1979 subjects with complete interview data. To estimate all the variance components in model (1), we use two linear relationships between the variances and covariances of X_{ir} and X_{jr} over the 100 replications of dose. If X_{ir} ($I = 1, \ldots, n$) is from model (1), then we then have

$$\mathrm{Cov}(X_{ir}, X_{jr}) = Z_iZ_j\sigma^2_{SM} + \sigma^2_{SA} \quad \text{and}$$

$$\mathrm{Var}(X_{ir}) = Z_i^2[(\sigma^2_{SM} + 1)(\sigma^2_M + 1) - 1] + \sigma^2_{SA} + \sigma^2_A.$$

By fitting linear regressions relating sample variances and covariances (calculated over the 100 replications r) to Z_j and Z_i, respectively, we have four equations (two estimated slopes and two estimated intercepts) in four unknowns to solve to estimate all four variance components. The results from this analysis for the subjects with complete data are

Model for variances	Estimate	SE
Intercept ($\sigma^2_{SA} + \sigma^2_A$)	−4.50247	24.72021
Slope [$(\sigma^2_{SM} + 1)(\sigma^2_M + 1) - 1$]	0.89530	0.00970
Model for covariances		
Intercept (σ^2_{SA})	−492.04371	12.86722
Slope (σ^2_{SM})	0.27173	0.00014

The estimate for σ^2_{SM} implies that shared error has some impact on power in the HTDS study. Assuming normality of $\hat{b}$, the standard formula for power is

$$Z_\beta = \frac{Z_{1-a}se_0(\hat{b}) - b_1}{se_1(\hat{b})} = \frac{Z_{1-a}se_0(\hat{b}) - b_1}{\sqrt{se_0(\hat{b})^2 + \sigma^2_{SM}}}. \quad (3)$$

Consider an analysis that ignores shared dosimetry error and assumes that there is power equal to 0.80 for a one-sided test with type I error rate $\alpha = 0.05$. This analysis will set $b_1 = (Z_{1-\alpha} + Z_{1-\beta})se_0$ ($\hat{b} = (1.64 + 0.84)\ se_0\ (\hat{b})$. Using Eq. (3), this analysis will in fact produce a true power, after accounting for shared dosimetry error, specified by

$$Z_\beta = \frac{1.64se_0(\hat{b}) - 2.48se_0(\hat{b})}{\sqrt{se_0(\hat{b})^2 + \sigma^2_{SM}(2.48se_0(\hat{b}))}} = -0.5139$$

so that power is reduced from 80% to 70% in this example. We compare the use of this simple power estimate to a simulation-based approach using the actual HEDR dose estimates in a hypothetical example below.

Power ignoring shared error	Simulation-based power	Power calculated under formula (3)
0.05	0.039	0.050
0.80	0.713	0.706
0.90	0.829	0.786
0.95	0.863	0.826

The correspondence between the power estimated in a simulation study using the actual HEDR doses with that arrived at using Eq. (3) is good for moderate levels of power (70%) but degrades as power increases further. The failure of Eq. (3) to fully capture the true power of the HTDS study at larger values of power is probably due to a failure of the normality assumption for $\hat{b}$ upon which Eq. (3) is based. Such a failure is expected in cases when the distribution of the shared error component ε_{SM} in model (1) is markedly non-normal and when true b is large enough that the term $b^2\sigma^2_{SM}$ dominates $Var(D)/NVar(Z)$ in Eq. (2). Nevertheless, we find that the simple shared and unshared dosimetry error model of Eq. (1) appears overall to provide a useful simplification of an extremely complex dosimetry system and may be useful for the purpose of making power calculations in other complex systems as well.

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Discussion

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As a number of speakers have pointed out, diagnostic medical X rays are the primary source of exposure of the U.S. population from man-made radiation. However, until this millennium, there has not regularly been an entire session of the ASA conference that has been devoted to radiographic exposure studies. A major reason for this lack is that the effects of such exposures are especially difficult to study, particularly in the U.S. For example, a prohibitively long and expensive study would be required to follow up children who received spiral CT to assess the long-term health effects of this exposure.

In Utah at the ASA meeting 2 years ago, I made an appeal for help in estimating doses for examinations had by subjects in a case–control study of adult-onset acute myelogenous leukemia (AML). We had derived dose estimates for most examinations using the medical literature, the web and consultations with local and other experts. The help we got from an attendee at the Utah meeting and from a colleague he referred us to

allowed us to complete the dose estimations for all 830 study subjects. We have now been able to finish our analyses, and we have findings I will share with you as an illustration of a possible new approach to studying radiogenic leukemias related to radiographic exposures.

AML is the most common of the adult leukemias, generally has a poor prognosis, and is one of three of the four major leukemia types shown in studies of heavily exposed populations such as A-bomb survivors to be caused by radiation. But studies of AML and radiographic exposures have had inconsistent findings. As for all leukemia, epidemiological studies have had limited success in identifying etiological factors. We believe that, for AML, which is a group of heterogeneous leukemias, this may be because analyses need to be specific for each subtype of AML. Indeed, cigarette smoking has been shown to be related to only one of the seven AML subtypes, M2. Our population-based AML study in Los Angeles County has confirmed the association between M2 and smoking and further suggests that radiation, in particular radiographic exposures, may be related specifically to AML subtypes M4 and M5A.

Preliminary subtype-specific analyses of our data on prior radiation treatment exposure showed an overall effect but suggested that the association was strongest for subtypes M4/M5A, which are both associated with 11q23 translocations. For diagnostic imaging procedures, no dose–response trends are apparent in analyses of all AML case–control pairs combined whether we restrict analyses to total number of high-dose (compared to low-dose) procedures or we use data based on interviews of patients or on medical charts. However, when analyses are restricted to M4/M5A pairs, AML risk increases with increasing number of high-dose procedures reported by patients and recorded in patients' charts. Similar trends are seen in a ''dose''–response analysis for this subtype.

''Doses'' to the active bone marrow from common high-dose examinations such as imaging of the GI tract using conventional X rays, fluoroscopic series, or CT scans are far higher than from common low-dose procedures such as chest X rays, mammography and X rays of the extremities. Most dose estimates are based on dosimetry surveys reported in the literature, but the range of doses reported in such surveys is huge for some procedures such as coronary angiography (2.14–38 mGy), and for over half of all procedures only one such estimate is available. For many examinations, the dose is simply assumed to be the same as the dose from a similar examination, and other doses are derived solely from the opinion of a radiology expert. Despite those difficulties and uncertainties, studies of radiographic exposures need to be done. The ASA can support efforts in this direction by continuing to regularly devote a session to radiographic exposures at its bi-annual meeting.

SENSITIVE SUBPOPULATIONS

Robert L. Ullrich, Chair

Genetic Susceptibility to Radiation Tumorigenesis: Problems and Prospects for Resolution

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Cancer risk is judged to be the most important consideration in radiation protection, particularly with respect to exposure at low doses and low dose rates. The central estimates of cancer risk are based upon epidemiological evaluation of irradiated human subgroups, but data from fundamental studies with cell and animal models add important support on some judgments (*1, 2*).

The potential effects of variation in genetic makeup on radiation cancer risk have been recognized for some time, but present knowledge is insufficient to allow genetic factors to be specifically accounted for within population risk. This whole issue has been reviewed by the ICRP (*3*) and explored further by UNSCEAR (*1, 2*). From these recent reviews, it is possible to identify two related human genetic issues on which judgments need to be developed.

Cancer-Predisposing Mutations of High Penetrance

Advances in cancer genetics continue to provide detailed information on heritable human mutations which are expressed strongly as cancer; i.e., their high penetrance is reflected in a lifetime risk of specific cancer types in carriers that may approach 100%; multiple tumors are also frequently expressed. Examples include the autosomal dominant, tumor suppressor, and/or DNA damage response gene mutations of retinoblastoma, Li-Fraumeni syndrome, adenomatous polyposis coli and *BRCA*-type familial breast cancer.

From knowledge of the molecular genetic mechanisms involved, studies with cell models/mouse genetic homologs and limited epidemiological/clinical investigations, it is possible to judge that most of the known strongly expressing cancer-predisposing mutations are likely to confer a significantly increased risk after irradiation—albeit with some expected further modification by genetic background and environmental factors. However, since such genetic disorders are very rare, their collective impact in the whole population will be small, and no significant distortion of low-dose risk estimates is anticipated (*3*). Nevertheless, there are implications for individual carriers presenting for high-dose radiotherapy: The risk of therapy-associated second cancers may be substantially elevated in some of these disorders.

Gene Polymorphisms and Modifier Genes

There is increasing evidence that the risk of development of many diseases including cancer is influenced, but not specifically determined, by weakly expressing variant genes (so-called polymorphisms and modifier genes). Individually, their phenotypic effects may be small, but the overall balance between multiple variant genes conferring cancer resistance and those conferring cancer susceptibility can in principle create substantial differences in cancer risk between individuals; this scenario seems likely to apply to spontaneous cancers and to those associated with carcinogen exposure.

On this basis, the following questions are relevant to the development of future judgments in radiological protection: (1) How many cancer-related genes fall into this category, and how common are the variant forms? (2) Which classes of variant genes are involved, and how strong are the gene–gene interactions that apply? (3) How tissue-specific and agent-specific are these genes? (4) From knowledge on the above issues, will it be possible to arrive at judgments on the distribution of cancer risk in the population and/or place individuals within a hierarchy of radiation risk?

Much effort is currently being expended on the use of genetic epidemiological approaches to address possible associations between specific variant genes and the risk of human disease, including cancer. However, in spite of advances in high-throughput genomics, there is much debate on the true power of such genetic association studies (*4*); the amount of work that has been necessary to clarify the relationship between heterozygosity for the *ATM* gene and breast cancer risk (see the next extended by abstract by M. Lavin) provides one example of the problems that are faced.

Given the limited knowledge on interactive variant human genes that are believed to modify the risk of induced cancer, there is much scope for proof-of-principle experimental studies in animal genetic models of carcinogenesis. Recent mouse genetic studies on chemical carcinogenesis highlight the importance and potential complexity of variant gene interactions. For example, in the mouse, around 60 germline loci with multiple interactions appear to be involved in lung cancer risk (*5*). Similar studies are under way on mouse genetic loci involved in radiation tumorigenesis (*6*), and this area of investigation shows much promise for the provision of initial guidance on future molecular genetic investigations in humans. In particular, mouse studies strengthen the view that selected surrogate

cellular phenotypes coupled with high-throughput assays can be informative about human cancer risk.

Overall, the technical and academic advances of recent years have provided a foundation on which to build a more complete understanding of the genetic factors that influence radiation cancer risk. In particular, knowledge on the potential role of weakly expressing variant genes involved in the DNA damage response and clonal proliferation/differentiation is now growing. In due course, this should facilitate the development of judgments on the likely distribution of radiation cancer risk within given populations. However, the indication from mouse studies that complex tissue-specific interactions between multiple variant genes are to be expected sounds a strong note of caution on the prospects for meaningful genetic predictions on individual cancer risk after irradiation.

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Ataxia Telangiectasia and the Complexity of Radiosensitivity

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To maintain the integrity of the genome, cells have evolved several mechanisms that recognize DNA damage and signal this to the DNA repair machinery, cell cycle checkpoints, and transcriptional control. While there have been exhaustive reports on the nature of the lesions arising in DNA in response to a variety of damaging agents and on the mechanisms of repair, the ability of the cell to recognize these lesions and signal to the appropriate cellular machinery is only recently being unraveled. The description of a number of human genetic disorders characterized by chromosomal instability and cancer predisposition has assisted in accelerating our understanding of the process of DNA damage recognition. One such syndrome, ataxia telangiectasia (AT), has been a focal point for these studies because of its universal sensitivity to ionizing radiation and the central role the gene product involved plays in radiation signal transduction. This syndrome is characterized by immunodeficiency, neurodegeneration, radiosensitivity, meiotic defects and cancer predisposition (*1*).

Increased sensitivity to radiation was first described for AT patients undergoing radiotherapy for tumors (*2, 3*). This sensitivity was subsequently observed in AT cells in culture (*4, 5*) and appears to be a universal characteristic, although the extent of sensitivity is influenced by the exact nature of the mutation in *ATM*, the gene mutated in this syndrome (*6*). The basis of the radiosensitivity remains unknown but appears to be due to a failure of AT cells to respond appropriately to double-strand breaks in DNA. Cornforth and Bedford (*7*) showed that AT cells were defective in premature chromosome condensation, and it was later demonstrated that residual breaks remained in DNA at long times postirradiation (*8*). While the majority of double-strand breaks are repaired by AT cells, some persist and may be converted into chromosome breaks which characterize this syndrome and account for the radiosensitivity. Clearly *ATM* is only one of the numerous genes involved in protecting cells against radiation damage to DNA. Mutations in other genes such as DNA-dependent protein kinase (*PRKDC*), its associated heterodimer Ku70/Ku80 (now known as *G22PI*/*XRCC5*), *NBS1*, mutated in the human genetic disorder Nijmegen breakage syndrome, and *MRE11*, mutated in AT like syndrome, are just a few of the many that lead to radiosensitivity.

ATM is activated primarily as a pre-existing protein by ionizing radiation and radiomimetic agents (*9, 10*). The exact mechanism of activation is as yet undescribed, but it is clear that this molecule undergoes autophosphorylation which is expected to be responsible for or contribute to activation (*11*). Agents that break DNA activate ATM, so it is likely that the initiating signal may be a relaxation of the superhelical density of chromatin which would be rapidly transmitted to ATM, present in complexes loosely associated with chromatin. The initiating event may be a conformational change and/or dissociation from other members of a protein complex such as BRCA1-associated genome surveillance complex (BASC) (*12*) which would allow access to ATP and protein substrates. In this context recent evidence points to a greater retention of a portion of ATM in nuclear aggregates, after irradiation (*13*).

Once activated, ATM phosphorylates a range of substrates involved in DNA damage recognition (NBS1, MRE11, RAD51, BRCA1) and in cell cycle checkpoint activation (TP53, CHEK2, NBS1, BRCA1, MDM2). Some of these proteins such as NBS1 and BRCA1 are involved in DNA break recognition and repair as well as cycle control.

Recent data suggest that oxidative stress arising as a consequence of loss of ATM may contribute to the AT phenotype. Evidence for oxidative stress in AT cells and in *ATM* gene-disrupted mice includes lipid and protein damage, elevated levels of enzymes involved in protecting against this form of stress, higher basal levels of TP53 and CDKN1A (p21/WAF1) proteins, and abnormalities in nicotinamide nucleotides (*14*). The use of antioxidants alleviates some of this oxidative stress and they are effective in protecting against radiosensitivity in AT cells. Antioxidants also have the potential to reduce the severity of the neurodegeneration and the increased tumor incidence that are characteristic of AT.

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Carcinogen Exposure and Inactivation of the RB Pathway: Does Inverse Dose Response Identify Susceptibles?

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Recent advances in the molecular biology of human cancer have elucidated multicomponent pathways that are pivotal in cancer etiology; prominent among these are cell cycle checkpoint controls and programmed cell death. As the details of each pathway are brought forth, additional questions concerning the link between environmental factors and the cancer process can now be asked. For example, is individual susceptibility to environmental insults reflected by the components of pathways inactivated in human cancers? Previous studies of TP53 mutational spectra in lung tumors indicated that within the TP53 component, mutational changes may reflect etiology (*1, 2*). Studies have suggested a positive association of exposure to cigarette smoke and TP53 mutations (positive dose response) (*3, 4*). Inverse dose response, however, has not been considered in somatic alteration occurring in lung cancer. If a specific component of a pathway confers susceptibility to lung cancer, then an inverse dose–response relationship between carcinogen exposure and gene alterations may be expected. As a corollary, age at diagnosis may be expected to be inversely related to these molecular changes in susceptible populations.

In addressing the role of exposure in affecting the pattern of alteration of multiple components within a single pathway in lung cancer we chose to examine the *CDKN2A* (p16INK4a)/*RB* genes. Several mechanisms exist to inactivate this pathway including CDKN2A mutation, methylation silencing, or deletion, RB mutation or deletion, and cyclin D1 amplification. CDKN2A protein detected by immunohistochemical analyses is a sensitive method for screening lung tumors for several of these alterations (i.e. deletion, methylation, mutation). Because CDKN2A mutation is extremely rare in lung cancer, CDKN2A immunohistochemical analyses mostly reflects the former modes of inactivation (i.e. deletion, methylation).

To characterize tobacco smoking dose response and inactivation at CDKN2A, we examined CDKN2A by immunohistochemistry and methylation-specific PCR in primary non-small cell lung tumors (NSCLC). CDKN2A methylation was positively associated with increasing levels of exposure to tobacco smoke. In contrast, deletion of the gene, in concert with loss of CDKN2A staining and no evidence of promoter methylation, was inversely related to measures of tobacco smoke exposure. Age at diagnosis was earlier in subjects in whom the gene was deleted compared to patients with tumors with evidence of methylation.

Inverse dose response of inactivation (loss of protein) of CDKN2A through a non-methylation mechanism and early age of diagnosis are consistent with the hypothesis of increased susceptibility to deletion events. Linking exposure history with somatic genetic analyses of tumors may help identify mechanisms of host susceptibility to exposure-induced cancers.

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Radiation and Genetic Susceptibility in Non-melanoma Skin Cancer

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Ultraviolet radiation is a clear etiological exposure in skin cancer development. Exposure to UVB radiation creates signature DNA lesions (pyrimidine dimers and 6,4-photoproducts) that are repaired through the nucleotide excision repair (NER) pathway (*1*). Inherited mutations in NER genes result in extreme photosensitivity and skin cancer susceptibility, as observed in the xeroderma pigmentosa syndrome. These rare inactivating NER mutations contribute very little to the high rate of nonmelanoma skin cancer in Caucasians. However, common genetic variation in these same genes may have an impact the efficiency of NER and may significantly affect individual susceptibility to keratinocyte carcinomas.

Due to the unique signature lesions and associated cancer syndromes, NER is often depicted as the principal DNA repair process after exposure to UV radiation. However, both UVA light and sunburns (inflammation) induce DNA damage that is repaired by alternative DNA repair pathways. Unlike NER, the base excision repair (BER) pathway does not have an identified cancer syndrome, and it has historically been thought to play a lesser role in cancer susceptibility.

Using a large, population-based case–control study of non-melanoma

skin cancer in New Hampshire, we are testing hypotheses of genetic susceptibility in these two DNA repair pathways. Non-melanoma skin cancer cases are identified using an incidence survey (*2*). A subset of these cases are recruited into the case–control study. Controls, identified through Department of Transportation and Health Care Financing Administration lists, are frequency-matched to cases by age and gender (*3*). Polymorphisms in the *XPC* (*4*), *XPD* (*5*), *XRCC1* (*6*) and *APE1* (*7*) genes have been assessed in approximately 1,200 study participants.

Our preliminary data suggest that NER polymorphisms may not play a dramatic role in skin cancer susceptibility. We have examined two polymorphisms in the *XPD* gene, asp312asn and lys751gln. For basal cell carcinoma (BCC), there was no risk associated with either the asn312asn genotype or the gln751gln genotype. Similarly, for squamous cell carcinoma (SCC), there was no significant effect of the codon 312 polymorphism or codon 751 polymorphism. However, there was a modest reduced risk of SCC associated with a poly-AT intronic insertion polymorphism in the *XPC* gene. Further, there was evidence that this polymorphism may interact with skin type, such that the reduced risk is observed only among those with a tendency to tan rather than burn.

Surprisingly, the strongest evidence for genetic susceptibility to common skin cancer was in the BER pathway. We have previously reported a significantly reduced risk of both BCC and SCC with the *XRCC1* codon 399gln polymorphism (*6*). We have expanded our sample size and added data on two other *XRCC1* polymorphisms (arg194trp, arg280his). For both BCC and SCC, the significantly reduced risk with the gln399gln genotype remained (OR 0.7 and 0.4, respectively). There was no significant association with the other two *XRCC1* polymorphisms that have a markedly lower prevalence ($<$10%). There was a nonsignificant trend for an interaction between both the 194trp and 399gln polymorphisms and therapeutic exposure to ionizing radiation for occurrence of BCC. In addition, although there were no main effects of the *APE1* 148glu polymorphism in BCC, there was a significant interaction between the *XRCC1* 399gln polymorphism and the *APE1* 148glu polymorphism, suggesting that both of these common variations may be contributing to the non-melanoma skin cancer burden.

The surprising result from these preliminary analyses is the relatively weak contribution of NER polymorphisms to skin cancer susceptibility. Further, we see a consistent reduced risk effect of common polymorphisms that have been associated with increased risk in studies of other malignancies. We propose that different cell types vary in their tolerance of DNA damage at the cell cycle checkpoints, and that this results in tissue-specific apoptotic thresholds. If keratinocytes have a relatively low threshold, this model would predict that when polymorphisms confer reduced repair capacity, keratinocytes with persistent damage would undergo apoptosis, protecting against neoplasia, whereas in other tissues which tolerate higher levels of DNA damage, cells would continue to divide and propagate pro-neoplastic mutations.

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KEYNOTE ADDRESS
Nuclear and Radiological Terrorism

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Nuclear terrorism is an attempt to cause a nuclear explosion. Radiological terrorism is an attempt to cause either (1) a nuclear reactor accident or (2) radiation casualties with a transuranic such as plutonium, a fission product such as ^{137}Cs, or an activation product such as ^{60}Co.

Nuclear Terrorism

Unfortunately, it is all too easy to make a nuclear explosive with highly enriched uranium. Plutonium is somewhat more difficult. Quantities of weapons-grade highly enriched uranium sufficient to make a nuclear weapon can be found at about 100 civilian locations around the world. These locations include research reactors, spent-fuel reprocessing plants, and nuclear weapons development and production facilities. Exercises with Special Forces have shown that highly enriched uranium can be stolen even from large U.S. nuclear weapons facilities. In addition to security upgrades, governments should give a much higher priority to converting research reactors to low-enriched uranium, drastically reducing the number of sites where highly enriched uranium can be found, and rapidly eliminating the very large excess stocks of highly enriched uranium that are a legacy from the Cold War (*1*).

Radiological Terrorism

As Hiroshima showed, the consequences of a nuclear explosion in an urban area could be 100,000 acute deaths. In contrast, the number of deaths due to high doses from a large release of radioactivity to the atmosphere is likely to be small—of the order of 100 or less. But the calculated number of long-term cancer deaths can be of the order of 10,000. According to calculations using the linear hypothesis, most of those deaths will not be statically significant additions to the background cancer rates. However, an order of magnitude increase in the incidence of non-fatal childhood thyroid cancer has been reported in heavily contaminated regions of Belarus after the 1986 Chernobyl accident (*2*).

The use of a linear dose–effect relationship in projecting radiation-induced cancers in large populations from their statistically measurable incidence at high doses therefore becomes a central issue in discussions of the consequences of radiological terrorism. The linear hypothesis was the subject of great controversy during the 1950s and 1960s in debates over the health impacts of the testing of nuclear weapons in the atmosphere and during the 1970s in debates over the consequences of large releases of radioactivity from nuclear reactor accidents.

The author has participated in a number of these controversies (*3*–*5*) and recently helped prepare testimony on the subject of radiological

terrorism for a hearing before the Senate Foreign Relations Committee.[3]

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MEDICAL RADIATION EXPOSURES IN OCCUPATIONAL STUDIES

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Overview of Occupational Medical Exposure

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Radiologists and radiological technologists are among the earliest occupational groups exposed to radiation. In 1902, only 7 years after the discovery of X rays, excessive occurrences of skin cancer, which was the first solid cancer linked to radiation, were noted among radiologists. In early 1950, excess mortality from leukemia among radiologists began to receive attention, and this, together with the rising concern about the effect of chronic radiation exposure from nuclear weapons tests, led to two landmark cohort studies of radiologists, one in the United Kingdom and the other in the United States. Today, a large number of professional and technical personnel in medicine, dentistry and veterinary medicine are occupationally exposed to radiation while administering various radiological procedures, i.e., diagnostic, therapeutic, interventional and nuclear medicine. The latest UNSCEAR report estimates that, worldwide, there are 2.3 million medical radiation workers—half of the entire workers exposed to man-made sources of radiation. Health risks from radiation exposure in such a large occupational segment of the population are clearly of special concern.

In the literature, there are eight major cohort studies of medical radiation workers: three in the United States and one each in Canada, the United Kingdom, Japan, China and Denmark. Two of these cohorts are exclusively radiologists, while the other six are predominantly radiological technologists. All together, these cohorts include more than 270,000 radiological workers. Radiological technologists typically began their careers when they were in their early 20s and late 30s, whereas radiologists joined the specialty society at somewhat older ages, i.e., in their mid-30s and mid-40s. While most of the cohorts are exclusively or predominately male, two cohorts, U.S. radiological technologists and Canadian medical radiation workers, include large numbers of women, offering a unique opportunity for providing risk data for females, which are lacking in other occupational populations. Because of the availability of professional and specialist society membership rosters and records, follow-up of the medical radiation workers is relatively straightforward. Medical workers are highly cooperative and this facilitates collecting data and biological specimens.

Cohort	Cohort size		Years worked	Years followed up
	Total	Female		
U.S. radiologists	6,500	—	1920–1969	1920–1969
UK radiologists	2,700	—	1897–1979	1897–1997
U.S. radiological technologist	143,000	105,000	1926–1982	1926–1997
U.S. Army radiation techs	6,500	—	1946–1963	1946–1974
Chinese radiological technologist	27,000	5,400	1950–1980	1950–1995
Danish radiotherapy personnel	4,100	3,400	1954–1982	1968–1985
Japanese radiological technologist	12,000	—	NA	1969–1993
Canadian medical radiation workers	73,000	26,300	<1950–1983	1951–1987

Most of the cohort subjects worked during periods of striking historical changes in radiation exposure. This creates a number of dosimetric and analytical problems that need to be addressed. A brief account, which follows, of the historical development of radiation safety standards illustrates the remarkable improvement in radiological protection and concomitant reduction in exposure. During the decades after the discovery of X rays in 1895, radiologists were exposed to such high doses that dermatitis and other radiation-induced injuries were common. The first dose limit was introduced in 1902, which was about 0.1 Gy per day (30 Gy per year!); this was not based on biological data but rather on the lowest observable amount, i.e. fogging of a photographic plate. Many of the subjects in the UK radiologist cohort were pioneering radiologists who were exposed to excessive doses of radiation during this early period. With accumulating evidence of the cancer and cell-killing effects of X rays, the American Roentgen Ray Society recommended in 1924 a tolerance dose of one-hundredth of an erythema dose per month for radiation workers, which is a 10-fold reduction from the one-tenth of an erythema dose per month (about 0.6 Sv per month) that the workers were receiving at that time. In 1934, the U.S. Advisory Committee on X ray and Radium Protection proposed the first formal standard of 0.1 R per day (0.3 Sv/year). The earliest radiologists in the U.S. radiologist cohort and some of the UK cohort worked during this period. One study estimated that radiological workers during the period of 1920–1930 could have been exposed to 100 R per year (1 Sv/year). The conditions must have improved in the late 1930s, since a survey of a large number of U.S. hospitals in 1940 showed that the average exposure ranged from about 0.01 to 0.25 Sv per year, depending upon how well the installations were protected. Levels of exposure may have improved further in the 1950s. Thus, in a 1953 survey of the radiological technologists at the Cleveland Clinic, the usual weekly exposure dose was usually >0.1 R (>0.05 Sv/year) and seldom >0.3 R (>0.15 Sv/year). Large numbers of subjects in the U.S. and Canadian radiological technologist cohorts worked during the period of 1940 through early 1950. In 1957, the International Commission of Radiological Protection recommended a dose limit of 0.05 Sv/year, which led to much lower levels of exposure that exist to this day.

Routine monitoring of radiation exposure was not introduced until 1950. Doses were not measured systematically in earlier years; therefore, the link between the cohort and dose cannot be made. For example, Landauer, Inc., the largest commercial dosimetry provider in the U.S., has

[3] Henry Kelly, Testimony before the Senate Committee on Foreign Relations, March 6, 2002, available on the web at http://www.fas.org/ssp/docs/030602-kellytestimony.htm.

dose information on medical workers only after 1958. Early cohort studies of radiologists and radiological technologists generally demonstrated an excess risk of leukemia and excess risks for some solid cancers (*1*, *2*), but the evidence is based on comparison of the standardized mortality ratios among subgroups working in different periods or between radiologists and other medical professionals working in the same period. In some studies, for example in Canada (*3*), measured doses were available but only for the period after the introduction of monitoring in 1951. Risk values based on such incomplete dose data are likely to be overestimated. In the absence of individual dose information, investigators have used a number of proxy measures. The proxy measures are typically based on work history, e.g., how long the subject worked as a radiological technologist, especially during the early years, and whether the subject administered fluoroscopic examinations and other diagnostic and therapeutic procedures. Data using these proxy measures that must take into account different periods, without dose estimates, clearly have limitations. However, several findings, such as the excess risk of breast cancer, leukemia, skin cancer, and more recently non-cancer diseases,[4] have provided new information on the risks associated with chronic radiation exposure, and they merit further study.

For further study, however, dosimetry is critically important. Currently, efforts are under way in at least three major studies to construct individual dose estimates. Dose reconstruction work carried out for the U.S. radiological technologist cohort will be discussed by subsequent speakers. Briefly, this involves construction of models using film-badge measurement data, extrapolation and modification of the models to earlier periods, and construction of doses for the earliest period using published, largely disconnected, information. These models, along with detailed radiological work history data obtained by questionnaires, are used to estimate individual organ doses. Retrospective dose reconstruction has also been attempted for the Chinese X-ray worker cohort, involving simulation of past working conditions with a phantom, interviewing of subjects for detailed work histories, mathematical models, and verification by chromosomal aberration data (*4*). Reconstruction of early doses is also being undertaken for the Canadian radiation worker cohort.

Medical radiation worker cohorts hold a unique position in radiation studies and offer one of the few chances for obtaining information regarding chronic radiation exposure. The chronic doses received range from a negligibly small to a considerably high level. The subjects represent a healthy working population of both sexes and a wide range of ages. Long-term follow-up is continuing in many studies. The subjects are cooperative and responsive to epidemiological studies and are agreeable to biologically motivated studies of gene–radiation interactions. Together, these open the possibility of gaining critically important insights into health risk of chronic exposure and their underlying mechanisms, about which so little is known at present.

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Retrospective Exposure Assessment for Radiological Technologists

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In 1982, the National Cancer Institute (NCI) initiated a study of cancer incidence and mortality among radiological technologists in the United States. A cohort of approximately 146,000 technologists who were certified by the American Registry of Radiologic Technologists (ARRT) for at least 2 years during the period 1926–1982 was identified for study. The cohort is predominantly female with a current average age of 53 years. The NCI staff have collected extensive work history and health outcome data for the cohort members through the administration of two separate surveys, both of which had more than 90,000 respondents. In addition, the NCI has obtained approximately 1.3 million annual dosimetry badge readings for cohort members from 1977 through 1998. Several reports on the health effects observed in the cohort have been published previously without a substantial assessment of exposure (*1*, *2*). One of these studies reported an excess of breast cancer associated with duration of employment which may be a surrogate for cumulative exposure.

In a collaborative agreement with the National Cancer Institute, researchers at the National Institute for Occupational Safety and Health have participated in an effort to retrospectively assess the occupational radiation exposure for this unique cohort. Because the quality, quantity and type of available exposure information varied considerably over time, it was recognized at the outset that several different exposure assessment strategies would be necessary. This is consistent with other studies that attempted to reconstruct exposures over long periods (*3*). Depending on availability of data, the assessment approach must incorporate the appropriate elements of either quantitative statistical or deterministic models. A summary of our findings for each of three exposure periods is presented below.

Assessment of Exposures between 1977–1998

The arithmetic mean badge dose for the cohort during this period was found to decrease in an approximately exponential manner from 2.9 mSv in 1977 to 0.3 mSv in 1998. This trend was in general agreement with that observed for medical workers (*4*). The geometric mean annual doses for this population were 0.5 and 0.04 mSv for 1977 and 1998, respectively. The percentage of workers with no detectable exposure increased from 20% in 1977 to almost 60% in 1998. Fewer than 1.6% of the measured annual doses were greater than 10 mSv. Within each year, the geometric standard deviations were very large (ranging from about 8 to 10).

An evaluation of the databases that contained the annual dosimetry results and the questionnaire responses revealed that at least partial information on exposure was available for about 51,000 of the 71,000 technologists who responded to both questionnaires. Using these exposure records and the information contained in the questionnaires, multivariate regression models were evaluated for their usefulness in assigning missing exposure information. Using a stepwise regression approach, the predictive value of candidate variables from the questionnaires was evaluated. The various predictors evaluated included the calendar year, the type of facility, the type of radiation procedure used, the frequency and duration of the use of the different procedures, the use of shielding, and the location of the dosimeter on the body. The statistical model that included responses from both questionnaires was found to explain at best about 30% of the variance in the data. Other models that relied on less complete

data were less predictive. The most strongly correlated predictors were type of facility (physician's office or hospital), year of exposure, and frequency of fluoroscopy use.

Assessment of Exposures between 1960 and 1976

There were considerably fewer electronic exposure records available for this period. A number of approaches were employed to collect data that might be useful in assessing exposures. These included (1) the collection of samples of microfilm records from a commercial supplier of dosimetry services, (2) the evaluation of exposure data collected previously from employers by the University of Minnesota, (3) a review of published exposure reports for similarly exposed populations, (4) the collection and evaluation of work practices and engineering controls descriptions, (5) collection and review of documents on the introduction of new technology and improvements in design, and (6) the evaluation of dosimetry records from government agencies and hospitals where retention of historical records was likely to be more conservative.

The above efforts resulted in the collection of approximately 3,800 annual exposure values from a combination of the data collected previously, new efforts on ascertainment of data, and published exposure summaries. A plot of the data collected by the University of Minnesota indicated that there was an almost level trend in the annual doses between 1960 and 1976, with an average dose of about 2.6 mSv. Published exposure summaries during this period tended to be considerably higher than those of the radiological technologists included in the University of Minnesota data. It is believed that this is due to the fact that the published data were collected at large teaching hospitals. This is consistent with our finding from the post-1977 period that radiological technologists who worked in physicians' offices had about one-half the exposure of those who worked in hospitals.

Assessment of Exposures prior to 1960

For exposures prior to 1960, very few individual monitoring results were found to exist. Because of this, statistical modeling of the exposures was not possible. It was decided that the base of this assessment would consist of a detailed literature review to document changes in regulations and technology. It was noted, for example, that the decrease in allowable exposure in the mid-1950s by a factor of three led to a significant reduction in worker exposure. Improvements in technology are also known to have resulted in decreased exposure per unit workload.

For this period, the available literature was sparse and tended to show great differences between workplace types. For example, annual means in large hospitals were reported to range from 30.0 to 50.0 mSv per year, while reported exposures at small medical clinics were less than 0.1 mSv per year. Data contained in seven of the early publications indicated an increasing trend in annual exposure going back in time from 1960. This trend appeared to roughly follow the changes in occupational exposure limits. Over the last year, the NCI has developed new exposure assessment models and approaches for risk estimation in the radiological technologist cohort.

Summary

Occupational radiation exposures for radiological technologists have been evaluated between 1940 and 1998. In this period, there has been a decreasing trend in annual exposure which prior to 1960 appears to follow changes in occupational exposure limits. In the most recent period (1977 through 1998), sufficient electronic information was available to conduct multivariate regression modeling. The most significant predictors of exposure during this time period were type of facility, year of exposure, and frequency of fluoroscopy use. Data were much more sparse in the earlier periods, prohibiting the use of regression modeling.

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Cancer Risks Associated with Employment as a Radiological Technologist

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Radiological technologists represent a unique occupational group with low-dose and low-dose-rate radiation exposure. Small and large cohorts of radiological technologists and other radiation workers have been assembled in Denmark, Japan, China, Canada and the U.S. that have been followed for cancer mortality and incidence. Women comprise variable proportions (range 20 to 82%) of the cohorts in Denmark, China, Canada and the U.S. We summarize here reported findings from the cancer mortality and incidence studies. Many cohorts have been updated recently and we have chosen to focus on the most recently published findings. In the case of the U.S. radiological technologists, we present selected published and unpublished data on cancer mortality and incidence.

Cancer Mortality Studies in Radiological Technologists

One of the earliest studies assessed cancer and other mortality risks among male radiological technologists ($n = 6{,}560$) serving in the U.S. Army during World War II. For comparison, men working as technologists in medicine or pharmacology or in a laboratory ($n = 6{,}826$) were also followed. Over the period 1946–1974, Jablon and Miller (*1*) found no differences in deaths from cancer or other causes in this cohort. Even though the mid-1940s was a period when work-related medical radiation exposures were relatively high, the exposure duration was short (averaging less than 3 years), suggesting that the average cumulative exposure was probably low.

A cohort of Japanese male radiological technologists assembled from licensing records ($n = 12{,}195$) was followed for 25 years, from 1969 to 1993 (*2*). Their cancer mortality experience was compared to corresponding cancer mortality rates in the general population of Japanese men and to a subgroup of Japanese men employed in professional/technical jobs. The calendar periods when the Japanese technologists worked are not known with complete certainty because licensing regulations were not instituted until 1968; many had presumably worked in previous years. Therefore, the cohort was divided, with the more highly exposed cohort comprised of radiological technologists born in 1933 or before and the second cohort born after 1933. Among those born prior to 1934 ($n = 4{,}595$), nonsignificant excess risks of death were observed for colon cancer, lymphoma, multiple myeloma and leukemia. Significant deficits were observed for all solid cancers combined and for cancers of the stomach and lung. The Japanese technologists who were born before 1934 likely worked variable amounts of time in the earlier calendar periods when occupational exposure to radiation was high and personal exposure was not monitored.

Using certification records of the American Registry of Radiologic Technologists, 143,517 U.S. technologists (73% female) certified for 2 or

more years during 1926–1982 were followed through 1990 (*3*). Cancer deaths were ascertained through the National Death Index and state mortality tapes, with the number of observed cancer deaths compared to the number expected based on U.S. general population mortality rates. All categories of causes of death and nearly all cancer site-specific risks were below unity, a pattern ascribed to the healthy worker effect in this relatively young cohort (median age in 1990 was 42 for men and 41 for women). Mortality analyses based on 7,354 deaths through 1990 and a subcohort mortality analysis of 1,103 technologists who were Catholic nuns revealed significantly elevated breast cancer risks among women who were first certified before 1940 and for a long time (30 or more years). However, risk was not related to the use of various commonly performed diagnostic or therapeutic procedures. Mortality risks were not elevated for any forms of leukemia or for lung cancer. Internal breast cancer mortality analyses conducted recently (through 1997) revealed increased risks for employment before 1950, and risk was also increased among women performing fluoroscopy or multi-film procedures before 1950 (compared to 1960 or later). In addition, the risk of acute, myeloid and monocytic leukemia combined was slightly, but not significantly, elevated for starting work before 1950 compared to 1960 or later.

Cancer Incidence Studies in Radiological Technologists

In Denmark, radiotherapy workers from two departments who were employed between 1954 and 1982 ($n = 4{,}151$) were followed from 1968 to 1985, and radiation doses were based on badge readings from monitoring that began in 1954 (*4*). The cumulative radiation dose was relatively low, with an average of 18 mSv. Cancers occurring in radiotherapy staff were ascertained by linking to the Danish Cancer Registry and expected cancers were calculated from Danish population rates. Only prostate cancer was statistically significantly elevated, but cancers of the breast, skin and brain and multiple myeloma were also somewhat increased. Cancer of the uterine cervix was about half of that expected. When the analyses were partitioned by dose categories, the relative risk estimates showed no discernable pattern, indicating low support for excess cancer risk in relation to occupational radiation exposure. Despite the small numbers of radiotherapy workers followed, the individual badge doses and the inclusion of women (82% of the cohort) are clearly study strengths.

A Canadian cohort of 191,000 radiation workers (including 110,000 dental and medical technologists) was assembled from dosimetry records spanning 1951 to 1988 (National Dose Registry of Canada) (*5*). Cancer incidence was determined by linkage with the Canadian Cancer Data Base over the years 1969–1988. Using Canadian population rates, standardized incidence ratios (SIRs) were computed. For males and females combined, nearly all SIRs were less than unity, including the leukemias and female breast cancer. The significantly increased SIRs for melanoma and thyroid cancer were somewhat difficult to explain, indicating that further evaluation was warranted. Internal cohort analyses revealed several elevated cancer site-specific excess relative risks (ERRs), including colon, rectum, pancreas, lung, testis, leukemia and all cancers in men. ERRs for women could not be reported separately because of a lack of numbers in the high-dose range. This cohort has badge doses for individual workers, an undisputed strength, but the cumulative doses are extremely low, yielding fairly high ERRs from internal analyses.

A cohort of medical X-ray workers in China was recently updated for cancer incidence between 1950 and 1995 (*6*). This study has followed 27,011 medical diagnostic X-ray workers and 25,782 medical specialists for cancer incidence using hospital employment records. Elevated risks were observed for leukemia, non-melanoma skin, female breast, lung, liver, bladder, esophagus and thyroid cancers. Slightly reduced risks were seen for oral cavity, colon/rectum and brain, but these did not achieve statistical significance. Work history characteristics supported conclusions that occupational radiation exposure was related to elevated risks of leukemia, skin, female breast and possibly thyroid cancers. In addition, physical and biological retrospective dose reconstruction was performed. Annual average doses were the highest before 1950 ($\sim$37 mGy/year) and dropped successively to $\sim$3 mGy/year by 1975. Comparison of biological dosimetry (using translocation frequencies from FISH) and physical dosimetry revealed fairly good agreement, although the biological dosimetry consistently underestimated the reconstructed cumulative physical doses.

A large study of radiological technologists in the United States is ongoing, and investigators have recently completed a number of incident cancer analyses, which are not yet published. An overall cancer incidence analysis was based on 90,305 technologists who completed a postal survey in $\sim$1984 and $\sim$1995 or died in the interim. Self-reported cancers were verified by medical record review, for which 74% of records requested were obtained, and cancer reports were confirmed in 89%. Incident cancer occurrence was compared to that expected based on U.S. population rates from the NCI's Surveillance, Epidemiology and End Results Program. The incidence of solid cancers was elevated in women and lower than expected in men. Women had a significantly elevated incidence of breast cancer of about 1.2-fold. Among both sexes, melanoma and thyroid cancers were elevated and decreased risks were observed for buccal cavity/pharynx, rectum and lung cancers. The elevated risks of melanoma, breast and thyroid cancers suggest they could be related to radiation; however, the observed excesses may reflect, at least in part, increased screening in a population with easy access to health care.

From separate internal analyses, incident cancer risk at the sites of the female breast, non-melanoma skin cancer (basal cell), and melanoma are increased for work in earliest calendar period (before 1940) after adjustment for known risk factors. An increased incidence of thyroid cancer was associated with the practice of holding patients >50 times compared to <50 times for X-ray procedures, although risk was not significantly elevated among those working in the earliest years.

Summary

Overall, several studies suggest an elevated risk for cancers of the breast and thyroid and leukemia, with increasing risks for workers in early calendar periods. Non-melanoma skin cancer was increased among Chinese X-ray workers, but this cancer site is difficult to evaluate across cohorts if cancer registries do not routinely collect this information. There is some evidence for multiple myeloma and melanoma, but the latter has not been observed consistently. Some of the inconsistencies across studies could be due to choice of referent populations, risk estimates based on very low radiation doses for which confounding or bias (about which we may know little) accounts for observed associations, incomplete cancer ascertainment, and chance. With regard to radiation dosimetry, it is unlikely that good individual exposure data will ever be available for workers employed in calendar periods predating routine badge use (about 1950), yet these workers would be the most informative for risk assessment.

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Evaluation of Work-Related Medical X Rays in Epidemiological Studies of Nuclear Workers

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Introduction

Occupational epidemiological studies provide an opportunity to evaluate the health risks from exposure to low levels of ionizing radiation. These studies rarely include exposures from medical sources. In two studies of atomic bomb survivors, the authors concluded that medical X-ray exposures should be evaluated to better understand the effects of low-level exposures to ionizing radiation (*1, 2*). The aim of this study was to investigate multiple sources of worker exposures to external ionizing radiation at a uranium enrichment plant (a low-level exposure facility) between the early 1940s and 1990s and determine if work-related X-ray exposures added substantially to their cumulative occupational dose.

Methods

Bone marrow doses from work-related X rays were estimated for 297 workers, who are cases and controls for a multiple myeloma study, at a gaseous diffusion plant between the early 1940s and the late 1990s. Only 45 of these workers had other occupational radiation exposures monitored with personal dosimeters. Radiation exposure from work-related X rays was determined by the number and type of X rays conducted on the 297 workers at the facility. Cumulative bone marrow doses due to these X-ray exposures were calculated by converting entrance skin exposures to bone marrow doses (*3*). Conversion factors account for different types and energy of radiation, partial-body irradiation, exposure times, orientation, type of X-ray examination, and the configuration and composition of the body.

Work-related X-ray exposure data from all 297 workers were evaluated to describe the distribution of bone marrow doses associated with X-ray techniques used in the medical surveillance program. A comparison of bone marrow doses from external radiation exposure and from work-related X rays was performed on the subset of 45 workers to investigate the significance of each source of radiation exposure to their respective cumulative dose. Also evaluated was the potential for misclassification resulting from excluding work-related X-ray exposures from the cumulative dose and the presence of any statistical relationships between these sources of radiation exposure.

Results

Several findings are noted as a result of this study: (1) Among these 297 workers, the chest X ray was performed most frequently (78.6%), followed by extremities (12.3%), lumbar spine (2.3%), and skull (2.2%). Seven different examinations account for the remaining X rays (4.6%). (2) Chest X rays using the photofluorographic technique during the 1940s and 1950s delivered a bone marrow dose that was two orders of magnitude greater than the conventional method [about 800 mrad (8 mGy) compared to $<$10 mrad (0.1 Gy), respectively]. (3) Among the subset of 45 workers having radiation exposure from both chest X rays and external sources, bone marrow doses from work-related chest X rays were about 50 times greater than the doses from occupational sources, accounting for over 90% of their combined-source cumulative dose estimate. (4) Over 75% of the 45 workers would have been misclassified among the five groups if work-related chest X-ray exposure had not been not included in their estimate of cumulative bone marrow dose. (5) As a group, radiation workers were expected to receive more work-related chest X rays because they were subject to more frequent medical monitoring than non-radiation workers. Thus it was expected that external radiation exposure measured with the personal dosimeter would be related to exposure from work-related chest X rays. However, no statistically significant relationship was identified.

Discussion

Previous occupational epidemiological studies of radiation workers have not included radiation exposure from work-related X-ray examinations for several reasons. First, the historical radiation monitoring records did not include work-related X-ray exposure estimates. Second, there is a perception that the contribution from chest X rays would be very low compared to other sources of radiation encountered at the workplace (*4*). Third, epidemiologists have traditionally assumed that exposure from work-related X rays would be distributed randomly throughout the working population, so effects associated with this exposure would not influence the analysis (*5*). Fourth, the time and effort necessary to retrieve, interpret and evaluate this source of radiation exposure is large and costly. More recently, the practice of excluding health-related radiation exposure from occupational exposure records has been supported by recommendations from technical advisory committees and federal regulations.

Excluding work-related chest X rays as a source of radiation exposure, the largest contributor to cumulative dose at this low-dose facility, resulted in many individuals being misclassified. Historical documents indicated that radiation workers received more chest X rays than other, nonexposed workers. This suggests that work-related chest X-ray exposures may not be distributed randomly among the population. Failure to detect this association in this study may be due to the limited number of workers in this analysis ($n = 45$). An assessment of the full study population would provide additional insights.

Conclusions

Radiation exposure from work-related chest X rays accounts for more than 90% of the cumulative bone marrow dose received by workers employed at a low-dose facility in the U.S. between the early 1940s and the late 1990s. The photofluorographic chest X-ray technique used in the medical surveillance program was responsible for delivering the large dose to the bone marrow compared to the conventional technique. This study suggests that work-related chest X-ray exposures should be considered as a source of radiation exposure in epidemiological studies involving workers with low cumulative doses (e.g. cumulative dose $<$20 cGy), especially when high-dose X-ray examinations of the workforce were routinely conducted.

The results of this study may be applicable to other facilities that followed similar medical surveillance activities or used similar technology to obtain X-ray images. Ongoing research at NIOSH suggests that these activities and technology have been employed at other sites under study, but they occurred at different periods in history and may vary with regard to surveillance frequencies. Therefore, generalization of the results of this study to other facilities must account for site-specific medical surveillance activities and technologies used over time.

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Medical Radiation Exposures in Occupational Studies: Discussion

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The presentations in this session are linked by the populations studied (occupational cohorts), by the exposure setting (incidental or intentional exposure to medical sources of ionizing radiation), and by the aim of the studies, which is to evaluate risk of cancer after exposure to ionizing radiation. Continued interest in the effects of low-dose exposure to ionizing radiation places these occupational radiation research studies at the forefront of the current debate about the limits of epidemiology. Among the most pressing aspects of these potential limits is the ability within low-dose studies to adjust for sources of bias (e.g. due to selection and information) and error (e.g. in measurement of exposures or confounding factors) (*1, 2*). All four presentations made in this session illustrate attempts to circumvent these limitations and to improve the ability to measure low-dose effects of exposure to ionizing radiation.

Studies of Low-Dose Radiation Exposure in Medical Workers

As noted in Dr. Mabuchi's presentation, early studies of medical workers exposed to ionizing radiation have provided substantial qualitative evidence for the causation of skin cancer and leukemia at relatively high doses of X rays. Most of these early studies focused on male workers. More recent studies of radiological technologists, discussed by Dr. Sigurdson, include large cohorts of female workers, and they may prove highly relevant for breast cancer and malignant melanoma risk estimation, especially for low-dose, fractionated exposures among a healthy Western population. Until recently, the lack of available quantitative exposure information limited the ability to evaluate risks in these studies quantitatively.

Challenges in Quantitative Exposure Assessment

Many of the sources of uncertainty identified in the previous session on diagnostic patient exposures apply to workers exposed to medical radiation sources. Some procedures (e.g. fluoroscopy and mammography) use very low-energy photon exposures to improve contrast in soft tissues. The doses from these exposures are highly dependent on features of the medical examinations, and they are specific to instrumentation as well as the characteristics of patient (*3, 4*).

The incidental nature of the radiation exposure of medical personnel makes exposure assessment in these cohorts similar to that conducted for nuclear worker studies. The recent linkage of cohorts to national databases containing badge dosimetry data should facilitate exposure assessment for these studies from the 1970s onward; however, uncertainties still exist regarding the placement of these badges with respect to protective shielding, their orientation with respect to source, and the adequacy of monitoring for the range of photon energies encountered. A greater challenge is the ability to obtain subject-specific information for exposures occurring during the 1940s and 1950s, when doses were likely highest and individual monitoring did not occur. Dr. Neton's approach to imputation and Dr. Cardarelli's evaluation of subjects' medical records suggest two reasonable exposure assessment alternatives in cohort and case–control studies, respectively.

Medical Exposures in Nuclear Worker Studies

Few studies have evaluated medical exposures in nuclear workers. A study of multiple myeloma among five nuclear worker cohorts indicated no change in the dose–response coefficient for external badge dose after qualitative information about medical X-ray exposures was incorporated (*5*). A sensitivity analysis of doses among Hanford workers also suggests that bias in the dose–response relationship would be minimal if distributed non-differentially with respect to measured exposure (*6*). Dr. Cardarelli's discovery that higher-dose photofluorographic X-ray procedures were used routinely before the 1960s at a uranium processing facility raises questions about how widespread these practices may have been across the DOE complex and whether their use is associated with the recorded occupational dose.

Considerations for Future Evaluation of Medical Radiation Exposures in Occupational Studies

It is anticipated that medical exposures in occupational studies will receive greater attention as techniques improve for reducing sources of bias and uncertainty in studies of low-dose ionizing radiation exposure. The ability to identify interactions (both exposure–environment and gene–exposure–environment) within studies of current radiological technologists and, within nuclear worker studies, to reduce important sources of exposure bias and uncertainty greatly increases the relevance of these studies in low-dose epidemiology and risk assessment of ionizing radiation.

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