Projecting the Lifetime Risk of Breast and Thyroid Cancer from Exposure to Diagnostic Ionizing Radiation for Adolescent Idiopathic Scoliosis

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ABSTRACT

Adolescent idiopathic scoliosis (AIS) is a disorder characterized by lateral curvature of the spine and is the most prevalent orthopedic disorder during growth. The diagnosis and management of scoliosis require multiple full-spinal radiographs, exposing adolescents to potentially high doses of ionizing radiation. The purpose of this study was to determine the cumulative doses of x-ray radiation to the thyroid gland and female breast from spinal radiographs and to estimate the number of cancers at these sites attributable to x-rays.

Subjects for this study were patients referred from 1960 to 1979 for AIS to Hôpital Ste-Justine, Montréal. The number of spinal radiographs, the radiant energy of the beam emitted from the x-ray machines, differences in the type of equipment used to make the radiographs, the view, the calendar period, and the subject's size were used in Monte Carlo simulations of photon energy depositions in human tissue to estimate organ-specific x-ray doses. These estimates of dose, published estimates of risk from the Fifth Committee on the Biological Effects of Ionizing Radiation, and Quebec cancer incidence and cancer mortality rates were then incorporated in a life table procedure to project the expected excess number of cancers.

About 85 percent of 2,181 subjects in the AIS cohort were first referred for scoliosis between the ages of eleven and seventeen years and the average time under observation at the hospital was about three years. The mean number of radiographs was about twelve. The mean cumulative dose to the thyroid gland and to the female breast was about three cGy. Seven excess breast cancer and thyroid cancer cases were projected to occur over the lifetime of the women; among these, two excess deaths from cancers were projected. In summary, approximately one in every 250 women in this cohort would be expected to develop breast or thyroid cancer over their lifetime, and one in every 900 women would be expected to develop a fatal cancer, due to spinal radiographs

for scoliosis.

Doses today from spinal radiographs are considerably lower than two decades ago, due to the installation of modern x-ray equipment. However, doses can be further reduced through the use of the posteroanterior view in place of the more traditional anteroposterior view. Moreover, spinal radiographs for scoliosis, as well as other radiological procedures, must be ordered judiciously rather than routinely.

RÉSUMÉ

La scoliose idiopathique des adolescents (SIA), un désordre caractérisé par une déviation latérale de la colonne vertébrale, est le trouble orthopédique le plus fréquent pendant la croissance. Pour établir un diagnostic et traiter la scoliose, il est nécessaire d'effectuer des radiographies multiples de toute la colonne vertébrale, exposant éventuellement les adolescents à des doses élevées de rayonnement ionisant. L'objectif de la présente étude était d'évaluer l'effet des doses cumulatives de rayonnement ionisant sur la glande thyroïde et sur le sein, et d'estimer les risques de cancer, reliés aux radiographies spinales.

Les sujets de cette étude étaient des patients (1,847 femmes et 334 hommes) qui avaient été adressés à l'Hôpital Ste-Justine à Montréal, entre 1960 et 1979. Pour chacun des sujets, une dose cumulative de rayonnement a été calculée pour le sein et la thyroïde à partir des radiographies spinales et du débit des rayons émis par les appareils de radiographie. Pour cela, l'auteur a tenu compte des différents appareils utilisés, de l'angle de la radiographie, de l'année d'utilization, et de la taille des sujets. Des simulations Monte Carlo de dépôts d'énergie photon dans les tissus humains ont permis d'estimer les doses spécifiques à chaque organe provenant de radiographies typiques. Afin de calculer une projection du nombre attendu de cancers excédentaires dans cette cohorte, une table de survie a été utilisée, basé sur les doses reçues, les risques associés à ces doses selon les données publiées par le Cinquième comité sur les effets du rayonnement ionisant en biologie (BEIR V), et de l'incidence du cancer et les taux de mortalité du cancer au Québec.

Environ 85 pour cent des 2,181 sujets de la cohorte SIA ont été examinés pour la première fois entre les âges de 11 et 17 ans, et la durée moyenne d'observation à l'hôpital était d'environ trois ans. Le nombre moyen de radiographies s'élevait à 12. La dose

cumulative moyenne touchant la glande thyroïde et le sein était de l'ordre de trois cGy. Nous estimons qu'il y aura sept cas supplémentaires de cancer du sein et de cancer de la thyroïde au cours de la vie de ces femmes. De plus, on prévoit deux décès supplémentaires parmi ces cas. Il faut donc envisager qu'environ une sur 250 femmes exposées à un rayonnement semblable à celui auquel a été exposé cette cohorte sera atteinte de cancer du sein ou de la thyroïde au cours de sa vie, et qu'une femme sur 900 décèdera des suites de ce cancer, et ceci, à cause des radiographies pour la scoliose.

Grâce à l'équipement actuel de haute technologie, les doses provenant de radiographies spinales sont considérablement inférieures à celles auxquelles étaient exposés les sujets il y a vingt ans. Ces doses peuvent être encore réduites lorsqu'on utilise une image postéroantérieure, et non l'image antéropostérieure plus traditionnelle. Les radiographies de scoliose, ainsi que d'autres interventions radiologiques, doivent être prises avec discernement et non de façon routinière.

PREFACE

Ionizing radiation is one of the few accepted causes of cancer. For the general population the greatest source of exposure to radiation, other than radiation from natural sources, is from diagnostic x-rays (NCRP87, NCRP89). In particular, persons with spinal deformities may be exposed to relatively large doses of x-rays because the diagnosis and management of their condition depends on visualizing the spine using full spinal radiographs over a long period of time. Adolescents with scoliosis are particularly vulnerable to the potential effects of radiation because the exposure occurs early in life, during a period of rapid growth, when they may be more susceptible to its effects (NAS90). Because of these concerns, this thesis was undertaken in order to assess the excess risk of cancer among individuals exposed to diagnostic x-ray radiation for the investigation of scoliosis.

This thesis was conducted as part of a retrospective cohort study of the impact of adolescent idiopathic scoliosis (AIS) on health and well-being in adulthood (Po87). The cohort comprised the 2,181 adolescents referred to Hôpital Ste-Justine, Montréal, from 1960 to 1979 for idiopathic scoliosis. The cohort has been followed to early adulthood and the prevalence of various indicators of health and fitness has been ascertained and compared with the prevalence in a population-based control group. At the time of follow-up, most individuals in the cohort were between twenty and forty years of age. Thus, it was not possible to investigate the relationship between diagnostic radiation and cancer because the incidence rates of cancer in this age range are low and insufficient time had passed to produce sufficient numbers of cancers (*i.e.* latency). Nevertheless, it is of interest to predict what the excess risk may be given the doses of radiation received by scoliosis subjects.

The female breast and the thyroid gland are known to be highly sensitive to radiation

carcinogenesis (NAS90). When subjects in the AIS cohort were being treated for scoliosis, it was usual for spinal radiographs to be taken using the anterior-posterior view, with breast and thyroid tissues unshielded. Thus, these organs received the largest doses of x-rays (Gr83) and the excess cancer risks at these sites are of primary interest. Thus, this thesis deals with projecting the lifetime risk of breast and thyroid cancer from exposure to diagnostic radiation. The methodology developed in this study used for the investigation of these two organs can be generalized to other sites of cancer.

The thesis is structured in six chapters, according to the following framework. Chapter one provides the background for the risk estimates from scoliosis radiography. Background information on a number of areas relating to AIS and on cancer risks from spinal radiographs is provided in chapter two, which also includes an overview of the major studies used in radiation risk assessment. The specific objectives of the study are presented in chapter three and chapter four describes the radiobiological and statistical methods used to attain the objectives. The results are described in chapter five. In chapter six, uncertainties in the risk projections are considered, the results are compared to other published studies, directions for future research are suggested, and a recommendation for lowering x-ray doses from scoliosis radiographs is given.

1. INTRODUCTION

Adolescent idiopathic scoliosis (AIS) is a disorder characterized by lateral curvature of the spine. AIS typically afflicts persons between ten and sixteen years of age and is more common among women than men (We89). The consequences of progressive AIS can include increased risk of right heart failure, decreased pulmonary function, chronic back pain, and adverse reproductive outcomes (We89). To straighten the curve a brace is often prescribed (Ka87). For some persons spinal bracing is successful in halting curve progression and maintaining the correction. For severe cases, however, a surgical intervention is often the only effective treatment. Treatment is determined by the subject's age, sex, and rapidity of curve progression. The spinal curve is measured on full-spinal radiographs and progression is monitored by following the curve over time. An adolescent referred for scoliosis is typically monitored at three to twelve month intervals (Ka87). Follow-up typically continues until curve progression stabilizes, and this usually occurs when the skeleton matures.

The use of diagnostic radiographs for evaluating scoliosis was first suggested in 1900 (Hi00), five years after the discovery of x-rays. Since that time, it has been considered "... the ideal discipline for evaluation of scoliosis, enabling precise measurement of scoliotic curves, facilitating the recognition of vertebral, related skeletal, and soft tissue deformities, and influencing the management of scoliosis." (Yo70). Radiological examination typically consists of at least one standing full-spinal radiograph. When making full-spinal radiographs, the organs exposed to the highest doses of x-rays are those that lie directly in the path of the x-ray beam and those that are closest to the skin. In the past, spinal radiographs for scoliosis were made with the patient facing the x-ray machine (anteroposterior) and, therefore, the doses delivered to the female breast tissue and the thyroid gland were much higher than doses from the posteroanterior view.

Although exposure to high doses of x-rays can cause acute sickness and even death, effects of exposure to diagnostic levels of x-rays are manifested long after exposure ceases. The long-term effects that have been demonstrated include genetically determined ill-health, developmental abnormalities and some degenerative diseases (*e.g.* cataracts; NAS90). Additionally, if germ cells are irradiated, exposure can result in hereditary defects to the offspring. However, the greatest risk posed by radiation exposure is believed to be cancer (NAS90).

The induction of cancer by radiation is thought to result from damage to the DNA. Briefly, when x-rays pass through DNA, enough energy is imparted to displace molecular electrons, thereby breaking the bonds that hold the molecules together (*i.e.* ionization). Ionization of cellular DNA strands can disrupt the sequence of molecules in the chain, causing mutations, and when the DNA strands divide, these mutations in the DNA code may be replicated. This in turn can result in the appearance of a malignant tumor in the affected tissue.

The potentially large number of radiographic examinations for scoliosis, the relatively high doses to the female breast and thyroid gland, and the dangerous effects of exposure to x-rays mean that adolescents with scoliosis may be at increased risk of developing cancer. This thesis will present a risk assessment of the carcinogenic effects of diagnostic radiation for scoliosis.

2. Literature Review

2.1 Scope of the review

This chapter provides background information on AIS and how radiographs are used for evaluating and managing the disorder. The material on scoliosis was obtained from the protocol of the AIS study (Po87) as well as several other recent review articles (Ka87, We89). A brief overview of the epidemiology of cancer of the female breast and cancer of the thyroid gland is presented, and this was assembled from review articles (Ke79, Ke88, Pe84, Ro82a). What follows is a description of the methods used for evaluating the risk of breast cancer and thyroid cancer from exposure to ionizing radiation. The relevant epidemiologic studies are reviewed and the statistical models used to summarize the cancer risk from radiation exposure are described.

2.2 Clinical characteristics, epidemiology and treatment of AIS

Scoliotic curves can result from either structural or non-structural malformations of the spine (Mo78). Most scoliotic curves are the result of a structural change, while the others are usually secondary to another problem such as disparity in the length of the legs or from vertebral osteoid osteoma (Ka87). Adolescent idiopathic scoliosis is the most prevalent form of scoliosis, accounting for approximately 80 percent of patients with a structural scoliosis (Ta90). AIS is characterized by progressive lateral curvature of the spine and rotation of the vertebrae that arrests upon skeletal maturity, but usually leaves the individual with a permanent deformity (Ca75). Persons referred for AIS are supervised by an orthopedic surgeon, who assesses the spinal curve, monitors curve progression and prescribes treatment.

AIS is classified according to the location and direction of the spinal curve (Mo78). This

classification gives a clinical portrait of afflicted individuals but does not refer to etiology. Location refers to the region of the spine containing the curve's apex, and is defined as follows: cervical (vertebrae C1 to C6), cervicothoracic (vertebrae C7 to T1), thoracic (vertebrae T2 to T11), thoracolumbar (vertebrae T12 to L1), lumbar (vertebrae L2 to L4) and lumbosacral (vertebrae L5 to S1; Ro82b). The direction of the curve is designated by the side of convexity of the deformity and can be either right or left (viewed from the back). Most scoliotic curves are convex to the right if the apex is thoracic and are convex to the left if the apex is lumbar (Mo78).

The extent of a scoliotic curve is measured from full spinal radiographs using either the method of Cobb (Co48) or the method of Ferguson (Fe45). The Cobb angle, recommended by the Scoliosis Research Society as the standard method of evaluation, measures the inclination between the superior surface of the uppermost vertebra and the inferior surface of the lowermost vertebra in the curve (Ki70, Yo70). The Cobb angle is measured in degrees on a full-spinal radiograph using a goniometer, a plastic device made of a transparent protractor and ruler. Estimates of the accuracy of measuring the Cobb angle indicate that it is repeatable 95 percent of the time within plus or minus five degrees (Go88).

AIS is the most prevalent orthopedic disorder during growth (Ca75, Ke82). In North America, estimates of prevalence for scoliotic curves greater than five degrees range from 10 to 140 per 1,000 adolescents. Women are affected twice as often as men (Le82, Mo78). For spinal curves requiring close supervision or treatment, *(i.e.* greater than about 20 degrees), estimates of prevalence range from three to nine per 1,000 adolescents (Br75, Ch86, Di83, Dr77, Mo78, Ro84b, Wi82), with women affected five to seven times as often as men (Ro84b, Mo85).

Scoliotic curves can either arrest spontaneously or progress during adolescence, but the curves never return to normal. The consequences of a rapidly progressing curve can be debilitating and may leave the individual with a permanent deformity (Ca75). Premature death from right heart failure, or *cor pulmonale*, is one of the possible late sequelae of scoliosis (Co69, Na68, Ni68, We81). Other potential consequences of untreated scoliosis include decreased pulmonary function (Bj73, Sh78a), chronic back pain (Co69) and adverse reproductive outcomes (Vi87).

Treatment for scoliosis is determined by the subject's age, sex, skeletal maturity, by the size and location of the curve, and the rapidity and extent of curve progression. Small curves, iess than 10 degrees, are generally left untreated or treated with exercise and orthoses. Moderate curves, between 10 and 40 degrees, are treated typically either by bracing or traction. Braces and night traction are sometimes useful for slowing the development of the curve (Ka87). Several plastic braces are available, and the best known are the Milwaukee and Boston braces. These braces are worn during the waking hours and straighten the spine by applying pressure to the neck and to the base of the spine. Traction consists of a set of weights attached to a corset worn by the patient, usually during the sleeping hours.

For curves greater than 40 degrees, it has been established that surgical intervention arrests curve progression and reduces the extent of the spinal curve (Co83, Ha73, Mo64, Mo80, Ri58). During the period 1960 to 1989, the most common surgical procedure at Hôpital Ste-Justine was that of Harrington (Ha73), accounting for over 95 percent of the surgical interventions for AIS. In the Harrington procedure, two metal rods were implanted alongside the spine to straighten the curve; a distraction rod on the concave side and a compression rod on the convex side. The spine was grafted using bony material shaved from the iliac crest. After surgery, the patient was placed in a plaster

cast and held immobile on a Stryker bed for up to two weeks. Subsequently, the patient was placed in a body cast for several months. Since the late 1980s, improvements in metal rod technology (*i.e.* Cotrel-Dubousset rods) have reduced the length of time that the patient must remain immobile and allow the patient to leave the hospital without a cast.

Thus, treatment for AIS is physically demanding for the patient and, when a surgical correction is required, carries the added risks of infection, pseudoarthrosis and neurologic complications. However, the consequences of not treating a progressive spinal curve are believed to outweigh the risks and discomforts of treatment (Bj82, Fo78, Lo84, Na68, Sh78a).

2.3 Epidemiology of breast cancer and thyroid cancer

Breast cancer poses a serious threat to the health of women and continues to be a major public health problem in Canada and other western countries. Breast cancer is very rare in the premenarchal period, with an annual incidence rate of less than one per 100,000 girls. Annual age-specific incidence rates of breast cancer remain low until the third decade of life when they are between 30 and 50 per 100,000, and thereafter rates rise rapidly until ages greater than 75, when the rates are over 300 per 100,000. In Canada, the standardized incidence of breast cancer among women aged 65 years and over increased by about twenty percent between 1970 and 1984; over the same period, breast cancer incidence was stable among women aged 25 to 64 years (NCIC89).

Both hereditary and environmental risk factors have been implicated in the etiology of breast cancer (table 2.1). Familial factors appear to be important components in the etiology of breast cancer; this is indicated by the observation that having a first degree relative with breast cancer increases the risk by about 1.5- to three-fold (An74, Ba80).

Although familial associations could conceivably be due to shared environmental risk factors, the approximately ten-fold risks observed in some familial patterns (*e.g.* a mother or sister with bilateral breast cancer at a young age) indicates that heredity probably plays a role in the etiology (Wi89). However, differences in rates between countries have been used to estimate that 80 percent of breast cancers in the United States may be attributed to non-hereditary factors (Do81).

A number of reproductive factors have been shown to increase the risk of breast cancer thus implicating hormones in the etiology. For example, higher parity (Ch77, Ka88) and first childbirth before age twenty (Mac73) have been associated with a decreased risk of breast cancer. Other studies have shown an association between early age at menarche and increased risk of breast cancer; typically, early menarche confers about a 1.5- to two-fold increase in risk as compared with late menarche (Ke79, Ka88). The risk of breast cancer is reduced among women with early menopause (Ka88).

Among demographic factors, increases in risk have been observed among women of high socioeconomic status and among Caucasians (Ke79). In addition, women with pre-existing proliferative breast diseases (Hu80, Pa78) and obesity (Le79) are at higher risk. Although it has been suggested that nutritional variables may be responsible for up to 50 percent of breast cancers in the United States (Do81), recent studies have shown that this is probably an overestimate (Wi88). The nutritional factors thought to confer higher risk include diets that are high in animal and vegetable fats and animal proteins. Recent evidence indicates that alcohol consumption is also associated with elevated risk of breast cancer (Ha87, Wi88). The estimated relative risks from daily alcohol consumption, pooled from five prospective studies, were about 1.4, 1.7 and 2.0, for one, two and three drinks daily, respectively (Lo88).

Table 2.1 Risk factors for breast cancer in women.

Factor	High risk	Low risk	Relative risk
Age	Old	Young	> 4
Country of birth	North America, Northern Europe	Asia, Africa	> 4
Family history of premenopausal bilateral breast cancer	Yes	No	> 4
History of cancer in one breast	Yes	No	> 4
Ionizing radiation	Large doses	Unexposed	2 - 4
Socioeconomic status	Upper	Lower	2 - 4
Age at first full-term pregnancy	≥ 30 years	≤ 20 years	2 - 4
History of fibrocystic disease	Yes	No	2 - 4
Any first-degree relative with breast cancer	Yes	No	2 - 4
History of primary cancer in ovary or endometrium	Yes	No	2 - 4
Oophorectomy	No	Yes	2 - 4
Postmenopausal body build	Obese	Thin	2 - 4
Marital status	Never married	Ever married	1 - 2
Place of residence	Urban	Rural	1 - 2
Race	White	Black	1 - 2
Age at menarche	Early	Late	1 - 2
Age at menopause	Late	Early	1 - 2
Daily alcohol intake	One drink or more	None	1 - 2

Adapted from Ke79, Ke88, Lo88

Cancer of the thyroid gland is a rarer and less virulent neoplasm than breast cancer, but like breast cancer, affects more women than men. The incidence of thyroid cancer has been rising in the past few decades (Po80, We79) and, in developed nations, at least part of this increase has been attributed to medical radiation exposure (Ro84a).

In Canada, the age-standardized rate of thyroid cancer is about five per 100,000 women and four per 100,000 men (NCIC91). Except for a few geographic areas with particularly high incidence rates, such as Hawaii, Iceland, Israel and Colombia, the incidence of thyroid cancer does not vary greatly by country (Ro84a). In Western countries, thyroid cancer accounts for one to two percent of all cancer cases, and less than one percent of all cancer deaths (Si88, NCIC91).

Like most solid neoplasms, thyroid cancer is rare during the first two decades of life, with an incidence of less than one case per 100,000 per year. The annual incidence rate rises with age, and among women, is about five cases per 100,000 at age 30, ten cases per 100,000 at age 60, and about fifteen cases per 100,000 at ages 75 years and over. As noted above, thyroid cancer is more frequent among women than among men, but this excess varies with histologic type of the tumor and with age (Fr79, Ha70, McG78, Sh77a, St72). The majority of benign thyroid disorders also occur more frequently in women (Ro84a).

The observation of a relative predominance of thyroid cancer among women may indicate that hormonal factors are implicated in its etiology, although diet, prior thyroid disease, and genetic susceptibility are also suspected (Ro84a). The differences in incidence between men and women also raises the possibility that women are more frequently exposed than men to one or a set of environmental carcinogens. However, the only established causal risk factor for thyroid cancer is ionizing radiation (Ro84a).

2.4 Radiation studies

For the purposes of estimating the excess risks of cancer in the AIS cohort, only the most recent analyses of the United States National Academy of Sciences Fifth Committee on the Biological Effects of Ionizing Radiation (hereafter referred to as BEIR V; NAS90) were used. A number of meta-analyses of studies of radiogenic cancers have been carried out (NAS72, NAS80, NAS90, UNS77, UN88, ICRP91), primarily for the purposes of risk assessment. The BEIR V report superseded the earlier reviews because it included more up-to-date data on exposed populations and used the revised dosimetry on the atomic bomb survivors (Ma86).

Estimates of the risk of cancer from exposure to low doses of ionizing radiation were extrapolated by the BEIR V Committee from observations of populations exposed to high doses. Aside from studies of the A-bomb survivors (Sh89, Sh90), the studies were carried out on persons who had a variety of medical conditions and who were intentionally exposed to x-rays for therapy or diagnosis. Radiation therapy involves the use of high energy x-rays to kill living tissue and, currently, its use is restricted to the treatment of malignant disease. In the past x-ray therapy was also used for treating infectious diseases and reducing inflammation, and persons were exposed for a variety of conditions including: tinea capitis (Ro84a, Ro89, Sh85); ankylosing spondylitis (Da87a); postpartum mastitis (Sh86b); enlarged thymus gland (Sh85); and, benign head and neck conditions such as enlarged tonsils and adenoids (Fa76). For diagnostic purposes, x-rays of lower energy were used to image anatomical structures, and the studies of persons exposed to diagnostic x-ray radiation include women with pulmonary tuberculosis who were monitored with fluoroscopic images (Hr89, Mi89), and women with scoliosis (Ho89).

Selected characteristics of the studies used to estimate thyroid cancer and breast cancer risks, attributable to radiation, are presented in table 2.2. With the exception of thyroid cancer among A-bomb survivors, breast cancer among women with scoliosis and among women with tinea capitis, all the studies in the table were used in analyses by the BEIR V Committee. One study used by the BEIR V Committee, that of persons with ankylosing spondylitis irradiated in the United Kingdom (Da87a), was not included in the literature review because organ-specific risks for breast and thyroid cancer were not estimable from the published report.

Atomic Bomb Studies

The most important study for estimating the cancer risk among persons exposed to ionizing radiation is that of 120,132 residents of Hiroshima and Nagasaki irradiated after the detonation of the A-bombs in 1945. (This study is referred to as the Life Span Study). There were 91,228 residents exposed to radiation. The remainder, who were exposed to low doses (< 1 cGy) or were not in the city at the time of the bombing, has served as a comparison group. Individual dose estimates were revised in 1986 (known as DS86) for a sub-cohort of 75,991 subjects (Ro87), replacing the older dosimetry (known as T65D) published in the 1960s (Mi68). The new estimates incorporated each subject's orientation and the amount of local shielding upon detonation. Absorbed whole-body doses ranged from zero to 600 cGy, with a mean whole-body dose of 295 cGy[1]. By 1985, this sub-cohort had been under observation for an average of 39 years, yielding some

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1 Radiation doses are presented using an SI unit called the gray, abbreviated *Gy*. The Gy has replaced the rad in the radioepidemiologic literature, and the conversion between the two units is one Gy equals 100 rad. In this thesis doses will be reported in centiGray (abbreviated *cGy*; one rad = one cGy).

2,185,000 person-years at risk[2] and approximately 6,000 cancer deaths among both men and women (Sh89, Sh90). This is the only cohort in which both women and men of all ages, including *in utero*, were exposed to radiation.

Subjects who were exposed *in utero* or as children are just now entering the age range in which solid tumors becomes an appreciable cause of death in the general population. Consequently, estimates of risk for solid tumors among younger subjects (less than ten years of age at the time of bombing) have greater uncertainty than estimates for subjects exposed later in life (Sh90).

Deaths have been ascertained routinely from the Japanese household registries, in which ascertainment is almost complete (Sh86a). Cancer mortality has most recently been analyzed from 1950 until 1985 for the DS86 sub-cohort (Sh89, Sh90) and these data comprised the largest source of information used by the BEIR V Committee. The reference group comprised those residents of Hiroshima and Nagasaki whose dose was less than one cGy and those persons who were not in the city when the bombs were detonated. For breast cancer, the relative risk for all exposed women was 1.6 (90% confidence interval, 1.3-1.5). Other cancers that showed a statistically significant ($p < 0.05$) increased mortality were leukemia, cancers of the esophagus, stomach, colon, lung, ovary, and the urinary tract, and multiple myeloma. Risks for cancers of the skin, rectum, gallbladder, pancreas, uterus, and prostate and malignant lymphoma were not elevated. The excess risk of breast cancer mortality per unit dose was 2.2% per cGy (90% confidence interval, 1.6% to 3.1%).

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2 This value does not correspond to the value in table 2.2 because it includes the person-years of both women and men.

Table 2.2 Selected characteristics of studies used to estimate the effect of ionizing radiation on breast cancer and thyroid cancer risks.

Study Cohort/ reference	Study (S) and referent (R) populations	Type of study[a]	Period exposed	Period of follow-up	Number of subjects		Proportion traced		Person-years of observation		Number of cancers		Mean dose (cGy)	Relative risk (exposed to unexposed)	95% CI
					Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed			
Female breast cancer															
USA thymus Hi89	S Infants irradiated for enlarged thymus R Unexposed sisters	I	1926-57	1926-85	1,201	2,469	90	90	38,200	87,202	22	12	69	3.6	1.8 - 7.3
USA mastitis Sh86	S Women irradiated for postpartum mastitis R Unexposed mastitis patients and sisters	I	1940-60	1945-82[e]	601	1,239	93	91	17,670	36,300	56	59	371	3.2	2.3 - 4.3[j]
Israel ringworm[b] Mo89	S Girls irradiated for tinea capitis R Population controls, unirradiated siblings	I	1949-59	1955-86	5,541	8,097	98	98	NE	NE	13	9	2	2.1	1.1 - 4.2
USA fluoroscopy Hr89	S Women irradiated during pneumothorax R Unexposed tuberculosis patients	M	1930-56	1930-80	1,044	698	98	97	30,932	21,486	55	19	96	1.9	1.2 - 2.8
A-bomb survivors To87	S Women irradiated during A-bomb attacks R Unexposed and low exposure (< 0.5 cGy)	I	1945	1950-80	63,275[c]	NA	> 96	> 96	1,339,300[f]	877,800[f]	154	258	309[d]	NE	NE
A-bomb survivors Sh89 Sh90	S Women irradiated during A-bomb attacks R Unexposed and low exposure (< 1 cGy)	M	1945	1950-85	25,252	20,305	> 96	> 96	602,930[g]	747,511[g]	98	57	240	1.5	1.3 - 1.6[j]
Canad. fluoroscopy Mi89	S Women irradiated during pneumothorax R Low exposure (< 10 cGy)	M	1930-52	1950-80	31,710[c]	NA	96[h]	96[h]	NE	NE	319	163	NE	1.4	1.1 - 1.7
USA scoliosis[b] Ho89	S Women irradiated for scoliosis R Cancer rates from Connecticut	I	1935-65	1938-86	1,030	NA	92	NA	21,691	NA	11	6[j]	13	1.8	1.0 - 3.0
Thyroid cancer															
USA thymus Sh85	S Infants irradiated for enlarged thymus R Unexposed siblings	I	1926-57	1953-82	2,413	4,819	88	88	59,034	118,157	27	1	123	49.1	17 - 225
Israel ringworm Ro84	S Children irradiated for tinea capitis R Population controls, unexposed siblings	I	1949-59	1955-78	10,842	16,262	100	100	367,289	612,198	29	8	9	5.4	2.7 - 10.8
A-bomb survivors[b] Pr82	S Persons irradiated during A-bomb attacks R Unexposed and low exposure (< 0.01 Gy)	I	1945	1959-78	98,610[c]	NA	NA	NA	44,531	54,079	70	42	NE[d]	2.2	NE

CI - confidence interval NA - not applicable NE - not reported or estimable in the published paper.

[a] Incidence (I) or mortality (M)

[b] Not included in the BEIR V analyses

[c] Includes both index cases and referents

[d] Based on older dosimetry system and not used for modelling risk (Mi68)

[e] Closing date of follow-up inferred

[f] Includes all women in the Life Span Study (Sh86a)

[g] Includes sub-cohort of women in the Life Span Study whose dose estimates were revised

[h] From estimates of the accuracy of probabilistic record linkage in Canada (Co92)

[i] Expected from population rates

[j] 90% confidence interval reported

The incidence of breast cancer was also evaluated in the Life Span Study cohort (To87), based on interim dose estimates calculated only for the breast tissue. The interim dose estimates were used because the dosimetry from the 1960s (T65D) was known to be incorrect and the new dosimetry (DS86) was not available to the investigators. The interim doses were about 20 percent higher than the revised DS86 estimates. The estimated increased risk of breast cancer incidence was about 1.7% per cGy (90% confidence interval, 1.4% to 2.0%)

Breast cancer among women with postpartum mastitis

Acute postpartum mastitis is an infectious inflammatory condition of the maternal breast that may occur at childbirth or during lactation. In the United States during the 1940s and 1950s x-rays were used to reduce inflammation. A typical course of therapy consisted of one to ten exposures of x-ray radiation over a period of several weeks (Sh77b, Sh86b). The risk of breast cancer among women with postpartum mastitis was investigated in a cohort of 601 women treated in New York State. The study included three unexposed comparison groups: one consisted of 663 sisters of the irradiated subjects; a second comparison group consisted of 384 postpartum mastitis patients treated by other means; and the third comparison group consisted of 192 siblings of the second group. Vital status and breast cancer incidence were ascertained using a postal questionnaire and other direct follow-up procedures (the response rate was over 90%). For each case of breast cancer reported, the diagnosis was verified from medical records. Records of the number of x-ray exposures were used to estimate the dose, which ranged from 40 to 1,200 cGy.

The dose-response curve appeared to be linear, with a diminution of risk at doses greater than 700 cGy. Significant increases in risk were observed for all ages at exposure (14 to

45 years old). The relative risk of breast cancer among exposed women compared to all referents was 3.2 (90% confidence interval, 2.3 to 4.3). A linear multiplicative relative risk regression model (Th81) was used to estimate an excess risk of 0.6% per cGy (95% confidence interval, 0.4% to 0.8%). Detailed analysis of the effects of fractionating the doses showed that neither the number of x-ray treatments, the number of days between treatments, nor the dose per treatment had any apparent effect on the increased risk of breast cancer. Although the number of breast cancer cases (n=56) was probably too small to detect the effects of dose fractionation, a finding of no effect is consistent with other studies.

Breast cancer and thyroid cancer among children with tinea capitis

Cancer incidence was ascertained in children treated with x-ray therapy for ringworm of the scalp (*tinea capitis*) in Israel during the 1940s and 1950s (Mo89, Ro84a, Ro89). Records from four treatment centers were used to assemble the cohort of 10,842 subjects. Two comparison groups were used. The first group consisted of children without tinea capitis selected from the Israeli Central Population Registry and the second group was composed of unexposed siblings of treated children. Records of all subjects were linked to the Israel Cancer Registry. For subjects identified as having a malignant tumor, confirmation was sought from the pathology records of the treating hospitals.

X-ray exposures were measured using plastic phantoms, under conditions similar to those employed during therapy (We68). The estimated mean dose to the thyroid gland was nine cGy and the mean dose to the female breast was 1.6 cGy. The average age at irradiation was seven years, and 96 percent of subjects were irradiated before fifteen years of age. Excess relative risks were observed for tumors of the thyroid gland (both benign and malignant), central nervous system cancers and leukemia (Ro84a). Subjects

irradiated under the age of five years were found to be at significantly higher risk to develop thyroid tumors than older children. A linear dose-response relationship was consistent with the data for thyroid tumors (Ro89).

In a separate analysis, a statistically significant excess of breast cancers was also observed in one subgroup, that of women who were five to nine years old when treated (Mo89). The observation that the relative risk of breast cancer was significantly increased is remarkable because of the relatively low dose to the breast (1.6 cGy). This translated into an estimated increased risk of breast cancer in this subgroup of 69.4% per cGy (90% confidence limits, 3.1% to 202.5%), which was higher, by an order of magnitude, than the risk observed in any of the studies used in the BEIR V analyses. It must be borne in mind that the excess risk was based on only a small number of cases (n=10), and it will be of interest to see if the risks remain as elevated in further follow-up of the cohort. Data on breast cancer incidence from this cohort were not used by the BEIR V Committee, presumably because the BEIR V analyses were conducted before the results were available.

Women irradiated as infants for enlarged thymus

During the first half of this century, a condition called *status thymicolymphaticus* that is characterized by enlargement of the thymus gland, was thought to cause sudden death in otherwise healthy infants (Sa60, Hi89). Diagnosis and treatment of this condition varied widely; in some institutions no treatment was given while in others all newborns were screened radiographically and were sometimes given x-ray radiation treatment if a supracardiac shadow was observed. Radiation treatment for thymic enlargement ended in the late 1950s when it was recognized that an enlarged thymus was not pathologic.

In order to assess the excess risk of breast cancer, Hildreth and colleagues carried out a cohort study of children living in Monroe County, New York who, between 1926 and 1957, received x-ray therapy for enlarged thymus (Hi89). About 1,200 women so irradiated were identified from medical records in hospitals and in private clinics. The comparison group consisted of non-irradiated sisters of study subjects. Postal questionnaires and telephone interviews were used to ascertain cases of breast cancer, and the diagnosis was verified by a pathologist who reviewed hospital records. Response rates were similar in both groups: about 85 percent of subjects were traced, five percent were deceased, and ten percent refused to participate or were lost to follow-up.

Radiation doses to the breast were estimated using the number and view of x-ray exposures, average energies of the x-ray beams used for therapy, and Monte Carlo radiation transport methods (Hi85, Pi63, Ro79). The estimated mean dose was 69 cGy. After an average of 36 years of follow-up, there were 22 breast cancers in the irradiated group and twelve among their sisters, yielding a relative risk of 3.6 (95% confidence interval, 1.8 to 7.3). Using population rates from upstate New York, the standardized incidence ratio was calculated and found to be similar to the relative risk. The dose-response relationship was compatible with linearity, and the increased risk of breast cancer was estimated at 2.5% per cGy (95% confidence interval, 1.1% to 5.2%).

Breast cancer among women with pulmonary tuberculosis

Women diagnosed with pulmonary tuberculosis in the 1930s and 1940s were commonly treated by pneumothorax (*i.e.* deliberate deflation of the lung, also called air collapse therapy). During therapy the lungs were monitored by fluoroscopic examination. Patients were typically treated every two weeks, sometimes for five years or more. Data have been collected on two groups of women treated in tuberculosis sanitaria, one

group in Canada and the other group in the United States.

In the first study, Hrubec and colleagues followed women treated in tuberculosis sanitaria in Massachusetts (Bo77, Hr89). Subjects were followed until 1980, and the breast cancer incidence among 1,044 women exposed to radiation at the time of pneumothorax therapy was compared to the incidence among 698 women who were treated for tuberculosis by other means but did not receive fluoroscopic examinations. Breast cancer cases were ascertained through postal questionnaires and through the use of hospital records and death certificates. On average, subjects were treated for 3.3 years and exposed to 102 fluoroscopic examinations. Doses to the breast were estimated from the number of fluoroscopies, reconstruction of exposure conditions, and Monte Carlo dose simulations (Bo78a). The cumulative mean dose to the breast was estimated at 96 cGy. The relative risk for exposed women was 1.9 (95% confidence interval, 1.2 to 2.8). The excess risk of breast cancer was 0.7% per cGy (95% confidence limits 0.0% to 1.4%). The dose-response curve was consistent with a linear relationship over the entire dose range (from zero to 400 cGy). The risk of breast cancer increased with decreasing age at exposure and was highest in those aged fifteen to nineteen years at exposure (table 2.3, page 30).

In the second study, breast cancer mortality was ascertained for a cohort of women treated in tuberculosis sanitaria in Canada (Ho84, Mi89). Records in all Canadian sanitaria were searched by trained clerks to identify patients admitted between 1930 and 1952. A total of 46 institutions contributed data from all provinces in Canada except Newfoundland. The records of the cohort were linked to the Canadian Mortality Data Base. This data base contains identifying information (e.g. name, sex, birthdate and date of death) and underlying causes of death for all persons deceased in Canada from 1940 onwards. More than 95 percent of deaths can be ascertained accurately using this

method (Go92). Deaths during the period 1940 to 1949 were identified through a record linkage and deceased subjects were eliminated from further follow-up. Thus, the period of follow-up used for the Canadian tuberculosis study was from 1950 to 1980, and the cohort comprised 31,710 women. Doses were estimated using similar techniques to those used for the Massachusetts fluoroscopy cohort (Sh78b).

The comparison group consisted of women exposed to less than 10 cGy (La79). This allowed the inclusion of women with no reported pneumothorax therapy, but who nevertheless may have had some radiation exposure from chest radiographs. Although risks may have been slightly underestimated because the reference group had some exposure, the exposed and referent groups were probably more comparable on other factors associated with breast cancer than otherwise would have been achieved through the use of an external reference group. The risk of breast cancer in exposed women compared to referents was 1.4 (95% confidence interval, 1.1 to 1.7). Risk was greatest among women who had been exposed to radiation between ten and fourteen years of age, where the estimated excess risk of breast cancer from radiation was 4.5% per cGy (95% confidence interval, 0.1% to 40.2%). A linear dose-response relationship was consistent with the data. The risk increased with decreasing age at first exposure, and the risk was greatest 25 to 34 years after first exposure (table 2.3, page 30).

Women diagnosed with x-rays for scoliosis

The risk of breast cancer from diagnostic irradiation for scoliosis has been estimated in only one study (Ho87, Ho89). The cohort consisted of 1,030 women diagnosed with scoliosis or kyphosis, from 1925 through 1965, in three hospitals and in one clinic in Minneapolis-St. Paul, Minnesota. The women were followed-up until 1986. Postal questionnaires and telephone interviews were used to obtain details on various medical

conditions including breast cancer and relevant risk factors. The response rate was over 92 percent. For each reported breast cancer, a pathological confirmation was obtained from the hospital where the diagnosis was made.

Breast doses were estimated using the number of full-spinal radiographs, the orientation of the patient (*i.e.* the view), and typical x-ray beam energies used to make the radiographs. An average of 41 full-spinal radiographs per woman were made, and this yielded a mean dose of 12.8 cGy to the breast. Among 1,030 women, eleven breast cancers were observed compared with six expected according to Connecticut Tumor Registry rates (He86), and the standardized incidence ratio was 1.8 (95% confidence interval, 1.0 to 3.0). The excess risk of breast cancer was estimated at 6.4% per cGy (90% confidence interval, 0.0% to 15.6%).

Summary of the observed risks of breast and thyroid cancer

In general, the risk of breast cancer increases with radiation exposure, and statistically significant increased risks have been observed to result from cumulative x-ray doses less than 15 cGy (Ho89, Mo89). There is no evidence for the existence of a threshold dose below which there are no increased risks (NAS90). The risk of radiation-induced breast cancer appears to be greatest among women exposed at ages younger than 20 years. There is evidence to suggest that breast tissue may be at increased risk when the breast cells are multiplying, such as during menarche and pregnancy (Bo78b). There is no evidence that cancers due to radiation occur before age 25 years, the age at which breast cancers from other causes usually appear (Hi89). There is no evidence of a change in risk when the cumulative radiation dose is received in multiple exposures rather than a brief single exposure *i.e.* fractionated doses appear to carry the same risks as single doses (Sh86b, Mi89). A latent period of at least ten years between first exposure and disease

expression has been observed in all the studies. The existence of a maximal latent period (*i.e.* a plateau) after which the risk decreases cannot be determined from available data; however, if one exists, it must be greater than 30 years (NAS90).

Table 2.3 presents a summary of the excess risks of breast cancer and thyroid cancer after exposure to radiation. Risks are expressed as the percent increase per cGy, and, where possible, according to age at exposure. For studies in which the excess risk per cGy was not presented, the parameter was estimated using the equation:

$$\% \text{ excess relative risk} = \frac{\text{Relative risk of cancer} - 1}{\text{mean organ dose (in cGy)}}$$

Thyroid cancer was the first of the solid tumors to occur at increased frequency among A-bomb survivors (Ho63, Pa74, Pr82, So63). Other than the A-bomb survivors, cohort studies of thyroid cancer after radiation therapy have been carried out among infants exposed for enlarged thymus in the USA (Sh85) and children exposed for tinea capitis in Israel (Ro84a, Ro89). In all three studies, the excess risks of thyroid cancer were observed to increase with cumulative radiation dose. The highest excess risks of thyroid cancer have been observed in persons exposed in their youth (Sh85). Statistically significant increased risks of thyroid cancer have been observed from doses as low as 6 cGy (Ro84a).

Table 2.3. Estimates of the lifetime excess risk of cancer percent per cGy in cohort studies of persons exposed to ionizing radiation.

Study Cohort (Reference)	Number exposed	Age at exposure (years)	% excess relative risk per cGy	(95% CI)
		Female breast cancer		
Scoliosis (Ho89)	1,030	All ages	6.4[a]	0.0 - 15.6[b]
	50	< 5	9.4[a]	-3.4 - 61.1[b]
	141	5-9	14.8[a]	-2.4 - 58.6[b]
	574	10-14	-3.5[a]	-7.9 - 7.9[b]
	265	≥ 15	21.0[a]	4.0 - 52.0[b]
Tinea capitis (Mo89)	5,541	1-15 (mostly 3-8)	69.4[a]	3.1 -202.5[b]
Postpartum mastitis (Sh86b)	601	14-49	0.6	0.4 - 0.8
Tuberculosis (Hr89)	1,044	All ages	0.7	0.0 - 1.4
		< 20	1.6	0.4 - 3.8[b]
Tuberculosis (Mi89)	31,710[c]	10-14	4.5	0.1 - 40.2
		15-24	0.8	0.0 - 6.1
		25-34	0.2	0.0 - 1.8
		≥ 35	0.1	0.0 - 1.2
Enlarged thymus (Hi89)	1,201	< 1	2.5	1.1 - 5.2
A-Bomb (To87)	63,275[d]	All ages	1.7	1.4 - 2.0
	NR	≤ 10	5.3	0.9 - 8.7
	NR	10-19	1.6	1.9 - 2.3
	NR	20-29	0.2	-0.2 - 0.6
	NR	30-39	0.4	-0.2 - 1.0
A-Bomb (Sh89, Sh90)	25,252[d]	All ages	2.2	1.6 - 3.1[b]
	NR	≤ 10	1.1	NE
	NR	10-19	2.2	NE
	NR	20-29	0.8	NE
	NR	30-39	1.0	NE
		Thyroid cancer		
Tinea capitis (Ro84)	10,842	All ages	48.9[a]	18.9 -108.9[b]
	3,762	0-5	56.7[a]	NE
	3,660	6-8	44.4[a]	NE
	3,420	9-15	11.1[a]	NE
Enlarged thymus (Sh85)	2,413	< 1	0.6	0.4 - 0.7
A-Bomb (Pr82)	98,119[c,e]	All ages	0.5[a]	NE

NE - not estimable; NR - not reported; CI - confidence interval.

[a] Excess risk not given in original article and was calculated for this thesis (see page 29).

[b] Values are 90% confidence limits.

[c] This value is the total number of persons of all ages in the cohort.

[d] Includes the value for both exposed women and referents of all ages.

[e] Excludes 491 subjects exposed to greater than 400 cGy.

2.5 Models used to estimate radiogenic cancer risk

Data on some of the populations described in section 2.4 were used by the BEIR V Committee to estimate the radiobiologic dose-response relationship for cancer. Continued follow-up of the A-bomb survivors has indicated that the risk of radiogenic cancer is modified by age at exposure, time since exposure, sex, and linear energy transfer of the radiation (Sh89, To87). This was reflected in the BEIR V risk models, that, in addition to dose, included terms for sex, age at exposure and time since exposure. The large number of strata meant that the number of cases of organ-specific cancers in each stratum was small. Because of this problem, individual cancers were grouped as follows: leukemias (International Classification of Diseases, Ninth Revision (ICD9) 204-207), female breast cancer (ICD9 174), cancers of the respiratory system (ICD9 160-163), cancers of the digestive system (ICD9 150-159), and all other cancers combined (ICD9 140 to 209, less those listed above).

Radiobiological theory posits that the probability of forming a biological lesion in DNA depends linearly on dose if a single event is required or on the square of dose if two events are required (NAS90). At very high doses radiation can cause cell death that competes with the process of malignant transformation. The following dose-response relationship incorporates these features:

$$M(D) = (a_1 D + a_2 D^2) \exp(-\beta_1 D - \beta_2 D^2) \qquad (2.1)$$

where D is the radiation dose, and M(D) is the relative risk or excess cancer mortality rate (depending on whether risks are multiplicative or additive), and a_1, a_2, β_1 and β_2 are coefficients estimated from the data. Doses greater than four hundred cGy were excluded so that cell death was assumed to be negligible (*i.e.* $\beta_1 = \beta_2 = 0$). The precise relationship between risk and radiation dose depends on the site of cancer under study. The BEIR V Committee assumed that for cancers other than leukemia, excess mortality

increased linearly (*i.e.* a_2 equal to zero). For leukemia, the observed data on mortality were more compatible with a linear-quadratic dose-response relationship (*i.e.* a_2 not equal to zero).

In the past, two types of models have been used to determine how excess risks from radiation relate to the background risk of cancer. The absolute risk model assumes that the risk of radiogenic cancer is increased over background by a constant additive amount for all ages after exposure. The relative risk model assumes that the age-specific risk in persons exposed is a multiple of the corresponding risk in those not exposed. This latter model implies that the excess risk of cancer increases proportionately with age because the background rate increases. Expressed mathematically, these models can be represented as follows:

$$\text{Absolute risk model: Risk } (A;D,E) = b_0(A) + M(D,A,E) \qquad (2.2)$$

$$\text{Relative risk model: Risk } (A;D,E) = b_0(A)\,[1 + M(D,A,E)] \qquad (2.3)$$

where $b_0(A)$ represents the baseline rate in unexposed persons, D is the dose, A is attained age and E is age at exposure. The function M(D,A,E) is estimated from the data. Among A-bomb survivors, the age-specific number of excess cancers induced by radiation increased with attained age, while the risk of radiogenic cancer relative to the background incidence remained relatively constant (Sh89). This finding led the BEIR V Committee to adopt relative risk models instead of absolute risk models to estimate excess cancers due to radiation. Generalizing the dose-response relation (2.1) to include terms for age at exposure and time since exposure yields a general relative risk model of the form:

$$M(D,A,E) = (a_1 D + a_2 D^2)\exp[c_1 f(A) + c_2 g(E) + c_3 h(A-E)] \qquad (2.4)$$

where D is dose, f(A) is a function of age at risk, g(E) is a function of age at exposure, and

h(A-E) is a function of time since exposure, and the coefficients a_1, a_2, c_1, c_2 and c_3 are estimated from the data.

The BEIR V Committee also incorporated a *latency period*, in which all cancer deaths and person-years of observation were excluded. Thus, it was assumed that any cancers caused by radiation could only occur after some minimum time has elapsed. The latency periods used by the BEIR V Committee were: ten years for solid tumors other than breast cancer, five years for breast cancer, and two years for leukemia. After incorporating these latency periods, the relative risk of cancer was assumed to be constant for all ages up to 100 years.

The BEIR V risk estimates were about three to five times larger for solid cancers and four to five times larger for leukemia than those reported by the BEIR III Committee (NAS80). These differences arose mainly from the revised A-bomb dosimetries (called DS86) and the increased length of follow-up of the A-bomb cohort. The new dosimetry accounted for individual shielding and orientation when the bombs were detonated (Ma86, Ro87). Overall, under the new dosimetry (DS86), average organ-specific doses were lower than earlier dose estimates (T65D; Sh89). Because the estimated average organ-specific doses were lower under DS86, the risk per unit dose increased. Higher risk estimates were also due to increased follow-up of the A-bomb cohort and due to the use of multiplicative risk models that included for solid tumors only a linear term for dose.

On the other hand, the life table method used by BEIR V yielded fewer excess cancer deaths than earlier Committees; given the same dose and the same estimate of relative risk, the method used by BEIR V tended to produce estimates of excess cancers that were about 20 percent lower than BEIR III (El91). In BEIR V, the lifetime number of excess cancer deaths was calculated as the difference between the total number of

deaths in an exposed and an unexposed population. In contrast, earlier Committees (NAS80, UN77, UN88) calculated the number of cancer deaths by applying the difference in cause-specific death rates between an exposed and an unexposed population to a hypothetical population at the beginning of each age interval. The total excess was obtained by summing over all age intervals. Because an exposed population has smaller survival probabilities, the method used by the BEIR V Committee produced fewer excess cancers (NAS90). Both methods are correct and the best measure of risk is probably found between the two estimates (El91).

Risk model for breast cancer

The BEIR V model for the risk of female breast cancer *mortality* was based on the analysis of risks observed in the Canadian Tuberculosis Fluoroscopy study (Mi89) and the DS86 subcohort of the Life Span Study of atomic bomb survivors (Sh89, Sh90). A similar analysis of breast cancer *incidence* was based on the Life Span Study cohort (To87), the New York acute postpartum mastitis study (Sh86), and the Massachusetts tuberculosis study (Hr89). Although the Committee stated that the mortality and incidence models predicted similar relative risks, only the Committee's final model for mortality was presented in the BEIR V report. The main difference between the two models was that incidence peaks at 15 to 20 years after exposure and mortality about five years later. In addition to dose, the important predictors of breast cancer mortality were age at exposure and time since exposure. Risks were highest among women under fifteen years of age at exposure and risks were lowest among women exposed at ages greater than 40 years (NAS90). The relative risk model for breast cancer mortality was:

$$\text{Relative risk} = 1 + f(D) \times g(A,E), \text{ where} \qquad (2.5)$$
$$f(D) = a_1 D$$

$$g(A,E) = \exp[\beta_1 + \beta_2 \ln((A-E)/20) + \beta_3 \ln^2((A-E)/20)] \quad \text{if age at exposure} \leq 15 \text{ years}$$
$$\exp[\beta_2 \ln((A-E)/20) + \beta_3 \ln^2((A-E)/20) + \beta_4(E-15)] \quad \text{if age at exposure} > 15 \text{ years}$$

The coefficients and their standard errors (in parentheses) were: a_1 = 1.220 (0.610), β_1 = 1.385 (0.554), β_2 = -0.104 (0.804), β_3 = -2.212 (1.376) and β_4 = -0.0628 (0.0321).

Risk model for thyroid cancer

To model the excess risk of thyroid cancer, the BEIR V Committee used data from the Israeli tinea capitis study (Ro84a, Ro89) and the Rochester thymus study (Sh85). Data from the Japanese cohort were not used because the most recent follow-up study of thyroid cancers (Pr82) was based on the older dosimetry. The BEIR V analyses indicated that relative risk models were more appropriate than absolute risk models for projecting excess thyroid cancers. The final model chosen by the Committee was based on a subgroup of the Israeli tinea capitis study consisting of Israeli-born children who were five to fifteen years of age at exposure. Because the BEIR V Committee did not publish the estimates of the standard errors associated with the coefficients for dose, it was decided to reanalyze the data. A relative risk model of thyroid cancer was obtained and was based on the entire Israeli tinea capitis cohort. Data from the Rochester thymus study (Sh85) were not used because the dose to that cohort (mean dose of 119 cGy) was much higher than in the tinea capitis study (mean dose of 9 cGy). Thus, exclusion of the Rochester thymus study did not adversely affect the ability to estimate risk at the low doses observed in this thesis.

For the analysis done for this thesis, the data from the Israeli tinea capitis study (table IV of Ro89) are reproduced in table 2.4 (columns one to four). The authors presented the data with both sexes and all ages grouped. Also presented in table 2.4 are the relative risks of thyroid cancer for each dose category (columns five to seven). Crude relative risks and those adjusted for sex, ethnic origin, and attained age were taken from the

original article (Ro89). Because the data were consistent with a linear dose term (NAS90), Poisson regression was used to model the natural logarithm of the rate of thyroid cancer as a linear function of dose. The addition of a quadratic term for mean dose did not significantly improve the fit of the data. It was not possible to examine how the risk of thyroid cancer was modified by sex, age at exposure, and time since exposure. The final risk model was:

$$\log(\text{incidence rate}) = a_0 + a_1 D \qquad (2.6)$$

where D is the dose (in Gy), $a_0 = -9.867$, and $a_1 = 9.540$ (standard error = 1.913). The coefficient a_1 is interpreted as the log relative risk of developing thyroid cancer per unit dose of radiation. The BEIR V Committee's final model for thyroid cancer, based on Israeli-born children aged five to fifteen years when treated, yielded $a_1 = 8.3$ (standard error not given) which was relatively close to the value obtained for this thesis. The final column of the table presents the estimates of relative risk obtained for each mean dose using the model derived for this thesis. The modelled relative risks were slightly lower than the crude and adjusted relative risks in the two lower dose categories, and slightly higher in the highest dose categories, but overall the estimates were consistent with those estimated by Ron *et al* (Ro89).

Table 2.4. Relative risks of thyroid cancer for children therapeutically irradiated for tinea capitis[1]

Dose range (cGy)	Mean dose (cGy)	Person-years of follow-up	Number of cases[2]	Relative Risk		
				Crude	Adjusted[3]	Modelled[4]
0	0	412,030	16	1.0	1.0	1.0
4-7	6.2	106,690	15	3.6	3.3	1.8
8-14	10.2	149,720	24	4.1	4.2	2.7
15-50	21.4	17,770	4	5.8	6.1	7.7

[1] Data from Table IV (Ro89).
[2] Cases of malignant thyroid cancer.
[3] Presented in Table IV (Ro89) and adjusted for sex, ethnic origin, and attained age.
[4] Predicted relative risks using the model obtained from the Poisson regression analysis.

3. OBJECTIVES

This thesis was undertaken in order to assess the risk of cancer among patients exposed to diagnostic x-ray radiation for the investigation of AIS. As indicated previously, the thesis is based on a follow-up study of subjects referred for adolescent idiopathic scoliosis to Hôpital Ste-Justine, Montréal, during the period 1960 to 1979. (The study group will be referred to as the "AIS cohort".)

The objectives of this thesis are:

1) to determine the frequency distribution of diagnostic spinal radiographs among subjects enrolled in the AIS cohort;

2) to estimate among AIS subjects the distribution of cumulative doses of x-ray radiation from spinal radiographs delivered to the female breast and the thyroid gland; and,

3) to estimate among AIS subjects the lifetime number of female breast cancers and thyroid cancers attributable to radiation from spinal radiographs.

4. Materials and Methods

4.1 The AIS Cohort

The AIS cohort included all persons referred to Hôpital Ste-Justine for idiopathic scoliosis between 1960 and 1979 (Po87). There were two characteristic time periods of enrollment for the cohort. From 1960 to 1964, only subjects with fairly severe scoliotic curves were referred to the hospital for treatment. In 1965, a scoliosis clinic was established at the hospital, and thus, from 1965 onwards, subjects having varying degrees of scoliosis were referred. While persons with other types of scoliosis were also referred to the clinic, the cohort included only subjects with AIS and excluded persons with the following concomitant conditions: paralytic or congenital scoliosis; spina bifida; polio; cerebral palsy; heart defects; and malignant or benign tumors.

4.2 Spinal radiographs for scoliosis

At the initial visit for scoliosis, patients were seen by an orthopedic surgeon and received one or more radiographs of the spine. Follow-up visits were scheduled every three to twelve months. During these visits full-spinal radiographs were taken to monitor the progression of the curve. Spinal radiographs for scoliosis were taken using large films (14 x 36 inches) in order to view as much of the spine as possible; it is recommended that radiographs for scoliosis include the area from the vertex of the skull to hip level (epiphyses of the iliac crests; Cl64). Spinal radiographs were taken with the patient positioned between the x-ray machine and the radiographic film, and oriented with respect to the x-ray beam. The x-ray tube was adjusted to the appropriate distance and angle, and the machine was set to the required energy level. Figure 1 shows the layout for a typical anteroposterior spinal radiograph for scoliosis.

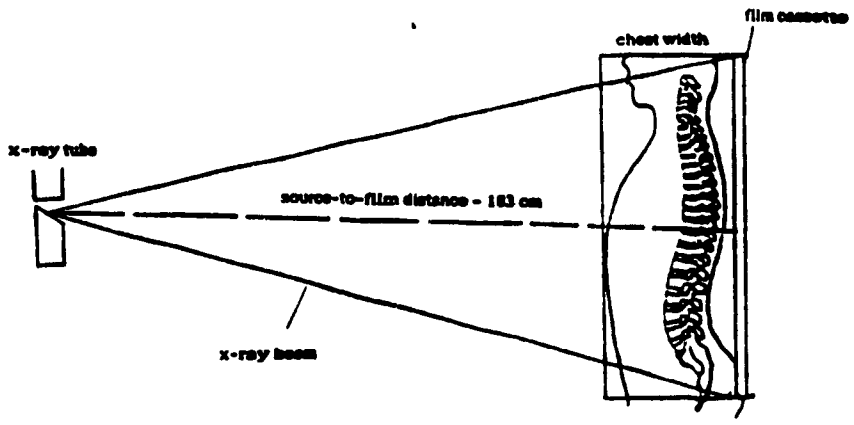

Figure 1. Setup for an anteroposterior full-spinal radiograph. Adapted from Bh81.

Scoliotic curves were measured from anteroposterior spinal radiographs taken in the standing position using the method of Cobb (Co48). Standing lateral and oblique views, taken with the patient's body rotated 90 degrees and 45 degrees with respect to the x-ray beam, respectively, were used to measure the degree of vertebral rotation. During surgery, only the posteroanterior view was taken because the patient was face down on the operating table.

The requisition form used to order the radiographs specified the projection (*i.e.* anatomical structure to be x-rayed) and the view (*i.e.* the orientation with respect to the x-ray beam; namely anteroposterior, lateral, oblique or posteroanterior). On the requisition form would be written the number of films of each view actually taken, including the number of radiographs that were repeated because of inferior images. A copy of the form was placed in the medical chart. For each spinal radiograph taken of each subject, the date, projection and view of each radiograph and the measured Cobb angle was abstracted from the medical chart. (In addition, the subject's sex, date of birth, and dates of first and last visits to the hospital were obtained.)

4.3 X-ray machine settings and geometric characteristics

Before describing the data used for projecting risk, it is useful to describe the physical processes involved in producing diagnostic radiographs and to introduce relevant terminology. The terminology that is used in calculating x-ray doses is summarized in table 4.1. X-rays are produced in x-ray tubes when electrons, accelerated by high voltage in a vacuum, collide with a metallic target of high molecular weight such as tungsten. The property that makes x-rays useful for diagnosis is their ability to penetrate matter. When passing through a human body, x-rays are transmitted, scattered and differentially absorbed by tissues. The amount of radiant energy absorbed depends on the tissue density and the energy of the x-ray photons. As bones are denser than soft tissues, they absorb more x-ray photons and thus fewer photons bombard the film. The number of photons striking the film is recorded by changes in the physical state of silver compounds coating the x-ray film.

Three characteristics that affect the energy of the emergent x-ray beam are the electrical current, the exposure time, and the voltage potential across the x-ray tube. The quantity of electrical current running through a filament circuit is defined by the amperage and, on an x-ray machine, the amperage is controlled by a rheostat in the circuit. The higher the amperage the greater the flux (or number of photons) of x-rays produced. The exposure time, measured in seconds (abbreviated *s*), is the amount of time in which the beam is discharged. Because milliamperage (abbreviated *mA*) represents the amount of current, multiplying mA by the exposure time s yields the total amount of electrical current flowing over that time. The intensity (or flux) of the x-ray beam integrated over time is proportional to mAs. The x-ray tube voltage is a measure of electrical energy. The frequency (or energy) of the emitted photons is proportional to the voltage (Fo72).

Table 4.1. Summary of terms related to organ-specific dose calculations.

Characteristic	Unit of measurement (abbreviation)	Groupings
Machine settings		
Peak tube potential	kilovolts (kV)	3 time periods: 1957-78, 1979-81, 1982-89 3 body sizes: children, adolescents, adults
Current	milliamperes (mA)	3 time periods: 1957-78, 1979-81, 1982-89 3 body sizes: children, adolescents, adults
Exposure time	seconds (s)	3 time periods: 1957-78, 1979-81, 1982-89 3 body sizes: children, adolescents, adults
Beam output	milliroentgens[1] per mAs (mR/mAs)	4 years: 1977, 1978, 1980, 1982
Geometric characteristics		
Source-to-film distance	centimeters (cm)	3 body sizes: children, adolescents, adults 2 views: anteroposterior, lateral
Source-to-skin distance[2]	centimeters (cm)	3 body sizes: children, adolescents, adults 2 views: anteroposterior, lateral
Film size	centimeters (cm)	1 size (35.6 by 91.4 cm)
Film cassette	centimeters (cm)	1 size (3 cm)
Other parameters required for dose calculations		
Half-value layer	millimeters aluminum (mm Al)	2 time periods: 1957-78, 1979-89
Skin exposure	roentgen (R)	3 time periods: 1957-78, 1979-81, 1982-89 3 body sizes: children, adolescents, adults 2 views: anteroposterior, lateral

[1] One roentgen is equivalent to 2.58×10^{-4} coulombs per kilogram of air
[2] Calculated as: {Source-to-film distance - (Source-to-skin distance + cassette width)}

When electrons strike an x-ray anode target, they impart different energies to the molecules in the target and, thus, the emitted x-ray beam comprises photons with a distribution of energies. The maximum voltage attained during an electrical cycle (referred to as "kilovolt peak", abbreviated kV) is the parameter used to characterize this energy distribution (Ca85). The parameters mAs and kV will be collectively referred to as the *machine settings*.

Machine settings were abstracted from log books at the hospital, and those data were supplemented by consultations with radiology technicians who had worked in Hôpital Ste-Justine since the 1970s and were familiar with the x-ray techniques. Machine settings were collected for the anteroposterior and lateral views; the machine settings for the oblique view were the same as those used for the anteroposterior view.

At the hospital, spinal radiographs were made in three rooms. All three rooms housed x-ray machines of the same type, and therefore, the machine settings for all three were assumed to be identical. Machine settings were unchanged from 1957 to 1978. In 1979, the hospital started using higher speed radiographic film and more sensitive types of screens that required x-ray beams of lower energy (*i.e.* lower mAs and lower kV). Modern three-phase x-ray machines were installed in the early 1980s to replace the older single-phase equipment. Three-phase x-ray machines produce an x-ray beam that has a higher average energy with few low energy photons than the beam from single-phase machines (Ca85), thus resulting in an increase in the *useful* proportion of x-rays. Machine settings were lower for the three-phase x-ray machines. Thus, there were three periods of time during which it was assumed that the machine settings were constant; *i.e.* 1957 to 1978, 1979 to 1981, and 1982 to 1989. Because of these changes x-ray exposures to the patient decreased considerably from era to era.

Machine settings also varied according to the size of the subject. In general, x-ray beams of higher energy and intensity (increased kV and mAs) were used for larger individuals. Subjects were classified into three anthropometric categories corresponding roughly to children, adolescents and adults. Thus, for each time period and radiographic view (*i.e.* anteroposterior and lateral), three sets of machine settings were collected corresponding to the three anthropometric categories.

The geometric characteristics needed to calculate organ-specific x-ray doses were the film size, the distance between the x-ray tube and the film (referred to as the source-to-film distance), and the distance between the x-ray tube and the patient (referred to as the source-to-skin distance). These characteristics remained constant over the whole study period; the film size was 17 by 36 inches (35.6 by 91.4 centimeters) and the source-to-film distance was 72 inches (183 centimeters) for all spinal radiographs. The three anthropometric categories, mentioned above with respect to machine settings, were incorporated into the geometric characteristics by subtracting the average anteroposterior chest diameter (also called the mediastinal diameter) from the source-to-film distance to obtain the source-to-skin distance. Children, adolescents, and adults were defined as having an average chest diameter of 14 centimeters, 17 centimeters, and 20 centimeters, respectively. These dimensions correspond approximately to ages less than 9 years, 10 to 17 years and 18 years or older, respectively, based on auxological data collected in the United States (Mo66). The average anteroposterior source-to-skin distances were: 166 centimeters for children, 163 centimeters for adolescents and 160 centimeters for adults. A similar calculation was carried out for lateral source-to-skin distances using a lateral chest diameter (also called the biacromial diameter) of 21 centimeters for children, 25 centimeters for adolescents and 30 centimeters for adults. These figures were based on the lateral chest diameter being approximately 50 percent greater than the anteroposterior thickness (ICRP75). The lateral source-to-skin distances were

therefore calculated as 159 centimeters, 155 centimeters and 150 centimeters for children, adolescents and adults, respectively.

Another parameter used in calculating organ-specific doses is the *half-value layer*, which is defined as the thickness of metal needed to attenuate the intensity of an x-ray beam by one half; it is usually measured in millimeters of aluminum (mm Al). The half-value layer can also be used as a measure of the penetration of the x-ray beam; the higher the half-value layer, the higher the average energy of the x-ray beam. The half-value layer is determined by the filtration of the x-ray machine. About one millimeter of filtration is typically considered the amount inherent in an x-ray tube; filtration may be augmented by inserting aluminum filters in the path of the beam. As there was no information on the amount of filtration added to the machines at Hôpital Ste-Justine, two assumptions about likely half-value layer values were made in consultation with a radiophysicist, Dr. Montague Cohen. In general, aluminum filters were used more sparingly until the late 1970s and, therefore, the half-value layer was assumed to be two millimeters aluminum for the period 1957 to 1978. The 1980s corresponded to more widespread use of filters, and therefore, for the period 1979 to 1989, a half-value layer of 2.5 millimeters aluminum was assumed. If the half-value layer was actually one millimeter of aluminum greater than assumed, the calculated doses would have underestimated the actual doses by fifteen to twenty percent.

4.4 X-ray machine energy output

In addition to machine settings and geometric characteristics of spinal radiographs, average beam energy outputs from the x-ray machines were needed in the dose calculations. Energy outputs were measured by hospital staff during periodic calibration studies of the x-ray machines and were available from the years 1977, 1978, 1980 and

1982. Energy outputs, expressed in units of milliroentgens[3] per 100 milliampere-seconds, were measured during the calibration studies using ionization chambers at a variety of tube potentials. In order to compare x-ray beam outputs between machines and between years, values were standardized to a distance of 100 centimeters using the inverse square law (table 4.2). For example, if the output was measured at 90 centimeters, the value was standardized to 100 centimeters by multiplying by $(90/100)^2$. In the 1980 report, outputs from machine II were measured twice, three months apart, and both sets of measurements were used in the calculations. Reference energy outputs published by the National Commission on Radiation Protection are also included in the table (NCRP68). The NCRP reference outputs for three-phase machines were obtained by multiplying the values from the single-phase machines by a factor of 1.8 (P. Caron, personal communication). The reference values can serve as guidelines for the proper functioning of an x-ray machine, and were obtained by NCRP under experimental conditions from machines that were calibrated with high precision. Under normal operating conditions, the x-ray energy output may vary considerably from the reference values.

From table 4.2 it is evident that there was some variability in energy output between the different x-ray machines used to make spinal radiographs: measured outputs ranged from 30 percent below to 30 percent above the NCRP reference values. Physical deterioration of the x-ray tube could have caused deviations from the ideal energy output; this supposition is substantiated by differences in output from the same machines between 1977 and 1978. X-ray tubes deteriorate with use and must be replaced every several years (the interval depends on the frequency of use).

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[3] The roentgen is not an SI unit but is used here because it is more tractable than the SI equivalent (*i.e.* units of coulomb per kilogram of air).

Table 4.2. Measured beam output[1] of x-ray machines at Hôpital Ste-Justine in milliroentgens/100 milliampere-seconds for 1977, 1978, 1980, and 1982.

Tube potential (kilovolt peak)	Energy output (mR/100 mAs) at 100 cm			
	Reference values[2]	Machine		
		I	II	III
Single-Phase Machines				
1977				
50	170	230	140	150
70	390	475	310	335
90	730	800	530	575
100	920	1225	-	-
110	1120	-	780	960
130	-	-	-	1475
1978				
50	170	277	170	168
70	390	563	465	367
90	730	1013	750	571
110	1120	1429	1075	963
130	-	1949	1400	1476
Faster Films and More Sensitive Screens				
1980[3]				
40	-	85	- 103	53
46	-	133	- -	-
50	170	-	- -	104
52	190	206	170 225	-
60	260	289	244 316	160
70	390	415	343 430	215
80	540	554	446 560	279
90	730	687	573 725	359
100	920	820	691 882	442
124	-	-	979 1200	652
Three-Phase Machines[4]				
1982				
40	-	131	-	-
50	306	242	-	356
60	468	366	-	504
70	702	500	-	667
80	972	656	-	860
90	1314	820	-	1037
100	1656	1022	-	1263
110	2016	1235	-	1490
125	2538	1560	-	1839

- indicates measurement not taken

[1] Energy output (mR/mAs) standardized to 100 centimeters

[2] According to the National Commission on Radiation Protection (NCRP68)

[3] Values for machine II were measured twice, three months apart.

[4] Reference values for three-phase machines were obtained by multiplying the values for single-phase machines by 1.8 (P. Caron, personal communication).

It was not possible to distinguish from the medical chart which machine was used to make each radiograph. Therefore, the values in table 4.2 were assumed to be representative of energy outputs used to make all spinal radiographs at Hôpital Ste-Justine. By using the entire range of tube potentials in the linear regression procedure, the relationship with output was obtained using all the information available rather than only averaging specific point estimates from the technical reports. In order to estimate the mean energy output as a function of the tube potential, multiple linear regression was used (Kl88). The results of the regression analysis are shown in table 4.3. Separate estimates were obtained for the three calendar periods by combining the data from 1977 and 1978 to calculate the dose from all radiographs made in the calendar period 1957 to 1978, by using the data from 1980 to represent the calendar period 1979 to 1981, and by using the data from 1982 to represent the calendar period 1982 to 1989. It should be noted that in the first calendar period the kilovoltages were between 88 and 102 kV, between 74 and 94 kV in second calendar period, and between 40 and 68 in the third calendar period.

Table 4.3. Estimated energy output (in milliroentgens/100 milliampere-seconds) of x-ray machines used to make spinal radiographs at Hôpital Ste-Justine for three calendar periods.[1]

Year of calibration study	Calendar period for dose calculation	Estimated intercept (β_0)	Estimated slope (β_1)	Standard error (β_1)
1977, 1978	1957-78	-719.1	16.8	1.3
1980	1979-81	-369.8	10.6	0.9
1982	1982-89	-672.8	18.4	1.1

[1] Based on the linear relationship: energy output = $\beta_0 + \beta_1$ (kV), for each calendar period separately.

4.5 Skin exposure

In the general sense, exposure refers to the production of ions by electromagnetic radiation; the basic quantity is the *roentgen*, defined as the x-ray or gamma radiation that produces a charge of 2.58×10^{-4} coulombs per kilogram of air (Ka89). Skin exposure is the exposure at the skin surface closest to the source. As an x-ray beam passes through the body it is attenuated by about two orders of magnitude, and the amount of radiant energy absorbed in tissue is the dose. Figure 2 shows a schematic of the energy transfer as diagnostic x-rays pass through the body during a typical radiographic examination.

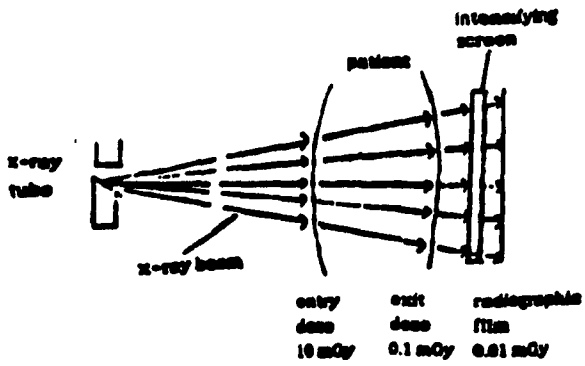

Figure 2. Schematic of energy transfer as diagnostic x-rays pass through the body. Adapted from Da84.

In order to calculate organ-specific doses, x-ray exposure at the skin was required. By using the machine settings, mean machine outputs and geometric characteristics, it was possible to calculate skin exposures. The following steps were followed: 1) the machine output at a distance of 100 cm for a given maximum kilovoltage was determined using the coefficients in table 4.3; 2) the output was adjusted for the actual source-to-skin distance using the inverse square law; and 3) this value was multiplied by the mAs to obtain the actual skin exposure.

Table 4.4 shows the relevant data used in the calculations of skin exposure.

Table 4.4 X-ray machine settings, estimated energy output (in milliRoentgens per milliampere-seconds), skin exposures in milliroentgens (mR), and 95 percent confidence limits (95% CL) from full-spinal radiographs, according to view, the AIS Cohort, 1960-1979.

Calendar period	Age[1]	Machine settings: Tube potential (kV)	Machine settings: Intensity (mAs)	Source-to-skin distance (cm)	Energy output at 100 centimeters (mR/mAs): Lower 95% CL	Energy output at 100 centimeters (mR/mAs): Estimate	Energy output at 100 centimeters (mR/mAs): Upper 95% CL	Skin exposure (milliroentgens): Lower 95% CL	Skin exposure (milliroentgens): Mean	Skin exposure (milliroentgens): Upper 95% CL
Anteroposterior View										
1957-78	Children	88	100	164	6.85	7.57	8.29	255	281	308
	Adolescents	88	140	162	6.85	7.57	8.29	365	403	442
	Adults	90	200	160	7.18	7.90	8.63	560	618	674
1979-82	Children	74	60	164	3.67	4.13	4.59	82	92	102
	Adolescents	74	80	162	3.67	4.13	4.59	112	126	140
	Adults	82	120	160	4.50	4.98	5.45	211	233	255
1983-89	Children	50	40	164	1.50	2.49	3.48	22	37	52
	Adolescents	58	40	162	3.12	3.97	4.82	47	60	73
	Adults	60	50	160	3.52	4.34	5.15	69	85	101
Lateral View										
1957-78	Children	96	140	156	8.15	8.91	9.67	469	512	556
	Adolescents	96	200	153	8.15	8.91	9.67	696	762	826
	Adults	102	300	150	9.09	9.92	10.75	1212	1323	1434
1979-82	Children	90	100	156	5.29	5.83	6.25	217	240	261
	Adolescents	90	120	153	5.29	5.83	6.25	271	299	323
	Adults	94	200	150	5.67	6.25	6.83	531	556	607
1983-89	Children	56	50	156	2.72	3.60	4.48	56	74	92
	Adolescents	62	50	153	3.92	4.71	5.49	384	101	117
	Adults	68	64	150	5.12	5.81	6.51	145	165	184

CL = confidence limit

[1] Children, adolescents, and adults were defined as being 0 to 8 years of age, 9 to 17 years, and 18 years and over, respectively.

The estimated mean energy output was calculated from the equation: machine output = $\beta_0 + \beta_1 \times (kV)$, using the parameter estimates from the linear regression models presented in table 4.3. Upper and lower 95% confidence limits for energy output were calculated according to the formula: Mean output + kV ($\beta_1 \pm t \times$ standard error; K188).

For example, consider an anteroposterior spinal radiograph taken of an adolescent during the period 1957 to 1978. The second row of the table shows the settings that were used: tube potential of 88 kV and an electric current of 140 mAs. The energy output standardized to 100 centimeters at this tube potential was calculated as 16.77 x 88 - 719.1 = 757 mR/100 mAs = 7.57 mR/mAs (from table 4.3; note that for presentation in the table the values were rounded to one decinal place so that 16.77 was written as 16.8). The skin exposure was obtained by multiplying the mAs by the energy output and adjusting for the source-to-skin distance; *i.e.* $140 \times 7.57 \times (100/162\ cm)^2 = 403.8$.

Energy output was calculated as a function of the tube potential and, therefore, within each calendar period the output was the same for the same tube potential. Upper and lower 95% confidence limits for skin exposure were calculated using the upper and lower limits on machine output. Thus, differences in machine output were the only source of uncertainty accounted for in the skin exposures.

From table 4.4, it can be seen that skin exposures increased with age and decreased for each subsequent calendar period. Exposures increased with age (a proxy for body size) because x-rays of higher energy were used to produce radiographs for larger individuals. Exposures decreased with calendar period because improvements in technology permitted x-ray beams with lower energies to be used.

4.6 Monte Carlo methods and the organ-specific x-ray doses

A Monte Carlo simulation procedure for estimating x-ray doses from diagnostic radiographs, developed at the Oak Ridge National Laboratory (Wa73), was used. The method simulates the transport of photons through a mathematically defined, heterogeneous human phantom. A computer program based on the Monte Carlo simulations was obtained from Dr. Marvin Rosenstein of the United States Center for Devices and Radiological Health (Pe89). Detailed descriptions of the Monte Carlo techniques and their applications in estimating organ-specific x-ray doses from diagnostic radiographs have been published elsewhere (An91, Ka86, Le88, Ra76, Ro76), but a brief resumé is given below.

The Monte Carlo method was first developed during the 1930s and 1940s to predict how atomic particles behaved under different conditions. Where applied to diagnostic radiography, the method simulates mathematically the trajectories of many photons having different energies being emitted from an x-ray tube. The Monte Carlo method accounts for the energy distribution of the x-rays, the distribution of different tissues in the human body and the different scattering and energy absorption processes that occur between x-ray photons and molecules. In the simulations the individual histories of millions of photons are followed as they pass through a mathematical representation of the human body called a phantom.

The phantom consists of three principal sections: an elliptical cylinder representing the trunk, torso, hips and arms; two truncated circular cones representing the legs and feet; and an elliptical cylinder capped by a hemi-ellipsoid representing the neck and head. Regions within the phantom representing the organs are defined using a system of Cartesian coordinates with the origin at the center of the base of the trunk. The organs

are given simple geometrical shapes whose dimensions and location are based on average values from western populations (ICRP75). Each organ within the phantom is considered to be homogeneous in composition and density. Separate elemental compositions for regions of the body are defined for: the skeleton, which consists of a mixture of bone and bone marrow and has an approximate density of 1.5 g/cm^3; the lungs which have an approximate density of 0.3 g/cm^3; and the remainder of the phantom which has an approximate density of 1.0 g/cm^3. (For comparison, the density of water is 1.0 g/cm^3). The typical elemental composition of each organ was based on tissue specimens obtained from autopsies of 150 adults in the United States (Ti66). Thus, the simulation accounts for the size, shape, composition, location and density of actual organs in the human body.

When interacting with matter, x-ray photons can ionize atoms through three stochastic processes: the photoelectric effect, Compton scattering, and positron-electron pair production. The first two processes predominate at the energy levels of diagnostic x-rays. In the simulation, each photon history contains several potential interaction sites, the actual number depending on the initial energy of the photon. At each interaction site a subroutine in the program is called to locate the organ in which the interaction occurred and the energy deposited is added to the total for that particular organ. Photon histories are terminated if the photon exits the phantom or if the energy of the photon falls below selected cut-off values.

The doses estimated from the Monte Carlo simulations depend on the initial energies of x-ray photons. These energies are estimated from the skin exposure, voltage, current and filtration and, thus, these were the parameters used as input values into the computer program. Also needed was the geometry of the radiograph to determine the organs that lay in the x-ray beam. Doses obtained from the simulation program were tabulated as a

function of the half-value layer (assumed to be 2.0 mm Al for the period 1957 to 1979 and 2.5 mm Al for the period 1979 to 1989).

Breast and thyroid doses were calculated for three views: anteroposterior, lateral and posteroanterior. As the doses from posteroanterior spinal radiographs were two orders of magnitude less than the other views and subjects almost never had more than one or two posteroanterior views, these radiographs were omitted from the calculations of cumulative dose. Radiographs of the oblique view were made using the same machine settings as the anteroposterior view. Although the geometry of an oblique radiograph differed slightly from the anteroposterior view, doses were assumed to be equal for the two views because they were made using the same machine settings. For the lateral view, x-ray doses to the female breast were not available from the simulation program. However, the average dose to the breasts from the lateral view has been measured and shown to be of the same magnitude as the dose from the anteroposterior view (Dr. M. Rosenstein, personal communication), and thus, doses from the two views were assumed to be equivalent.

For both the anteroposterior and lateral views, separate estimates of x-ray dose to each organ were determined for both sexes (except the breast in males), three calendar periods and three age groups. For each stratum, plausible "minimum" and "maximum" doses were calculated using the estimated lower and upper 95% confidence limits of skin exposure, respectively. Doses for each strata were incorporated into a matrix that was indexed by organ, age group, sex, calendar period and view. (This matrix will hereafter be referred to as the *dose-matrix*.) Each cell of the dose-matrix contained three entries, representing the "lower estimate", "mean estimate", and "upper estimate" of dose.

Organ-specific doses to subjects were calculated as follows. For each radiograph taken

of each subject, the view was obtained from the x-ray requisition form, the calendar period was determined from the date of the radiograph and age at time of the radiograph was calculated by subtracting the date of birth from the date of the radiograph. Using these values, the lower, mean and upper estimates of dose to each organ were extracted from the appropriate cell of the dose-matrix. Cumulative mean doses and the lower and upper estimates were calculated for each subject by summing over all radiographs listed in the medical chart.

4.7 Life table procedure for projecting excess cancers

The excess lifetime risk of breast cancer and thyroid cancer in the AIS cohort was estimated using a life table procedure. The procedure incorporated all-cause and organ-specific cancer mortality rates and used the relative risk models for radiation exposure derived by the BEIR V Committee. The calculations were carried out using the life table computer program written by Drs. Duncan Thomas and David Hoel for the BEIR V Committee (NAS90).

The life table was calculated using standard methods (*e.g.* Ch84), but modified to account for cancer deaths attributable to radiation. The departure point was a hypothetical cohort of 100,000 persons, followed from age at exposure until age 100 years. At the beginning of each five-year age interval the number of persons was equal to the number at the start of the previous interval less the number of deaths due to other causes (referred to as *baseline*) and due to radiation exposure. The number of baseline deaths was calculated by multiplying sex- and age-specific cancer mortality rates by the number of persons alive at the start of each age interval. Cancer deaths due to radiation (for the thyroid gland, female breast, bone marrow, respiratory system, digestive system, and all other sites combined) were calculated using the BEIR V Committee relative risk

models (see section 2.5, page 31 *ff*). These models assume that cancer deaths due to radiation are a multiple of the age-specific cancer deaths expected from background rates.

The input parameters used for the life table calculation were age-specific mortality rates and the dose of radiation. However, it was assumed that all tissues in the body were irradiated by the same dose of radiation (*i.e.* whole body exposure). For a spinal radiograph this assumption is not entirely correct although doses to the thyroid gland and breast were approximately the same (see table 5.8, page 72). Cancers for organs other than the thyroid gland and breast were not tabulated.

The age at exposure was set to fifteen years for the entire cohort, and exposure was assumed to have been delivered instantaneously. Accounting for different latency periods, the excess risk of cancer was zero until age seventeen years for leukemia, until age twenty years for breast cancer and until age 25 years for thyroid cancer. (Also calculated in the life table procedure were deaths from exposure at eight other ages (5, 25, 35, ..., 85) using the same latency periods).

Calculations were carried out at one cGy dose intervals, using the mid-point of the integer dose intervals, *i.e.* 0.5 cGy, 1.5 cGy, ..., 15.5 cGy. (It was therefore assumed that, within a dose interval, all subjects received the dose at the mid-point of the interval.)

Quebec cancer mortality rates and incidence rates were calculated using data from Statistics Canada and the Quebec Tumor Registry, respectively. The numerators were the average annual age-, sex- and site-specific numbers of all-cause and cancer deaths from 1980 to 1984 and incident cancer cases from 1981 to 1983. The denominators were the number of persons alive in 1986 in Quebec according to age and sex, obtained from the

1986 Canadian census. By averaging several years of cancer mortality and incidence data, the effect was to reduce the impact of year to year variations. By using Quebec rates, it was assumed that the AIS cohort will experience the same baseline rates as the general Quebec population, and that cross-sectional mortality rates from the early 1980s will apply throughout the lifetime of the cohort.

The life table program was first tested, using United States rates, by reproducing the projected number of excess cancer deaths published in the BEIR V report. After successfully completing this test, age- and sex-specific Quebec cancer mortality and all-cause mortality rates and the risk model for thyroid cancer were incorporated into the program. Separate calculations were carried out for women and for men. For each cancer site under consideration (*i.e.* breast and thyroid), the difference between the total number of baseline deaths and deaths due to baseline plus radiation was divided by 100,000 to obtain the fraction attributable to radiation. To obtain the number of excess cancer deaths in the AIS cohort, the number of subjects in each dose interval (tables 5.10 and 5.11, pages 74 and 75) was multiplied by the fractional excess projected for that dose (table 5.13, page 77), and, then, summing over all dose intervals.

In order to obtain a plausible range of estimates to the excess numbers of deaths, calculations were repeated incorporating two different sources of uncertainty. First, uncertainty in the dose estimates was included using the dose distributions obtained from the lower and upper estimates for skin exposure. Second, statistical uncertainty in the estimates of the coefficient for dose was accounted for by using the lower and upper 95% confidence limits (*i.e.* dose coefficient $\pm$ (1.96 * standard error)); the coefficients and their standard errors are given for breast cancer on pages 34 and 35 and for thyroid cancer on page 36. Only the uncertainty in the coefficient for dose was taken into account (and not the other coefficients in the risk model). In summary, the excess number deaths from

breast cancer and thyroid cancer in the AIS cohort was calculated using three different doses, and for each of these, using the three different coefficients for dose in the risk models.

To estimate the number of incident cases of cancer attributable to radiographs for scoliosis, the life table procedure was repeated using Quebec incidence rates for breast cancer and thyroid cancer. In so doing, incident cases for these tumors were removed from the life table population in the same fashion as cancer deaths, and this implied that radiation could not cause cancer more than once in the same person. Censoring from all other causes was accounted for through incorporation of all-cause mortality rates and cause-specific cancer mortality rates for other organs.

5. RESULTS

5.1 Description of the AIS cohort

The AIS cohort was composed of 1,847 women and 334 men. The ratio of women to men in the cohort is similar to that observed in other studies of AIS (Le82, Mo78). Less than three percent of the cohort were referred prior to the opening of the scoliosis clinic (1965), and over 80 percent of the cohort were referred during the 1970s. Table 5.1 (page 65) shows the distribution of age at first referral by sex. About 85 percent of individuals in the cohort were first referred for scoliosis between the ages of eleven and seventeen years.

The mean time under observation was 3.5 years for women and 2.6 years for men (table 5.2; page 66. Approximately fifteen percent of women and 22 percent of men were seen only once for AIS. About 30 percent of subjects seen only once had no scoliotic curve. There is a clear trend showing that the length of time under observation was inversely related to age at first referral. This can be explained by the fact that scoliotic curves of individuals referred at a young age, particularly before puberty, tend to progress more than those of older persons. Table 5.3 (page 67) shows that the angle of spinal curvature at first referral was larger among subjects who were first referred at older ages. The mean curve at first referral among women was about 35 degrees, but there was a wide spread about the mean (standard deviation 21 degrees).

5.2 Description of spinal radiographs

Table 5.4 (page 68) shows that a total of 22,217 and 3,320 radiographs were taken of women and men, respectively, with the anteroposterior view being the most common (about 76% of spinal radiographs for both sexes). The number of spinal radiographs is

tabulated by three calendar periods (1957 to 1978, 1979 to 1981, and 1982 to 1989) that represent intervals during which radiological practices and equipment remained the same. Approximately 80 percent of radiographs were taken during the first period (1957 to 1978). Table 5.5 (page 69) shows the distribution of the number of radiographs according to sex and view. About four percent of subjects were not exposed to x-rays and 96 percent of subjects received at least one radiograph; an oblique view was taken for only three percent of subjects.

Table 5.6 (page 70) shows the mean and median number of spinal radiographs according to the extent of spinal curvature at first referral. The mean number of radiographs generally increased monotonically with increasing spinal curvature. Women were radiographed an average of twelve times and men an average of ten times. The distribution of ages when the radiographs were taken is presented in table 5.7 (page 71). About 75 percent of the radiographs taken of women, and 69 percent of radiographs taken of men, were made between the ages of twelve and seventeen years.

In summary, over 25,000 spinal radiographs were taken of the 2,181 AIS cohort subjects. This yielded an average of twelve and ten spinal radiographs taken of women and men, respectively, and the majority were made using the anteroposterior view. Few posteroanterior and oblique spinal radiographs were taken. In addition, the majority of radiographs were made between the ages of twelve and seventeen years.

5.3 Cumulative organ-specific doses

Table 5.8 (page 72) shows the estimated x-ray doses (in cGy) to the thyroid gland and female breast from anteroposterior and lateral views, for children, adolescents and adults. The doses for the three time periods were estimated using the data in table 4.4

(page 49) as input values to the Monte Carlo simulation program. Minimum, mean and maximum doses were calculated using lower 95% confidence limit, average and upper 95% confidence limits of skin exposure, respectively. As the average dose to the breasts from the lateral view has been measured and shown to be of the same magnitude as the dose from the anteroposterior view, the dose from the two views was assumed to be the same. The doses calculated for the thyroid gland were identical for men and women for both anteroposterior and lateral views.

For both views and all three time periods, the dose from spinal radiographs was lowest for children, intermediate for adolescents, and highest for adults; the dose to adults was approximately twice that of children. Doses increased with age because the intensity and energy of the x-ray beam was increased to account for larger body sizes, and because of shorter source-to-skin distances. During the period 1957 to 1978, the mean dose to both the thyroid gland and the female breast from one anteroposterior or lateral radiograph was approximately 0.2 cGy in children, 0.3 cGy in adolescents and 0.4 cGy in adults. Thyroid and breast doses decreased with calendar period and by 1982, doses had been reduced by a factor of five because of the adoption of faster films and more sensitive x-ray screens in the late 1970s and because of replacement of older single-phase x-ray machines with more modern three-phase equipment (see page 42).

As indicated in table 5.4, the posteroanterior view was rarely taken of subjects over the period of study. Table 5.9 (page 73) shows that for the most recent period (1982 to 1989) the estimated doses to the breast and thyroid gland from the posteroanterior view are approximately 1/20th of those from the anteroposterior view.

For each subject in the AIS cohort, cumulative organ-specific x-ray doses to the thyroid gland and breast (for women) were calculated by summing the doses from each

radiograph taken. The distributions of doses are shown in tables 5.10 and 5.11 (pages 74 and 75). For both organs, more individuals were exposed to lower doses; this resulted in median values that were consistently lower than the mean dose estimates. Mean doses to the thyroid gland and female breast ranged from 2.5 to 3.4 cGy. The range in the dose estimates extended from about ten percent below to ten percent above the mean. The mean cumulative thyroid dose was slightly lower for men than women because men received, on average, fewer spinal radiographs.

5.4 Projections of excess cancer incidence and mortality

The BEIR V Committee life table procedure was used to project the number of breast and thyroid cancers in the AIS cohort attributable to radiation. Using Quebec mortality rates, table 5.12 (page 76) shows the number of excess cancer deaths for a theoretical population of 100,000 persons exposed to single dose of one cGy of radiation to the whole body at various ages at exposure. The values in the table represent the excess numbers of cancer deaths attributable to radiation per 100,000 persons exposed. Table 5.12 can be compared to table 4-3 of the BEIR V report (page 175 of NAS90) which shows the results of a similar calculation using United States cancer mortality rates and an exposure to ten cGy. For comparison with the table in the BEIR V report, the number of deaths in table 5.12 must be multiplied by ten to account for different doses. In both the BEIR V calculations and table 5.12, the total number of excess number of deaths generally declines with increasing age at exposure. The projected number of excess cancer deaths in Quebec is between ten and twenty percent higher than in the United States, which is due mainly to the higher baseline mortality rates of digestive and respiratory cancers in Quebec and the risk models that are relative to (*i.e.* a multiple of) the baseline rate. For women at all ages at exposure, the projected excess number of breast cancer deaths using Quebec rates is similar to the number using United States rates. The

largest projected excess number of breast cancer deaths in both calculations occurs from exposure at age fifteen, and at this age, the value is identical for Quebec and United States women (29 per 100,000 women exposed to one cGy).

Using Quebec rates, the projected number of excess thyroid cancer deaths was the same for ages at exposure fifteen through 45 years (table 5.12; page 76). The constancy of these values is due to the absence of a term for age at exposure in the relative risk model. At ages older than 45 years, the excess number of thyroid cancers declines because of other, competing causes of death. It was not possible to compare the excess number of thyroid cancers between Quebec and the United States because BEIR V did not report these data.

Table 5.13 (page 77) shows the number of breast cancers and thyroid cancers attributable to a single exposure of radiation at age fifteen years, according to different doses. As the dose was assumed to be whole-body, the calculation of excess breast and thyroid cancers accounted for the induction of other types of cancers (*i.e.* bone marrow, respiratory, digestive, and all other cancers combined). The actual numbers of subjects in the AIS cohort in each cumulative dose category (tables 5.10 and 5.11) were multiplied by the projected excess numbers in table 5.13, and divided by 100,000 to obtain the total projected number of excess cancers in the cohort. The results of the calculations are shown in table 5.14 (page 78), which shows the projected lifetime number of incident and fatal cancers attributable to diagnostic radiation for scoliosis.

Using the life table procedure to project deaths in the cohort in the absence of radiation, the lifetime number of breast cancers occurring among women in the absence of radiation was 162 cases and 73 deaths. About five excess incident cases and 1.5 excess deaths from breast cancer attributable to radiation for scoliosis were projected to occur; this

represented about a three percent increase over the lifetime expected numbers (*i.e.* 5/162 = 3%). The expected number of thyroid cancer cases and deaths among women was thirteen and 3.5, respectively. For thyroid cancer the number of cases among women attributable to radiation was 2.3 cases and 0.6 deaths, representing about a fifteen percent increase (*i.e.* 2/13 = 15%) above expected. The combined effects of the small number of men in the cohort and lower rates of thyroid cancer among men resulted in very low projected excess number of thyroid cancers, in the order of 0.1 incident cases.

In order to show how dose has been reduced over time because of changes in equipment and procedures, comparisons were made of the number of spinal radiographs needed to deliver a given dose to the female breast and thyroid gland for an adolescent patient, according to view (table 5.15; page 79). Also included in the table are the lifetime excess risks of breast and thyroid cancer, based on the life table calculation, for each dose. For example, the third line of the table shows that to accumulate a dose of 3.5 cGy to the female breast required thirteen anteroposterior spinal radiographs during the period 1957 to 1978, and 76 anteroposterior radiographs and 1,458 posteroanterior radiographs during the period 1982 to 1989. This dose of 3.5 cGy would result in a risk of 3.24 excess breast cancer cases and 1.01 excess deaths per 1,000 women exposed. From the table it is clear that considerable reductions in dose occur when the posteroanterior view is used instead of the customary anteroposterior view.

In summary, female and male AIS patients were shown to receive an average of twelve and ten spinal radiographs, respectively (table 5.6). The radiographs were made over an average period of 3.3 years for women and 2.6 years for men (table 5.2). Over 70 percent of subjects were exposed between the ages of twelve and seventeen years (table 5.7). The mean cumulative organ-specific doses were: 2.9 cGy to the breast of women; 3.1 cGy to the thyroid gland of women; and 2.7 cGy to the thyroid gland of men (tables 5.11

and 5.12). Almost all excess cancers were projected to occur among women in the cohort, among whom about five excess cases of breast cancer and two excess cases of thyroid cancer were projected to occur from radiographs for scoliosis; these values represent about three and fifteen percent increases in risk, respectively (table 5.14).

Table 5.1. Distribution of age at first referral by sex, the AIS Cohort, 1960 - 1979.

Age at first referral (years)	Women		Men	
	Number	%	Number	%
≤ 10	111	6.0	43	12.9
11-13	730	39.5	97	29.0
14-17	883	47.8	167	50.0
≥ 18	123	6.7	27	8.1
All ages	1847	100.0	334	100.0

Table 5.2. Distribution of time under observation, by sex and age at first referral, the AIS Cohort, 1960 - 1979.

Time under observation	Age at first referral <=10 %	10-13 %	14-17 %	>=18 %	All ages %
			Women		
1 visit only	8.1	8.6	16.6	39.8	14.5
< 1 year	9.9	9.7	12.8	13.8	11.5
1 - 2 years	11.7	8.8	13.7	15.4	11.7
2 - 3 years	8.1	9.0	12.1	8.9	10.5
3 - 6 years	21.6	34.5	33.2	17.1	31.9
≥ 6 years	40.5	29.3	11.5	4.9	19.7
Total	99.9	99.9	99.9	99.9	99.8
Mean (years)	5.1	4.3	2.9	1.5	3.5
Standard deviation	4.0	3.2	3.4	2.1	3.4
Median (years)	4.4	4.1	2.5	0.7	3.1
			Men		
1 visit only	16.3	21.6	22.2	25.9	21.6
< 1 year	20.9	17.5	14.4	25.9	17.1
1 - 2 years	0.0	13.4	12.6	11.1	11.1
2 - 3 years	7.0	8.2	16.8	18.5	13.2
3 - 6 years	18.6	27.8	26.3	14.8	24.8
≥ 6 years	37.2	11.3	7.8	3.7	12.3
Total	100.0	99.8	100.1	99.9	100.1
Mean (years)	4.5	2.5	2.3	1.6	2.6
Standard deviation	4.2	2.5	2.2	1.8	2.7
Median (years)	4.1	1.6	2.0	0.8	2.0

Due to rounding, column totals may not necessarily sum to exactly 100 percent.

Table 5.3. Distribution of spinal curves measured at first referral, by sex and age at first referral, the AIS Cohort, 1960-1979.

Spinal curve at first referral (degrees)[1]	Age at first referral (years) <=10 %	10-13 %	14-17 %	>=18 %	All ages %
		Women			
0 - 9	31.5	10.5	5.9	10.6	9.6
10 - 19	23.4	17.0	10.8	4.9	13.6
20 - 29	18.9	16.7	21.3	13.8	18.8
30 - 39	13.5	16.8	21.2	18.7	18.8
40 - 49	7.2	14.8	17.8	21.9	16.2
50 - 59	3.6	11.9	11.3	16.3	11.4
≥ 60	1.8	12.2	11.8	13.8	11.5
Total	100.0	99.9	100.1	100.0	100.0
Mean curve (degrees)	19.2	34.0	36.3	40.9	34.6
Standard deviation	16.7	21.0	19.0	24.9	20.6
Median (degrees)	17	32	35	40	33
		Men			
0 - 9	44.2	40.2	13.8	7.4	24.8
10 - 19	18.6	27.8	13.8	14.8	18.6
20 - 29	13.9	11.3	12.0	7.4	11.7
30 - 39	13.9	10.3	18.0	14.8	15.0
40 - 49	4.6	4.1	10.8	33.3	9.9
50 - 59	4.6	3.1	16.2	11.1	10.5
≥ 60	0.0	3.1	15.6	11.1	9.5
Total	100.0	99.9	100.2	99.9	99.9
Mean curve (degrees)	15.6	16.0	36.0	38.4	27.7
Standard deviation	15.5	16.9	23.8	21.5	23.1
Median (degrees)	11	12	34	42	25

Due to rounding, column totals may not necessarily sum to exactly 100 percent.

[1] The spinal curve at first referral is defined as the largest Cobb angle on the date of first visit for scoliosis.

Table 5.4. Distribution of spinal radiographs by calendar period, sex and view, the AIS Cohort, 1960 - 1979.

Calendar period [1]	Number of radiographs				All views
	Antero-posterior	Lateral	Postero-anterior	Oblique	
			Women		
1957-78	13238	3224	500	111	17073
1979-81	2880	935	70	24	3909
1982-89	874	332	17	12	1235
Total	16992	4491	587	147	22217
Percent	76.5	20.2	2.6	0.7	100.0
			Men		
1957-78	2059	569	71	32	2731
1979-81	320	94	5	0	419
1982-89	121	43	4	2	170
Total	2500	706	80	34	3320
Percent	75.3	21.3	2.4	1.0	100.0

[1] The calendar periods correspond to intervals in which radiological practices and equipment remained constant.

Table 5.5. Distribution of number of spinal radiographs per subject by view and sex, the AIS Cohort, 1960 – 1979.

Number of spinal radiographs	Number of subjects			
	Antero-posterior	Lateral	Postero-anterior	Oblique
	Women (n=1847)			
0	78	283	1331	1792
1–5	660	1341	516	50
6–10	374	184	0	5
11–15	369	38	0	0
16–20	244	1	0	0
21–25	77	0	0	0
26–30	31	0	0	0
31–35	8	0	0	0
> 35	6	0	0	0
	Men (n=334)			
0	16	44	262	322
1 – 5	164	262	72	11
6 – 10	58	27	0	1
11 – 15	49	0	0	0
16 – 20	32	1	0	0
21 – 25	7	0	0	0
26 – 30	3	0	0	0
31 – 35	5	0	0	0
> 35	0	0	0	0

Table 5.6. Mean and median number of spinal radiographs per subject, by spinal curvature at first referral[1] and sex, the AIS Cohort 1960 - 1979.

Spinal curve at first referral (degrees)	Number of subjects	Spinal radiographs per subject		
		mean number	standard deviation	median number
Women				
0 - 9	177	5.5	5.4	4
10 - 19	251	8.1	7.5	6
20 - 29	348	9.3	8.8	7
30 - 39	348	10.4	8.7	7
40 - 49	300	15.4	9.7	16
50 - 59	211	17.2	9.3	19
≥ 60	212	19.2	9.7	20
All curves	1847	12.0	9.7	9
Men				
0 - 9	83	5.5	5.3	4
10 - 19	62	5.9	4.6	4
20 - 29	39	11.3	11.8	8
30 - 39	50	12.9	10.6	11
40 - 49	33	8.9	8.2	5
50 - 59	35	14.4	9.1	16
≥ 60	32	19.1	7.3	20
All curves	334	9.9	9.1	6

[1] The spinal curve at first referral is defined as the largest Cobb angle on the date of first visit for scoliosis.

Table 5.7. Distribution of the number of spinal radiographs according to sex and to the age of subjects at the time when spinal radiographs were taken, the AIS Cohort, 1960 – 1979.

Age (years)	Women (n=1847)		Men (n=334)	
	Number of radiographs	%	Number of radiographs	%
0–5	35	0.2	24	0.7
6–7	189	0.8	112	3.4
8–9	448	2.0	113	3.4
10–11	1320	5.9	217	6.5
12–13	4748	21.4	492	14.9
14–15	7007	31.5	894	26.9
16–17	4806	21.6	796	24.0
≥18	3664	16.5	672	20.2
All ages	22217	99.9	3320	100.0

Due to rounding errors, column totals may not necessarily sum to exactly 100 percent.

Table 5.8. Estimated radiation doses (in cGy) to the thyroid gland and female breast of children, adolescents and adults, calculated using Monte Carlo simulations for minimum, mean and maximum x-ray exposures at skin entrance, for anteroposterior and lateral views of full-spinal radiographs.[1,2]

	Anteroposterior view Dose for skin exposures:			Lateral view Dose for skin exposures:		
	Lower estimate	Mean	Upper estimate	Lower estimate	Mean	Upper estimate
FEMALE BREAST[3]						
1957-1978						
Children	0.176	0.193	0.212	0.176	0.193	0.212
Adolescents	0.251	0.277	0.304	0.251	0.277	0.304
Adults	0.386	0.425	0.464	0.386	0.425	0.464
1979-1981						
Children	0.062	0.070	0.077	0.062	0.070	0.077
Adolescents	0.085	0.096	0.106	0.085	0.096	0.106
Adults	0.161	0.177	0.194	0.161	0.177	0.194
1982-1989						
Children	0.017	0.028	0.039	0.017	0.028	0.039
Adolescents	0.036	0.046	0.055	0.036	0.046	0.055
Adults	0.052	0.064	0.077	0.052	0.064	0.077
THYROID GLAND[4]						
1957-1978						
Children	0.186	0.205	0.225	0.177	0.194	0.210
Adolescents	0.267	0.294	0.323	0.263	0.288	0.312
Adults	0.409	0.451	0.492	0.458	0.500	0.542
1979-1981						
Children	0.067	0.076	0.084	0.088	0.097	0.106
Adolescents	0.092	0.104	0.115	0.110	0.121	0.131
Adults	0.175	0.193	0.211	0.215	0.225	0.245
1982-1989						
Children	0.018	0.030	0.043	0.022	0.029	0.037
Adolescents	0.039	0.049	0.060	0.033	0.040	0.047
Adults	0.057	0.070	0.083	0.058	0.066	0.073

[1] Children, adolescents, and adults were defined as being 0 to 8, 9 to 17, and 18 years of age or over, respectively.

[2] Half-value layer of 2.0 millimeters of aluminum for the period 1957 to 1978, and 2.5 millimeters of aluminum for the period 1979 to 1989 were assumed.

[3] The breast dose resulting from the lateral view was assumed to be the same as from the anteroposterior view.

[4] For the two views, the dose to the thyroid gland was the same for males and females.

Table 5.9. Comparison of radiation doses (in cGy) for the breast and thyroid gland from posteroanterior and anteroposterior full-spinal radiographs estimated from skin exposures in the period 1982 to 1989.[1,2,3]

	Posteroanterior view Dose for skin exposures:			Anteroposterior view Dose for skin exposures:		
	Lower estimate	Mean	Upper estimate	Lower estimate	Mean	Upper estimate
Female breast						
Child	0.001	0.001	0.002	0.017	0.028	0.039
Adolescent	0.002	0.002	0.003	0.036	0.046	0.055
Adult	0.003	0.003	0.004	0.052	0.064	0.077
Thyroid gland[4]						
Child	0.001	0.002	0.002	0.018	0.030	0.043
Adolescent	0.002	0.003	0.003	0.039	0.049	0.060
Adult	0.003	0.004	0.005	0.057	0.070	0.083

[1] These are the doses that are currently delivered from full-spinal radiographs.
[2] Children, adolescents, and adults were defined as being 0 to 8, 9 to 17, and 18 years of age or over, respectively.
[3] Doses were assumed to have a half-value layer of 2.5 millimeters of aluminum.
[4] The dose to the thyroid gland was the same for males and females.

Table 5.10. Number of subjects by cumulative radiation dose[1] (in cGy) to the thyroid gland, by sex, the AIS Cohort, 1960-1979.

Cumulative dose range (cGy)	Estimated skin exposure: Lower estimate number	%	Mean number	%	Upper estimate number	%
Women						
0	78	4.2	78	4.2	78	4.2
> 0–1	410	22.2	384	20.8	363	19.7
> 1–2	410	22.2	374	20.2	356	19.3
> 2–3	249	13.5	261	14.1	238	12.9
> 3–4	178	9.6	156	8.4	165	8.9
> 4–5	169	9.1	164	8.9	154	8.3
> 5–6	159	8.6	170	9.2	149	8.1
> 6–7	85	4.6	101	5.5	133	7.2
> 7–8	46	2.5	68	3.7	74	4.0
> 8–9	32	1.7	36	1.9	61	3.3
> 9–10	11	0.6	26	1.4	26	1.4
> 10–11	11	0.6	10	0.5	21	1.1
> 11–12	4	0.2	10	0.5	11	0.6
> 12	5	0.2	9	0.5	18	1.1
All doses	1847	99.8	1847	99.8	1847	100.1
Mean (cGy)	2.82		3.10		3.38	
Standard deviation (cGy)	2.39		2.63		2.86	
Median (cGy)	2.09		2.30		2.54	
Men						
0	16	4.8	16	4.8	16	4.8
> 0 – 1	99	29.6	92	27.5	88	26.3
> 1 – 2	88	26.3	88	26.3	79	23.7
> 2 – 3	25	7.5	27	8.1	34	10.2
> 3 – 4	33	9.9	25	7.5	23	6.9
> 4 – 5	22	6.6	23	6.9	24	7.2
> 5 – 6	19	5.7	18	5.4	20	6.0
> 6 – 7	10	3.0	16	4.8	13	3.9
> 7 – 8	15	4.5	12	3.6	11	3.3
> 8 – 9	0	0.0	10	3.0	11	3.3
> 9 – 10	3	0.9	0	0.0	8	2.4
> 10 – 11	3	0.9	3	0.9	0	0.0
> 11 – 12	1	0.3	2	0.6	3	0.9
> 12	0	0.0	2	0.6	4	1.2
All doses	334	100.0	334	100.0	334	100.1
Mean (cGy)	2.46		2.71		2.96	
Standard deviation (cGy)	2.35		2.58		2.81	
Median (cGy)	1.59		1.75		1.92	

Due to rounding errors, column totals may not sum to exactly 100 percent.

Table 5.11. Number of subjects by cumulative radiation dose[1] (in cGy) to the female breast, the AIS Cohort 1960–1979.

Cumulative dose range (cGy)	Estimated skin exposure: Lower estimate number	%	Mean number	%	Upper estimate number	%
0	78	4.2	78	4.2	78	4.2
> 0 - 1	422	22.8	401	21.7	377	20.4
> 1 - 2	442	23.9	406	22.0	370	20.0
> 2 - 3	228	12.3	237	12.8	242	13.1
> 3 - 4	197	10.7	178	9.6	174	9.4
> 4 - 5	205	11.1	172	9.3	155	8.4
> 5 - 6	119	6.4	166	9.0	173	9.4
> 6 - 7	80	4.3	81	4.4	107	5.8
> 7 - 8	30	1.6	58	3.1	70	3.8
> 8 - 9	23	1.2	29	1.6	37	2.0
> 9 - 10	12	0.6	18	1.0	29	1.6
> 10 - 11	5	0.3	12	0.6	12	0.6
> 11 - 12	2	0.1	5	0.3	12	0.6
> 12	4	0.2	6	0.3	11	0.6
All doses	1847	99.7	1847	99.9	1847	99.9
Mean (cGy)	2.63		2.91		3.20	
Standard deviation	2.23		2.46		2.70	
Median (cGy)	1.93		2.13		2.35	

Due to rounding errors, column totals may not sum to exactly 100 percent.

Table 5.12. Projected excess number of cancer deaths using the BEIR V Committee life table procedure incorporating Quebec rates, for 100,000 persons exposed at a given age to an instantaneous dose of one cGy.

Age at exposure (years)	Number of excess deaths due to radiation						
	Total	Leukemia	Breast	Respiratory	Digestive	Thyroid	Other[1]
			Women				
5	190	10	11	4	91	9	65
15	192	8	29	6	91	9	50
25	151	2	4	11	95	9	30
35	65	4	5	18	10	9	20
45	62	7	2	24	9	9	10
55	58	11	0	25	9	8	5
65	46	13	0	18	7	7	1
75	27	12	0	8	4	3	0
85	11	7	0	2	1	1	0
			Men				
5	144	11	-	0	49	5	79
15	132	10	-	5	50	5	61
25	111	3	-	14	53	5	36
35	65	6	-	29	3	5	23
45	72	9	-	45	2	5	11
55	73	15	-	51	1	4	3
65	57	18	-	36	1	3	0
75	30	16	-	12	0	2	0
85	14	11	-	3	0	0	0

- not estimated

[1] Other cancer sites include: skeleton, brain and nervous system, ovary, uterus, testis, prostate, urinary tract, parathyroid glands, nasal cavity and sinuses, skin, lymphoma and multiple myeloma, salivary glands and pancreas.

Table 5.13. Projected lifetime number of organ-specific excess incident and fatal cancers per 100,000 persons exposed to a single exposure of ionizing radiation at age 15 years.

Dose (cGy)	Women		Men
	Thyroid gland	Breast	Thyroid gland
	Mortality		
0.5	4	15	2
1.5	14	43	7
2.5	24	72	13
3.5	36	101	19
4.5	48	130	26
5.5	62	159	33
6.5	77	187	41
7.5	94	216	50
8.5	112	245	60
9.5	132	273	71
10.5	154	301	83
11.5	178	330	96
12.5	205	358	110
13.5	234	386	126
14.5	266	414	144
15.5	302	442	163
	Incidence		
0.5	17	47	6
1.5	53	139	19
2.5	92	232	33
3.5	135	324	49
4.5	183	415	67
5.5	235	506	86
6.5	293	596	107
7.5	356	686	130
8.5	425	775	155
9.5	501	863	183
10.5	585	951	213
11.5	676	1038	247
12.5	777	1124	284
13.5	887	1209	325
14.5	1009	1292	369
15.5	1142	1375	418

Table 5.14. Projected excess lifetime number of incident and fatal cancers of the thyroid gland and female breast among 2,181 subjects assumed to be exposed at age 15 years to a single x-ray dose, the AIS Cohort, 1960-79.

Dose parameter[1]	Excess incidence for exposure estimate: Minimum	Mean	Maximum	Excess mortality for exposure estimate: Minimum	Mean	Maximum
Breast - Women						
Lower 95% CL	0.0	0.0	0.0	0.0	0.0	0.0
Central estimate	4.2	4.6	4.9	1.4	1.5	1.6
Upper 95% CL	8.8	9.6	10.3	2.8	3.0	3.2
Thyroid - Women						
Lower 95% CL	1.2	1.4	1.5	0.3	0.4	0.4
Central estimate	2.1	2.3	2.6	0.6	0.6	0.7
Upper 95% CL	3.3	3.8	4.3	0.9	1.0	1.1
Thyroid - Men						
Lower 95% CL	0.0	0.0	0.0	0.0	0.0	0.0
Central estimate	0.1	0.1	0.2	0.1	0.1	0.1
Upper 95% CL	0.2	0.2	0.2	0.1	0.1	0.1

CL - confidence limit

[1] The central estimates were derived using the risk models and coefficients published by the BEIR V Committee. The lower and upper confidence limit were calculated using the lower and upper 95% confidence limits, respectively, on the BEIR V coefficient for dose.

Table 5.15. Comparison of the number of anteroposterior (AP) and posteroanterior (PA) spinal radiographs taken at age 15 years that would produce a given dose of radiation to the thyroid gland and female breast, and the projected excess risk of cancer for that dose.

Dose (cGy)	Number of radiographs to produce a given dose: AP 1957–78	AP 1982–89	PA 1982–89	Excess cancer risk Incidence (per 1,000)	Mortality (per 1,000)
Breast – Women					
0.5	2	11	208	0.5	0.1
1.5	5	33	625	1.4	0.4
3.5	13	76	1458	3.2	1.0
7.5	27	163	3125	6.9	2.2
11.5	41	250	4792	10.4	3.3
15.5	56	337	6458	13.7	4.4
Thyroid – Women					
0.5	2	10	179	0.2	0.0
1.5	5	31	536	0.5	0.1
3.5	12	71	1250	1.3	0.4
7.5	25	153	2679	3.6	0.9
11.5	39	235	4107	6.8	1.8
15.5	53	316	5536	11.4	3.0
Thyroid – Men					
0.5	2	10	179	0.1	0.0
1.5	5	31	536	0.2	0.1
3.5	12	71	1250	0.5	0.2
7.5	25	153	2679	1.3	0.5
11.5	39	235	4107	2.5	1.0
15.5	53	316	5536	4.2	1.6

6. Discussion

The major finding of this thesis was that because of diagnostic radiographs for scoliosis about five excess cases of breast cancer and about two cases of thyroid cancer would be expected to occur over the lifetime of the 1,847 women in the AIS cohort. Thus, the lifetime risk of developing breast cancer was increased between three and five percent, and the risk of fatal breast cancer was about one percent greater than the numbers expected in the absence of radiation. For women and men, the excess risk for developing thyroid cancer was about 15 percent over baseline.

6.1 Methodological considerations of the investigation

Several limitations related to the dose estimates and the risk projections may have affected the results of this study. One source of uncertainty that could have affected the cumulative dose estimates consisted of errors in transcribing information from the medical chart (*i.e.* date of birth and the number and date of spinal radiographs). In order to evaluate recording errors, the number and date of x-rays and the date of birth were reviewed for a five percent random sample of medical charts. Of 106 medical charts that were reviewed a second time, four errors in the number of radiographs were found, and one subject was assigned an incorrect date of birth. Using the binomial distribution, we would expect 82 medical charts of 2,181 subjects to contain errors in radiographic data (95% confidence interval, 28 to 194; Ar85). If these errors are assumed to be random, which seems reasonable, these recording errors probably had little effect on the dose estimates.

It was impossible to evaluate non-transcription errors in the medical chart information (*i.e.* missing or incorrect data entered by the hospital staff). However, we can speculate on the probable direction of this error; it seems reasonable that the radiographs listed in

the medical chart were actually made, and that if any errors occurred, they likely involved the omission of radiographs from the medical chart. If that were the case, the actual x-ray doses and excess cancer risks would be higher than estimated here.

Assumptions in the dose calculation

The Monte Carlo methods used in this thesis should not be used to attribute dose to individuals unless certain parameters, such as body size, machine settings and actual machine outputs are known precisely. In this thesis organ-specific x-ray doses and excess cancer risks for the AIS cohort were estimated by making certain assumptions that were applied in a systematic way to each subject. In theory, the results of the thesis do not refer specifically to the subjects under study but rather to an ensemble of persons having certain average attributes. In practice, however, it seems reasonable to believe that the results are directly applicable to the AIS cohort.

In order to obtain x-ray doses the following assumptions were made. First, the calendar periods chosen for the study (*i.e.* 1957 to 1978, 1979 to 1981, and 1982 to 1989) represented time periods when the equipment and radiologic practices were constant in the hospital. However, the actual dates that the transitions took place were not known and could only be inferred. Thus, doses assigned from some radiographs may have been made using different machine settings and machine outputs than those used in the calculations. The first period was assumed to have ended on December 31st, 1978. If the actual date of change was January 1st, 1978, then doses would have been overestimated by about four percent. This figure, obtained by multiplying the six percent of radiographs made in 1978 by a dose reduction of about two-thirds (table 5.8), represents the largest amount of error that could have been introduced by using incorrect transition dates.

Second, the values used for average skin exposures comprised another source of uncertainty in the dose calculations. The skin exposures were calculated from the machine settings, the geometry of the radiograph and the average machine output. The assumption that the machine settings were constant within each calendar period may have been incorrect if the machine operator used different machine settings than specified for the procedure or if the machine was improperly calibrated. Neither of these can be confirmed explicitly.

Third, machine outputs were obtained from the results of calibration studies. As it was not possible to match any radiograph with a particular x-ray machine, values of energy output averaged over all machines were used. Although using the average value for energy output may have under- or overestimated the true value for a particular subject, given the large number of subjects, it was unlikely that there were any large distortions of dose across all subjects.

Fourth, no data were available to indicate the correct values for the half-value layers. Instead, plausible values were chosen for this thesis on the basis of typical practices for the time periods under study. If the half-value layer was actually one millimeter of aluminum greater than assumed, the calculated doses would have underestimated the actual doses by fifteen to twenty percent.

Fifth, it was assumed that breast doses from lateral spinal radiographs were the same as those from the anteroposterior view. Direct measurements bear out that this assumption is correct (M. Rosenstein, personal communication). A similar situation, with one breast partially shielding the other and altering the dose distribution, occurs with the oblique view. In both cases, the breast closest to the machine receives a higher dose than from the anteroposterior view, the shielded breast receives a lower dose, and the

mean is approximately the same. Another issue concerns doses from posterior anterior radiographs which were about an order of magnitude lower than from anteroposterior radiographs (table 5.9 page 73). Thus, it was assumed that the organ doses using the posteroanterior view contributed negligibly to the cumulative doses and were consequently excluded.

Assumptions in the risk projection

According to the BEIR V Committee, the statistical models of excess cancer risk were subject to three types of uncertainty (NAS90). The first was random error owing to sampling variation; the Committee believed this to represent the largest component of uncertainty. To account for this variability, lower and upper confidence interval of the coefficient for dose were used in the life table calculations. Uncertainties in the temporal modifying variables were not taken into account (*i.e.* time since exposure), because the data needed to make these calculations (*e.g.* covariance matrices, likelihood-based confidence intervals) were not available. The second type of uncertainty was the correct form of the risk model Before selecting their preferred risk models (*e g.* equation 2.5 shows the model for breast cancer, pages 34 and 35), the BEIR V Committee tested a variety of other models that contained different combinations of the terms for age. Some of the alternative models for other sites were included in the BEIR V report, but no alternative models were presented for breast cancer. It was therefore not possible to evaluate the affects on the life table projections that different risk models may have had. Third, there were various potential biases in the data sets used for modelling risk by the BEIR V Committee (*i.e.* dosimetry errors, population differences). As these biases could not be quantified precisely, they were not considered (NAS90). However, it has been estimated that if the BEIR V Committee had incorporated model misspecification, dosimetry errors and population differences in their risk models, the 90% confidence

intervals of the risk estimates may have been increased by a factor of 1.4 (EI91). If this were the case, the upper confidence limit on the risk of breast cancer may have been increased by about the same value.

The life table calculations entailed two assumptions regarding the age at exposure and the effects of dose fractionation. The first was that all subjects were assumed to have been exposed at age fifteen years. The mean age at referral in the AIS cohort was fourteen years, and the average length of time under observation was approximately three years. Furthermore, over 70 percent of individuals were first exposed between fourteen and seventeen years of age. Thus, one effect of assuming the age at exposure was fifteen years was to overestimate the number of years at risk by one or two. Given that individuals in the cohort were projected to have a typical life expectancy of over 60 years more at age fifteen, it is unlikely that this had any material effect on the results. The other possible effect of underestimating age at exposure was that, for breast cancers, the risk model projected the greatest risks for age at exposure less than sixteen years. If the actual excess risk dropped off rapidly after that age, then the risks associated with radiographs made of women older than fifteen years may have been overestimated. The second assumption was that the x-ray doses were delivered from a single exposure to radiation while, in fact, they were delivered over a period of several years. For low energy ionizing radiation like x-rays, there is some evidence that dividing a given dose into a number of fractions spread over a period of time reduces the risk of some cancers when compared to a single dose. However, on the basis of the United States and Canadian studies of fluorscopic examinations and breast cancer, the BEIR V Committee concluded that "... the epidemiological data reveal little or no decrease in the yield of tumors when the total radiation dose is received in multiple exposures rather than a single, brief exposure" (NAS90). It was not possible to evaluate the effect of dose fractionation on thyroid cancer risk because all published studies were of individuals

irradiated over a short period of time.

In the life table calculations, doses were taken as whole-body so that all organs were assumed to be exposed to the same amount of radiation. The calculation therefore accounted for cancers of other organs (digestive, respiratory, bone marrow). In fact, these organs received much lower doses than the thyroid gland and female breast. The effect of incorporating these other cancers was to reduce the cancer risks to the breast and thyroid gland because the other cancers were a competing source of mortality or incidence (Va90).

Although the risk models presented by the BEIR V Committee were derived for cancer mortality, the same models were applied to project cancer incidence. In the risk calculation, incident breast cancers and thyroid cancers were therefore censored from the life table population. Thus, subjects developing a breast cancer or thyroid cancer were assumed not to be at risk of developing a second cancer. Although this assumption is not correct, it probably did not seriously affect the results because the probability of developing two incident cancers over a lifetime is relatively low.

Another uncertainty was the appropriateness of using general population rates to predict the number of cancers expected in a population of scoliotics. For mortality from other causes than cancer, there is some evidence that scoliotics have elevated mortality rates, but this finding was limited to untreated populations in the past (Na68, Ni68). For breast cancer, it is not known whether differences in other risk factors exist between scoliotics and the general population (Ho89). Differences in other risk factors for cancer, such as the inability to carry out a pregnancy to term which is also associated with increased risk of breast cancer, would probably affect only women with more severe scoliosis. Thus, given that the cohort consisted of many individuals with a scoliosis that was not

considered severe, and that severe cases received surgical interventions that may have reduced the risk of reproductive and pulmonary complications, use of population rates is justified.

6.2 Comparison of results with data from the literature

Subjects in this study received on average about ten spinal radiographs during the diagnosis and management of AIS. The distribution of radiographs has been reported in three other articles (He83, Ho89, Na79). The largest average number of spinal radiographs taken for scoliosis was 41.5, of women in Minnesota (Ho89). This relatively large value was due to these women having more severe scoliotic curves (average Cobb angle during treatment of 56 degrees), a longer period of observation (nine years), and referral occurring before 1965 when x-rays were used more freely. In another study, Nash *et al* estimated that, on average, 22 spinal radiographs would be taken of a typical patient undergoing Milwaukee brace treatment during a three year period of observation (Na79). This number was based on a series of thirteen female subjects for whom the average curve was not given. Although the length of follow-up in the AIS cohort was also about three years, the number of spinal radiographs was approximately half that reported by Nash, due in part to the AIS cohort comprised about five percent of individuals who were not radiographed. In a third study from Sweden, the number of spinal radiographs for treatment of scoliosis was estimated between ten and twenty (He83), a value that is compatible with the results of this study.

The value of 22 spinal radiographs for scoliosis published by Nash *et al* (Na79) has some importance in that the value given has been used in several studies estimating the excess cancer risk from scoliosis radiographs (De81, Dr83, Du90, Ra84). As the estimate was obtained from only thirteen subjects, risks projected using this estimate may not reflect

scoliosis patients seen in clinics today. Since the advent of screening programs, more persons are referred with small scoliotic curves that do not progress and require less follow-up (and fewer radiographs). For subjects whose curves progress, follow-up is extended over a longer period of time (requiring more radiographs). Overall, it is likely that the values obtained in this thesis (twelve radiographs for women and ten for men) are more accurate because they were based on a large number of subjects with all degrees of scoliotic curves.

In table 6.1 (page 88), information on the techniques, skin exposures and breast doses from anteroposterior spinal radiographs at Hôpital Ste-Justine is shown and compared to values published in other studies. The table also shows how the skin exposure measurements were made and summarizes the method used to obtain a value for breast dose. There was wide variation in organ doses reported in the literature that was probably due to differences in the type of x-ray machines used and the methods of calculating dose from skin exposure. The type of x-ray equipment surely affected the doses in all studies, yet surprisingly, the type of machine was only listed in one study (a single-phase machine; Bh81). To estimate the average breast dose, most studies simply multiplied the skin exposure by a constant value to represent the photons' attenuation of energy through the body. Using Monte Carlo calculations to obtain the organ dose is preferable to other methods because it describes the energy deposition of x-rays in human tissue more realistically. Overall, the doses from anteroposterior radiographs at Hôpital Ste-Justine in the most recent period are of the same order as the lowest doses reported in the literature. Those studies were probably carried out using three-phase x-ray equipment similar to the machines currently in use at Hôpital Ste-Justine. The doses estimated for the period 1957 to 1978 were compatible with values from one study (Ho89), and lower than the values from two other studies (Bh81, Na79).

Table 6.1. Comparison of anteroposterior spinal radiographic techniques, skin exposures, and organ specific dose estimates.

Location (Reference)	Year	Machine settings: Maximum tube potential (kV)	Machine settings: Current (mAs)	Machine settings: Filtration (mm Al)	Source to film distance (cm)	Skin exposure (mR)	Skin exposure measurement: Instrument	Skin exposure measurement: Placement	Method of calculating dose from skin exposure	Dose (cGy): Breast	Dose (cGy): Thyroid
Present study[1]	1957-78	88	140	2 0	183	403	IC	In air	Monte Carlo methods	0 277	0 294
Present study	1979-82	74	80	2.5	183	126	IC	In air	Monte Carlo methods	0 096	0 104
Present study	1983-89	58	40	2.5	183	60	IC	In air	Monte Carlo methods	0 046	0 049
Pennsylvania[3] (Bh81)	na[2]	90	100	3.0	183	283	IC	In air	Arithmetic correction	0 790	0 914
Ohio (Na79)	na[2]	na	na	na	183	1129	TLD	On patient	Arithmetic correction	0 620	na
Ontario (Dv82)	na[2]	74-87	na	na	119-186	26-147	TLD	On patient	Arithmetic correction	0 035-0 061	0 039-0 117
Sweden (He83)	na[2]	80-88	40-320	na	300	250	IC	Plastic phantom	Arithmetic correction	0 022-0 035	na
Virginia (Du90)	na[3]	80	150	na	183	na	TLD	Plastic phantom	TLD measurements taken at a depth of 3 cm	0 015-0 029	na

na - not available
IC = ionization chamber, TLD = thermoluminescent dosimeters
[1] In the present study the values are for adolescent subjects
[2] Probably from late 1970's or early 1980's.
[3] Probably mid-1980's.

A number of authors have reported estimates of the risk of developing breast cancer from spinal radiographs for scoliosis (De81, Du90, Na79). Nash *et al* estimated that the dose to breast tissue (average of 22 spinal radiographs) was 14 cGy (Na79), approximately three times as high as the dose estimated in the present study. Based on estimates from the 1972 BEIR I Committee (NAS72), these authors found the risk of breast cancer to be about 110 percent in excess. The relatively high risks estimated in that study were due to the large dose estimates. In another study (De81), the average breast dose was 1.3 cGy based on an average of 22 spinal radiographs for scoliosis, and the excess risk of breast cancer was estimated to be 35 percent based on a linear relative risk model. Risks in that study were estimated using information from a study by Boice *et al* (Bo79), that gave risk estimates of breast cancer similar to those from the BEIR I Committee (NAS72). Thus, the large difference in breast cancer risks estimated by DeSmet *et al* compared with Nash *et al* (35% versus 110%) is due in large part to the 10-fold difference in dose. In a third study (Du90), it was estimated that the risk of breast cancer incidence from an average of 22 spinal radiographs for scoliosis was increased 0.22 percent based on a linear relative risk model and 0.4 percent based on an absolute risk model. The much lower risks projected in that study were the result of very low dose estimates (table 6.1, page 88) and the use of risk estimates from the BEIR III Committee that were much lower than estimates from the BEIR V Committee (see section 2.5, page 31 *ff*). In summary, there is a difference of three orders of magnitude between the highest and lowest published estimates of risk of breast cancer from scoliosis radiographs. The main reasons for the large discrepancies are the wide range of dose estimates from spinal radiographs and the different estimates of risk of radiogenic breast cancer. The excess risks found in this study, approximately a three percent increase in breast cancer risk, were intermediate between the lowest and highest risk estimates.

6.3 Future studies

A follow-up study of the AIS cohort would permit evaluation of the accuracy of the risk projections made here. For such a follow-up study, cancer incidence or mortality would be ascertained and compared to that in a selected comparison group or to that in the general population. A fundamental question is whether there would be sufficient statistical power to make such a study worthwhile. A quantity related to statistical power is the minimum detectable relative risk. Under the assumption that the control group would be drawn from the general Quebec population, the minimum detectable relative risk (for a one-sided alpha of 0.05 and power of 0.8), was calculated using the excess number of cancers in the absence of radiation obtained from the life table program (table 6.2, column 2). The detectable excess (column 4) was obtained using the relationship: expected number of cancers * (relative risk - 1). For example, the first row in the table shows that about 162 breast cancers are expected to occur over the lifetime of 1,847 Quebec women in the absence of a cohort-specific exposure (like exposure to diagnostic x-rays); a minimum of about 32 excess cancers are needed to detect a statistically significant relative risk of 1.20; about five excess cancers (upper 95% confidence limit of about ten) were estimated for the cohort. The table shows that for both thyroid and breast cancer, the projected number of excess cancers, as well as the values projected using the upper 95% confidence limit, are well below the minimum number of excess cancers needed to detect a significant relative risk. Thus, the projected excess cancers due to x-ray radiation will probably not become statistically detectable over the lifetime of the AIS cohort.

Table 6.2. Lifetime expected background number, minimum detectable excess, and projected number of cancers among women needed to detect a significant relative risk (RR), the AIS Cohort, 1960-79.[1]

Cancer site	Expected lifetime number of cancer cases in the absence of radiation	Minimum detectable RR[2]	Detectable excess with this RR	Excess projected[3] (upper limit)
Breast, incidence	162.5	1.20	32.5	4.6 (9.6)
Breast, mortality	73.1	1.31	22.8	1.5 (3.0)
Thyroid, incidence	12.9	1.81	10.5	2.3 (3.8)
Thyroid, mortality	3.5	2.77	6.2	0.6 (1.0)

[1] In a cohort of 1,847 women with Quebec rates.
[2] Estimated using the method presented in Armstrong (Ar87), assuming a one-sided significance level of five percent ($z_\alpha = 1.645$) and 80 percent power ($z_{1-\beta} = -0.842$).
[3] Excess attributable to x-ray radiation for scoliosis

6.4 Reducing x-ray doses

Given the relatively high risks from diagnostic x-rays found here and the relatively high prevalence of scoliosis in the population, it is important to consider practical ways to reduce doses. A large portion of the excess risk was due to high doses received in the 1970s. Doses from spinal radiographs have been reduced considerably since that time through the installation of modern x-ray equipment. Nevertheless, doses could be further reduced by an order of magnitude if spinal radiographic examinations for scoliosis were taken using the posteroanterior rather than the anteroposterior view (table 5.15; page 79).

Nash *et al* first mentioned using the posteroanterior spinal examinations for scoliosis, and found a three-fold reduction in x-ray dose using that view (Na79). In that study, the estimated excess risk of breast cancer was reduced from 110 percent using the

anteroposterior view to 3.8 percent using the posteroanterior view. On the basis of that finding, those investigators suggested that the posteroanterior view be adopted for managing scoliosis. However, this was not the conclusion reached by DeSmet *et al* (De81), who showed that significant reductions in breast dose could be achieved by changing the radiologic techniques (machine settings, increased shielding) used to make anteroposterior spinal radiographs. They suggested that use of the anteroposterior view be continued because of concern that there would be difficulties in accurately measuring spinal curvature. In another study reported by DeSmet *et al* (De82), the Cobb angles of 128 curves measured in 78 patients were measured on paired anteroposterior and posteroanterior spinal radiographs that had been taken on the same day. The angles measured from the two views were highly correlated; the angles on the posteroanterior radiographs were systematically larger than the anteroposterior radiographs by a mean of 2.4 degrees for thoracic curves and 1.7 degrees for lumbar curves and only thoracolumbar Cobb angles measured essentially the same on the two views (De82). However, these differences are of the same order as the inter-observer differences in the Cobb angle reported elsewhere (Go88). Thus, the differences in curves observed by De Smet *et al* (De82) can be explained by observer variation, calling into question the previous assertion that anteroposterior radiographs are required for accurate measurement of spinal curvature. Other investigators have indicated that details are equally well visualized on anteroposterior and posteroanterior spinal radiographs (Gr83) and that posteroanterior radiographs are of adequate quality for routine follow-up of scoliosis patients (Ar80). Therefore, the majority of investigators have recommended posteroanterior spinal radiographs for scoliosis (An82, Ar80, Bu82, De85, Dr83, Fr83, Gr81, Gr83, He83, Le89, Ra84).

6.5 Conclusions

Using modern techniques for estimating organ-specific doses of x-rays from diagnostic radiographs and the most up-to-date risk models, this study showed that substantial excess breast cancer and thyroid cancer risks, between three and fifteen percent, are imparted from diagnostic levels of x-rays for scoliosis to subjects seen for scoliosis from the 1970s through the 1980s. The methodology developed here can be generalized to estimate risks from other radiographic procedures and to other organs. Over the past twenty years, doses of x-rays from spinal radiographs for scoliosis have been lowered by about 90 percent using modern x-ray equipment. However, doses to sensitive organs such as the breast and thyroid gland may be reduced even further through the use of the posteroanterior view, without substantial increases in risk to other tissues and without any loss in the diagnostic information used to manage scoliosis. Thus, the posteroanterior view should be requested instead of the anteroposterior view to diagnose and manage subjects with AIS and, all radiographs, whether for scoliosis or for other conditions, should be ordered judiciously rather than routinely.

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