I. INTRODUCTION

Objective. The aim of this review is to describe major epidemiological studies of medical irradiation and cancer risk. Two major categories of medical irradiation are reviewed: radiation therapy (RT) for both benign and malignant conditions; and diagnostic radiography, including dental x-rays and prenatal diagnostic procedures. Carcinogenic effects in both adults and children are considered. A section summarizing the most often-studied radiation-induced malignancies concludes the review. We have attempted to include all major epidemiological studies in these areas. Some smaller epidemiological studies as well as reports on clinical series have also been included.

Limitations. Only articles published in English that were readily attainable at a major medical school library in California (US) were reviewed. Studies were largely limited to those that provided relative risk estimates or other pertinant information; studies of survival analysis or lifetime incidence estimation were excluded. No attempts were made to evaluate and critique study methodologies. Results from both positive and negative studies are presented as objectively as possible. No attempts were made to contrast cancer risk against the potential benefits of medical irradiation. Cancer was the only outcome considered. Biological mechanisms by which radiation-induced carcinogenesis occurs are not discussed.

Background. It has been suggested that more data are available on radiation and cancer risk than are available on any other human carcinogen (Darby 1995). Medical irradiation is by far the largest source of exposure to man-made ionizing radiation. Shortly after the discovery of x-rays in 1895 by W.C. Roentgen, it was observed that radiation could be used to treat but could also cause cancer (Despeignes 1896, Freiben 1902). In fact, most existing data on cancer caused by medical irradiation are from cohorts of cancer patients treated with RT. These data are not generalizable to large segments of the population because exposures were at very high levels and delivered at high dose rates. However, a tremendous amount of knowledge on radiation-induced human carcinogenesis has been gained by studying these types of cohorts. Radiation is now an undeniable causal factor in many human cancers. Less is known, however, about low-dose exposures, such as from diagnostic radiography, which are much more relevant to the population in general. Cancer risk from low-dose medical irradiation is far less studied and is somewhat controversial; after all, a single chest x-ray delivers the equivalent of about six days of exposure from natural background radiation (Smart 1997). Nonetheless, some studies of low-dose exposures have observed some interesting findings, and the possibility of increased cancer risk from low-dose diagnostic procedures in light of background radiation exposure levels is one important issue to be resolved. It is noteworthy that a lower threshold, below which radiation-induced cell damage will not occur, has yet to be established (International Commission on Radiological Protection 1990).

The studies contained in this review cover a wide variety of exposure levels and anatomical sites of exposure and cancer occurrence, which is necessitated by the

inconsistency with which radiation acts as a carcinogen. A model does not exist that could be applied to all cancers. Certain anatomical sites, such as bone marrow and the thyroid gland, are highly sensitive to radiation, while others, such as the prostate, appear to be highly resistant to its carcinogenic effects. Several other factors are important determinants of cancer risk, such as age at exposure and latency.

This review is arranged in three major sections: 1) Radiation Therapy, 2) Diagnostic Radiography, and 3) Common Radiation-Induced Malignancies, which serves as an overall summary of the review. Radiation Therapy is subdivided into two subsections, Benign Conditions and Malignant Conditions. Benign conditions reviewed are ankylosing spondylitis, gynecological disorders, breast disorders, head/neck conditions, and hemangioma. Included in Malignant Conditions are Hodgkin's disease; non-Hodgkin's lymphoma; and gynecological, breast, testicular, prostate, and childhood cancers. Diagnostic Radiography has five subsections: special cohorts (chest fluoroscopy and scoliosis), general diagnostic radiography, dental x-rays, prenatal irradiation, and preconception irradiation. Common Radiation-Induced Malignancies reviewed are leukemia; Hodgkin's disease; non-Hodgkin's lymphoma; multiple myeloma; breast cancer; gynecological cancers; cancers of the kidney, ureters, and bladder; colon cancer; sarcomas; thryoid cancer; lung cancer; central nervous system tumors; and skin cancer.

II. RADIATION THERAPY

Benign Conditions

Ankylosing Spondylitis. One of the first medically-irradiated cohorts to be extensively studied was the ankylosing spondylitis (AS) cohort treated between 1935 and 1954 in the United Kingdom (UK). This is considered to be the most important study of late effects of RT for benign disease (Court-Brown 1957, 1965; Boice 1988b). During this time, typical treatment for AS was a course of RT over a two-week period aimed at the mid- and lower spine. Of the 15,577 patients in the AS cohort, 14,556 received at least one course of RT with nearly half of the cohort receiving two or more courses. Mean total body dose for the initial course has been estimated at 1900 rad, with the vertebrae and pelvic bones receiving the highest doses (14,400 rad and 9400 rad, respectively) (Weiss 1994). Lower mean doses were estimated for subsequent courses (mean total body dose = 1500 rad; mean dose to vertebrae and pelvis = 8800 rad and 7400 rad, respectively).

The most recent analysis of the AS cohort covers, on average, 25 years of follow-up (Weiss 1994). When compared to the general UK population, irradiated AS patients experienced significant excess cancer mortality (relative risk [RR] = 1.3, 95% confidence interval [CI] = 1.2,1.4), while unirradiated AS patients did not (RR = 0.8, CI = 0.6,1.0). Specific cancer sites and types for which excess mortality among irradiated AS patients was significant five years after first treatment to end of follow-up are shown in Table 1. For each of these sites/types, mean organ dose was likely to have exceeded 200 rad. In addition, significant excess mortality among irradiated AS

patients was observed for Hodgkin's disease when time since first treatment was limited to 5 to 24.9 years (RR = 1.9, $p < 0.05$) and for thyroid cancer when elapsed time was limited to at least 25 years (RR = 4.4, $p < 0.01$). For all cancers combined excluding leukemia, maximum RR was attained 5 to 9 years after first treatment, with significant decreases in RR over time for non-Hodgkin's lymphoma and for colon, breast, and lung cancer.

Table 1. Sites/types of significant excess cancer mortality 5 or more years after first radiation treatment for ankylosing spondylitis, 25 years average follow-up.[1]

Cancer site or type	RR	(95% CI)
Bone[2]	3.3	(1.6,5.9)
Connective/soft tissue	2.8	(1.4,5.0)
Leukemia	2.7	(2.1,3.5)
Esophagus	1.9	(1.5,2.4)
Non-Hodgkin's lymphoma	1.7	(1.2,2.4)
Pancreas	1.6	(1.3,1.9)
Multiple myeloma	1.6	(1.1,2.5)
Kidney	1.6	(1.1,2.3)
Bladder	1.5	(1.2,1.9)
Prostate	1.4	(1.1,1.7)
Colon	1.3	(1.1,1.6)
Lung	1.2	(1.1,1.3)

[1] (Weiss 1994)

[2] 5 of 7 cases with sufficient detail on their death certificates to discern specific site of bone cancer were cancers of the pelvic bones or lower vertebrae

Analysis by specific leukemia type revealed that increased leukemia risk excluded chronic lymphatic leukemia (CLL) (Weiss 1995). For non-CLL, overall RR among irradiated patients was 3.11 (CI = 2.4,4.1) and was highest 1 to 5 years post-treatment (RR = 11.1, CI = 5.3,21.0) with significant decline thereafter ($p < 0.001$). Whereas risk of solid tumors appeared to relate to high-dose exposure, non-CLL risk was highest among subjects who received total bone marrow doses of 10 to 99 rad (RR = 6.6, CI = 2.2,16.0). This suggests sterilization of potentially leukemic cells in subjects who received substantially higher doses, such as doses received by marrow in the pelvis and mid- to lower spine (about 800 rad).

The lack of risk association for breast cancer is noteworthy because 1) female patients received high ovarian doses (mean of 560 rad), which likely resulted in ovarian inactivation and thus affected occurrence of breast cancer; and 2) previous studies have found that risk of radiation-induced breast cancer is highest when exposure

occurs around the time of puberty (National Research Council 1990), and few AS patients were treated before 20 years of age.

The observed excesses in lung and colon cancer are particularly susceptible to confounding effects in this cohort which must be considered. Smoking histories were not available for the AS patients. However, lung cancer RR among unirradiated patients was 0.8 (CI = 0.5,1.1). Since it is unlikely that irradiated patients differed from unirradiated patients with respect to smoking habits, it does not appear that smoking confounded the elevated lung cancer RR observed for the irradiated patients. AS is associated with ulcerative colitis which, in turn, is associated with colon cancer. Again, the unirradiated patients did not experience excess colon cancer mortality (RR = 0.5, CI = 0.6,1.1) suggesting that the observed increased RR among irradiated patients was not confounded.

Gynecological Disorders. Women treated with RT for benign gynecological disorders (BGD) are another important group for studying late effects of RT for benign disease. The first such cohort identified consisted of 2067 women treated in Scotland between 1940 and 1960. The majority of the cohort (97%) was treated for dysfunctional uterine bleeding (termed „metropathia haemorrhagica" at that time) and was exposed to a mean ovarian dose of 500 rad (Darby 1994). Other sites receiving 500 rad mean dose were the uterus, bladder, and rectum; the vagina, colon, and small intestine received mean doses between 250 and 400 rad. The most recent analysis of this cohort covers, on average, 28 years of follow-up (Darby 1994). Specific cancer sites and types for which excess mortality was significant 5 years after treatment to end of follow-up are shown in Table 2.

Table 2. Sites/types of significant excess cancer mortality 5 or more years after radiation treatment for benign gynecological disorders, Scottish cohort (28 years average follow-up).[1]

Cancer site or type	RR	(95% CI)
Bladder	3.0	(1.8,4.6)
Multiple myeloma	2.6	(1.2,4.9)
Leukemia[2]	2.1	(1.1,3.6)
All pelvic sites[3]	1.5	(1.2,1.7)
Colon	1.4	(1.1,1.9)

[1] (Darby 1994)

[2] two or more years after treatment

[3] ovary, all of uterus, bladder, rectum, colon, and other pelvic sites

Mean active bone marrow dose has been estimated at 130 rad, however this varied substantially by specific site. Sacral and pelvic marrow received the highest mean

doses (550 and 310 rad, respectively), while sites far from the pelvis received very little dose (5 rad for thoracic spine marrow, 0.3 rad for cranial marrow). Although population mortality rates for specific leukemia types were not available, there was no evidence of increased risk of CLL in this cohort. No excess cancer mortality was observed for sites considered lightly irradiated ($\leq$ 4 rad) when these sites were analyzed as a group (RR = 1.1, CI = 0.8,1.4). Ovarian cancer RR was only elevated for ovarian dose 480 to 500 rad and was in fact reduced for doses over 600 rad.

Excess cancer mortality for heavily irradiated sites was generally highest 5 to 9 years post-treatment and, for pelvic sites, remained high 30 years post-treatment, largely due to bladder cancer (RR_{30+} = 4.9, $p < 0.001$). Increased leukemia RR peaked at 10 years post-treatment but did not disappear altogether, even after 30 years. RR was highest 30 years post-treatment for multiple myeloma (RR = 3.7, $p < 0.05$) and Hodgkin's disease (RR = 10.5, $p < 0.05$).

Breast cancer mortality was significantly decreased (RR = 0.5, CI = 0.3,0.8), and the trend relating breast cancer mortality to increasing ovarian dose was significantly negative ($p < 0.001$). Reduced breast cancer risk is an expected result of ovarian inactivation. The reduced RR was greatest for women over age 50 at treatment, suggesting that ovarian irradiation caused a complete cessation of estradiol and progesterone production and/or a reduction in androgen production, neither of which occur with natural menopause (Metcalf 1982, Vermeulen 1976).

A study of United Status (US) women treated in Connecticut with either x-ray or radium implants for BGD between 1935 and 1966 produced similar results (Wagoner 1984), with significant increased cancer risk observed for genital organs (RR = 2.0, $p < 0.01$), urinary organs (RR = 2.0, $p < 0.01$), and lymphatic and hematopoietic system (RR = 2.3, $p < 0.01$). No excess cancer risk was observed for lightly irradiated sites. RR for leukemia and for all hematopoietic sites was highest and only significant for mean marrow dose between 40 and 126 rad (for leukemia, RR = 3.2 [$p < 0.05$]; for hematopoietic sites, RR = 3.0 [$p < 0.05$]). In an expanded study that included additional Connecticut patients plus patients from other New England states followed an average of 25 years, risk was significantly elevated for acute, myelocytic, or monocytic leukemias combined (RR = 1.7, 90% CI = 1.3,2.3); risk was highest within 5 years post-treatment but remained elevated after 30 years (Inskip 1993). There was no clear relationship between risk and radiation dose. Risks were not elevated for CLL, Hodgkin's disease, non-Hodgkin's lymphoma, or multiple myeloma.

A subset of the aforementioned BGD patients from New England states other than Connecticut consisted of over 4000 women treated with only radium implants between 1925 and 1965, followed for an average of 26.5 years (Inskip 1990). Consistent with previous BGD studies, excess cancer mortality was significantly high for the heavily-irradiated pelvic sites (RR = 1.5), which received 100 to 1000 rad, and for leukemia (RR = 2.0). RR was highest after 10 years post-treatment for solid cancers and within the first 9 years for leukemia. Excess mortality from solid cancers remained elevated 30 to 40 years post-treatment. Dose-response relationships were evident for colon and

bladder cancer. Most deaths from cancer of genital organs other than the cervix were from ovarian cancer, and dose-response was positive up to 400 rad. Excess RR of breast cancer mortality at least 5 years post-treatment decreased with increasing ovarian dose, but not significantly.

Cancer predisposition is a potential confounding factor among women with BGD. Ideally, this would be tested by comparing cancer rates among irradiated BGD patients to those in unirradiated BGD patients. Unfortunately this is not possible since the alternative BGD treatment to radiation was hysterectomy with or without oophorectomy. Thus, unirradiated BGD patients were not anatomically comparable to irradiated patients. The fact that increased cancer risk among irradiated BGD patients appears limited to those sites most heavily irradiated, however, tends to refute the possibility of general cancer predisposition.

Breast Disorders. Risk of breast cancer following RT for benign breast conditions has largely been studied in two cohorts: US women treated for acute postpartum mastitis (APM) between 1940 and 1960 in Rochester, New York (Shore 1977, 1986c), and women treated for various benign breast conditions during the 1920s through the 1950s at Radiumhemmet in Stockholm, Sweden (Baral 1977, Mattsson 1993).

In the New York cohort, most subjects were 20 to 40 years of age. Mean dose to irradiated breasts was 377 rads, while mean dose per subject was 247 rads (about two-thirds received RT to only one breast). Sisters of irradiated APM cases, unirradiated APM cases, and sisters of unirradiated APM cases were used as unirradiated controls. Mean follow-up was 29 years. Cases and controls had similar rates of breast cancer. Women in the RT group, however, were significantly more likely than controls to develop breast cancer (RR = 2.2, 90% CI = 1.6,3.0), and RR peaked 15 to 24 years post-treatment. Further, irradiated breasts were more likely than unirradiated breasts to develop breast cancer (RR = 3.2, 90% CI = 2.3,4.3). The relationship between dose and RR was linear at doses less than 700 rad, and RR decreased at higher exposure levels. There was no evidence that greater fractionation reduced risk. Neither age at irradiation nor age at first pregnancy were effect modifiers. No excesses of other cancers in the RT group were reported, although these results were not presented by time since RT.

In Stockholm, breast cancer risk was evaluated for 1416 irradiated women and 2023 women who had benign conditions but were not irradiated. For both treatment groups, fibroadenomatosis was by far the most common presenting condition. Median age at exposure and/or diagnosis in the RT and non-RT groups was 40 and 36 years, respectively. Most irradiated women had only one breast treated (88%). Mean doses were 580 rad to treated and 30 rad to untreated breasts. Compared to Stockholm population rates, breast cancer risk was significantly elevated in irradiated (RR = 3.3, CI = 2.8,3.8) but not unirradiated (RR = 1.0, CI = 0.8,1.2) subjects. Excess risk was confined to the treated breast (RR = 3.6, CI = 2.8,4.6 vs. RR = 1.2, CI = 0.8,1.8 in the untreated breast), which tends to refute the argument that that women given RT for certain benign breast conditions have underlying factors that predispose to breast

cancer. RR peaked at about 25 years post-treatment and decreased thereafter, yet risk was still significantly elevated more than 40 years post-treatment ($p < 0.0001$). A significant decrease in RR with increasing age at exposure was observed ($p = 0.005$). This contrasts with the New York study and may reflect underlying differences in the two cohorts (women in the New York cohort had recently given birth and were generally younger than the Swedish women). There was a clear trend of increasing risk with increasing dose up to 825 rad mean dose followed by decreasing risk at higher levels.

Head and Neck Conditions. Cohorts of subjects treated for tinea capitis (TC), or ringworm of the scalp, have provided large amounts of data and allow a unique assessment of lifetime cancer risk after childhood irradiation. From about 1910 to 1959, the treatment for TC often included scalp irradiation for thorough and painless hair removal to expose the scalp so that an antifungal agent could be applied; this treatment was used worldwide. Two specific cohorts have been followed and extensively studied: children treated in Israel between 1948 and 1960 and children treated at New York University Hospital in the US between 1940 and 1959. The Israeli cohort is by far the larger of the two, consisting of over 10,000 irradiated and a similar number of unirradiated TC patients, as well as over 5000 sibling controls.

The most recent analysis of the Israeli cohort included an average of 33 years of follow-up (Ron 1988a). The average age at irradiation was 7 years. Both groups of unirradiated subjects were combined for analysis. It was estimated that one course of treatment delivered 121 to 139 rad to the upper layer of the brain hemisphere, 95 to 121 rad to the 2.5-cm second layer of the brain hemisphere, and 400 rad to the skull bone marrow. Most of the cohort (91%) received a single course of treatment. Excess cancer mortality among irradiated subjects was entirely attributable to head and neck sites (attributable risk [AR] = 70%) and leukemia (AR = 57%); there were no cases of CLL. RT between the ages of 5 and 9 years produced the highest RRs (head/neck tumor RR = 15.1, leukemia RR = 3.7; $p < 0.05$ for both); RR was highest within the first 5 years post-treatment for leukemia and 15 to 19 years post-treatment for head and neck tumors. RR of head and neck tumors significantly increased with increasing number of treatment courses ($p = 0.001$), while all leukemia cases among irradiated subjects received only one course. Leukemia RR was exceptionally high for Moroccan-born subjects (6 irradiated and 0 unirradiated subjects, lower CI = 2.3), who have a higher incidence of ataxia telangiectasia (AT) than other Israelis. AT patients, i.e. homozygous for the AT gene, have extreme sensitivity to radiation (Gotoff 1967, Morgan 1968, Feigin 1970) and substantial increased risk of leukemia and lymphoma (Taylor 1992). AT carriers, i.e. heterozygous for the AT gene, may also have an increased risk of cancer (Swift 1991).

Most of the increased risk of head and neck tumors was attributable to central nervous system (CNS) tumors (AR = 60%), and the highest RR was for benign nerve sheath tumors (RR = 33.1, CI = 9.4,116.5) (Ron 1988b). RR was 4.8 (CI = 1.9,12.0) for all malignant head and neck tumors, 9.5 (CI = 3.5,25.7) for meningiomas, and 2.6 (CI = 0.8,8.6) for gliomas. RR of brain tumor increased with increasing dose to the brain up to 300 rad and decreased thereafter. Average latency was 21 years for meningiomas

and 14 years for gliomas. The precise locations of tumors were unknown, however most were in the upper cranium which received the highest dose.

A case-control study using subjects who had been diagnosed with intracranial meningioma between 1952 and 1981 was conducted in Israel; case status was determined by exposure to low-dose RT to the head (Soffer 1989). Forty-two cases were identified, all of whom had received RT for TC. Average latency after RT was 37 years. Case meningiomas were significantly more likely to occur in calvarial locations ($p < 0.001$), which received substantially higher doses than the basal regions. Further, cases had a higher proportion of multiple meningiomas, a higher recurrence rate ($p < 0.02$), and more malignant meningiomas ($p < 0.01$).

Two of the head/neck tumors were bone cancers and three were soft tissue sarcomas; RR of bone and connective tissue cancer was 9.0 (CI = 1.3,208.4). These cancers are typically associated with high dose radiation, suggesting a possible extrasensitivity among children to radiation-induced cancers of bone and soft tissue.

Thyroid tumor occurrence was of particular interest because of the well-known radiosensitivity of the thyroid and the rarely-studied effects of low-dose exposures (about 10 rad to the thyroid in TC patients). Risk was significantly increased for both malignant (RR = 4.0, CI = 2.3,7.9) and benign (RR = 2.0, CI = 1.3,3.0) thyroid tumors in the Israeli cohort, with significant linear dose-response for both and a steeper dose-response curve for malignant tumors (Ron 1989). Time since exposure was not a significant effect modifier, but risk was highest for children irradiated at younger ages (< 5 years).

Skin cancer was also more prevalent among irradiated subjects in the Israeli cohort (Ron 1991). For melanoma, RR was 3.0 but was based on only three melanoma cases. For nonmelanoma skin cancer, RR was 4.2 (CI = 2.3,7.6), and nearly all tumors were basal cell (RR for basal cell = 4.9, CI = 2.6,8.9). Basal cell tumors, in general, are associated with lower radiation doses and typically develop on the head or neck (Traenkle 1963). In the RT group, 53% of basal cell tumors arose within the radiation field, compared to 36% in the non-RT group. The trend relating risk to dose was significantly linear ($p < 0.001$). The only significant risk modifier was age at exposure, with risk increasing with decreasing age. In a follow-up case-control study of 38 of the skin cancer cases, significant predictors of skin cancer development were sun exposure (OR = 2.6, CI = 1.1,6.1) and alopecia or dermatitis (OR = 3.4, CI = 1.3,8.8). Regarding the latter, the authors hypothesized that actual radiation dose for the skin cancer cases might have been higher than what was recorded.

The most recently reported data from the New York cohort included 1981 irradiated and 1395 unirradiated TC patients followed for an average of 20 years (Shore 1976). As in the Israeli cohort, the only tumors significantly in excess among the irradiated subjects were of the head and neck. Six irradiated and no unirradiated patients developed thyroid adenomas ($p = 0.05$). Four cases of leukemia (all non-CLL) occurred in the irradiated groups versus one (CLL) in the unirradiated group (Shore 1976). Forty-one

RT subjects developed skin cancers of the head and neck, all basal cell, compared to only three non-RT subjects (Shore 1984). Excess risk first appeared 20 years post-treatment and rose sharply thereafter. The New York cohort was more heterogeneous in complexion than was the Israeli cohort, and all 41 of the head/neck skin cancers in the RT group occurred in white subjects, yet 25% of RT patients were black. Further, a disproportionate number of skin cancers developed near the hairline compared to the larger, hairy surface of the scalp, suggesting an interactive effect with UV radiation.

Several studies have analyzed long-term effects of RT for other benign head and neck conditions. Infants with enlarged thymus glands, at one time thought to be a dangerous condition, were often given RT and have provided confirmatory data on the extreme radiosensitivity of the thyroid gland. A large US cohort from Rochester, New York, treated from 1926 to 1957, consisted of 2657 patients followed for a minimum of 5 years (Shore 1993). Compared to sibling controls, cases had a substantially elevated risk of thyroid cancer (RR = 18.2, CI = 8.5,43.0) with a significant linear dose-response effect. Latency ranged from 6 to 49 years. Median age at exposure was 5 weeks; and median dose to the thyroid was 30 rad. Similar results were observed in a smaller enlarged thymus cohort from Boston consisting of 511 cases (RR of thyroid cancer = 32.8, CI = 4.0,120.0) (Janower 1971). Women from the Rochester cohort also had a significantly increased risk of breast cancer (RR = 3.6, CI = 1.8,7.3) for which a strong linear dose-response effect was demonstrated ($p < 0.0001$) (Hildreth 1989). Mean dose to the breast was estimated at 69 rad; the first breast cancer among irradiated women occurred 28 years post-treatment.

Two cohorts of US children treated for various benign head and neck conditions have also shown that RT to the head and/or neck results in increased risk of developing thyroid cancer (Maxon 1980, Schneider 1993). Mean thyroid dose was estimated at 524 rad in one of these cohorts and 59 rad in the other. Both had average follow-up periods of more than 20 years. In one of the cohorts (Schneider 1993), risk significantly declined with increasing age at exposure, and dose-response was linear up to 200 rad.
A Swedish Cancer Registry study found a significantly increased risk of thyroid cancer among infants irradiated for skin hemangioma between 1920 to 1959 (RR = 2.3, CI = 1.3,3.7) (Lundell 1995). One other early study of children given head/neck RT, most of whom received small doses (150 rad) for prophylactic purposes, found no cancer occurrences using data from follow-up interviews of family members (Conti 1960). This study, however, had serious methodological limitations. Length of follow-up was not explicitly given, but a maximum of 20 years was implied. Perhaps more importantly, if the interview respondent said that the treated subject was presently „in good health," no further questions were asked. Since thyroid cancer in particular has a relatively good prognosis, the interview method is likely to have incorporated a conservative bias into the study results.

In a case-control study of 159 cases from the Connecticut Tumor Registry, the OR for thyroid cancer after head/neck RT was 2.8 (CI = 1.2,6.9) (Ron 1987). Risk was highest when RT occurred at less than 10 years of age and significantly declined with

increasing age at exposure. Excess thyroid cancers occurred only after 20 years post-treatment. After adjusting for other potential factors in thyroid cancer development, such as goiter and nodules, the effect of head/neck RT was essentially unchanged. Results from another case-control study of only female thyroid cancer cases from Washington state in the US are similar: OR for head/neck RT was 16.5 (CI = 8.1,33.5); risk was substantially higher for younger ages at exposure, and mean tumor latency was 22 years (McTiernan 1984).

Excess salivary gland malignancies have also been observed in cohorts irradiated for benign head/neck conditions (Ju 1968, Modan 1974), including both US cohorts of irradiated children cited above (Schneider 1977, Maxon 1981). Among 1922 patients treated at a Chicago, Illinois hospital who were irradiated in the tonsil-nasopharyngeal area, eight salivary gland carcinomas were observed, compared to 0.2 expected (Schneider 1977). Tumors began to appear 5 years post-RT but occurred with increased frequency after 15 years and continued up to 35 years post-RT. Latency decreased with increasing dose and significantly decreased with increasing age at exposure ($p = 0.02$). Among 554 patients treated in the Cincinnati, Ohio area who were classified as having received „probable" RT exposure to the salivary glands, three salivary gland malignancies were observed compared to none in non-RT patients treated for similar conditions and none in RT patients with low probability of having received exposure to the salivary glands (Maxon 1981).

Hemangioma. Effects of radiation exposure early in life have been studied in a large cohort (over 18,000) of infants treated for skin hemangioma in Sweden between 1920 and 1959 (Furst 1988). Eighty-five percent of the cohort was treated with RT; most were less than 1 year of age at treatment. The most common hemangioma sites were the head and neck (45%) and the abdominal (30%) regions. Most of the irradiated patients were treated with radium-226, while smaller proportions received orthovoltage or contact x-ray treatment; the latter delivered negligible doses to adjacent tissues. Absorbed target dose was 600 to 900 rad from radium-226 and 500 to 1000 rad from x-ray treatments.

Significant increased risks for breast cancer (RR = 1.7, CI = 1.3,2.1) and for soft tissue sarcomas (RR = 2.7, CI = 1.2,5.4) were observed among patients treated with radium-226 or orthovoltage x-rays but not among those treated with contact x-rays or no RT at all. Latency ranged from 24 to 59 years for breast cancer and 11 to 54 years for soft tissue sarcomas. The average breast dose was 39 rad,and dose-response was significantly linear ($p < 0.003$) (Lundell 1996). Neither age at exposure nor ovarian dose modified risk of breast cancer. RR of thyroid cancer was also elevated and marginally significant (RR = 1.9, CI = 1.0,3.2); latency ranged from 19 to 35 years. RRs for cancer sites known to be radiosensitive were higher among patients treated more than once. There were no cancers for which risk was significantly high among contact x-ray treated patients or patients not given RT.

Malignant Conditions

Hodgkin's Disease. Intensive curative therapies for Hodgkin's disease (HD) were initiated in the 1960s. HD was associated with increased risk of secondary cancer, primarily skin cancer, before then (Berg 1967); however, the new treatment regimens consisting of chemotherapy (CT) and RT, have increased the secondary cancer risk despite improving the overall cure rate of HD. The first report of secondary cancers in HD patients after CT and/or RT was based on a case series (n = 452) treated at the National Cancer Institute (NCI) in the US, in which risk of secondary cancer was elevated for both CT and RT individually, but was substantially elevated among patients who received combined modality treatment (CMT), i.e. both CT and RT (Canellos 1975). CMT was introduced to achieve complete remission as well as to prevent relapse. Since the NCI report, several other studies have examined the relationship between HD treatment and secondary cancer risk. Results have been mixed and are presented in Table 3.

Among second malignancies developing in HD patients, acute non-lymphocytic leukemia (ANLL) is associated with the highest RR and comprises 91% of all leukemias in HD patients (Kaldor 1990). Incidence peaks four to eight years post-treatment and declines thereafter (Tura 1991). Most studies have found an association with CT but not RT (see Table 3). However, in one French study, extent of RT was the only significant independent predictor of ANLL risk (Andrieu 1990). Also, some investigators have reported an increased ANLL risk with CMT compared to CT alone (Tucker 1988, Cimino 1991, Abrahamsen 1993, Biti 1994).

Seven studies (Baccarani 1980, Nelson 1981, Coleman 1982, Valagussa 1982, Henry-Amar 1983, Boivin 1984, Tester 1984) were pooled to form a cohort of 6513 HD cases to analyze risk of secondary solid tumors (Boivin 1988). Among irradiated subjects, risk was generally unaffected by CT exposure. Results are shown in Table 4; the „radiotherapy" group includes subjects with and without CT. Risk for several cancer sites was significantly increased in the RT group, while none were significantly increased in the CT group. Risk for only two cancers was elevated in both groups: cancer of the respiratory system and non-Hodgkin's lymphoma (NHL). Both of these cancers have been associated with immunosuppression, which accompanies HD (Blattner 1985, Kinlen 1982, Fraumeni 1977).

Table 3. Summary of studies relating second malignancy development to treatment in Hodgkin's disease patients.

Reference	Cohort	Diagnosis Years	# HD Cases	Median Followup	Major Finding(s)
Nelson 1981	Strong Memorial Hospital Rochester, NY	1960-1977	248	5.3 years	CMT almost doubled RR of any second cancer compared to RT alone; RR (CI) = 4.2 (1.5,9.2) for RT alone and 7.6 (2.1,19.4) for CMT
Brusamolino 1982	Pavia, Italy	1970-1979	251	4 years	No patients with RT only developed ANLL compared to 6 with CMT
Glicksman 1982	Cancer and Leukemia Group B	1966-1974	798	3.8 years	CMT increased risk of non-AML cancers only: RR = 1.3 ($p = 0.30$) for CT alone and 3.3 ($p = 0.0008$) for CMT; extent of RT not a modifier
Aisenberg 1983	Massachusetts General Hospital Boston, MA	1967-1981	408	7.5 years	No patients with RT only developed ANLL compared to 8 with CT or CMT
Bartolucci 1983	Southeastern Cancer Study Group (U.S.)	1971-????	209	4.3 years	No patients with RT only developed AML compared to 4 with CT only
Tawil 1983	Montreal, Canada	1969-1977	227	7.2 years	No patients with RT only developed leukemia compared to 4 with CT or CMT
Curtis 1984	U.S. cancer registries	1973-1980	4366	not given	No patients with RT only developed leukemia compared to 5 with CT only or CMT
Pedersen-Bjergaard 1987	Denmark	1970-1981	391	not given	CMT was not a significant ANLL risk factor compared to CT alone; no cases of ANLL occurred in patients given RT only
Tucker 1988	Stanford University Stanford, CA	1968-1985	1507	6.2 years	CMT increased risk of leukemia but not solid tumors or lymphoma; for leukemia, RR = 1.1 (0.0,6.3) for CT alone and 4.4 (2.8,6.7) for CMT; extent of RT was not a modifier
Colman 1988	Royal Marsden Hospital, UK	1963-1978	583	not given	CMT did not produce higher risk of AML than CT alone: RR = 191.0 ($p < 0.001$) for CT alone and 154.9 ($p < 0.001$) for CMT

Table 3. Summary of studies relating second malignancy development to treatment in Hodgkin's disease patients (cont'd).

Reference	Cohort	Diagnosis Years	# HD Cases	Median Followup	Major Finding(s)
Prior 1988	Birmingham and West Midlands, U.K.	1950-1979	2999	7.7 years (mean)	CMT did not produce higher risk of ANLL than CT alone: RR = 37.5 ($p < 0.001$) for CT alone and 25.0 ($p < 0.001$) for CMT; for all cancers combined, RR was significant only for CT alone; for lung cancer, RR was significant only for RT alone (RR = 2.5, $p < 0.01$).
Andrieu 1990	Saint Louis Hospital Paris, France	1972-1980	441	6.5-8 years (mean)	In a Cox regression with sex, age, histology, splenectomy, MOPP, and RT extent as covariates, only RT extent was a significant independent predictor or ANLL ($p < 0.002$)
Kaldor 1990	**Collaborative case/control European/Canadian**	**not given**	**29552**	**N/A**	**CMT did not increase risk of acute and nonlymphocytic leukemias compared to CT alone**
Cimino 1991	Italy	1969-1979	947	10.5 years	No patients with RT only developed leukemia compared to 14 with CT or CMT; risk was higher for CMT than CT
Abrahamsen 1993	Norwegian Radium Hospital	1968-1985	1152	8 years (mean)	CMT increased risk of 1) ANLL: RR = 22.2 (CI = 2.7,80.3) for CT alone and 53.9 (CI = 21.7,111.0) for CMT (there were no ANLL cases among subjects with RT alone); 2) solid tumors: RR = 1.2 (CI = 0.7,1.9) for RT alone, 1.1 (CI = 0.5,2.1) for CT alone, and 2.0 (CI = 1.3,3.0) for CMT; for lung cancer, risk was elevated only among subjects receiving RT alone (RR = 4.3, CI = 1.4,10.1) or CMT (RR = 3.9, CI = 1.3,9.1)
Biti 1994	Florence Radiotherapy Dept. Florence, Italy	1960-1988	1121	> 9 years (mean)	CMT increased risk of 1) acute leukemia: RR = 9.9 ($p = 0.10$) for CT alone and 13.4 ($p = 0.02$) for CMT; 2) solid tumors if RT involved subtotal or total nodal irradiation: RR = 4.3 ($p = 0.01$) for CT alone and 5.8 ($p = 0.001$) for CMT

Table 3 Summary of studies relating second malignancy development to treatment in Hodgkin's disease patients (cont'd).

Reference	Cohort	Diagnosis Years	# HD Cases	Median Followup	Major Finding(s)
van Leeuwen 1994	The Netherlands	1966-1986	1939	9.2 years	CMT was not a significant leukemia risk factor compared to CT alone; increased risks for solid tumors were evident for RT but not CT; highest risk for leukemia, non-Hodgkin's lymphoma, and solid tumor was for subjects who received salvage treatment after initially receiving CMT
Boiven 1995	Collaborative U.S./Canadian	1940-1987	9280	8.1 years	RT, adjusted for CT (and splenectomy), was not a significant leukemia or solid tumor risk factor: RR = 1.2 (CI = 0.6,2.1) for leukemia and 0.9 (CI = 0.6,1.4) for solid tumors

HD patients are often reported to have a predisposition, irrespective of treatment, to developing NHL (Tucker 1988). This has not, however, been a consistent finding, possibly because primary NHL may often be misdiagnosed as HD recurrence. In a cohort of HD patients in the Netherlands, risk of NHL was associated with salvage therapy after initial CMT (van Leeuwen 1994). This study avoided the possible bias of NHL misdiagnosis by reviewing all slides of both the HD and the NHL for patients who developed NHL.

Table 4. Risk of secondary solid tumors after radiotherapy and/or chemotherapy for Hodgkin's Disease.[1]

Cancer Site	Radiotherapy RR (95% CI)	Chemotherapy RR (95% CI)
All sites	2.2 (1.9,2.6)	1.1 (0.5,1.9)
Bones and joints	20.0 (5.5,51.2)	0.0 (0.0,123.0)
Soft tissue	18.3 (9.1,32.8)	0.0 (0.0,46.1)
Non-Hodgkin's lymphoma	8.1 (4.3,13.9)	5.0 (0.1,27.9)
Melanoma	6.7 (3.2,12.3)	0.0 (0.0,18.5)
Buccal cavity and pharynx	4.1 (2.0,7.3)	2.0 (0.1,11.1)
Central nervous system	3.6 (1.2,8.3)	0.0 (0.0,18.5)
Thyroid	2.7 (0.7,6.8)	0.0 (0.0,18.5)
Respiratory system	2.5 (1.6,3.6)	2.6 (0.9,6.1)
Digestive system	1.8 (1.2,2.6)	0.8 (0.1,2.8)
Urinary system	1.5 (0.5,3.2)	1.4 (0.0,8.0)
Female genital system	1.2 (0.5,2.3)	0.0 (0.0,3.7)
Male genital system	1.1 (0.4,2.5)	0.0 (0.0,4.1)
Breast	0.9 (0.4,1.8)	0.0 (0.0,2.8)
Eye/orbit	0.0 (0.0,18.5)	0.0 (0.0,123.0)
Multiple myeloma	0.0 (0.0,5.3)	0.0 (0.0,36.9)

[1] (Boivin 1988)

In the Netherlands cohort, risk of solid tumors was observed for RT but not CT (van Leeuwen 1994). RR increased gradually over the first 15 years post-treatment and was highest after more than 15 years among patients who only received initial RT. In this group, RR after 15 years was 6.9 (CI = 0.8,25.1) for lung cancer and 3.7 (CI = 1.2,8.5) for all other solid tumors. Patients receiving salvage therapy after initial CMT had nearly a twofold risk of solid tumor development (RR = 4.0 [CI = 2.4,6.3] vs. 2.3 [CI = 1.4,3.2] for all others). The proportion of tumors within the irradiated field was highest for melanoma (100%), soft tissue sarcoma (100%), and lung cancer (84%). Approximately 45 to 50% of colorectal, stomach, gynecological, and genitourinary tumors occurred within the irradiated field. In a Cox regression, the only solid tumor for which RT was an independent significant predictor of risk was lung cancer. However, comparisons using the Cox model are restricted to within the patient group. Seventy-

seven percent of the lung cancer cases smoked, a potential confounder yet to be fully evaluated in the context of HD treatment.

A collaborative study involving 14 centers from the US and Canada further explored RT for HD and risk of subsequent solid tumors by analyzing the relationship between RT to specific anatomic sites and risk of subsequent cancer at that same site (Boivin 1995). After at least 10 years of follow-up, significant elevated RRs were observed for cancer of the respiratory system and intrathoracic organs after RT to the thorax (RR = 2.7, CI = 1.1,6.8) and for cancer of the female genitals after RT to the abdomen (RR = 2.4, CI = 1.1,5.4).

In a cohort of HD patients treated at Stanford University in the US, RT alone did not increase risk of solid tumors overall (Tucker 1988). However, sparse numbers prevented analyses of individual tumor sites, and cancers of the stomach, bone, and soft tissue occurred exclusively within the irradiated field. Most solid tumors occurred in the lung; RR of solid tumors increased over time but became elevated earlier than expected (within 5 to 9 years post-treatment), which the authors hypothesized may relate to immunosuppression that accompanies HD. All lung cancer cases were smokers and all received RT.

A European/Canadian collaborative case-control study was conducted to specifically assess relationships between lung cancer risk and several other factors, such as CT, in HD patients (Kaldor 1992). Compared to patients treated with RT alone, those treated with CT alone had a significantly higher risk of lung cancer (RR = 2.1, $p = 0.04$); RR of CMT was not significantly different than that of CT alone. Further, among the RT-only patients, lung cancer risk was not related to radiation dose. This was one of the few studies that was able to evaluate possible modifying effects of smoking; none were noted.

A very important factor to be considered in interpreting studies that analyze risk of solid tumor after HD treatment is that CT is typically administered for more advanced cases of HD. Therefore, CT patients may not survive long enough for solid tumors to appear since solid tumors have a longer latency than ANLL. For example, in the seven-study pooled analysis cited above, patients treated with CT alone accounted for only 10% of the total accumulated person-years. However, the most frequently observed solid tumors have been of the lung, esophageal, stomach, skin, and bone (Tucker 1988), sites likely to be within the radiation treatment field (Prior 1988).

Thyroid disease is the most common complication of HD treatment (Hancock 1991). Thyroid cancer after HD has mostly been associated with RT rather than CT or CMT, with typical latency between 15 and 30 years (Moroff 1986). Most subjects in the Stanford cohort received 4400 rad to the cervical lymph node areas. In this study group, RR of thyroid cancer after RT was 15.6 (CI = 6.3,32.5), based on six cases; two of the six received CMT (Hancock 1991). Risk first became elevated 10 years post-treatment and remained elevated thereafter. Age at exposure did not appear to be an effect modifier. Mantle irradiation for HD delivers an estimated 200 to 600 rad to the

breast (Dershaw 1992). Thus, breast cancer in HD patients is a concern, given the radiosensitiviy of breast tissue. Among 885 female HD patients in the Stanford cohort, followed for an average of 10 years, significantly more breast cancers occurred than predicted by population rates (RR = 4.1, CI = 2.5,5.7) (Hancock 1993); nearly all (97%) of the HD patients received RT, either alone or with CT. Age was a substantial modifier; RR for women irradiated before the age of 15 was 136 and significantly declined with increasing age thereafter ($p < 0.0001$), yet remained significantly elevated for women less than 30 when irradiated. Analysis of latency produced another significant temporal trend, with an RR of 13.6 (CI = 7.9,18.2) after 15 years of followup compared to 2.0 (CI = 1.0,3.5) 5 to 14 years post-treatment (p trend < 0.0001). Risk was higher for CMT (RR = 5.9, CI = 3.2,9.9) than for RT alone (RR = 3.5, CI = 1.8,6.0), though this difference was not significant. Modifying effects of radiation dose could not be assessed since most patients in this cohort received the same dose (4000 to 4500 rad to a mantle field).

The age and latency effects of RT on breast cancer risk were also observed in the US/Canadian collaborative study (Boivin 1995) and in the Netherlands cohort (van Leeuwen 1994). Further supportive data of an RT effect on secondary breast cancer risk after HD was provided by US studies at Memorial Sloan-Kettering in New York (Dershaw 1992) and a cohort consisting of HD patients from the Connecticut Tumor Registry (CTR) and from the NCI SEER program (Curtis 1988). In the Sloan-Kettering case series, 29 women developed breast cancer after HD and all 29 were treated with RT. Average age at onset was 48 years, compared to women treated for primary breast cancer at Sloan-Kettering who presented at an average age of 57 years. In the CTR/NCI cohort, RR of breast cancer at least 10 years post-RT was 4.3 (CI = 2.0,8.2) based on nine breast cancer cases; eight of the nine were less than 40 years of age at time of treatment.

There is some evidence to suggest that breast cancer risk is greatest in tissue that is shielded with a block. In RT for HD, the unshielded midline mantle field typically receives 3600 to 4000 rad, while the central and inferolateral areas receive a much lower dose of 300 to 1200 rad because of shielding (Janjan 1992, Zellmer 1991). In comparisons between women given RT for HD and for primary breast cancer, the HD patients had significantly higher incidences of tumors in the shielded half of the breast than did the primary breast cancer patients.

Non-Hodgkin's Lymphoma. All non-Hodgkin's lymphoma (NHL) patients treated at Duke University in the US from 1970 to 1981 (n = 686) were followed for a median of 5.5 years (Lavey 1990). Risk of ANLL was significantly elevated among subjects who received CMT (RR = 11.9, CI = 3.2,30.6), and risk associated with CT only was very similar (RR = 10.6, CI = 3.4,24.8). Since no ANLL cases occurred in subjects with RT only, CT appears to be the critical risk factor. This is supported by four previous studies in which only one case of ANLL (among 305 NHL cases) was reported (Pedersen-Bjergaard 1985, MacDougall 1981, Gomez 1982, Monfardini 1980). In the Duke study, there was no increased risk for solid tumors overall nor for any single

tumor site in any treatment group. No previous studies analyzed risk of solid tumors by treatment.

Gynecological Cancers. Women who received RT for cervical cancer have been largely studied in relationship to long-term effects of radiation for several reasons (Boice 1985b): they constitute sizeable cohorts, treatment is usually successful, unirradiated cases are available, and organ doses are well-estimated. The International Radiation Study of Cervical Cancer (IRSCC) included over 181,000 (> 96,000 invasive; > 85,000 in situ) cervical cancer patients from 15 cancer registries in eight countries followed for an average of 7.6 years (Boice 1985b); over 80,000 received RT by external beam, brachytherapy, or both for invasive cervical cancer (in situ cervical cancers were mostly treated with surgery only). A typical radiation treatment delivered 2000 to 7000 rad to the middle of the pelvis. Organs in close proximity to the target area, the cervix, generally received doses in the thousands of rads, while organs farther from the cervix received doses in the hundreds. Distant organs received doses in the tens of rads. Table 5 shows relative risks among irradiated women followed for at least 10 years for various sites categorized by distance from the cervix. Overall risk of secondary cancer was similar for all three groups (RT invasive, non-RT invasive, in situ).

Table 5. Relative risk of secondary cancer after radiation treatment for cervical cancer, International Radiation Study of Cervical Cancer (Boice 1985b).

Close Sites		Intermediate Sites		Distant Sites	
Site	RR	Site	RR	Site	RR
Uterine corpus	1.0	Stomach	1.0	Breast	0.7[1]
Ovaries	0.9	Pancreas	1.2	Lung	2.3[1]
Colon	1.1	Kidney	0.8	Thyroid	1.4
Rectum	1.8[1]	Gallbladder	0.8	Buccal cavity	1.7[2]
Small intestine	2.4[2]	Liver	0.9	Salivary gland	1.7
Bladder	3.5[1]			Brain	0.6[2]

[1] $p < 0.001$

[2] $p < 0.05$

In the RT group, excess cancers of close sites only occurred 10 or more years post-treatment, significantly increased with time thereafter ($p < 0.001$), and remained elevated even after 30 years of observation. No such temporal pattern was observed in the non-RT groups. Women under 30 years of age at RT were at higher risk than older women; further, in older women, RR remained constant over time, suggesting that RT at older ages may multiply, rather than interact with, the underlying cancer risk.

Bone marrow near the cervix also received substantial doses; dose to the active marrow (averaged over the entire body) was between 300 and 1500 rad, with distant marrow likely receiving less than 100 rad. Risk of non-CLL was significantly elevated in the RT group 1 to 4 years post-treatment (RR = 2.0, $p < 0.05$) and declined thereafter. To further study the specific dose-response of leukemia incidence after RT for cervical cancer, the IRSCC data were combined with other hospital series and a nested case-control study was performed (Boice 1987). Cases were cervical cancer patients who later developed leukemia at least 1 year after their original diagnoses; controls were cervical cancer patients from the same registry or series as the case who did not develop any secondary cancer. Results showed that leukemia risk after RT peaked at about 400 rad (RR = 2.5, 90% CI = 1.1,6.0) and declined thereafter. The model that best fit the data summed incremental risks to individual active marrow sites and incorporated a cell-killing effect at high doses. Risk was highest for women under age 45 at RT (RR = 4.6, 90% CI = 0.8,28.0) and decreased with increasing age.

For multiple myeloma, a plasma cell malignancy, risk increased significantly with time in the RT group ($p < 0.001$) but did not occur in excess until 10 years post-treatment; this may reflect the long prodromal phase of this cancer (Boice 1985b).

The lack of increased RR for the uterine corpus and ovaries is not surprising since many cervical cancer cases have these organs surgically removed. It has been estimated that 35% of women treated for cervical cancer with RT have hysterectomies and that many of these also have oophorectomies. For both uterine corpus and ovarian cancer, RR among the RT group significantly increased over time ($p < 0.001$ for both). For other genital sites (e.g., vulva, vagina), RR increased with time in the RT group but not significantly. In the non-RT groups, RR was also overall significantly increased but decreased over time. Describing cancers of these sites as secondary in cervical cancer patients is problematic because of the potential for misclassifying metastases and recurrent disease.

Many of the increased RRs among distant sites were for smoking-related cancers and were also elevated in the non-RT groups. Smoking is strongly associated with sexual activity in most cultures and therefore may act as a confounder (Doll 1996, Phillips 1994). Alternatively, there is some evidence to suggest that tobacco-specific N-nitrosamines are an important co-factor in the development of cervical cancer (Prokopczyk 1997). Either way, cervical cancer cases are more likely than the general population to have smoked. Thus, becauses of the high background rates, increased risks of lung and other smoking-related cancers due to RT would be very difficult to detect given the low level of radiation exposure to these sites.

The deficit of breast cancers was not unexpected because of the well-known protective effects of artificial (surgery or radiation) ovarian inactivation. Both younger (< 50 years) and older women had significant breast cancer deficits. Similar results were observed among women given RT for benign gynecological conditions as described previously, although in the cervical cancer cohort, younger (< 50 years) rather than older women had a lower RR. A subsequent case-control study nested within the IRSCC cohort was

conducted to further explore the reduced breast cancer risk in cervical cancer patients (Boice 1989). Separate analyses were done for women with and without intact ovaries; breast cancer risk was reduced only for women with intact ovaries (RR = 0.7, CI = 0.4,1.0), and risk reduction peaked at an ovarian dose of 600 rad.

Although the increased thyroid cancer risk in the RT group was not significant, it was higher than in the non-RT groups ($p = 0.07$). Since the thyroid is highly radiosensitive, it seems possible that the slight excess in thyroid cancers in the RT group was due to RT. The deficit of brain cancers was also observed in the in situ group and was unexplained. However, cervical cancer cases tend to be of lower socioeconomic status (SES) (Logan 1982), and high SES has been associated with brain tumor incidence (Preston-Martin 1989).

A cohort study of radiation effects after cervical cancer treatment conducted in Japan (Arai 1991) compared secondary cancer rates between 7694 subjects treated with irradiation (1969 of whom had post-operative RT) and 4161 subjects treated with surgery alone. RT delivered an estimated minimum dose of 5000 rad to the pelvic organs. Results were very similar to those from the international study. Among sites close to the cervix, significant cancer excesses in the RT but not the surgery group were observed for the bladder (RR = 2.1, $p < 0.05$) and rectum (RR = 1.9, $p < 0.05$) but not the colon (RR = 0.5, $p < 0.05$). There was an overall significant deficit of uterine cancers (RR = 0.5, $p < 0.01$) with excesses appearing 15 years post-treatment (RR = 2.5, $p < 0.10$), paralleling the findings related to uterine corpus cancer in the international study. Fewer than expected ovarian cancers were also observed. The temporal patterns for bladder and rectal cancer were somewhat different from the international study, with excesses occurring 2 to 5 and 5 to 10 years post-treatment, respectively. As in the international study, risk of both cancers increased over time. A significant excess of leukemia (RR = 2.6, $p < 0.01$) was observed in the Japanese study, however specific types were not distinguished from each other. Leukemia risk began 2 to 5 years and peaked 6 to 15 years post-treatment. There were no significant excesses for intermediate sites (e.g., stomach). Among distant sites, lung cancer risk was significantly increased (RR = 1.9, $p < 0.05$) while thyroid cancer risk was moderately elevated (RR = 1.4). Unlike the international study, there were no deficits of breast or brain cancer.

Another Japanese cohort study of 1767 and 1377 cervical cancer cases treated with and without RT, respectively, in Osaka between 1966 and 1970 also found overall significant excesses of bladder (RR = 9.9, $p < 0.01$) and rectal (RR = 4.8, $p < 0.01$) cancer in the RT but not the non-RT group (Hiyama 1985). Excesses in cancers of smoking-related sites (buccal cavity and lung) were elevated in both groups; lung cancer was higher and significantly increased in the RT group (RR = 4.5, $p < 0.01$; in the non-RT group, RR = 1.5). Colon cancer RR was the same in both groups (1.6, $p > 0.05$), and both groups had a deficit of breast cancers. There were no observed leukemias in this cohort.

Leukemia risk after RT was studied using a case-control study nested within an international cohort of 110,000 women from nine cancer registries diagnosed with cancer of the uterine corpus from 1935 to 1985 (Curtis 1994); most (83%) were endometrial cancers. There were 161 and 57 cases of non-CLL and CLL, respectively, matched to uterine corpus cancer cases who did not develop a second cancer by the time of the leukemia diagnosis of the corresponding case. RT for uterine corpus cancer was typically delivered by external beam, brachytherapy, or both. About two-thirds of the study subjects received RT. RT was a significant risk factor for non-CLL (RR = 1.9, CI = 1.3,2.9) but not CLL (RR = 0.9, CI = 0.4,1.9). Among the non-CLL leukemias, the increased risk was largely confined to ANLL (RR = 2.3, CI = 1.4,3.7). Similar findings were observed in a combined analysis of uterine cancer cases from nine US cancer registries (ANLL RR = 4.0, CI = 1.9,7.3) (Curtis 1984). No clear relationship with time since treatment was established, however risk was significantly increased as early as 1 to 4 years post-treatment.

Overall, no definitive dose-response was apparent, and at least twofold risk increases were observed at both low and high doses. However, among women treated with brachytherapy, RR peaked at about 120 rad (RR = 2.6) and declined (but remained elevated) thereafter, while RR slightly increased with dose among women receiving external beam therapy. Thus, the difference in dose-response may relate to differences in mode of therapy: Brachytherapy is administered at low doses and at low dose rates, compared to external beam therapy which is fractionated and given at high dose rates. Also, RR was highly elevated for several women in the external beam group who received substantial doses to the bone marrow in the trunk (RR = 5.5, CI = 2.0,15.1), and the authors hypothesized that this may have influenced the upward trend in risk in this group.

Breast Cancer. There are generally three classes of potential secondary cancer risk following RT for primary breast cancer: 1) a „second primary," i.e. a breast tumor not resulting from metastasis of the original tumor, 2) sarcomas, and 3) other secondary malignancies.

Breast cancer patients, regardless of type of treatment, have a threefold risk of developing a second primary; age is an important factor, with younger patients (< 45 years) having a fivefold risk. Most studies of second primary breast cancer relate only to the contralateral breast because, historically, breast cancer was treated with radical mastectomy combined with RT. Currrently, the typical treatment for early-stage breast cancer is local excision with RT and/or CT. Despite this, dose to the contralateral breast is similar to dose delivered to the contralateral breast in mastectomy patients; thus, earlier studies are relevant to current concerns regarding scatter radiation. Also, the lower dose received by the contralateral breast may be the most comparable to cumulative lifetime exposure from mammography. However, it is important to note the differences in exposure between scatter from RT for breast cancer and a lifetime of mammographies. Breast cancer RT delivers 100 to 300 rad to the contralateral breast over a short period of time (Basco 1985, Benedick 1985, Fraass 1985), compared to 0.5 rad for a single mammogram which accumulates over several years (Storm 1992).

Several case series have been observed to assess risk of a second primary after breast cancer treatment and have consistently reported a lack of an RT effect. In Ontario, Canada, women given prophylactic postoperative RT (for more advanced stages of disease) between 1953 and 1971 were compared to women treated with surgery only during the same time period (McCredie 1975); the two treatment groups did not differ in second primary incidence. This finding was confirmed in two separate analyses of cases treated in Houston, Texas in the US (Schell 1982, Montague 1984).

Clinical trials have also attempted to assess cancer risk associated with RT. In a combined analysis involving data from several different trials, it was noted that overall survival 10 years post-treatment was significantly lower ($p < 0.001$) in breast cancer patients who had received RT compared to those treated with surgery only (Cuzick 1987); however, causes of death were unknown and the validity of pooling these particular trials has been questioned (Levitt 1988). One of the trials included in the combined analysis was the Manchester trial, conducted from 1949 to 1955 in the UK. Breast cancer patients were followed for 34 years and no significant difference in mortality from breast or any other cancer between groups treated with and without RT was observed (Jones 1989). Similar conclusions were reached in the British Cancer Research Campaign Randomized Trial (Haybittle 1989). Both the Manchester and the British trials have been criticized for improper randomization techniques and non-standardized treatment regimens (Levitt 1991).

One of the first case-control studies of second primary breast cancer was conducted in British Columbia, Canada (Basco 1985). Cases were breast cancer patients originally diagnosed between 1946 and 1982 who subsequently developed a second primary ($n = 194$); controls were breast cancer cases who did not develop a second primary. The study found that cases and controls had received similar radiation doses in treatment of their primary breast cancers. Further, second primaries that occurred in the cases were not more likely to develop in the most heavily irradiated areas of the second breast (i.e., the inner half), as might be expected if RT was a causal factor.

Epidemiological data on the role of RT for the original tumor in second cancer risk largely come from two population-based registries: the Connecticut Tumor Registry (the oldest registry in the SEER program of the National Cancer Institute in the US) and the Danish Cancer Registry.

The original analysis of the Connecticut cohort included 6690 patients treated with RT plus surgery and 19,034 patients treated with surgery alone (Hankey 1983); diagnosis years ranged from 1935 to 1975. An increased RR of a second primary among the RT group was mostly confined to the first 5 years of follow-up and thus not likely attributable to RT since latency for radiation-induced breast cancer is thought to be between 5 and 15 years. Increased risk of a second primary associated with RT among subjects with 10 or more years of follow-up was not observed. Further, no clear pattern of risk by age, original tumor stage, or length of follow-up was apparent. In two separate case-control studies nested within the Connecticut cohort, however, some interesting temporal patterns have emerged. In the first of these case-control analyses, second primary risk among the RT group peaked between 5 and 15 years post-

treatment (depending on method of analysis) and declined thereafter (Horn 1987). Such a decline has not been observed in studies of radiation-induced primary breast cancers. In the second case-control analysis, risk was increased for women less than 45 years of age at exposure (RR = 1.6, CI = 1.1,2.4) and for the period 10 to 14 years post-treatment (RR = 2.0, CI = 1.3,3.1) (Boice 1992). Further, dose-response was significant in both of these groups. Risk estimates from this study were comparable to those from a tuberculosis cohort given chest fluoroscopies (Boice 1991a), suggesting that primary breast cancer patients are not at increased risk of radiation-induced breast cancer.

The Danish study, which included 56,237 primary breast cancer cases, also found temporal patterns in second primary risk that differed between RT and non-RT subjects (Storm 1986). For RT subjects, there was a two- to threefold increased risk during the first 20 years post-treatment, rising to a fourfold increase at 30-plus years post-treatment. For the non-RT subjects, risk was highest during the first 14 years post-treatment and declined thereafter (but also increased at 30-plus years post-treatment). Excluding the first 9 years post-treatment, RR was 30% (CI = 10%,40%) greater in the RT group than in the non-RT group (RR = 2.6 vs. 2.0). Also, there was some evidence that RT risk was greater among women 45 to 54 years of age; however, there were few women in the cohort less than 45 years of age. In a subsequent nested case-control study of this cohort, detailed exposure data were ascertained for 691 case-control matched pairs (Storm 1992). In this analysis, RT was not a significant risk factor and no significant temporal patterns were observed. Further, there was no relationship between risk and dose, nor were second primaries more heavily distributed in the area of the breast receiving the highest dose. Adjustment for other potential risk factors such as chemotherapy and family history did not alter the results. The authors hypothesized that the discrepant findings between the cohort and the case-control studies were due to treatment misclassification in the cohort study; specifically, RT was sometimes incorrectly indicated in the cancer registry records, and the case-control but not the cohort study made the necessary corrections.

Analysis of RT and risk of secondary non-breast cancers in the Connecticut cohort included cases diagnosed through 1982 (Harvey 1985a); 11,691 patients given RT for primary breast cancer were compared to 29,418 patients treated with other methods. Both treatment groups had a significantly elevated risk of developing any second cancer, but risk was higher for the RT group (RR = 2.0, CI = 1.9,2.1 vs. RR = 1.5, CI = 1.5,1.6 for the non-RT group) until 20 years post-treatment, at which time RRs for the two groups converged. Other secondary cancers for which overall RR was higher in the RT group are shown in Table 6 (confidence intervals were not reported). Specific areas of irradiation and dosages were not available for this study.

Lung cancer risk was higher in the RT group for two time periods: 10 to 19 years (RR = 2.3 vs. 1.5) and especially 20 to 29 years (RR = 4.8 vs. 1.8) post-treatment. The lung receives a substantial dose in breast cancer RT, however the lung is also a common site of breast cancer metastasis (Kamby 1984). Smoking information was available only for breast cancer cases registered between 1986 and 1989. In a case-control

study using only these cases, lung cancer risk after RT was greatly increased among smokers (OR = 32.7, CI = 6.9,154.0) compared to non-smokers (OR = 3.2, CI = 0.6,17.4) (Neugut 1994). This finding is consistent with studies of smoking and uranium mining (National Research Council 1988). Among Connecticut breast cancer patients, risk among smokers was confined to the ipsilateral lung (OR = 76.6, CI = 8.1,724.0).

Table 6. Secondary non-breast cancers for which irradiated patients had higher relative risk than unirradiated patients, Connecticut Tumor Registry, 1935-1982.[1]

Secondary Cancer	Irradiated RR	Unirradiated RR
Esophagus	1.7	0.7
Kidney	1.9[2]	0.7
Soft tissue sarcoma	4.2[2]	1.8
Non-Hodgkin's lymphoma	1.7[2]	0.7[2]
Chronic lymphocytic leukemia	1.2	0.4[2]
Acute nonlymphocytic leukemia	2.5[2]	1.2

[1] (Harvey 1985a)
[2] $p < 0.05$

Increased risk limited to ANLL among irradiated patients in this cohort is consistent with a radiation effect. In a case-control study using data from nine US cancer registries, including Connecticut, ANLL risk was significantly related to previous irradiation for breast cancer (RR = 3.7, $p < 0.01$); risk of non-ANLL was not elevated (Curtis 1984). In these studies, however, only the treatment first administered was considered; thus, CT was not well controlled. Although ANLL risk is associated with CT, there is evidence to suggest that the observed relationship between RT and ANLL risk in these studies was not confounded. In the study of nine cancer registries, treatment groups of cases were reassigned if their medical records indicated a „suggested" treatment but no record of that treatment existed. For example, a breast cancer case whose records only showed RT but CT was recommended would have been reassigned to the RT + CT group. This revised analysis resulted in essentially unchanged risk estimates. Another case-control study using data from several cohorts, including Connecticut, ascertained detailed treatment data so that joint effects of RT and CT for breast cancer could be specifically assessed (Curtis 1992). ANLL risk after receiving both RT and CT was higher (RR = 17.4, CI = 6.4,47.0) than risk of CT alone (RR = 10.0, CI = 3.9,25.2), and this difference was significant when CT and RT doses were considered ($p = 0.02$). Further, there was a significant trend of increasing risk with increasing RT dose after adjustment for alkylating agents. Average dose to the total bone marrow was 720 rad.

Radiation-induced sarcoma in breast cancer patients was first reported in 1936 (Warren 1936). As of 1995, a total of 81 cases had been reported in the literature (Pendlebury 1995). Doses to the affected areas were not well-reported for the 81 cases but ranged from 1800 to 10,000 rad. In general, osteosarcomas are the most common after RT, and the bone most frequently involved is the scapula; mean latency for RT-induced bone sarcomas is 11 years (Pendlebury 1995). The most common site of RT-induced soft tissue sarcomas is the irradiated conserved breast, and most of these are angiosarcomas (Pendlebury 1995). However, the breast is one of the more frequent sites of angiosarcoma irrespective of RT (Liberman 1992). Lymphedema of the upper extremities is associated with mastectomy and may predispose to lymphangiosarcoma (Stewart 1948). Thus, the soft tissue sarcomas observed after breast cancer RT must be interpreted cautiously. A recent Swedish case-control study, however, observed a significant correlation between RT dose and soft tissue sarcoma occurrence ($p = 0.008$) which remained significant after adjustment for arm edema (Karlsson 1996). RT-induced breast sarcomas have a shorter latency than those occurring in bone (mean = 5.5 years) but have similar latency to other soft tissue sarcomas (mean = 8 years) (Pendlebury 1995). RT-induced sarcomas are rare; it has been suggested that risk is comparable to that of death from surgery and/or anesthesia (Parker 1990). However, they are one of the most fatal complications of RT, which may be an important consideration given the high survival rate for breast cancer patients.

Two smaller US cohorts have also been studied to compare secondary cancer incidence between women treated for primary breast cancer with RT and those treated with surgery alone: breast cancer patients from the University of California at Los Angeles (UCLA) Tumor Registry (Parker 1988) and from the Duke University Medical Center (Lavey 1990). The UCLA cohort (diagnosis years 1975 to 1979) included 836 women treated with RT (with or without surgery) and 648 women treated with surgery alone. No excess second primaries were observed for the RT group. The Duke cohort (diagnosis years 1970 to 1981) included 140 RT subjects and 407 surgery subjects. Risk was not elevated in the RT group for second primaries or any other second malignancy. For these smaller studies, it should be emphasized that few, if any, subjects with long-term follow-up were available.

Testicular Cancer. Like Hodgkin's disease, testicular cancer (TC) is highly curable, but curative treatment may result in increased risk of secondary cancer. Until the 1970s, RT was used in the treatment of both seminomatous and nonseminomatous germ cell cancers and is still the standard treatment for low-stage seminomas (Bokemeyer 1995); specifically, treatment involves orchidectomy with RT to the paraaortic and ipsilateral pelvic nodes with a usual fractionated dose of 2500 rad (Steinfeld 1990). About half of all TCs are seminomas which typically occur in younger men (Vallis 1995). Thus, even though RT doses and treatment fields have been reduced, it may be important to consider the potential for RT-induced second malignancies. Investigation of RT-related malignancies in TC patients is limited by the fact that few are unirradiated. Thus, most studies can only compare cancer rates in TC patients to population rates, which then leaves cancer predisposition unaccounted for. Nonetheless, several studies of treatment-related long-term effects have been undertaken.

The first cohort of TC cases investigated for radiation-induced secondary cancers included all TC patients given RT in Scotland from 1950 through 1969 (Hay 1984). Rates of cancers occurring at least two years after TC diagnosis among 517 subjects were compared to cancer rates in the Scottish population; mean follow-up was 15.4 years. Overall, TC cases had nearly twice as many secondary cancers than expected (RR = 1.9, $p < 0.001$). Cancer risk for sites within the field of high dose volume (RR = 1.9, $p < 0.05$) was similar to risk for sites outside of the high-dose field (RR = 2.0, $p < 0.01$). No excess leukemia was observed. Most of the increased risk of cancers outside the field was due to skin cancers, and the excess was hypothesized by the authors to be attributable to greater likelihood of detection in the TC cohort compared to the general population. Within the field, increased risk was confined to transitional cell carcinomas of the kidney, ureter, and bladder; RR was highest 10 to 14 years post-treatment (RR = 2.9, $p < 0.01$). Without a comparison group consisting of unirradiated TC patients, an RT causal effect for cancers within the field can only be postulated, i.e. TC patients may be predisposed to transitional cell carcinomas in these areas.

Similar findings have been observed in subsequent studies. Among cases in the Connecticut Tumor Registry treated between 1935 and 1982 and followed for an average of 8 years, there was a significant twofold increased risk of a second cancer, but this was observed both in irradiated and unirradiated men (Kleinerman 1985). Leukemia risk was comparable between the RT and non-RT groups. Cancers for which risk was elevated in the RT but not the non-RT group were pancreas (RR = 3.9), kidney (RR = 3.8), bladder (RR = 3.5), and lung (RR = 2.2). Among TC patients treated at Memorial Sloan-Kettering Cancer Center (New York, US), risk of leukemia was elevated but was significantly high only in men treated solely with CT (Redman 1984). In a random sample of cases from 163 US facilities treated in 1973 or 1974, RR of a second cancer was significantly high but did not differ by treatment (Hanks 1992); half of these patients were followed for at least 15 years. One study conducted in Norway did observe an overall increased risk of second cancer associated with RT (RR = 4.1, $p < 0.01$), and, for solid tumors, this risk was highest 5 to 14 years post-treatment (Fossa 1990). In men who received extended RT, significant elevated risks were found for malignant melanoma (RR = 7.7, $p < 0.01$) and cancers of the lung (RR = 7.7, $p < 0.01$) and stomach (RR = 8.3, $p < 0.05$). Among all cases treated at Geneva University between 1951 and 1986, an elevated but non-significant RR was observed for sites within the irradiated field (RR = 2.2, $p = 0.11$); however, there were no unirradiated TC patients available for comparison (Hellbardt 1990).

Prostate Cancer. Prostate cancer, the most common cancer in men, is typically treated either by external beam RT or radical prostatectomy. To date, only one epidemiological study has been conducted to determine long-term cancer risk due to RT (Neugut 1997). Combining data from 10 US population-based cancer registries resulted in 141,761 prostate cases diagnosed from 1973 to 1990, of whom 24.6% had been treated with RT. The *a priori* hypotheses included only four cancers: bladder, rectal, ANLL, and CLL. Of these four, only bladder cancer was significantly elevated in the RT group, and only after 8 years post-treatment (RR = 1.5, CI = 1.1,2.0). During

the relevant time period, RT for prostate cancer was targeted at the pelvis and typically delivered 4500-5000 rad followed by a boost to the prostate. Since then, however, the recommended RT limits exposure to only the prostate and thereby greatly limits dose to the bladder (Peschel 1996).

Childhood Cancers. The Late Effects Study Group (LESG) is an international cohort formed to study second cancers in children (less than 16 years old) previously treated for cancer. In general, the LESG defines radiation-associated solid malignancies as those arising in an irradiated field and radiation-associated leukemias as leukemias developing after RT (Meadows1988). In the most recent review of LESG subjects with second cancers (n = 297), 68% of second cancers were „radiation associated"; the most common of these were sarcomas, leukemias, lymphomas, and thyroid cancers (Robison 1993). It should be noted that leukemias and lymphomas were also commonly associated with CT, as were brain tumors. Most Hodgkin's disease (HD) patients who developed a second cancer were given a combined modality treatment (CMT) of CT and RT. Sixteen of 18 solid tumors in HD patients were radiation-associated.

Case-control studies have been done using the LESG data to further investigate treatment-related second cancer risk. Risk of secondary leukemia, most of which were ANLL, increased with increasing CT but not RT dose. The average active bone marrow radiation dose was 1000 rad. Bone sarcoma, on the other hand, was significantly related to RT for a previous cancer (RR = 2.7, CI = 1.2,7.7), and 83% of bone sarcomas occurred within the irradiated field (Tucker 1987). Risk increased with increasing dose up to 8000 rad but decreased thereafter, and no increased risk was evident for doses less than 1000 rad. Bone sarcoma risk was also independently and significantly related to prior CT (RR = 4.7, CI = 1.0,22.3) and increased with increasing CT dose. Thyroid cancer was related to previous RT but not CT. Most thyroid cancers arose within the irradiated field, and all of these were associated with exposure of at least 100 rad. RR of thyroid cancer after exposure to at least 200 rad was 13.1 ($p < 0.05$), and risk did not decrease with increasing doses.

Second cancers in children previously treated for cancer have also been studied in a similar cohort in the UK, the Childhood Cancer Research Group (Hawkins 1990). Second tumor risk was significantly elevated among subjects treated with neither RT nor CT (RR = 3.9, CI = 1.9,7.1) but was higher among subjects treated with RT alone (RR = 5.6, CI = 3.8,8.1) and was higher still among subjects given CMT (RR = 9.3, CI = 4.5,17.1). Subjects initially treated for Wilms' tumor had an overall eightfold risk of developing a second tumor, compared to a 12-fold risk among those given RT but not CT; six of the seven tumors in this RT subgroup occurred within the irradiated field. Among subjects initially treated for CNS tumors, RR of second tumors was significantly elevated for those given RT only (RR = 6.2, CI = 3.0,11.3) but not for subjects given neither RT nor CT (RR = 1.0, CI = 0.0,5.6); however, the latter group included very few survivors of medulloblastomas and ependymomas since these are almost always treated with RT. Thus, the results related to CNS tumors are likely to be confounded. Another potential problem with this cohort is that CMT subjects were followed for

substantially less time than those treated with RT alone (mean 3.8 versus 9.8 years). In a follow-up study that matched cases of secondary leukemia to controls in which a secondary cancer did not develop (with length of follow-up as one of the matching factors), RR increased significantly with exposure to a particular chemotherapeutic agent (epipodophyllotixins) and with average active bone marrow dose of radiation (Hawkins 1992).

In France, a case-control study was conducted to analyze treatment effects on second cancer risk among childhood cancer patients (de Vathaire 1989). Thirty-two of 634 subjects diagnosed with cancer between 1943 and 1969 developed a second cancer and were matched to controls (children who did not develop a second cancer). A dose-response effect was observed for RT regardless of CT exposure, however this trend was significant ($p < 0.01$) among subjects who were also treated with CT. Compared to children who had not received RT or had received less than 1000 rad of RT to a given anatomical site, patients who received both CT and at least 1000 rad to that site had a 15-fold increased risk of developing a second cancer at that site ($p = 0.05$).

A study involving over 1000 children from eight European cancer centers who developed second cancers after RT for a previous cancer attempted to demonstrate temporal patterns of risk (de Vathaire 1995). However, observed rates were compared to population rates of cancer occurrence; thus, a possible predisposition to second cancers among patients previously diagnosed with cancer could not be controlled analytically. Nonetheless, in this cohort, RR of solid tumor was highest 15 to 19 years post-RT (RR = 8.1, CI = 3.8,15.1) and declined thereafter. In terms of age at exposure, RR was significantly increased for children less than 10 years old at time of RT but was highest for children less than 5 years old (RR = 8.6, CI = 5.3,13.3). Sites at which solid tumors occurred most frequently were the thyroid, breast, brain, soft tissue, and skin.

RT effects after treatment for acute lymphocytic leukemia (ALL) were studied in a cohort of children (n = 981) from five Nordic countries diagnosed between 1958 and 1985 with median follow-up of 10.5 years (Nygaard 1991). Eight subjects developed a second malignancy, all but one at a site previously irradiated; latency ranged from 7.5 to 16.5 years. Compared to non-RT patients, RR of a second cancer among RT patients was elevated (6.7) but non-significant (CI = 0.8,57.7). Compared to population rates, RR among ALL patients given RT was 9.8 (CI = 3.2,22.9) for any cancer and 26.7 (CI = 5.5,78.1) for CNS tumor. Among non-RT patients, these RRs were not elevated. Leukemias and lymphomas as second cancers were excluded to avoid bias due to misclassification of relapses.

A collaborative US/Canadian study also investigated second tumors after ALL treatment in childhood (Neglia 1991). The cohort, consisting of nearly 10,000 childhood ALL cases, was substantially larger than the Nordic cohort but was followed for a shorter length of time (median = 4.7 years). Forty-three patients developed second tumors; in 32 of these patients, the tumor occurred in a previously irradiated field. Twenty-four patients developed CNS tumors, and all 24 had been treated with 1800 to 2400 rad to the cranium. Among RT patients, there was no evidence that

second tumor occurrence had peaked by 15 years, whereas in non-RT patients, no second tumors developed more than 4 years after ALL diagnosis.

Analysis of a cohort of HD survivors from Memorial Sloan-Kettering Cancer Center (New York, US), which also used general population cancer rates as the comparison, found RRs of 8.6 (CI = 2.4,22.1) for all second malignancies and 9.3 (CI = 2.5,23.9) for solid cancers among irradiated children, compared to RRs of 56.3 (CI = 24.3,110.9) and 31.5 (CI = 8.6,80.6) overall and for solid cancers, respectively, among children given CMT (Kushner 1988). Unfortunately, the RT group included children given single-agent CT. No leukemias or bone sarcomas were observed in the RT group.

Radiation-induced cancer after RT for retinoblastoma, a rare pediatric eye tumor, is difficult to assess because of the low incidence and the well-known predisposition for secondary cancer among patients with inherited retinoblastoma (IR), 40% of all retinoblastoma cases (Vogel 1979). However, case reports suggest that RT further increases secondary cancer risk among patients with IR. Two-thirds of second tumors in IR patients develop within the radiation field, and most of these (66-72%) are sarcomas (Abramsom 1984). Both within and outside of the field, the most common sarcoma occurring as a second tumor is osteogenic sarcoma (ibid). Sixty percent of osteogenic sarcomas after RT for IR develop in the orbit and periorbital region (the irradiated area); less than 5% of spontaneous osteogenic sarcomas occur in this region (Regelson 1965, Dahlin 1978). Further, median latency for osteogenic sarcoma after RT in IR patients is 10 years (Schwarz 1988), compared to less than 5 years for spontaneous osteogenic sarcoma occurring in patients with other primary cancers (Pickren 1963). It is thought that IR results from a mutation on chromosome 13 (Yunis 1978), which is also hypothesized to be an important chromosome in development of osteogenic sarcoma (Hansen 1985). Thus, the higher prevalence of osterogenic sarcomas within the irradiated field may indicate a mutation-promoter role for radiation.

The few epidemiologic data available to test the hypothesis of increased second tumor susceptibility among irradiated IR cases are supportive. In a series of 919 IR patients treated at various facilities in New York and Boston in the US, those who received RT had a threefold risk of mortality from second tumors (mostly sarcomas) than non-RT cases (RR = 2.9, CI = 2.2,3.7) (Eng 1993). Another study from the Netherlands of 237 cases given RT for IR found a significantly greater number of secondary cancers developing within the irradiated field than outside the field (p = 0.03) (Moll 1996). In the LESG data, IR patients who developed a second tumor were matched to IR control patients in order to factor out the genetic component in an analysis of treatment effect on bone cancer risk (Tucker 1987); it was found that bone cancer risk among these patients increased with increasing RT dose. Futher, RT effect on second tumor risk was no different in IR patients than in subjects originally treated for other types of tumors.

A recent nested case-control study conducted in France investigated the potential interactive effects of familial cancer predisposition and RT for a previous cancer in children (Kony 1997). Prior to this study, such a hypothesis had only been tested in IR

patients, as referenced above, in which it was observed that second cancer risk after RT was essentially the same as in patients treated for other, non-genetic cancers (Tucker 1987). The French study supported this finding: significant, increased risk from RT remained unchanged after adjustment for familial aggregation. Data from the National Wilms' Tumor Study (NWTS), which includes almost all Wilms' tumor patients in the US, also suggest a lack of an interactive effect between RT and genetic predisposition (Breslow 1988). Fifteen patients of 2438 registered between 1969 and 1982 developed a second malignancy. While four of the 15 had a characteristically genetic form of Wilms' tumor, the same is true of 25% of all NWTS patients. Further, among patients treated with RT, RR for a second cancer was 10.8 (CI = 5.6,18.9), compared to 5.0 (CI = 1.0,14.6) among non-RT patients.

III. DIAGNOSTIC RADIOGRAPHY

Special Cohorts. At one time, treatment for pulmonary tuberculosis (TB) often involved repeated (usually over a five-year period) injections of air into the pleural space or peritoneal cavity followed by inspection using fluoroscopic x-rays. Thus, cohorts of irradiated TB cases are unique in that exposure consisted of several low-dose applications over a period of several years rather than a few high-dose treatments over a shorter period of time, as is the case with RT. Two large cohorts, one Canadian and one from the US, have been studied to determine long-term cancer risk.

The first study of chest fluoroscopy in TB patients involved a Nova Scotian cohort (MacKenzie 1965) which was later combined with additional Canadian cases to form a larger study population (Miller 1989). Over 30,000 female tuberculosis (TB) cases treated in Canada between 1930 and 1952, 26% of which had chest fluoroscopy, were included in the combined analysis. The irradiated group had a significantly increased risk of death from breast cancer compared to the unirradiated group (RR = 1.4, CI = 1.1,1.7). No other cancer resulted in excess deaths among irradiated cases. RR of breast cancer increased linearly with dose, and RR was significantly elevated above 70 rad. Women x-rayed between the ages of 10 and 14 had the highest risk (RR = 4.5, CI = 1.1,41.2), and risk decreased substantially for women who were older when irradiated.

Similar findings were observed in the US study which consisted of nearly 5000 women, about half of whom had chest fluoroscopy, treated for TB from 1925 to 1954 at one of 12 Massachusetts hospitals (Boice 1991a). Mean age at exposure was 26 years, and mean follow-up was 22 years. Dose to the breast averaged 79 rad. Compared to unirradiated patients, irradiated TB patients were significantly more likely to develop breast cancer (RR = 1.4, $p < 0.05$). Risk was first significantly increased for the irradiated group 20 to 29 years post-treatment (RR = 1.5) and remained elevated beyond 50 years of follow-up. Girls irradiated between the ages of 15 and 19 years had the highest RR (2.3, $p < 0.05$); for older ages at exposure, RR declined with increasing age until 30 years of age, after which no differences between irradiated and

unirradiated subjects were noted. The minimum dose interval for which RR was significantly higher in the irradiated group was 100 to 199 rad (RR = 1.7). Dose-response was significantly linear: RRs for patients receiving less than 100, less than 200, less than 300, and 300 or more cumulative rad were 1.2, 1.7, 2.2, and 3.8, respectively.

The entire Massachusetts cohort, i.e. both men and women, were also studied with regard to excess mortality from cancers other than of the breast (Davis 1989). Nearly 14,000 subjects were included and followed an average of 25 years. For all subjects combined, only one cancer site, the esophagus, was associated with significantly increased risk in the irradiated but not the unirradiated group (RR = 2.1, CI = 1.2,3.6), and risk decreased over time. A clear dose-response effect was not demonstrated, although excess risk appeared greatest at a minimum of 50 rad absorbed dose to the esophageal tissue. An important limitation to this finding is that confounding effects of smoking and alcohol could not be evaluated; all cases of esophageal cancer among five-year survivors were smokers. The breast was the only site of significant cancer risk in irradiated but not unirradiated women (detailed above). Among men, bone cancer risk was elevated in both groups, but significantly so among those irradiated (RR = 4.2). Notably, lung cancer risk among all subjects with no record of lung surgery was not elevated (RR = 0.8, CI = 0.6,1.1), and this was true in both smokers and non-smokers; average dose to the lung was 84 rad. The findings related to breast and lung cancer are consistent with animal studies, which have shown that the breast is more susceptible than the lung to the effects of fractionated, low-dose radiation (Ullrich 1987).

Diagnosis of scoliosis requires periodic monitoring of the spine through x-ray examinations, typically anteroposterior and lateral views. This is particularly important during adolescence, when bones are developing at their peak growth rate. A cohort of US women diagnosed with scoliosis in Minnesota from 1935 to 1965 was formed to study breast cancer risk after multiple diagnostic x-rays to the spine (Hoffman 1989). 973 subjects less than 20 years old at diagnosis with no prior history of cancer or RT were included. Average age at scoliosis diagnosis was 12.3 years; average length of follow-up was 25.6 years. Subjects were exposed to an average of 41.5 total x-rays, with an average cumulative breast dose of 12.8 rad. Compared to population rates, risk of breast cancer was elevated overall (RR = 1.8, 90% CI = 1.0,3.0), with a significant increase in risk over time (p trend = 0.02); excess breast cancers first appeared 15 years after diagnosis, and RR after 30 years was 2.4 (90% CI = 0.9,5.0). A dose-response effect was also demonstrated, both by number of total x-rays and cumulative dose to the breast. Among women who received 20 or more total rad to the breast, RR of breast cancer was 3.4 (90% CI = 1.2,7.8). Independent effects of time since exposure and total dose were not evaluated. Age at first exposure was not an effect modifier.

Currently, scoliosis patients are exposed to lower cumulative dose than were the subjects in this cohort. Several modifications have resulted in lower radiation exposure levels: fewer x-rays are taken; x-ray beam collimation and filtration has been improved

to reduce excess radiation; intensifying screens have reduced the amount of necessary exposure required to produce interpretable radiographs; and breast exposure has been reduced by breast shields and by different patient positioning. Thus, while the Minnesota scoliosis cohort provided valuable data on breast cancer risk after relatively low doses of radiation exposure, results are not entirely generalizable to currently diagnosed scoliosis patients.

General Diagnostic Radiography. Most of the population exposure from man-made sources of ionizing radiation is from diagnostic x-rays (National Research Council 1980). It has been suggested that a large percentage (more than 50% in the US and 20% in the UK) of all procedures performed are unnecessary because of 1) the low probability that they will provide useful clinical information (such as employment-related chest screenings), and 2) a substantial number of exams are repeats of previous exams for which original films were misplaced or of poor quality (Abrams 1979, National Radiological Protection Board 1990). Thus, it is essential to evaluate possible adverse health effects, particulary cancer risk, associated with diagnostic radiography. Most of what is known about radiation-induced carcinogenesis is from studies of much higher exposures and dose rates, such as in A-bomb survivors and RT cohorts, than is associated with diagnostic radiography. Extrapolation from these „high dose" studies to estimate risk from low-dose exposure is probably not valid, providing further impetus for epidemiological study of diagnostic radiography and cancer risk.

Studies examining long-term effects of diagnostic x-rays on cancer risk are subject to some noteworthy methodological obstacles. First, exposure ascertainment is problematic. Unlike therapeutic radiation, diagnostic x-rays are a relatively common exposure and are less likely to be accurately recalled. Therefore, interview data are vulnerable to extensive misclassification. Further, misclassification bias is a concern since cancer cases may be more thorough in their recall of prior radiation exposure in their attempts to explain their cancer diagnoses. Ascertainment of exposure history through medical records alleviates some of the concern associated with retrospective data but is far from ideal. Ascertainment bias may still exist if, for example, medical records of cancer cases are more complete or more readily attainable than records of controls (Boice 1979). Also, data on medical providers are often collected from case and control respondents and are thus subject to the same biases as if subjects were providing exposure data. A second problem with studies of cancer risk and diagnostic x-rays is the potential confounding effect of x-ray exposure due to early cancer symptoms. Epidemiological studies attempt to deal with this by examining risk by various latency periods. However, when latency of radiation-induced cancer is short, as in leukemia, this may not be possible. Finally, individual dose from a given diagnostic procedure varies widely, depending on such factors as the number of films taken, the exposure field, whether or not fluoroscopy was used, and the duration of fluoroscopy.

Most studies of cancer risk from diagnostic x-rays have focused on leukemia. In the US, incidence rates for all types of leukemia combined have remained relatively stable over time, but rates of myeloid and monocytic leukemia have increased (Devesa 1987).

Despite successful efforts to reduce radiation exposure from specific medical radiographic procedures, the annual per capita mean active bone marrow dose among US adults has also increased because diagnostic procedures are ordered more frequently than in past decades and some procedures have been introduced that result in higher bone marrow exposure (e.g., CT scans) (Public Health Service 1973, 1986). Most relevant to leukemia risk are x-rays to the trunk, which contains nearly 90% of all active bone marrow in adults (Martin 1958).

One of the first studies to investigate potential cancer risk from diagnostic x-rays was conducted in the UK and focused on adult leukemia (Stewart 1962). Leukemias were divided into two groups: the „L" series, consisting of lymphatic leukemias and lymphosarcomas, and the „M" series, consisting of myeloid, monocytic, and all other leukemias. Acute and chronic leukemias were not differentiated in the analyses presented. In this study, M series cases had an excess number of diagnostic x-rays to the trunk but not to peripheral anatomical sites during each of the 5 years before diagnosis. Illnesses reported in excess among leukemia cases compared to controls who had been diagnosed with other cancers were responsible for only a small proportion of trunk x-rays; also, for each reason given for trunk x-rays, M series cases had more exposures than both cancer and healthy controls. Risk appeared greatest for a 3- to 4-year latency. One drawback to this early study is that only one-eighth of all leukemia cases that occurred during the specified time period (1958-1960) were ascertained.

Another early study from New Zealand was able to include a substantial proportion (87%) of leukemia cases diagnosed between 1958 and 1961 due to the partial use of proxy respondents (Gunz 1964). CML cases were significantly more likely to have had high-dose diagnostic x-rays. Dose distribution among these cases was highly skewed, which may suggest that risk is associated only with very high exposure from diagnostic x-rays. No other leukemia group was associated with excess exposure from diagnostic procedures, although ALL and AML were considered as a single group. Excess exposure among acute leukemia cases was confined to adults.

The Tri-State Leukemia Study in the US included adult leukemia cases from selected counties from New York, Minnesota, and Maryland diagnosed between 1959 and 1962 who were matched to population controls to assess risk from diagnostic x-rays (Gibson 1972). Exposure data were ascertained by either direct or proxy interviews and then confirmed through medical records. Exposure histories of almost all acute (92%) and most chronic leukemia (66%) cases were collected by proxy interviews. Excess risk for any leukemia type was not observed among females, a finding most likely related to inaccurate reporting by male spouses as proxies (Pickle 1983). Among males, risk was significantly related to dose among AML and CML cases, particularly for diagnostic x-rays to the trunk; it was calculated that 9% of AML/CML cases in males is attributable to exposure to more than 10 diagnostic films. Excess exposure was evident in each of the four 5-year intervals in the 20 years before diagnosis. Risk of CLL was significantly increased for exposure to more than 20 films to the trunk, but this finding was not consistent across all age groups. Risk was not increased for ALL.

Risk was significantly increased among children in the Tri-State Leukemia Study who were x-rayed at more than one site (RR = 2.1, p = 0.003), however a dose-response with number of films was lacking (Graham 1966). In Shanghai, acute leukemia risk was significantly elevated among children exposed to postnatal x-rays (OR = 1.6, CI = 1.0,2.6), and dose-response relating risk to number of exams was marginally significant (p = 0.07) (Shu 1994a).

A US study from the Mayo Clinic in Minnesota found no association between leukemia risk and diagnostic radiography (Linos 1980). An advantage in this study was that reliance on recall was not necessary since most of the community population received their medical care from the Mayo Clinic. Thus, it was argued by the authors, the observed lack of an association was more valid than increased cancer risks observed in previous studies. However, using controls from patient registers of health care facilities may have introduced another type of bias into the results, that of a comparison group that may have been more likely to have been exposed than the population in general.

A US population-based case-control study conducted in Los Angeles County investigated the role of diagnostic x-rays in risk of CML (Preston-Martin 1989). 137 cases, diagnosed between 1979 and 1985, were individually matched to neighborhood controls. Data on diagnostic x-ray exposure were ascertained by personal interview. Eleven cases and one control had had five or more back x-rays 3 to 20 years before diagnosis (OR = 12.0, p < 0.01). A single x-ray of the lumbar region delivers an estimated 0.35 rad to the active bone marrow (Schleien 1978). For all diagnostic x-rays combined, the period 6 to 10 years before diagnosis carried the greatest risk; it was estimated that 17% of all CML cases were attributable to x-rays during this period, and that 23% of CML cases were attributable to x-rays taken 3 to 20 years before diagnosis. The primary concern in interpreting these findings is the potential for confounding from symptoms related to CML that would necessitate diagnostic x-rays. Bone pain can be a symptom of CML, although fatigue, pallor, sweating and low-grade fever are the most commonly reported symptoms, which become persistent and progressively worse 2 to 6 months before diagnosis (Rundles 1977). In analyses that included the year and the 2 years prior to diagnosis, cases had more x-rays for ill-defined reasons than did controls. However, cases and controls were comparable with regard to this category of x-rays when these years just prior to diagnosis were excluded. Another concern with interview data is the potential for recall bias. This study used a highly structured, scripted questionnaire to minimize recall bias as much as possible; however, since the data were not validated through medical records, recall bias cannot be excluded as an influencing factor on the study results.

A case-control study using health maintenance organization (HMO) data was conducted to evaluate the effect of diagnostic x-rays on risk of leukemia, lymphoma, and multiple myeloma (Boice 1991b). The use of HMO data essentially eliminates recall bias but prevents evaluation of lifetime exposure and may result in a control series with higher exposure than the general population, as discussed above. 565

cases of leukemia, 318 cases of non-Hodgkin's lymphoma, and 208 cases of multiple myeloma from two US HMO facilities (one in Oregon, one in California) diagnosed between 1959 and 1979 were matched to 1390 controls. Analyses of leukemia risk discriminated between CLL and non-CLL. Cases less than 15 years old at diagnosis were excluded, as were cases previously treated with RT or CT. Diagnostic x-ray data for each subject were extracted from the HMO medical records. Overall, no risk associations with diagnostic x-rays were observed. However, among women from the California HMO, RR of multiple myeloma considering a 10-year lag between any x-ray exposure and diagnosis was 1.5 with a borderline significant dose-response ($p = 0.05$). Dose-response analyses were based on „exposure scores," a categorical assignment defined by total number of diagnostic procedures, which relies on the assumption that number of procedures equates to cumulative bone marrow dose.

Most recently, a case-control study from Japan found no association between diagnostic x-rays and leukemia; leukemias specifically studied were AML, ALL, and CLL (Yuasa 1997). Controls were hospital-based and exposures were ascertained by self-administered interviews.

Data from the Connecticut Tumor Registry were used to evaluate risk of thyroid cancer from diagnostic radiography (Ron 1987). 251 thyroid cancer cases, diagnosed between 1978 and 1980, were matched to controls from the general population. Exposure information was collected by personal interview. There were no significant associations between increased risk and specific diagnostic procedures, however a dose-response effect for number of thyroid scans was apparent. Compared to subjects who never had a thyroid scan, ORs for subjects receiving one and more than one scan were 1.6 and 2.5, respectively (p trend = 0.10). OR for ever having had a mammogram was 1.8 (CI = 0.9,3.6).

A Swedish case-control study that avoided many of the pitfalls of diagnostic radiography exposure ascertainment did not support the Connecticut finding (Inskip 1995). The public health care system in Sweden makes medical care accessible to all citizens, regardless of socioeconomic status. 95% of all diagnostic procedures were performed at facilities that were part of the public health care system (Leitz 1990), and rosters of all procedures were stored at and readily available from these facilities. Underascertainment was most likely for mammograms and x-rays of the chest and extremities. Procedures performed during the 5 years before diagnosis were excluded since, based on prior knowledge, radiation exposure during this period would most likely not be related to thyroid cancer. Among 484 thyroid cancer cases matched to population controls, disease status was not related to history of x-rays to areas nearest the thyroid (neck, upper spine, skull, face, chest, and upper gastrointestinal tract). Cases were not more likely to have had x-rays in earlier calendar years, when doses would have been higher, nor were cases more likely to have been x-rayed before age 20 (although a small proportion of x-rays had been administered to children). Trend relating RR to cumulative dose was non-significant. Thyroid scans were excluded because these were not documented in radiology records, however another Swedish study found no association between scans and thyroid cancer (Hall 1996). The authors

hypothesized that thyroid doses resulting from diagnostic radiography may not be high enough to induce cancer because most previous studies of radiation-induced thyroid cancer involved much higher doses. Also, very few diagnostic procedures expose the thyroid to radiation, whereas active bone marrow, for example, is exposed to varying degrees by many different procedures.

Dental Radiography. In the US, dental x-rays are the most common form of diagnostic radiography (U.S. Department of Health, Education, and Welfare 1973) and involve radiation exposure to body parts other than teeth. This was particularly the case before the 1960s, when faster film speeds and narrower fields reduced radiation exposures (Richards 1981). For example, in the 1940s and 1950s, 100 to 300 rad was absorbed by the skin during a full-mouth series, which typically involves 16 to 20 x-rays (Nolan 1953); further, in regions where radiation lines intersect, such as in the brain in full-mouth and panoramic x-rays, higher exposures result.

The first and most detailed case-control studies to examine brain tumor risk in relationship to dental radiography were conducted in the US in Los Angeles County. The first of these related specifically to adult meningioma and included 185 women diagnosed between 1972 and 1975 and 120 men diagnosed between 1972 and 1979 (Preston-Martin 1980, 1983); cases were neighborhood-matched to controls, and exposure data were ascertained by personal interview. In the female study, cases and controls were comparable on ever having had a full-mouth x-ray. However, cases were more likely to have had relatively frequent (more than five) full-mouth x-rays than controls (OR = 1.6, $p = 0.14$) and were four times more likely to have had their first full-mouth x-ray before the age of 20 ($p < 0.01$). Further, tumor location was increasingly likely to be in the tentorial or subtentorial region with increasing frequency of full-mouth x-ray (p trend = 0.01); these regions are likely to be within the x-ray beam during full-mouth x-rays. A significant association was also found for women who had had their first full-mouth x-ray before 1945 (OR = 2.1, $p = 0.03$), when doses were considerably higher than in more recent decades. Independent effects of age and year of first exposure could not be evaluated. In Los Angeles County men, meningioma risk was highest among subjects first exposed before 1945 who had frequent (five or more) full-mouth x-rays (OR = 2.7, one-sided p-value = 0.11). Among the subgroup with exposure before 1945, OR for tentorial or subtentorial tumor location was 3.1, compared to an OR of 1.3 for other tumor locations (CIs unavailable). A later study of adult brain tumor in Los Angeles County included 202 glioma and 70 meningioma cases diagnosed between 1980 and 1984 and neighborhood matched to similar controls (Preston-Martin 1989). Trends of increasing risk with increasing frequency of full-mouth x-rays after age 25 were evident for both glioma (p trend = 0.04) and meningioma (p trend = 0.06). Very few subjects in this study had full-mouth x-rays before age 25, and effect of calendar year of exposure was not evaluable. A limitation to these studies is the probable poor recall of dental x-rays, though it seems unlikely that controls would recall fewer x-rays than cases. Thus, any misclassification would conservatively bias risk estimates.

A case-control study of adult brain tumor in Australia also evaluated risk of dental x-rays as well as amalgam fillings (Ryan 1992a). Cases were diagnosed between 1987 and 1990 and frequency-matched to controls selected from the general population. Significant, unexplained protective effects were observed for amalgam fillings and, particulary for glioma, for ever having had a dental x-ray. Considering that these findings persisted after restricting analyses to non-proxy, good quality interviews and after adjusting for several potential confounders (e.g., socioeconomic status), an unknown bias is a likely explanation for these peculiar results. Nonetheless, among non-proxy subjects with good quality interviews, RR of ever having had a full-mouth or panoramic x-ray was 2.7 (CI = 0.9,8.7) for glioma; no risk association was observed for meningioma. The investigators did not evaluate frequency or calendar year of full-mouth (or panoramic) x-rays, nor was any attempt made to assess tumor location in relationship to regions likely to have been exposed during full-mouth x-rays, i.e. at or below the tentorium.

For pediatric brain tumor, risk has also been shown to significantly relate to frequency of full-mouth x-rays. In a case-control study of 68 Los Angeles County cases diagnosed at age 15 or older from 1972 to 1977 in which exposure data were obtained by personal interviews with mothers, OR for having had at least five full-mouth x-rays starting at least 10 years before diagnosis was 2.5 (p = 0.04) (Preston-Martin 1982). During the period that these subjects had their first full-mouth x-ray (before 1964), a full-mouth series delivered a total exposure of approximately 20 rad (U.S. Department of Health, Education, and Welfare 1973).

The only known risk factor for salivary gland cancer in humans is ionizing radiation. About 85% of cumulative parotid dose from diagnostic radiography comes from dental x-rays; the parotid gland may be in the primary beam when periapical or bitewing x-rays of the ipsilateral molars are taken, will likely be in the beam when anterior contralateral x-rays are taken, and will always be in the beam when panoramic x-rays are taken (Preston-Martin 1988). A case-control study of salivary gland risk and medical radiography conducted in Los Angeles County investigated exposure from dental x-rays as well as other medical radiography to the head and neck (ibid). 414 cases diagnosed between 1976 and 1984 were neighborhood-matched to controls. Exposure data were ascertained through personal interview. Dose estimates were based on published dosimetry surveys. Thirty-seven percent of all subjects were exposed to at least 5 rad to the parotid gland. Dose-response effects were demonstrated for salivary gland cancer risk and cumulative parotid dose 1) from all sources (p trend = 0.002); 2) from diagnostic radiography, i.e. including dental x-rays but excluding RT to the head or neck (p trend = 0.05); 3) from dental x-rays (p trend not given); and 4) from diagnostic radiography excluding dental x-rays (p trend not given). In a multivariate analysis, three factors emerged as independent predictors of risk: prior RT to the head or neck (RR = 5.8, p = 0.002, attributable risk [AR] = 14%), cumulative parotid dose from diagnostic radiography (including dental x-rays) (p = 0.04, AR = 15%), and prior cancer (RR = 11.7, p = 0.001, AR = 14%). In a validation component of this study, recall of dental x-rays during the most recent 20 years was found to be quite good. 76% of

subjects accurately reported dental visits within one visit and, most importantly, differential recall was non-existent (Preston-Martin 1985).

Prenatal Radiography. Ultrasound has essentially replaced radiography in obstetric applications, largely because of studies of prenatal radiography and childhood cancer risk. Although the question of a causal effect was not and perhaps never will be resolved, prenatal diagnostic procedures were changed based on the conservative assumption that there was a causal relationship and because radiography did not offer any benefit over the use of ultrasound. Early studies, then, of prenatal irradiation are perhaps less relevant than they were in the past. However, because abdominal x-rays may still be indicated for non-obstetric reasons in pregnant women, findings from these studies still have limited relevance. There is considerable uncertainty as to the amount of exposure delivered in prenatal radiography, but it has been estimated at a maximum of 1 to 2 rad (Ayres 1985).

The first and the largest case-control study of risk of childhood cancer from prenatal exposure to medical radiography was the Oxford Survey of Childhood Cancer (OSCC), consisting of 14,500 cases born between 1940 and 1978 in England, Scotland, or Wales individually matched to an equal number of controls (Stewart 1956, 1958). The OSCC analyzed data was originally collected because of concerns during the 1950s about the potential for fetal genetic damage from prenatal x-rays. In fact, the primary risk of prenatal x-rays was not to the fetus but to the child, and that was an increased risk of childhood cancer. Mothers were interviewed on abdominal and pelvic x-rays during their pregnancies, and interview data were validated against medical records where possible. Approximately 15% of all x-rays were pelvimetries. ORs and number of films per examination by birth cohort are shown in Table 7 (Mole 1990).

Table 7. Prenatal x-rays and risk of childhood cancer, Oxford Survey of Childhood Cancer,[1] 1940-1976.

Birth Cohort	Ever Exposed OR (90% CI)	Number Films Per Exam Cases	Controls
1940-1947	1.9 (1.4,2.6)	2.6	1.7
1948-1957	1.6 (1.4,1.8)	2.2	2.1
1958-1965	1.2 (1.1,1.3)	1.6	1.4
1966-1969	1.2 (1.0,1.5)	1.3	1.5
1970-1973	1.5 (1.2,2.0)	1.2	1.4
1974-1976	1.6 (1.0,2.8)	1.1	1.5

[1] Mole 1990

As can be seen in Table 7, number of films per examination generally decreased over time, but this had little effect on risk. The most important risk factor was whether or not exposure occurred rather than a dose-response effect. Risk appeared to decrease with increasing time since exposure (not shown) although, for the earlier cohorts, remained

significantly elevated after 15 years. The abrupt decrease in risk after 1958 was likely due to a decrease in prenatal x-raying rates during that time because of heightened concern for fetal genetic damage. For the 1954-1957 cohort, 19.1% of case and 12.2% of control mothers had been x-rayed, compared to 12% of case and 9.5% of control mothers in the 1958-1961 cohort. By 1970, however, x-raying rates had risen to levels above the pre-1958 rates (20.9% of case and 15.5% of control mothers).

In a subanalysis including only subjects for whom prenatal x-rays were confirmed through medical records (58%, not necessarily matched pairs), risk was elevated only for exposure during the first trimester (OR = 2.7, $p < 0.05$) and, as suggested by the data in Table 7, there was no relationship between risk and number of films per exam. Nearly all first-trimester x-rays were for non-obstetric purposes, and about 25% of non-obstetric pelvic or abdominal x-rays involve fluoroscopy and are therefore likely to result in substantially higher doses to the fetus.

Several potential confounding effects were evaluated in the OSCC data, such as drugs and maternal illness, and results were essentially unchanged. Twin studies of prenatal x-rays are important since mothers suspected of carrying twins are likely to be x-rayed, but not for conditions that may indicate a predisposition to subsequent cancer development in the child. In the OSCC data, there was no difference in cancer risk between twins and singletons (Mole 1974).

Several studies of prenatal x-rays and childhood cancer risk were launched as a result of the OSCC findings first published in 1956 (Stewart 1956). The first US study to assess risk of prenatal x-rays (MacMahon 1962, Monson 1984) included 1342 singleton children born between 1947 and 1960 in the New England and mid-Atlantic states who died of cancer before age 20. A 1% sample of singleton children born in the same hospitals was used as the comparison group. Exposure was defined as pelvimetry, flat-plate abdominal x-rays, upper or lower gastrointestinal series, intravenous pyelogram, or gallbladder series. Among younger children (less than 10 years old), ORs for death from leukemia and from solid tumors were 1.5 (CI = 1.2,2.0) and 1.3 (CI = 1.0,1.7), respectively; these were not statistically different from each other. Excess risk was not observed among older children. Elevated risk was limited to birth years 1947 to 1957 for leukemia and birth years 1951 to 1954 for solid tumors. For leukemia, exposure during the third trimester appeared most critical in terms of increased risk, whereas exposure during the first and second trimesters carried the highest risk for solid tumors. Actual exposure levels, including number of films taken, were not available. However, increased leukemia risk was most associated with pelvimetry; no clear pattern was observed for solid tumors. Pelvimetry results in slightly more than a twofold whole body dose to the fetus than does an obstetric abdominal x-ray (1.1 versus 0.5 rad) (Mole 1990).

The Tri-State Leukemia Study included 319 children diagnosed with leukemia between 1959 and 1962 in the designated geographical regions who were matched to 884 controls (Graham 1966). RR of leukemia in offspring was 1.4 (CIs not provided) for radiography to the abdomen and 2.0 specifically for pelvimetry. Risk was significant for

the combined effect of *in utero* exposure together with maternal exposure before conception (RR = 1.9, p = 0.006). This was particularly evident for second or later pregnancies, and consideration for prior miscarriages or stillbirths did not alter the finding.

A Chinese case-control study observed an elevated risk of childhood cancer for prenatal abdominal x-rays but was based on very small numbers (OR = 2.1, CI = 0.7,7.0) (Shu 1994a). A US case-control study from the Childrens Cancer Group found an elevated risk associated with prenatal x-rays for AML (OR = 1.6, CI = 0.8,3.1) but not ALL (Shu 1994b). However, AML risk was slightly lower when exposure was limited to lower abdominal x-rays or pelvimetry (OR = 1.5, CI = 0.2,9.5).

Another US study analyzed prenatal x-ray risk using twin data, with cases identified by the Connecticut Tumor Registry that were born between 1930 and 1969 and diagnosed before the age of 16 years (Harvey 1985b). A total of 31 twins with childhood cancer were included, matched to 109 twin controls. Exposure data were ascertained through medical records. Exposure was defined as any x-ray of the abdominal region. Fetal dose ranged from 0.16 to 4 rad, with an average dose of 1 rad. Forty-two percent of all x-rays were pelvimetries, and all exposures occurred during the third trimester. OR for childhood cancer, adjusted for birth weight, was 2.4 (CI = 1.0,5.9). Adjusted ORs for leukemia and solid tumors were 1.6 (CI = 0.4,6.8) and 3.2 (CI = 0.9,10.7), respectively. Birth weight, the only covariate that appreciably affected risk estimates, was positively correlated with cancer and negatively correlated with x-ray exposure. Age at diagnosis was not an effect modifier.

A twin study was also conducted in Sweden based on all twin births from 1936 to 1967 (Rodvall 1990). Of 83,316 twins, 95 childhood cancer cases were included in the analysis and matched to control twins. Risk was not significant when all diagnostic prenatal x-rays were considered, nor when only abdominal x-rays were considered. However, in general, RR for abdominal x-rays was higher than for all x-rays combined (RR = 1.4, CI = 0.8,2.5 versus RR = 1.2, CI = 0.7,2.1). This discrepancy was limited to leukemia (RR = 1.7, CI = 0.7,4.1 versus RR = 1.0, CI = 0.4,2.6) and central nervous system tumors (RR = 1.5, CI = 0.5,4.2 versus RR = 1.1, CI = 0.4,2.6). Also, RR was higher for earlier birth years when exposures were likely to be higher (RR for 1936-1959 = 1.6, CI = 0.8,3.4 versus RR for 1960-1967 = 1.1, CI = 0.4,2.7). Adjustment for potential confounders, such as previous miscarriages, did not alter the findings.

Case-control studies of pediatric brain tumor investigating various potential risk factors have reported on risk of prenatal x-rays, though not with the same degree of detail as the OSCC and US studies specifically designed to analyze fetal irradiation. Most found no association (Howe 1989, Kuijten 1990, Bunin 1994), however the only of these studies that specifically analyzed pelvimetry found an elevated but non-significant brain tumor risk (OR = 1.3, one-sided p = 0.21) (Preston-Martin 1982).

The causal relationship between prenatal exposure to x-rays and subsequent childhood cancer has been viewed with skepticism for several reasons. Perhaps the most

compelling of these is selection bias; that women x-rayed while pregnant or children x-rayed *in utero* were somehow different, possibly in ways that would predispose to childhood cancer, than were the unexposed women and children. For example, in the OSCC cohort, it has been shown that case mothers were more likely to have smoked and to have had illnesses during their pregnancies, previous miscarriages or stillbirths, grandparents who died of cancer, and children with non-infectious illnesses and congenital defects (Totter 1981). Case mothers were also of higher socioeconomic status and were more likely to have been x-rayed in general, and the possibility was raised that better medical care among case mothers, by eliminating competing causes of death through a reduction in infant mortality, actually contributed to an increased cancer risk (Totter 1981). The twin studies provided the strongest evidence against this argument, however the mere occurrence of a twin pregnancy still does not exclude other possible cancer-predisposing reasons for x-rays (Ayres 1985).

There are several other reasons for questioning findings of increased risk of cancer among children exposed prenatally to diagnostic radiation (Harvey 1985b): 1) increased cancer risk among subjects exposed to A-bomb radiation *in utero* has not been observed (Jablon 1970); 2) experimental data do not indicate an increased susceptibility to radiation-induced leukemia in fetuses (Upton 1960); 3) exposed children have similar risk increases (about 40%) for all cancers, which is highly suspect since underlying incidence rates are very different for different cancer sites (MacMahon 1980); and 4) childhood cancer rates in twins are lower than cancer rates in singletons, the opposite of what would be expected if a causal relationship existed (Inskip 1991).

For each of these arguments, there is contrasting evidence in favor of a causal relationship: 1) Average *in utero* dose received in the A-bomb cohort was 31 rad (Yoshimoto 1988), much higher than exposure from prenatal diagnostic radiography; thus, the possibility of cell sterilization must be a consideration (Doll 1997). Other considerations are that (a) A-bomb survivors have been monitored only since 1950, leaving the possibility that early cases of childhood cancer were unrecorded; (b) Infections are early signs of childhood leukemia, which may have resulted in death among A-bomb survivors living in less than optimal conditions in the years immediately after the bombing; and (c) More recent studies of adults who were exposed *in utero* to A-bomb radiation have observed a slight, although non-significant, increased risk for cancer in adulthood (Yoshimoto 1995). Thus, the possibility exists that lifetime cancer risk is affected (and may be demonstrated with further followup of the A-bomb cohort), a result that was never considered in the prenatal x-ray studies (Doll 1997); 2) While experimental data has not shown an increased leukemia susceptibility among subjects irradiated *in utero*, there is evidence of an increased cancer risk, albeit at higher doses than 1 to 2 rad (Morin 1989, 1991; Benjamin 1986); 3) Cells that contribute to incidence of typical childhood cancers other than leukemia are capable of dividing, if at all, only for a short time after birth (Doll 1997). Therefore, carcinogenic effects of radiation may be very different in fetuses than in children; 4) The cancer risk deficit in twins may relate to low birth weight, since high birth weight has been associated with childhood cancer (Daling 1984). Another possibility is increased fetal or neonatal death among twins, in which case cancer incidence in twins would be underestimated. Given the

current rarity of prenatal diagnostic irradiation, it seems unlikely that the question of a childhood cancer risk association will ever be resolved through epidemiological study.

Preconception Radiography. Findings from studies of preconception medical radiography and cancer risk in offspring have been inconclusive. The first controlled study to investigate this relationship was the Tri-State Leukemia Study (Graham 1966). Parents of 319 childhood leukemia cases diagnosed between 1959 and 1962 were compared to parents of 884 population controls on diagnostic x-ray history before conception. After adjustment for birth year, mother's age, and birth order, maternal exposure to diagnostic radiation significantly increased risk (RR = 1.6, p = 0.003). RR was either unchanged or slightly higher when adjustment was made for pregnancy order or history of miscarriage or stillbirth. Restricting exposure to diagnostic x-rays of the abdomen, pelvis, spine, and femur resulted in an RR of 2.1 ($p < 0.001$). Stratified analysis by pregnancy order revealed that risk was confined to second or later pregnancies. Preconception paternal x-ray exposure was associated with an increased but non-significant risk (RR = 1.3, p = 0.16), and exposure to both parents did not increase risk above that associated with maternal exposure only.

A study from Shanghai observed a similar risk estimate for leukemia in children whose mothers had at least 10 diagnostic x-rays before conception (OR = 1.5, CI = 0.6,3.4) (Shu 1994a). An OR of 1.5 was also observed for all cancers combined and was marginally significant (CI = 1.0,2.3). However, no increase in risk was observed when exposure was confined to x-rays of the abdominal or pelvic regions. Paternal x-rays before conception was not related to leukemia in offspring and moderately increased risk of all cancers when exposure period was restricted to the 2 years before conception (OR = 1.3, CI = 1.0,1.8); risk was highest among children less than 2 years old (OR = 1.7, CI = 1.0,2.6). As with maternal exposure, increased risks were not observed when exposure was restricted to x-rays of the abdominal or gonadal regions.

In contrast to the above studies, a study involving the Childrens Cancer Group in the US found that risk of infant leukemia in particular was more strongly associated with paternal rather than maternal x-ray exposure before conception (Shu 1994b). Cases were diagnosed between 1983 and 1988 and were at most 18 months of age; controls were randomly selected from the population. Exposure histories were ascertained by telephone interviews. Significant risk associations were evident particularly for paternal lower gastrointestinal and abdominal x-rays, and this was especially true for ALL compared to AML. After adjusting for x-rays to other body sites, OR for ALL for two or more lower GI x-rays was 2.9 (CI = 1.1,7.6), and OR for abdominal x-rays was 4.5 (CI = 1.6,12.5). Risk relationships were unchanged after adjustment for occupational radiation exposure. Only maternal preconception exposure incurred during the month before conception was significantly related to leukemia risk (OR = 4.5, CI = 1.1,19.3) but lacked a dose-response effect. Further, increased risk was largely due to reported x-rays of the chest and head/neck region. Paternal and maternal exposure did not confound nor interact with each other.

Cancer risk among offspring of survivors of childhood cancer who received RT has also been a research topic of interest. Most studies of cancer in offspring of cancer survivors involved very few offspring and observed few or no cancer cases among offspring (Li 1979, Li 1984, Nygaard 1991, Hawkins 1995). One of the largest studies included 2308 offspring of cancer survivors compared to 4719 offspring of sibling controls (Mulvihill 1987). However, even in a study of this size, only seven offspring among cases developed cancer; thus, comparisons by cancer treatment of the parents was not possible.

IV. COMMON RADIATION-INDUCED MALIGNANCIES

Leukemia. It has been well-established that radiation-induced leukemias are limited to types other than CLL and that usual latency is shorter (generally 2 to 10 years) than any other radiation-induced malignancy (although latency can be quite extended). Results from most studies suggest a cell-killing effect at high active bone marrow doses. For example, in the cohort of patients treated for ankylosing spondylitis, the highest RR for leukemias other than CLL was observed for subjects who received a total dose in the range of 10 to 99 rad, yet other subjects received substantially higher doses when radiation was delivered to the pelvic and lumbar marrow (Weiss 1995). In cervical cancer patients, RR peaked at about 400 rad (Boice 1987). In women treated for benign gynecological disorders (BGD), RR was only significant for lower average marrow doses between 40 and 126 rad (Wagoner 1984). In uterine cancer patients, RR peaked at about 120 rad among women treated with brachytherapy, which is administered at low doses and at low dose rates (Curtis 1994). On the other hand, in uterine cancer patients treated with external beam therapy, which is administered in high doses at high dose rates, RR slightly increased as dose increased. Thus, the dose-response relationship may depend on dose distribution and dose rate. Interestingly, despite different dose levels and delivery rates among cervical and uterine cancer patients and BGD patients, the leukemia RR in irradiated versus unirradiated patients is comparable among all of these cohorts (two- to threefold increase). In other words, high doses delivered at high dose rates are less leukemogenic, per unit dose, than low doses at low dose rates. It has been hypothesized that high doses are so destructive that cells are unable to divide, which results in cell death. Experimental data supports this theory. In a small study of stable chromosome aberrations in women previously treated with gynecological RT, BGD cases had the same frequency of aberrations as cervical cancer cases, despite a ten-fold lower dose exposure in BGD patients. This suggests that a larger proportion of chromosomally aberrant stem cells survived in the BGD cases (Kleinerman 1994).

Leukemia risk after cancer treatment is often difficult to evaluate because many cancer therapies, such as for Hodgkin's disease and breast cancer, involve both RT and CT, i.e. combined modality treatment (CMT), and CT is a proven risk factor for leukemia. There is some evidence, however, that CMT may increase leukemia risk beyond the risk associated with CT alone (Tucker 1988, Cimino 1991, Abrahamsen 1993, Biti 1994, Curtis 1992). Among cancer cases diagnosed at one of nine US cancer registries between 1973 and 1980, secondary ANLL risk was 2.5, 4.5, and 7.4 for cases

initially given RT, CT, and CMT, respectively (Curtis 1984). Some studies have observed a significant RT effect independent of CT (Andrieu 1990, Curtis 1992).

Some studies have suggested that younger age at radiation exposure increases non-CLL risk. In an analysis of leukemia cases previously treated with RT for cancer, non-CLL RR was 2.1 (CI = 1.1,4.0) for exposure at less than 60 years of age and 1.2 (CI = 0.7,2.1) for older ages (Boivin 1986). In women given RT for cervical cancer, non-CLL risk was highest for women under 45 years old at exposure (RR = 4.6, 90% CI = 0.8,28.0) and decreased with increasing age (Boice 1987). It should be noted, however, that RT exposure in older age groups has not been well-studied (Curtis 1994).

Increased risk of leukemia in children has been associated with RT for benign but not malignant conditions. Children irradiated between the ages of 5 and 9 for tinea capitis had nearly a fourfold increased risk of non-CLL (Ron 1988a). In fact, 57% of non-CLL cases in this cohort were attributable to tinea capitis RT. Children exposed to x-rays, especially from pelvimetry, *in utero* also appear to have an increased risk of leukemia (Graham 1966, Monson 1984), although this remains a controversial finding. A Shanghai case-control study found a significant increased risk of acute leukemia following post-natal x-rays, and there was evidence of a dose-response effect (Shu 1994a). On the other hand, the Late Effects Study Group, specifically formed to analyze second cancers in childhood cancer cases, found a dose-response leukemia effect for CT but not RT (Meadows 1988). Some studies of childhood leukemia have found risk to be related to diagnostic radiography experienced by the parents prior to conception (Graham 1966, Shu 1994b), but this has not been consistently observed (Shu 1994a).

Several studies of radiation-induced leukemia discriminate between ANLL and all other leukemia types. This designation, however, may mask a radiation effect on risk of CML. An early study conducted in the UK observed that non-lymphatic leukemia cases had a high prevalence of RT to the trunk, and the majority of these were chronic cases (Stewart 1962). Another early study from New Zealand found a significant excess of therapeutic irradiation among acute, chronic myeloid, and chronic lymphocytic leukemia cases (Gunz 1964). Upon closer inspection, however, it was observed that RT was given to all of the CLL cases for a prior malignancy, thus weakening the evidence for a causal effect of RT in this group. A US population-based case-control study of leukemia occurring after RT for a previous cancer found a significant increased risk of CML, particularly after RT for cancers in the trunk region (RR = 2.9, CI = 1.1,7.3) (Boivin 1986). Another US case-control study observed an association between CML and relatively low-dose exposure (Preston-Martin 1989) from frequent (at least five) diagnostic x-rays of the back (a lumbar x-ray delivers an estimated 0.35 rad to active marrow).

Other studies of adult leukemia risk from diagnostic radiography have not been conclusive. The UK study cited above observed an association between non-lymphatic leukemias and trunk x-rays (Stewart 1962). This association was also observed for

AML and CML in the Tri-State Leukemia Study, but only among males (Gibson 1972). The New Zealand study reported a correlation between CML risk and high-dose x-rays, although only a few cases accounted for the high exposure levels (Gunz 1964). Some studies have found no increased risk for any leukemia type due to exposure from diagnostic x-rays (Boice 1991b, Yuasa 1997). Groupings of leukemia subtypes are often inconsistent, however, making comparisons across studies difficult.

Hodgkin's Disease and Non-Hodgkin's Lymphoma. Increased risk of lymphomas following RT has been infrequently reported. A significant increased risk of Hodgkin's disease (HD) was observed in the ankylosing spondylitis (AS) cohort (RR = 1.9) during the 5 to 25 years post-treatment (Weiss 1994); average active marrow dose in this cohort was estimated at 438 rad. Among women treated for benign gynecological disorders (BGD), a much higher RR (10.5, $p < 0.05$) of HD was observed 30 years post-RT in the cohort from Scotland in which average active bone marrow dose was 130 rad (Darby 1994). However, no increase in HD risk 25 years post-treatment was observed among irradiated BGD patients from the Connecticut Tumor Registry (Inskip 1993). An increased risk of non-Hodgkin's lymphoma (NHL) 5 years post-RT was also observed in the AS cohort (RR = 1.7, CI = 1.2,2.4), with a significant decline in risk over time (Weiss 1994). A significant RR of NHL of the same magnitude was also observed in irradiated breast cancer patients in Connecticut, and no increase in risk was observed among unirradiated patients (Harvey 1985a). Average dose to active bone marrow in RT-treated breast cancer patients has been estimated at 720 rad (Curtis 1992). Thus, there is sparse evidence that RT may be associated with increased risk of lymphoma.

Multiple Myeloma. Increased risk of multiple myeloma (MM) has been reported following RT for both benign and malignant conditions. In the ankylosing spondylitis cohort, in which average active bone marrow dose was 438 rad, risk was significantly elevated 5 years post-RT (RR = 1.6, CI = 1.1,2.5) (Weiss 1994). Also after 5 years, women given RT for benign gynecological disorders (BGD) in Scotland had a significant risk of MM (RR = 2.6, CI = 1.4,4.9), and risk continued to increase 30 years post-RT (RR = 3.7, $p < 0.05$); average active marrow dose was 130 rad (Darby 1994). No such elevation in MM risk was observed in irradiated BGD patients from the Connecticut Tumor Registry (Inskip 1993). In the large international cervical cancer cohort, MM risk increased significantly over time among women given RT ($p < 0.001$), and excesses did not begin to appear until 10 years post-treatment (Boice 1985b). Average active bone marrow doses in this cohort ranged from 300 to 1500 rad. In men given extended RT (3600 to 4000 rad to the abdominal field and 3000 to 4000 rad to the mediastinal field) for testicular cancer, RR of MM was 7.7 ($p < 0.01$) (Fossa 1990). In a US case-control study of patients from a California health maintenance organization (HMO), risk of RT resulted in a twofold increased risk of MM (RR = 1.9, CI = 0.9,4.2) (Freidman 1986). Another case-control study from the UK observed that 10 MM cases versus only two controls had had RT for a malignant condition at least 1 year before diagnosis; eight of the 10 cases had first had RT at least 10 years before diagnosis (Cuzick 1988).

One study has suggested a possible increased MM risk after low-dose diagnostic radiography exposure (Boice 1991b). Among women treated at a HMO, a borderline significant ($p = 0.05$) dose-response effect was observed when total number of diagnostic procedures at least 10 years before MM diagnosis was considered. In both the California HMO study and the UK study referenced above (Freidman 1986, Cuzick 1988), no associations between diagnostic x-rays and MM risk were observed.

Breast Cancer. Breast cancer risk from medical radiography for a variety of conditions has been well studied, and one factor consistently appears as a critical risk modifier: age at exposure. In female tuberculosis (TB) patients examined with chest fluoroscopies, young age at exposure clearly increased breast cancer risk. In Canadian women, RR was 4.5 (CI = 1.1,41.2) among those exposed between the ages of 10 and 14 years and decreased substantially for women who were older at exposure (Miller 1989). In a similar US cohort, the highest RR occurred among women exposed between 15 and 19 years of age (Boice 1991a); risk decreased with increasing age until the age of 30, at which point no differences in risk between irradiated and unirradiated TB patients were observed. RT for Hodgkin's disease (HD) at a young age has also been shown to modify breast cancer risk. In the Stanford cohort, RR was 136.0 for women younger than 15 years at time of HD treatment with a strong decline in risk at older ages of exposure ($p < 0.0001$) (Hancock 1993). Similar findings related to age at HD treatment were observed in a US/Canadian collaborative study (Boivin 1995) and in a cohort from the Netherlands cohort (van Leeuwen 1994). In combined data from the Connecticut Tumor Registry and the National Cancer Institue, nine breast cancer cases occurred among women irradiated for HD, and eight of the nine were less than 40 years of age at time of treatment (Curtis 1988); the proportion of women in the combined cohort less than 40 years old was not indicated. Increased risk at younger ages is thought to be related to the increased proliferation of breast tissue during adolescence (Boice 1977).

In women irradiated for breast cancer, risk of a second primary breast cancer has generally not been demonstrated. However, second primary breast cancer risk was significantly high among Connecticut women who were less than 45 years old at time of RT for their original breast cancer (RR = 1.6, CI = 1.1,2.4), and dose-response in this subgroup was also signficant (Boice 1992). This age effect was not observed in a Danish cohort of breast cancer cases (Storm 1992). Among women irradiated for benign breast disease in Stockholm, a significant decrease in breast cancer risk with increasing age at exposure was observed ($p < 0.0001$) (Baral 1977, Mattsson 1993). No such age effect was found for US women treated for benign breast disease (Shore 1977, 1986c). The Stockholm and US cohorts were quite different, however, with respect to hormonal status and, to a lesser degree, age. The US cohort consisted of women treated for acute postpartum mastitis, whereas the Stockholm women were treated for various benign breast conditions, the most common of which was fibroadenomatosis, and were generally older.

Studies of second primary breast cancer among women given RT for breast cancer mostly relate only to the contralateral breast, which receives 100 to 300 rad scatter

radiation (Basco 1985, Benedick 1985, Fraass 1985). Findings have been very inconsistent. In several case series, no RT effect has been suggested (McCredie 1975, Schell 1982, Montague 1984). Case-control studies done in British Columbia (Basco 1985) and in Denmark (Storm 1992) found no association between RT and risk of second primary breast cancer. However, a Connecticut Tumor Registry study found risk to be significantly elevated when analysis was restricted to 10 to 14 years post-RT (RR = 2.0, CI = 1.3,3.1), and a significant dose-response effect was demonstrated (Boice 1992). As noted above, risk was also significant among women exposed at younger ages (less than 45 years) in this cohort.

Mantle irradiation for Hodgkin's disease (HD) delivers 200 to 600 rad to the breast (Dershaw 1992); however, an RT effect on breast cancer risk is difficult to evaluate since many HD patients treated with RT are also treated with CT. Some notable observations among women given RT for HD, however, include the modifying effect of age previously described, as well as latency effects. For example, in the Stanford cohort, RR of breast cancer was much higher 15 years post-treatment (RR = 13.6, CI = 7.9,18.2) than 5 to 14 years post-treatment (RR = 2.0, CI = 1.0,3.5). Similar latency effects were observed in the US/Canadian collaborative study and in the Netherlands cohort. Because there is little variation in total dose received among patients given RT (typically 3600 to 4500 rad), dose-response analyses are generally not possible. However, shields are used to protect regions outside of the target area, and these regions receive 300 to 1200 rad; some studies have shown that women treated for HD are more likely to develop breast cancer in these shielded, lower-dose regions than would be expected, based on data from primary breast cancer patients (Janjan 1992, Zellmer 1991).

The inherent relationship between hormonal status and breast cancer is well known. Breast cancer deficits have been observed in cervical cancer patients (Boice 1985b, Hiyama 1985), women treated for benign gynecological disorders (BGD) (Darby 1994), and among women in the ankylosing spondylitis (AS) cohort (Weiss 1994). These deficits are thought to relate to ovarian inactivation from RT. In the AS cohort, average ovarian dose was 560 rad; further, few patients were treated at young ages (younger than 20 years) when radiation-induced breast cancer risk would be greatest. In the Scottish BGD cohort, a significant trend of decreasing risk with increasing ovarian dose was observed ($p < 0.001$). In the International Radiation Study of Cervical Cancer, a reduction in breast cancer risk was apparent only for women with intact ovaries (RR = 0.7, CI = 0.4,1.0), and the reduction in risk was greatest at an ovarian dose of 600 rad. A study of subjects treated for adenoid hypertrophy in childhood found a deficit of breast cancers among women who had been given RT (0 in the RT group versus 5 in the non-RT group) (Sandler 1982), which delivered about 78 rad to the pituitary gland. This finding was also observed in an earlier study of subjects given nasopharyngeal radium (Hazen 1966).

Breast irradiation from RT for benign conditions has been more associated with breast cancer risk than RT for breast cancer. In both the Stockholm and US cohorts of benign breast disease patients, a two- to threefold increase in breast cancer risk was clearly

evident. Mean breast doses were 377 (US cohort) and 580 (Stockholm cohort) rad. In both cohorts, a linear-dose response was observed, with risk peaking at 700 (US) and 825 (Stockholm) rad. RR was highest 15 to 24 years post-RT in the US cohort; in Stockholm, RR peaked at 25 years post-RT but remained significant 40 years post-RT ($p < 0.0001$). RR was highest and of a similar magnitude in both cohorts in the treated breast (in the U.S., RR = 3.2, 90% CI = 2.3,4.3; in Stockholm, RR = 3.6, CI = 2.8,4.6).

Among women examined by chest fluoroscopy for TB, increased risk of breast cancer was observed at much lower dose ranges: 70 rad in the Canadian cohort and 100 to 199 rad in the US cohort. In both of these TB cohorts, RR increased linearly with dose. In the US cohort, excess breast cancer cases first appeared 20 to 29 years after exposure, and RR remained elevated beyond 50 years of follow-up. Increased breast cancer risk at even lower doses has been noted among women diagnosed with scoliosis and thus exposed to frequent diagnostic spinal x-rays (Hoffman 1989). Average cumulative breast dose was only 12.8 rad, and a dose-response effect was demonstrated. Excess breast cancers first appeared 15 years after diagnosis; after 30 years, RR was 2.4 (90% CI = 0.9,5.0). It is noteworthy that the average age of scoliosis diagnosis was 12 years.

Other benign conditions for which children are irradiated that have been associated with increased breast cancer risk are enlarged thymus (Hildreth 1989), hemangioma (Furst 1988, Lundell 1996), and tinea capitis (Modan 1989). Infants irradiated for enlarged thymus received an estimated dose to the breast of 69 rad. RR of subsequent breast cancer among female patients was 3.6 (CI = 1.8,7.3) with a strong linear dose-response effect ($p < 0.0001$). Breast cancer excesses first appeared 28 years post-RT. RT for hemangioma delivered an estimated 39 rad to the breast. RR was 1.7 (CI = 1.3,2.1) and a significant linear dose-response was also evident; latency ranged from 24 to 59 years. In the Israeli tinea capitis cohort, significant increased risk was found among women who had been irradiated between 5 and 9 years of age; dose to the breast was estimated at 1.6 rad.

A recent US study investigated risk of male breast cancer and medical radiography and found that risk was mildly associated with increasing frequency of chest x-rays, that risk was increased in men who had at least three radiographic examinations and in men who had been given RT to the chest and adjacent body areas (Thomas 1994). Further, the period of increased risk was limited to 20 to 35 years after first exposure and declined thereafter.

Estimates of cumulative risk from mammography have been based on data from cohorts of women exposed to much higher doses than those resulting from mammograms, i.e. TB patients given fluoroscopic chest examinations, the BGD cohorts, and A-bomb survivors (Upton 1977). Adjusting for age at exposure, the incremental risk of breast cancer among women aged 35 years and older is estimated to be 3.5 to 7.5 cases per million person-years per rad (combined exposure to both breasts), with a latency of 10 years. Currently in the US, a single mammogram entails two or three views of each breast, and typical absorbed dose per view is roughly 0.06

rad for low-dose and 0.4 rad for high-dose systems (Gohagan 1986). Thus, a mammographic examination results in 0.12 to 1.2 rad absorbed dose to each breast, depending on the system used and the number of films taken.

Gynecological Cancers. Women treated with RT for benign gynecological disorders had an increased risk of gynecological cancer, particularly of the ovaries. Data from these cohorts suggest that risk peaked at an ovarian dose range of 400 to 600 rad (Darby 1994, Inskip 1990). Genital cancer risk was difficult to evaluate in cervical cancer patients since many subjects had experienced surgical removal of the relevant organs. However, in the International Radiation Study of Cervical Cancer, RR of both uterine corpus and ovarian cancer significantly increased over time ($p < 0.001$ for both); these organs generally received exposure in the thousands of rads (Boice 1985b). Increased risk of cancer of the female genitals has also been observed in women given RT to the abdomen in the treatment of Hodgkin's disease (RR = 2.4 after 10 years of follow-up, CI = 1.1,5.4) (Boivin 1995).

Cancers of the Kidney, Ureters, and Bladder. Increased risk of cancers of the kidney, ureters, and bladder (KUB) after RT has been established in several studies. In the ankylosing spondylitis cohort, similar RRs 5 years post-RT were observed for both the kidney (RR = 1.6, CI = 1.1,2.3) and bladder (RR = 1.5, CI = 1.2,1.9) (Weiss 1994). Substantial doses were delivered to the pelvic region, with the pelvic bones receiving 9400 rad during a single course of treatment. Cohorts of women irradiated for benign gynecological disease (BGD) have uniformly observed a two- to threefold increased risk of KUB cancer. In the Scotland cohort (Darby 1994), bladder cancer risk was highest among women followed for at least 30 years (RR = 4.9, $p < 0.001$); mean dose to the bladder in this cohort was 500 rad. A dose-response relationship for bladder cancer was evident among women treated for BGD with radium implants (Inskip 1990). In women treated for cervical cancer, pelvic organs generally received doses in the thousands of rads. Significant bladder cancer risk was observed in the International Radiation Study of Cervical Cancer (Boice 1985b) as well as cohorts of cases from Japan (Hiyama 1985, Arai 1991). In the international study, RR was significantly elevated 10 years post-RT (RR = 3.5, $p < 0.001$), significantly increased thereafter ($p < 0.001$), and remained elevated at 30 years post-RT.

Consistent results relating to KUB cancer have also been observed in cohorts of men irradiated for testicular and prostate cancer (TC). Typical RT for TC involved 2500 rad to the paraaortic and ipsilateral pelvic nodes. In Scotland, KUB were the only organs within the field of radiation associated with increased cancer risk, and RR was highest 10 to 14 years post-RT (RR = 2.9, $p < 0.01$) (Hay 1984). In this study, a group of unirradiated TC patients was not available for comparison. However, a study of TC cases in the Connecticut Tumor Registry revealed significant excesses of kidney and bladder cancers (RR = 3.8 and 3.5, respectively) in radiated but not unirradiated men (Kleinerman 1985). In an analysis of combined data from 10 US cancer registries, men irradiated for prostate cancer had a significantly high risk of bladder cancer, but only after eight years of follow-up (RR = 1.5, CI = 1.1,2.0); RT was targeted at the pelvis and typically delivered 4500 to 5000 rad followed by a boost to the prostate (Neugut 1997).

Colon Cancer. Similar RRs for colon cancer after RT were observed in the ankylosing spondylitis cohort (RR = 1.3, CI = 1.1,1.6) and in women treated for benign gynecological disorders (BGD) (RR = 1.4, CI = 1.1,1.9) (Weiss 1994, Darby 1994). A dose-response effect was observed among women treated with radium implants for BGD (Inskip 1990). Doses to the colon in these cohorts were in the hundreds of rads. In contrast, increased colon cancer risk was not observed in women treated with RT for cervical cancer, who generally received colon doses in the thousands of rads (Boice 1985b, Arai 1991, Hiyama 1985).

Sarcomas. Sarcomas are a well-established consequence of RT, and, although rare, they are extremely fatal. Poor prognosis appears to be related to resectability (Mark 1994) and possibly delayed diagnosis, since sarcomas are difficult to differentiate from physical changes associated with RT (Souba 1996). Centrally-located sarcomas, such as those occurring after RT for Hodgkin's disease (HD) and breast cancer, have the worst prognosis. In HD patients, sarcomas almost always occur within the irradiated field (Tucker 1988, van Leeuwen 1994) and have not been associated with chemotherapy (Boivin 1988). In an analysis of seven pooled studies of HD cases, no sarcomas occurred in patients treated only with chemotherapy, while patients reated only with RT had about a 20-fold increased risk of sarcoma (for cancer of bones and joints, RR = 20.0, CI = 5.5,51.2; for soft tissue sarcomas, RR = 18.3, CI = 9.1,32.8) (Boivin 1988).

In breast cancer patients, most sarcomas after RT develop in the bone, most commonly the scapula, with a mean latency of 11 years (Pendlebury 1995). The most common site of soft-tissue sarcoma is the irradiated conserved breast, and the majority are angiosarcomas (ibid). However, the breast is one of the more frequent sites of angiosarcoma irrespective of RT (Liberman 1992), thus a radiation effect is less obvious. A Swedish study found a significant correlation between RT dose and development of soft tissue sarcoma ($p = 0.008$). This remained significant after adjustment for arm edema (Karlsson 1996), which may predispose to soft tissue sarcoma in breast cancer patients (Stewart 1948). Among cases in the Connecticut Tumor Registry, RR for soft tissue sarcoma was 4.2 ($p < 0.05$) in irradiated patients and 1.8 ($p > 0.05$) in unirradiated patients (Harvey 1985a). Average latency for soft tissue sarcoma in breast cancer patients is 5.5 years (Pendlebury 1995). Doses to areas in which sarcomas typically develop range from 1800 to 10,000 rad (ibid).

Among 531 cases treated for soft tissue sarcoma at a cancer center in Poland, 13 had been previously irradiated for uterine cancer (Ruka 1991). Soft tissue tumors in all 13 arose within the irradiated field; median latency was 18 years.

Bone sarcomas were found to relate to RT for a previous childhood cancer in the Late Effects Study Group (LESG) (Tucker 1987). Bone sarcoma RR after RT was 2.7 (CI = 1.2,7.7), and 83% of these tumors occurred within the irradiated field. Risk increased with dose up to 8000 rad and declined at higher doses. No increase in risk was evident for doses less than 1000 rad. Most secondary tumors that develop in retinoblastoma

patients are bone sarcomas (Abramsom 1984). Sixty percent of bone cancers in patients with inherited retinoblastoma develop in the orbit and periorbital regions, while less than 5% of spontaneous bone sarcomas in patients with other primary cancers occur in these areas (Regleson 1965, Dahlin 1978). In the LESG study, bone cancer risk among inherited retinoblastoma cases increased with increasing RT dose (Tucker 1987).

Increased sarcoma risk has also been observed in cohorts of subjects irradiated for benign conditions. In the ankylosing spondylitis cohort, RR of bone sarcoma 5 years post-RT was 3.3 (CI = 1.6,5.9) (Weiss 1994). Five of the seven bone sarcomas occurred in the pelvic bones or lower vertebrae, the areas that received the highest doses (thousands of rads). RR of soft tissue sarcoma 5 years post-RT was 2.8 (CI = 1.4,5.0). In the Israeli tinea capitis cohort, RR of all sarcomas combined (both bone and soft tissue) was 9.0 (CI = 1.3,208.4) (Ron 1988a). This was an unexpected finding given the relatively low levels of exposure in this cohort. In a cohort of children given RT for hemangioma, RR of soft tissue sarcoma was 2.7 (CI = 1.2,5.4), with a latency range of 11 to 54 years (Furst 1988).

Because sarcomas are so rare, much of the published literature is on series of sarcoma cases known to have received RT in the past (Tountas 1979, Basso-Ricci 1985, Souba 1986, Bechler 1992, Mark 1994, Cafiero 1996). Among osteosarcoma patients treated at Sloan-Kettering (New York, US), median latency in children was shorter (8.7 years) than in adults (13.5 years) (Huvos 1985). In a series of childhood cancer cases who later developed radiation-associated sarcoma, cases who had been treated with RT only had a significantly longer average latency than cases treated with both RT and chemotherapy (17.4 years versus 7.6 years, p = 0.01) (Bechler 1992). Experimentally, latency has been shown to be positively correlated (higher doses = longer latency) with doses above 4000 rad (Kim 1978); however, this has not been supported in human studies (Bechler 1992, Cafiero 1996).

Thyroid Cancer. Since an association between thyroid cancer and radiation was first suggested in 1950 (Duffy 1950), several studies of cohorts of subjects exposed to RT for various benign conditions of the head or neck have demonstrated an increased risk of thyroid cancer. Thyroid doses generally ranged from 10 to 525 rad. The largest risk estimates have been reported for RT given to infants for enlarged thymus (Janower 1971, Shore 1993). In the US Rochester cohort, median dose was 30 rad, and risk increased linearly with dose (Shore 1993); latency ranged from 6 to 49 years. Significant linear dose-response was also observed in the Israeli tinea capitis cohort, in which irradiated subjects were exposed to about 10 rad to the thyroid (Ron 1989). One study of RT for general head/neck benign conditions reported linear dose-response up to but not beyond 200 rad (Schneider 1993). Increased risk for younger ages at exposure has been consistently observed (McTiernan 1984; Ron 1987, 1989; Schneider 1993). Increased thyroid cancer risk has also been reported after RT for hemangioma (Furst 1988). No increased thyroid risk was observed, however, among children given RT for adenoid hypertrophy (Sandler 1982); most thyroid doses in this cohort were below 20 rad. In adults, ankylosing spondylitis is the only benign condition that has been associated with increased thyroid cancer risk after RT (Weiss 1994).

Malignant conditions for which RT has been linked to thyroid cancer risk include Hodgkin's disease (HD), cervical cancer, and general childhood cancer. The Stanford HD cohort consisted of both childhood and adult cases who received 4400 rad to the cervical lymph nodes (Hancock 1991). RR of thyroid cancer was significantly elevated for RT subjects 10 years post-treatment; however, this was based on only six subjects (age range at exposure = 5 to 32 years), two of whom also received chemotherapy. In the International Radiation Study of Cervical Cancer, thyroid cancer RR was higher in the RT group than in the non-RT group (Boice 1985b); this difference was of borderline significance ($p = 0.07$). An elevated RR was also observed in a Japanese cervical cancer cohort (Arai 1991). Cervical cancer patients given RT are exposed to thyroid doses in the tens of rads (Boice 1985b). The Late Effects Study Group found that most thyroid cancers in children previously irradiated for cancer arose in the irradiated field (Tucker 1987); all cases received thyroid doses of at least 100 rad, and risk did not decrease with doses above 200 rad.

One study has reported on the effect of diagnostic radiographic procedures on thyroid cancer risk and included both children and adults (Ron 1987). Using data from the Connecticut Tumor Registry, a dose-response effect for number of thyroid scans was observed (p trend = 0.10); OR for ever having had a mammogram was of borderline significance (OR = 1.8, CI = 0.9,3.6). Case-control studies conducted in Sweden, where health care is very controlled and health histories are relatively easy to reconstruct, have failed to find an overall association between thyroid cancer and thyroid exposure from diagnostic radiography (Inskip 1995, Hall 1996). However, one Swedish study observed a significantly increased thyroid cancer risk among women who were 50 years old or younger at diagnosis and who had been exposed to more than 0.059 rad from diagnostic radiography (OR = 2.7, CI = 1.2,6.6) (Hallquist 1994).

Lung Cancer and Mesothelioma. Two cohorts frequently studied for RT effects on lung cancer risk are breast cancer and Hodgkin's disease (HD) patients. In HD patients, findings have been inconsistent. In a European/Canadian collaborative study, patients treated with chemotherapy alone had a significantly higher lung cancer risk than those treated with RT alone (Kaldor 1992); in the latter group, a dose-response effect was not evident. Further, lung cancer risk in patients given combined modality treatment was the same as those given chemotherapy alone. In a combined analysis of seven separate studies, RT had the same effect on lung cancer RR as chemotherapy (Boivin 1988). Two studies, however, have reported an apparent RT effect. In a study conducted in the Netherlands, RT was the only independent predictor of lung cancer risk, and 84% of lung cancers occurred within the irradiated field (van Leeuwen 1994). In a US/Canadian collaborative study, radiation to intrathoracic organs or to the thorax produced significant RRs at least 10 years post-treatment (Boivin 1995).

In breast cancer patients, the lung receives a substantial dose from RT but the lung is also a common site of metastatic disease (Kamby 1984). Among Connecticut Tumor Registry cases, RR was higher in the RT group than in the non-RT group 10 to 29 years post-treatment, with the highest RR 20 to 29 years post-treatment. (Harvey 1985a). Among RT patients, risk was substantially higher in smokers than non-smokers (Neugut 1994), which is consistent with interactive effects of tobacco smoke and radon observed in uranium miners (National Research Council 1988). Risk among smokers was confined to the ipsilateral lung.

Mesothelioma is a very rare cancer that has primarily been associated with asbestos exposure. In addition, there are at least 35 reports of mesotheliomas at or near the site of previous irradiation (Cavazza 1996). Most radiation exposure is from cancer RT, and the most frequently-reported initial cancer was Hodgkin's disease. Average latency was 19.5 years. Due to the low incidence of mesothelioma, it has not been possible to fully analyze RT effects on risk with consideration for other potential risk factors, such as chemotherapy and prior malignancy.

Central Nervous System Tumors. Central nervous system (CNS) tumor risk has been strongly associated with RT for ALL in children (Nygaard 1991). Among 10,000 patients from a US/Canadian collaborative study, there were 24 cases of CNS tumors, all of whom had been given 1800 to 2400 rad to the cranium. Significant CNS tumor risk was also observed in a combined analysis of seven Hodgkin's disease studies in which all CNS tumors occurred in subjects given RT, while none developed in patients given chemotherapy (Boivin 1988). In the Israeli tinea capitis cohort, brain tumor risk increased with brain doses up to 300 rad and declined thereafter (Ron 1988b). Risk was higher and latency was longer for meningiomas than gliomas. Although the precise brain tumor locations were unknown, most were in the upper cranium which received the highest doses. This was confirmed for meningiomas in a study that compared meningioma cases who had and had not received RT to the head (all exposed subjects had RT for tinea capitis) (Soffer 1983); also in this study, it was shown that exposed subjects were more likely to have multiple, malignant, or recurrent

meningiomas; were slightly younger at diagnosis than controls; and had a less pronounced female-to-male ratio than controls.

A review of meningiomas occurring at sites of RT for a previous brain tumor also suggests that these meningiomas are different from those occurring spontaneously (Soffer 1989); age at diagnosis was substantially younger in RT subjects and the female-to-male ratio was less pronounced. Meningiomas after high-dose RT (at least 800 rad) appear to have a shorter latency than meningiomas occurring after lower-dose RT (mean 20.8 versus 36.8 years), and even shorter latency has been evident in children given high-dose RT (mean 15.3 years) (Starshak 1996). Age at glioma diagnosis was significantly younger among patients who received prior RT (mostly for ALL) than among patients with spontaneous gliomas (Salvati 1994); mean RT dose was 3340 rad, mean age at RT was 12.9 years, and mean latency was 9.6 years. In general, meningiomas are more frequently associated with low-dose irradiation while gliomas are more often reported after higher doses of RT (Hubert 1993).

In a cohort of 411 patients treated with RT for pituitary adenomas (prescribed dose = 45-50 Gy) between 1962 and 1986 and followed for a median of 10.5 years, five subjects developed secondary brain tumors (Brada 1992) which, when compared to population rates, equates to an RR of 9.4 (CI = 3.1,21.9). It should be emphasized that the most appropriate control group would be unirradiated pituitary adenoma cases. Despite the lack of epidemiologic studies, case reports suggest that there may be an increased risk of parasellar fibrosarcoma after RT for pituitary adenoma (Plowman 1995).

In a US cohort of 2925 subjects treated in Maryland from 1943 to 1960 for adenoid hypertrophy and followed an average of 24 years, 904 (31%) had been given RT to reduce the size of the adenoids and thus reduce the frequency of ear, nose, and throat infections (Sandler 1982). In irradiated patients, the pituitary gland and lower region of the brain received about 78 rad. Four subjects in the RT group compared to no subjects in the non-RT group developed a malignant head/neck tumor (lower CI = 1.4), three of which occurred in the brain; latency for all three brain tumors was between 15 and 20 years post-RT (histological types not given).

Several case-control studies have examined the relationships between RT and diagnostic x-rays to the head or neck and brain tumor risk in both adults and children. A US study of meningiomas among men in Los Angeles observed a significant increase in risk for RT to the head during childhood (Preston-Martin 1983), while a German study of adult brain tumor found no increased risk for RT to the head at least 5 years before diagnosis (Schlehofer 1992). Among female meningioma cases in Los Angeles, OR was 1.5 (p = 0.10) for head or neck x-rays at least 5 years before diagnosis (P-M 1980).
A Toronto adult brain tumor study observed elevated risks for head x-rays (OR = 2.7, p = 0.23) and x-rays of the shoulder or neck (OR = 6.0, p = 0.12) but did not report ORs with consideration for latency (Burch 1987). No increased risk was observed among adult brain tumor cases in Germany (Schlehofer 1992). An Australian study of adult

brain tumor found elevated risk of meningioma for diagnostic head or neck x-rays 2 to 20 years before diagnosis; increased risk was significant 2 to 10 years before diagnosis, and risk was not significantly elevated for any latency period for gliomas (Ryan 1992b).

Diagnostic skull x-rays at least 5 years before diagnosis significantly increased risk among pediatric brain tumor cases in Toronto (OR adjusted for chest x-rays = 6.7, CI = 1.7,27.3), and dose-response considering number of films was significant (p = 0.004) (Howe 1989). Subsequent pediatric brain tumor studies did not support this observation (Kuijten 1990, Bunin 1994, McCredie 1994).

In Los Angeles County, associations have been observed between brain tumor and dental x-rays for both adults and children (Preston-Martin 1980, 1982, 1983, 1989). Risk was related to frequent full-mouth series, which, prior to 1964, delivered an estimated total exposure of 20 rad (U.S. Department of Health, Education, and Welfare 1973). A correlation was noted between frequency of full mouth x-rays and probability of meningioma location in the tentorial or subtentorial regions, which are likely to be within the x-ray beam during a full-mouth series. Brain tumor risk and dental x-rays have been explored in other populations, though not with the level of detail used in Los Angeles. It is clear that a simple binary exposure variable (i.e., exposed versus unexposed) is not sufficient to detect risk effects of dental x-rays.

Weak associations have been found between pediatric brain tumor risk and prenatal exposure to pelvic x-rays. In Los Angeles County, an elevated but non-significant OR (1.3, one-sided p = 0.21) was observed specifically for pelvimetry (Preston-Martin 1982). Several studies that asked only about prenatal abdominal or pelvic x-rays (not necessarily pelvimetry) found no association with pediatric brain tumor risk (Choi 1970, Howe 1989, Kuijten 1990). One study that asked about „x-rays of the lower abdomen" found no overall association, although five cases and no controls were exposed during the first trimester (Bunin 1994).

Skin Cancer and Malignant Melanoma. Skin cancer was the first malignancy ever associated with ionizing radiation exposure (Freiben 1902). The most important predictor of radiation-induced non-melanotic skin cancer appears to be sun or ultraviolet (UV) radiation exposure. Most spontaneous non-melanotic skin cancers are associated with UV radiation and are usually basal cell, as opposed to squamous cell, carcinomas (Shore 1990). Basal cell carcinomas are more common in the head and neck region, and squamous cell carcinomas are more typically found on the arms and hands (ibid). It has been suggested that cohorts irradiated at body sites typically shielded from UV radiation do not have increased risks of skin cancer, whereas cohorts treated with radiation at unshielded body areas have significant skin cancer risk (ibid). Increased risk appears to exist over the entire lifetime of patients irradiated at these body sites (Martin 1970). Among „shielded" cohorts for which skin cancer risk was not elevated are tuberculosis patients exposed to multiple chest fluoroscopies (ibid) and women treated for benign gynecological disorders (Shore 1986, 1990) and cervical cancer (Boice 1985b). Excess skin cancers were observed in a cohort of men treated

for testicular cancer, although the authors attributed this to detection bias since the excess skin cancers were not confined to the treated field (Hay 1984).

Exposure to RT at anatomical areas unshielded from UV radiation typically involve benign conditions of the head or neck. While several studies indicate an increased skin cancer risk in patients given RT for various benign head/neck conditions (Hildreth 1985, Schneider 1985, Van Vloten 1987), perhaps the most conclusive evidence is from the tinea capitis cohorts in Israel and New York. In the Israeli cohort, RR for non-melanoma skin cancer was 4.2 (CI = 2.3,7.6); nearly all tumors were basal cell (Ron 1991). Risk increased with increasing dose ($p < 0.001$) and decreasing age at exposure. Significant risk predictors within the RT group were sun exposure (OR = 2.6, CI = 1.1,6.1) and alopecia or dermatitis (OR = 3.4, CI = 1.3,8.8). Similar results were observed in the New York cohort (Shore 1984). Forty-one of 2226 RT and three of 1387 non-RT subjects developed skin cancers of the head or neck, and all were basal cell tumors. Excess risk first appeared 20 years post-treatment and rose sharply thereafter. Complexion appeared to be a risk modifier, as all 41 skin cancer cases in the RT group were white and 25% of patients who received RT were black. A disproportionate number of skin cancers occurred near the hairline compared to the larger, hairy surface of the scalp, also suggesting an interactive effect with sun exposure.

RR of melanoma was 3.0 in the Israeli tinea capitis cohort, but was based on only three cases (Ron 1991). Increased melanoma risk has been observed among Hodgkin's disease (HD) patients treated with RT. In an analysis of seven pooled studies, RR was 6.7 (CI = 3.2,12.3) among subjects given RT, compared to 0.0 (CI = 0.0,18.5) among those given chemotherapy (Boivin 1988). Among HD cases treated with RT in the Netherlands, all melanomas that developed occurred within the irradiated field (van Leeuwen 1994).

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Anhang/Appendix K

Follow-up studies of patients who received radiation therapy (RT) for both benign and malignant conditions have advanced our understanding of radiation-induced human carcinogenesis. Consistent patterns of tumor development related to latency and dose have been observed in several cohorts of subjects treated with high doses of radiation. For example, solid tumors that occur at specific sites have been associated with high doses of RT at that site; leukemias other than chronic lymphatic leukemia (CLL) appear related to dose to the active bone marrow in a complex way that suggests a cell-killing effect. Latency appears to be shorter for these leukemias than for solid tumors.

Radiation-induced breast cancer has some unique features. Risk increases with decreasing age at exposure, and young age at exposure is also associated with very long latency. High ovarian dose, likely to result in ovarian inactivation, reduces breast cancer risk after RT; this was observed in both the ankylosing spondylitis and the benign gynecological disorder cohorts (as well as in A-bomb survivors). Data from benign breast disorder and Hodgkin's disease (HD) cohorts suggest that a cell-killing effect may be a factor, as with leukemia. Most studies that have found increased risk of radiation-induced breast cancer have involved lower-dose exposures for benign conditions.

Not all RT cohorts have provided conclusive findings. For example, studies of HD patients have produced widely inconsistent results. One of the main reasons for this is that many HD patients are given RT plus chemotherapy (CT), which is a well-known carcinogen. Many studies of breast cancer patients report no RT effect on second primary breast cancer risk, however temporal patterns that are consistent with an RT effects have also been observed. Findings from cohorts of testicular cancer patients have been inconclusive, likely due to the fact that few cases exist who were not given RT to serve as a comparison group. Leukemia in children treated for a prior cancer has been found to both relate to CT only and to RT with evidence of dose-response.

Low-dose exposure, such as from diagnostic radiography, is much more generalizeable to the population but has been less studied and is somewhat controversial. There have been some significant cohort studies, however, that have demonstrated similar radiation effects as those from RT cohorts. Two of the most notable are the tuberculosis and the scoliosis patient cohorts. Both cohorts were exposed to low doses over prolonged periods of time and both showed excessive breast cancer risk with particularly high risk associated with young age at exposure. Studies of general diagnostic radiography have largely focused on leukemia, for which trunk x-rays are most relevant in exposed adults, and associations have been found for the myeloid leukemias. This has not been consistently observed, but exposure assessment is often problematic in these types of studies. Dental radiography has been mostly studied in relationship to brain and salivary gland tumors, and high doses delivered during these procedures in past decades appear to have been related to risk. Similarly, there is evidence of increased childhood cancer with exposure to prenatal radiography which has essentially been replaced by ultrasound. Studies of maternal and/or paternal preconception radiography and risk of childhood cancer have been inconclusive.

In conclusion, risk of radiation-induced cancer has been well-established for high dose exposure, such as that received from radiation therapy for benign or malignant conditions. Cancer risk from lower-dose exposure has also been observed, but not consistently for diagnostic radiography, which is the more prevalent exposure. Diagnostic radiography studies, however, have not been as tightly controlled as studies of radiation therapy. Much more research needs to be conducted in the area of low-dose exposure before any conclusions can be confidently formulated.