Study details	Participant details	Outcomes measured	Results	Comments on quality
Cox 1964[42] **Type of publication:** Journal article **Country of origin:** Canada **Source of funding:** Supported by a research grant allocated by the Province of Ontario under the National Grants Programme **Study design:** Controlled cohort study **Aim of study:** To detect any indications of genetic damage from radiation in the offspring of women treated during childhood for congenital dislocation of the hip	**Inclusion/exclusion criteria** **Cases**: Married women who were at least 20 years of age at the onset of the study, who had been patients at The Hospital for Sick Children for congenital dislocation of the hip in 1925 or later were eligible for inclusion. Patients who lived more than 200 miles away from Toronto, or who could not be located or personally consulted were excluded **Control subjects**: Married male and female siblings of the cases **Dates of recruitment:** 1925 – NR (although participants had to be at least 20 years of age at the onset of the study) **No. recruited:** 91 cases and 157 control subjects **Age:** All cases were aged 20–40 years at the onset of the study (none were aged > 40 years at follow-up) **Male (%):** 0 cases and 77 (49) control subjects **Disease characteristics:** Cases: Childhood congenital dislocation of the hip	**Outcome measures** 1. Mean X-ray dose per child 2. Number and type of X-rays received since childhood 3. Details of pregnancies and offspring **Methods used for collecting data** 1. Mean X-ray dose per child was estimated using the mean number of films per child and the mean dose from an AP film The mean number of pelvic X-ray exposures for both married and unmarried female patients was estimated using medical records and X-ray films that were still on file at The Hospital for Sick Children. For each film the age of the child, type of projection, and whether or not the pelvis was enclosed in a plaster cast were recorded. Data were available for 30 patients Mean X-ray dose was estimated using tissue-equivalent wax phantoms. Ionisation chambers were used to measure the dose absorbed in the region of the ovaries in three phantoms, representing sizes for 6 months, 4 years and 12 years. Present techniques were altered to approximate techniques of the 1920–40 period using maximum field size, removing filters (with the exception of 1-mm aluminium, which was an integral part of the machine), and the value for milliampere seconds (mAs) was increased by a factor of four to account for increases in film and screen speeds. The focus field distance was 40 inches for all measurements. Films were made in the AP position and the LAT position 2. Number and type of X-rays received since childhood 3. Details of pregnancies and offspring	**Cases** **Mean no. of pelvic X-ray exposures during the course of treatment and follow-up:** 37.4 (at age 0–2 years: 8.7, at age 3–7 years: 13.9, at age 8–11 years: 8.1, at age 12–16 years: 6.7) **Mean no. of exposures while patient in plaster:** 11.4 **Mean X-ray dose measured on phantoms:** age 6 months AP: 108 mrads, age 4 years AP: 140 mrads, age 12 years AP: 180 mrads **Total mean X-ray dose per child:** 6.1 rads [5.58 rads (at age 0–2 years: 0.96 rads, at age 3–7 years: 1.95 rads, at age 8–11 years: 1.46 rads, at age 12–16 years: 1.21 rads) + 0.51 rads owing to increase in exposure of average 45 mrads for each exposure through a plaster cast]. The authors state that this estimate is subject to a number of errors and is probably considerably lower than the actual mean dose received **No. and type of X-rays received since childhood:** 56 cases had received pelvic X-rays prior to conception of their last child; 33 exposures during pregnancy and 58 exposures when not pregnant. The authors estimated the mean adult ovarian radiation dose as 1.4 rads per woman, making the total estimated mean ovarian dose per patient a minimum of 7.5 rads (up to a maximum of 20) **Cases and control subjects:** **Details of pregnancies and offspring:** There was no significant difference between cases and control subjects in the number of offspring (201 vs 402) or the proportion of male offspring (49% vs 53%) **Stillbirths (at least 28 weeks' gestation) and neonatal deaths (within 28 days after birth):** There was no significant difference between cases and control subjects in the number of stillborn offspring [4 (2%) vs 3 (0.8%); $p = 0.34$] or neonatal deaths [0 vs 8 (1.9%); $p = 0.10$]	The estimate of total mean X-ray dose is unlikely to be a reliable estimate; the authors acknowledge that it is subject to a number of errors The majority of cases had received pelvic X-rays prior to conception of their last child; including 33 exposures during pregnancy, which may have had an impact on pregnancies and offspring Details of pregnancies and offspring were obtained by personal interview/questionnaire, which may be subject to recall bias. The authors acknowledge that information on spontaneous abortion is unlikely to be accurate; early miscarriage may have been forgotten or unrecognised. However, causes of stillbirths and neonatal deaths and diagnosis of abnormalities requiring hospitalisation were confirmed objectively Using siblings as control subjects appears to be appropriate, as they share a greater similarity in social, economic and genetic background than unrelated controls subjects Other factors that may have influenced birthweight and congenital abnormalities were not reported, such as illness/injury during pregnancy, pre-term birth, family history, etc. The authors do not report the reasons for the 33 X-ray exposures amongst the cases during pregnancy

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		Cases: Personal histories were obtained by interview, usually in the participant's own home. If the participant had died as an adult, a member of their immediate family was interviewed. Participants were asked similar information about their married siblings (the control group) **Control subjects:** The control group were interviewed (*n*=57) or sent a questionnaire (*n*=96) in order to verify and add information about themselves and their families. If the participant had died as an adult, a member of their immediate family responded. Four control group participants were not surveyed **Cases and control subjects:** Causes of stillbirths and neonatal deaths were confirmed by the office of the Registrar General of the Province of Ontario. Each diagnosis of abnormalities requiring hospitalisation was confirmed by the hospital at which treatment was carried out **Statistical analyses:** Chi-squared tests were used **Length of follow-up:** NR	**Spontaneous abortions (earlier than 28 weeks' gestation):** There was no significant difference between cases and controls in the number of spontaneous abortions [23 (10.3% of pregnancies) vs 38 (8.6% of pregnancies); $p=0.58$] **Frequency of abnormal offspring (including stillborn offspring):** There was a statistically significant difference in the proportion of offspring with abnormalities between cases and control subjects [26 (12.9%) vs 23 (5.7%); $p=0.004$]. There was a statistically significant difference in the proportion of offspring with more severe abnormalities (i.e. those requiring hospitalisation, and excluding hernia) [15 (7.5%) vs 10 (2.5%); $p=0.008$] The congenital abnormalities requiring hospitalisation for offspring of cases were: anencephalus, hydrocephalus, Down syndrome, intestinal atresia, harelip and cleft palate, haemangioma of scrotum, facial pigmented naevus, cavernous plantar haemangioma, shoulder and abdominal haemangiomata, Duchenne muscular dystrophy, torticollis, undescended testes, bilateral clubfoot, bilateral nerve deafness (in two siblings). Abnormalities not requiring hospitalisation for offspring of cases were: inguinal hernia (*n*=4), umbilical hernia, inguinal hernia and umbilical hernia, strabismus, flexion deformity of toe, overlapping toes, haemangioma (*n*=2) The congenital abnormalities requiring hospitalisation for offspring of control subjects were: anencephalus (*n*=2), hydrocephalus (*n*=2), spina bifida, pyloric stenosis (*n*=2), dermoid cyst of orbit, congenital heart disease, tracheo-oesophageal fistula with immaturity. Abnormalities not requiring hospitalisation for offspring of control subjects were: inguinal hernia (*n*=3), umbilical hernia, epigastric hernia, hernia unspecified, strabismus (*n*=4), shortening of leg, bilateral tibial torsion, metatarsus varus	

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			Birthweight: Mean birthweight for male offspring was lower for cases than control subjects (3175 g vs 3320 g; $p > 0.025$). However, when birthweights were compared within birth orders, there were no significant differences. Mean birthweight for male offspring was lower than the Ontario population mean birthweight using birth data from 1960 (3385 g; $p < 0.001$) There was no significant difference in mean birthweight for female offspring between cases and control subjects (3149 g vs 3212 g), or the Ontario population mean birthweight (3255 g) **Authors' conclusions:** The frequencies of stillbirths, infant deaths and spontaneous abortions were similar for irradiated mothers and control subjects. The proportion of males tended to be lower among the offspring of cases than among offspring of control subjects. The frequency of abnormal offspring was significantly higher among the exposed mothers. The mean birthweights of offspring, particularly males, appeared to be lower for the offspring of exposed mothers than of control subjects	

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Goldberg *et al*. 1998[43] **Type of publication:** Journal article **Country of origin:** Canada **Sources of funding:** Atomic Energy Control Board of Canada, Université de Montréal, and Le Fonds de la recherché en santé du Québec (FRSQ) **Study design:** Controlled retrospective cohort study **Aim of study:** To assess the association between exposure to low-dose ionising radiation from diagnostic radiography received in adolescence and subsequent adverse reproductive outcomes in adulthood	**Inclusion/exclusion criteria** *Cases:* Female patients included in the Ste-Justine Adolescent Idiopathic Scoliosis Cohort Study were eligible for inclusion. The Ste-Justine Adolescent Idiopathic Scoliosis Cohort Study included 2092 children and young adults referred to Ste-Justine Hospital, Montreal, for the diagnosis and management of adolescent idiopathic scoliosis. Of the 1793 females included, the authors were able to trace 88.8%, of which 80.3% returned their questionnaires (1292) *Control subjects*: 1134 women selected randomly from the general population, identified using residential, non-confidential telephone numbers. Control subjects were approximately frequency-matched to cases according to age and general area of residence **Dates of recruitment:** Cases were recruited to the Ste-Justine Adolescent Idiopathic Scoliosis Cohort Study from 1960 to 1979. Dates of recruitment of the control group are not stated **No. recruited:** 1292 cases and 1134 control subjects **Age:** 15 to > 45 years. The majority of patients were aged 25–39 years **Male (%):** 0 **Disease characteristics:** Cases: adolescent idiopathic scoliosis	**Outcome measures** 1. Organ-specific doses from diagnostic radiography for adolescent idiopathic scoliosis 2. Adverse reproductive outcomes **Methods used for collecting data** 1. For each spinal radiograph (35.6 × 91.4 cm films) the authors abstracted the data of the radiograph and the orientation (AP, LAT PA or oblique) from the hospital chart. Absorbed X-ray doses to the ovaries were calculated by incorporating characteristics of the radiographs with data from a Monte Carlo procedure that provided estimates of the absorption of energy in human tissue. The organ-specific doses for each radiographic view, age group and sex were calculated. Then doses were assigned for each radiograph and summed for each patient 2. Participants completed a postal questionnaire that included questions on the following reproductive outcomes: lack of success in becoming pregnant after attempting to do so, and result of each pregnancy (live birth, spontaneous abortion or stillbirth). For each live birth, participants were asked the birthweight and whether the baby was diagnosed as having a congenital malformation. Low birthweight was categorised as < 2500 g) **Statistical analyses:** The authors used logistic regression to analyse unsuccessful attempts at pregnancy. Other binary pregnancy outcomes were analysed using logistic regression that accounted for the clustered nature of data through the Generalised Estimating Equations GEE framework, as clustering can occur from women having multiple pregnancies, with the consequence that multiple adverse outcomes are positively correlated	Cases and control subjects were fairly evenly matched in terms of education, marital status, alcohol consumption, self-perception of health, body mass index and physical recreational activity. A higher proportion of cases lived in Montreal, fewer cases were aged 15–24 years, more cases were aged 30–34 years, and there was a higher proportion of 'never smokers' among the cases **Organ-specific radiation dose:** The mean dose to the ovaries was 0.925 (SD 0.760) cGy **Reproductive outcomes:** Difference between cases and controls in the number of: Unsuccessful attempts at pregnancy 49 (3.8%) vs 32 (2.8%) adjusted OR 1.33, 95% CI 0.84 to 2.13 Stillbirths 6 (0.5%) vs 19 (1.5%) adjusted OR 0.38, 95% CI 0.15 to 0.97 Low-birthweight infants 74 (6.4%) vs 94 (7.6%) adjusted OR 0.84, 95% CI 0.59 to 1.21 Infants with congenital malformations 47 (4.0%) vs 36 (2.9%) adjusted OR 1.20, 95% CI 0.78 to 1.84 Spontaneous abortions 209 (12.8%) vs 158 (9.7%) adjusted OR 1.35, 95% CI 1.06 to 1.73 Subgroup analysis (quartiles of dose, cGy): When comparing adolescent idiopathic scoliosis patients at higher organ-specific doses to those in the lowest dose group (0–0.312 cGy), none of the reproductive outcomes was significantly different between groups. However, the outcome low birthweight (< 2500 g) almost reached statistical significance when the highest-dose group (≥ 1.444 cGy) was compared with the lowest-dose group: 33 (8.5%) vs 9 (3.6%); adjusted OR 2.34, 95% CI 1.0 to 5.6 **Authors' conclusions:** Associations between adverse reproductive outcomes and radiotherapy have been observed previously, but this is the first study in which an association with birthweight has been found with diagnostic radiography	This was a large cohort study; however, some of the events were rare (such as stillbirth) Details of pregnancies and offspring were obtained by postal questionnaire, which may be subject to recall bias. None of the responses on reproductive outcomes was validated objectively. The authors acknowledge that this study is open to errors in recall, in particular information on spontaneous abortion is unlikely to be accurate; early miscarriage may have been forgotten or unrecognised The authors presented the results as adjusted ORs, with no indication of which results were statistically significant, and which were likely to be because of chance The authors also acknowledge that other factors may have affected reproductive outcomes, such as age of the mother and smoking during pregnancy The authors acknowledge that chance or some undetected bias in selecting persons into the control group may account for the fact that they observed a dose–response relationship in the adolescent idiopathic scoliosis group for low birthweight, but there was a lower proportion of low-birthweight infants in this group than in the control group. Other factors may have been involved, such as medical conditions during pregnancy, gestational age or sex of the infant

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		Analyses were conducted using cumulative ovarian dose as a continuous linear variable, and according to quartiles. Analyses were conducted using the control group as a baseline category (no radiation exposure in adolescence from scoliosis), and excluding the control group, but comparing within the cases between levels of dose. GEE was used to analyse birthweight as a continuous variable, assuming a Gaussian error structure. Sensitivity analyses were conducted to verify assumptions about cut-points and linearity Sixteen pairs of twins were excluded from the analyses (because of their lower birthweight) Covariates included in the final models were those variables found from univariate logistic regression analysis to be associated with each of the outcomes under consideration (e.g. education, alcohol consumption, smoking status, body mass index and occupation) **Length of follow-up:** NR		

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US Scoliosis Cohort Study (pilot) 1989[34] **Type of publication:** Journal article **Country of origin:** USA **Sources of funding:** Public Health Service contracts from the National Cancer Institute, National Institutes of Health, Department of Health and Human Services; the Scoliosis Research Society; the Twin Cities Scoliosis Research Fund; and the Medical Education and Research Foundation of Gillette Children's Hospital, St Paul, MN **Study design:** Uncontrolled retrospective cohort study **Aim of study:** To determine whether or not X-ray exposures during scoliosis treatment in the past might be associated with a detectable risk of breast cancer	**Inclusion/exclusion criteria:** Women with a confirmed diagnosis of scoliosis or kyphosis who were seen at one of four medical facilities in the Minneapolis-St Paul, MN area. Patients were excluded if they were diagnosed after 1965, were aged > 19 years at diagnosis, survived < 3 years after diagnosis, or had a history of cancer or radiotherapy Dates of recruitment: 1935–65 (year of diagnosis 1922–65) **No. recruited:** 1030, of which 856 responded to the questionnaire/telephone interview (either in person (818), or a surrogate response was received for deceased patients (38); 973 patients were included in the analyses, as 51 patients could not be located, and dates of radiographs were missing for six patients **Age:** Mean age at follow-up was 41.4 years **Male (%):** 0 **Disease characteristics:** 60% of participants had idiopathic scoliosis	**Outcome measures** 1. Radiation dose estimation 2. Observed and expected breast cancers **Methods used for collecting data** 1. Information on diagnosis and treatment of scoliosis were abstracted from medical records from the participating hospitals. Counts of all radiographs were obtained by reviewing actual films or estimating numbers from radiology reports in the medical records, film jackets or radiology log books. The authors collected data on whether or not the breasts were in the primary X-ray beam for particular X-ray procedures for a sample of patients, and then estimated this for the entire population. Data on stage of breast development was obtained from photographic, descriptive or X-ray evidence Radiation doses to the breast (and other organs) were estimated using data on the number of radiographs per patient, the type of examination and the machines and techniques in use at the time of radiography. The dose absorbed by breast tissue was estimated by medical physicists (AP exposure assumed) 2. Participants completed a telephone interview or postal questionnaire on various medical conditions, breast cancer and relevant cancer risk factors. Pathological confirmation of breast cancer cases was obtained from the hospital of diagnosis or treatment. A subgroup of women ($n = 465$) attended one of the medical facilities for a scoliosis follow-up examination or sent a current radiograph for review	**Radiation dose estimation:** The average number of radiographs taken per patient was 41.5 (range 0–618) and were given over an average of 8.7 years. Among the 951 women for whom a dose of radiation to the breast could be estimated, the average dose was 12.8 rad (range 0–159 rad). Average doses to the thyroid and active bone marrow were 6.9 rad and 3.3 rad, respectively **Observed and expected breast cancers:** The proportion of patients who had a history of breast cancer was higher than the number expected (11 vs 6 expected cases; SIR 1.82, 90% CI 1.0 to 3.0) **Subgroup analyses:** When examining the number of cases of breast cancer by age, time since first radiograph, and radiation exposure, there was a higher incidence of breast cancer than the expected incidence, for patients aged ≥ 15 years at the time of their first radiograph (SIR 3.1, 90% CI 1.4 to 6.2), patients for whom time since first radiograph was 30 years or more [SIR 2.4 (90% CI 0.9 to 5.0) trend for increased risk with time $p = 0.02$], patients who received a total of 30 or 60 radiographs or more (SIRs 2.0, 90% CI 0.07 to 4.7 and 3.1, 90% CI 1.1 to 7.1 respectively) and patients who had a radiation dose to the breast of 20 rad or more (SIR 3.4, 90% CI 1.2 to 7.8) (trend for increased risk with increased dose $p = 0.08$) No patients were diagnosed with breast cancer within 15 years of their first radiograph, which was expected. Risk of breast cancer increased with increasing radiation dose to the breast within both the group of women who had had a full-term pregnancy, and the group of women who had not. Patients with more severe scoliosis were less likely to have had a full-term pregnancy	This was a large cohort study; however, there were only 11 cases of breast cancer. The authors acknowledge that their findings require confirmation by larger studies The authors acknowledge that the radiation dose estimation may be subject to error Other factors that may have influenced breast cancer incidence were not adjusted for, such as age at menarche, history of benign breast disease and family history of breast cancer The authors acknowledge that factors associated with severe scoliosis, such as inability to carry a pregnancy to term, might influence the results, since nulliparous women are at higher risk for breast cancer. Therefore, the observed association between higher number of radiographs (more common for more severe scoliosis) and breast cancer may have been influenced by this risk factor

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		Statistical analyses: Person-years of follow-up began 3 years after the date of the first X-ray exposure or scoliosis diagnosis and ended at the date of breast cancer diagnosis, death or date of last known vital status. Expected numbers of breast cancers were calculated by multiplying age-, sex- and calendar time-specific breast cancer incidence rates from the Connecticut Tumor Registry by the appropriate person-years of follow-up. The SIR (the ratio of observed cases to expected cases) was calculated, with 90% CIs. Tests of trend of increasing SIR with time and dose were performed by applying the multiplicative models of Breslow *et al.*[a] Tests were one-sided **Length of follow-up:** The average length of follow-up for the 973 patients with usable follow-up information was 25.6 years	**Authors' conclusions:** These data suggest that frequent exposure to low-level diagnostic radiation during childhood or adolescence may increase the risk of breast cancer	

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US Scoliosis Cohort Study 2000[35] **Type of publication:** Journal article **Country of origin:** USA **Source of funding:** The National Cancer Institute, US Public Health Service, Bethesda, MD **Study design:** Uncontrolled retrospective cohort study **Aim of study:** To evaluate patterns in breast cancer mortality among women with scoliosis, with special emphasis on risk associated with diagnostic radiograph exposures	**Inclusion/exclusion criteria:** Women with a confirmed diagnosis of scoliosis, kyphosis, lordosis or kyphoscoliosis, who were seen at any of 14 large orthopaedic medical centres in the USA (including those patients enrolled in the pilot study).[34] 161 patients with congenital scoliosis were included in the pilot study; however, no additional patients with congenital scoliosis were enrolled in this study. Exclusion criteria included patients who were diagnosed after 1965, were > 19 years of age at diagnosis, or had a history of cancer or radiotherapy or other characteristics that could have been associated with multiple radiograph exposures at other institutions **Dates of recruitment:** Not stated (year of diagnosis 1912–65) **No. recruited:** 5573, of which vital status was determinable for 4971 patients. 5466 patients were included in the subgroup analyses, as 34 patients contributed no woman-years of follow-up, 18 patients had missing exit dates and 55 were known to have died but the cause of death was unknown **Age:** Mean age at follow-up was 51 (range 2–89) years **Male (%):** 0 **Disease characteristics:** The vast majority of patients had scoliosis (92.7%). Around half of patients (49.2%) had idiopathic disease. Most patients were diagnosed at the age of 10 years or above (62.7%)	**Outcome measures** 1. Radiation dose estimation 2. Mortality rates 3. Breast cancer mortality rates **Methods used for collecting data** 1. Information on diagnosis and treatment of scoliosis were abstracted from medical records from the participating hospitals. Data on date of radiograph, field, view, position, presence of an orthosis, radiograph size, whether or not the breast was in the X-ray beam and radiograph machine parameters were collected from radiology reports, radiographs, radiograph jackets and radiology log books Dose to the breast was estimated for each examination in which the breast was definitely or probably in the radiation beam (89% X-rays); examinations in which the breast was not exposed to the beam were assumed to contribute no dose. The breast dose was estimated for pre-teens (aged < 13 years) at a depth of 1.0 cm, and for adults (aged ≥ 13 years) at 2.5 cm. Doses were calculated for each examination according to the year of X-ray examination (separately for the years 1920–39, 1940–59, 1966–75 and 1976–89) Information was not sufficient to estimate doses for 13.5% radiographic examinations, they were assigned the mean dose for all other examinations received by the same patient or other similar patients 2. and 3. Follow-up data were obtained from the Social Security Administration, Health Care Financing Administration, National Death Index, town books, motor vehicle bureaus, credit companies, the US Postal Service, telephone directory assistance, commercial telephone listings and neighbour search databases. Death certificates were obtained for decedents from state vital statistics offices and causes of death were coded by trained nosologists Mortality rates of patients were compared with those of white females in the USA	**Radiation dose estimation:** The total number of radiographs recorded was 137,711. Most X-rays (77.3%) were of the spine and approximately 64% were AP. The average number of radiographs taken per patient was 24.7 (range 0–618). The average estimated cumulative dose to the breast per patient was 10.8 (range 0–170) cGy Mortality rates: 985/4971 patients (20%) were confirmed deceased with death certificate, 61 (1%) were presumed deceased with cause of death unknown There was a statistically significant increase in the risk of dying of all causes for patients with scoliosis, compared with the general population (SMR 1.71, 95% CI 1.6 to 1.8), primarily of infectious, circulatory, respiratory and musculoskeletal conditions There was a statistically significant increase in the risk of dying of breast cancer for patients with scoliosis, compared with the general population (77 vs 45.6 expected deaths; SMR 1.69, 95% CI 1.3 to 2.1) The risk of dying of leukaemia or lung cancer were not significantly different between patients with scoliosis and the general population (SMR 1.21, 95% CI 0.6 to 2.3; nine cases and SMR 0.73, 95% CI 0.5 to 1.1; 29 cases, respectively) Significant dose response relationships were observed for deaths from infectious, circulatory, respiratory, digestive and musculoskeletal conditions **Subgroup analyses:** Breast cancer deaths by scoliosis characteristics: There was a statistically significantly higher risk of dying of breast cancer, compared with the expected number of deaths, for patients aged ≥ 10 years at the time of diagnosis (SMR 2.01, 95% CI 1.5 to 2.6), patients diagnosed between 1940 and 1959 (SMR 2.35, 95% CI 1.6 to 3.3), patients with neuromuscular scoliosis (SMR 2.09, 95% CI 1.4 to 3.1) or unknown aetiology (SMR 2.61, 95% CI 1.1 to 5.1), patients with a maximum curve magnitude	

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		Statistical analyses: Person-years of follow-up began at the date of scoliosis diagnosis for patients from the 10 expanded study centres and 3 years after scoliosis diagnosis for the pilot study patients. Follow-up ended at the date of death, date of last known vital status or 1 January 1997 Expected numbers of deaths, by cause, were calculated by multiplying the age- and calendar-specific woman-years at risk, in 5-year intervals, by the corresponding mortality rates in the general population. SMRs were calculated by dividing the number of observed deaths by the number of deaths expected Exact and asymptotic methods were used to calculate 95% CIs and statistical significance levels for SMRs, RRs, and tests for non-homogeneity and trend among different levels of factor **Length of follow-up:** The average length of follow-up was 40.5 years	of 30–59 °(SMR 2.29, 95% CI 1.3 to 3.8) or unknown magnitude (SMR 1.55, 95% CI 1.2 to 2.0), patients who had surgery (SMR 2.52, 95% CI 1.7 to 3.6) and patients who had a higher number of surgeries (two surgeries: SMR 2.79, 95% CI 1.4 to 5.0, three surgeries: SMR 3.83, 95% CI 1.7 to 7.5) Statistical tests for trend when adjusted for radiation dose were only statistically significant for age at scoliosis diagnosis, $p = 0.02$ **Breast cancer deaths by radiation exposure characteristics:** There was a statistically significantly higher risk of dying of breast cancer, compared with the expected number of deaths, for patients with a higher number of radiographs, particularly patients receiving ≥ 50 radiographs (SMR 3.86, 95% CI 1.9 to 6.9), patients with a higher cumulative radiation dose to the breast, particularly patients with a cumulative dose of ≥ 20 cGy (SMR 3.36, 95% CI 2.0 to 5.3), those aged 10–13 years at the time of their first radiograph (age 10–11 years, SMR 3.36, 95% CI 2.1 to 5.1; age 12–13 years, SMR 1.85, 95% CI 1.2 to 2.8), those with a longer time since their first radiograph (30–39 years, SMR 2.43, 95% CI 1.6 to 3.6; ≥ 40 years, SMR 2.07, 95% CI 1.5 to 2.8) and those who were older at study exit (45–49 years, SMR 2.19, 95% CI 1.2 to 3.6; ≥ 50 years, SMR 1.74, 95% CI 1.3 to 2.3) Statistical tests for trend when adjusted for radiation dose were only statistically significant for age at first radiographic examination ($p = 0.01$) **Authors' conclusions:** These data suggest that exposure to multiple diagnostic radiographic examinations during childhood and adolescence may increase the risk of breast cancer among women with scoliosis; however, potential confounding between radiation dose and severity of disease and thus with reproductive history may explain some of the increased risk observed	

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US Scoliosis Cohort Study 2008[40] **Type of publication:** Journal article **Country of origin:** USA **Source of funding:** Intramural Research Program of the NIH, National Cancer Institute, Division of Cancer Epidemiology and Genetics **Study design:** Uncontrolled retrospective cohort study **Aim of study:** To quantify the radiation dose–response relationship for fractionated exposures at a vulnerable age, assess whether or not known breast cancer risk factors modify dose response, and explore possible developmental intervals of increased radiation sensitivity	**Inclusion/exclusion criteria:** US Scoliosis Cohort Study patients (see above)[35] Of the 5573 eligible patients, 19% were lost to follow-up and 16% were deceased. The authors contacted 3620 (65%) patients; 3121 patients (86%) participated in the health survey; 6% refused, 4% were unable to participate owing to illness, language problems or other reasons and 4% did not respond. An additional 111 patients were excluded because they had congenital scoliosis, so were likely to have had radiographic examinations for concomitant medical conditions in other hospitals **Dates of recruitment:** Not stated (year of diagnosis 1912–65) **No. recruited:** 3010 female patients with scoliosis (analysis cohort) **Age:** Mean age at follow-up was 51 (range 30–84) years **Male (%):** 0 **Disease characteristics:** 59% patients had idiopathic scoliosis. Mean age at scoliosis diagnosis was 11 (range 0–19) years	**Outcome measures** 1. Radiation dose estimation 2. Breast cancer risk **Methods used for collecting data** 1. Information on diagnosis and treatment of scoliosis were abstracted from medical records from the participating hospitals. Data on date of radiography, field, view, position, presence of an orthosis, radiograph size, whether or not the breast was in the X-ray beam and radiograph machine parameters were collected from radiology reports, radiographs, radiograph jackets and radiology log books. (As Doody *et al.* 2000[35]) Dose to the breast was estimated for each examination in which the breast was definitely or probably in the radiation beam (89% X-rays); examinations in which the breast was not exposed to the beam were assumed to contribute no dose. The breast dose was estimated for pre-teens (aged < 13 years) at a depth of 1.0 cm, and for adults (aged ≥ 13 years) at 2.5 cm. Doses were calculated for each examination according to the year of X-ray examination. (As Doody *et al.* 2000[35]) 245 scoliosis patients had no radiographs recorded in their medical records, these patients were recorded as having a breast dose of 0 cGy and were the ‘minimally exposed’ group in the analyses 2. Participants completed a telephone interview (live patients with a US telephone number) or postal questionnaire (patients who were included in the original pilot study[34] or who had no telephone number available) on medical and reproductive history, family history of cancer and other characteristics. Treating physicians were contacted for written medical confirmation of self-reported breast cancers. Family history of breast cancer was defined as breast cancer in a first- or second-degree blood relative (mother, sister, daughter, grandmother or aunt) as reported by the patient. Age at breast budding was estimated as 3 years prior to the age at menarche, as reported by the patient	**Radiation dose estimation:** The mean number of breast-exposed radiographs taken per patient was 26.8 (range 0–332). The mean estimated cumulative dose to the breast per patient was 12.1 (range 0–111) cGy **Breast cancer:** 88 women reported breast cancer and one woman reported a non-defined cancer; invasive breast cancer was confirmed for 68 women. Eleven women had a confirmed diagnosis of in situ breast cancer, which was not included in most of the analyses; 78 confirmed or non-denied invasive breast cancers were included in the analyses Compared with patients who received 1–9 radiographs (mean total dose 3 cGy), patients who received ≥ 60 radiographs (mean total dose 33.5 cGy) had a statistically significantly higher risk of breast cancer (RR 3.14, 95% CI 1.33 to 7.44). *p*-value for trend for total number of radiographs = 0.12 Compared with patients who had a baby when aged < 25 years, patients who had no children, or had children aged ≥ 35 years had a statistically significantly higher risk of breast cancer (RR 2.13, 95% CI 1.21 to 3.75 and RR 3.02, 95% CI 1.03 to 8.87, respectively). *p*-value for trend for age at first live birth = 0.03 Postmenopausal women were at a significantly higher risk than pre-menopausal women (RR 3.13, 95% CI 1.38 to 7.09). *p*-value for trend = 0.004 Women with an annual household income of ≥ US$60,000 were at a significantly higher risk than women with a household income < US$30,000 (RR 2.84, 95% CI 1.52 to 5.30). *p*-value for trend for household income = 0.003 Women with a second-degree relative affected by breast cancer were at a significantly higher risk than women with no known family history of breast cancer (RR 2.71, 95% CI 1.57 to 4.66). *p*-value for trend for family history of breast cancer = 0.008	This was a very large cohort study; although there were still only 78 confirmed or non-denied cases of breast cancer The authors acknowledge that the estimate of cumulative radiation dose to the breast may be subject to error The authors also acknowledge that breast cancer rates among patients with scoliosis may be higher than the general population, owing to risk factors other than radiation exposure (such as reproductive characteristics) The authors also acknowledge the potential for bias, when relying on self-report for breast cancer and family history of breast cancer. They state that the risks associated with family history of breast cancer may be overestimated in the study, as patients with breast cancer are more likely to report complete family histories of breast cancer, than women without breast cancer

Study details	Participant details	Outcomes measured	Results	Comments on quality
		Statistical analyses: Woman-years of follow-up began at the date of scoliosis diagnosis until the date of first breast cancer diagnosis or survey completion. All woman-years were cross-classified by time-dependent variables for age, total breast dose, and by breast cancer risk factors and scoliosis characteristics. ERR per unit dose was calculated. Subgroup analyses were used to assess whether or not the dose response differed according to specific epidemiological characteristics (breast cancer risk factors). Enhanced sensitivity to radiation according to breast development stage (before breast budding, between breast budding and menarche, between menarche and birth of a first child and after birth of a first child) was also assessed. Results were presented as RRs with 95% CIs **Length of follow-up:** The mean length of follow-up was 39.5 (range 13–68) years	Women with three to five relatives with breast cancer were at the highest risk (RR 5.65, 95% CI 1.73 to 18.5), while women with one or two relatives with breast cancer were also at a significantly higher risk than those with no known relatives with breast cancer (RR 2.12, 95% CI 1.32 to 3.41). *p*-value for trend for number of relatives with breast cancer = 0.0003 Women with a family history of early-onset breast cancer (diagnosed before the age of 50 years) were at a significantly higher risk than women with no known family history of early-onset breast cancer (RR 2.84, 95% CI 1.10 to 6.03). *p*-value for trend for family history of early-onset breast cancer = 0.03 There were no statistically significant differences associated with curve magnitude, parity, education level or reported alcohol use or smoking status. The authors report that risk was not related to age at menarche, oral contraceptive use or hormone replacement therapy (data not shown) Adjustment for age at birth of first child, menopausal status at questionnaire completion, household income and family history of breast cancer significantly improved the statistical fit of the model; therefore, these factors were included as additional baseline term covariates in all subsequent analyses Compared with patients with breast doses of < 10 cGy, those with doses of 20–29 or ≥ 30 cGy had a statistically significant double risk of breast cancer. The radiation dose response for breast cancer was statistically significantly modified by any family history of breast cancer ($p = 0.03$): ERR/Gy = 8.37 (95% CI 1.50 to 28.16) There was no evidence of variation in the risk of breast cancer when assessing subgroups according to breast development stage	

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US Scoliosis Cohort Study 2010[41] **Type of publication:** Journal article **Country of origin:** USA **Source of funding:** Intramural Research Program of the National Institutes for Health, National Cancer Institute, Division of Cancer Epidemiology and Genetics **Study design:** Uncontrolled retrospective cohort study **Aim of study:** To describe the spectrum of cancer mortality after an average follow-up of 47 years, 8 years longer than the earlier report.[35] In addition, to evaluate risks for all cancers and assess potential confounding	**Inclusion/exclusion criteria:** US Scoliosis Cohort Study patients (see above)[35] Of the 5573 eligible patients, the authors were able to determine vital status for 5513 (99%) **Dates of recruitment:** Not stated (year of diagnosis 1912–65) **No. recruited:** 5573, of which vital status was determinable for 5513 patients Risk of dying from cancer was assessed for the subgroup of 3121 women who completed the health survey in the previous study[40] **Age:** Mean age at follow-up was 58 (range 2.1–96.5) years **Male (%):** 0 **Disease characteristics:** The mean age at curvature diagnosis was 10.6 (range 0–19.9) years	**Outcome measures** 1. Radiation dose estimation 2. Cancer mortality rates **Methods used for collecting data:** 1. Information on diagnosis and treatment of scoliosis were abstracted from medical records from the participating hospitals. Data on date of radiography, field, view, position, presence of an orthosis, radiograph size, whether or not the breast was in the X-ray beam and radiograph machine parameters were collected from radiology reports, radiographs, radiograph jackets and radiology log books. (As Doody *et al.* 2000[35]) Cumulative radiation doses to the breast, thyroid gland, lung, ovary and bone marrow were estimated for each patient based on their age at examination, year of examination and the characteristics of the radiograph, listed above. (As Doody *et al.* 2000[35]) 2. Vital status was determined up to 31 December 2004; causes of death were obtained from death certificates or the National Death Index Risk of dying from cancer in the subgroup of 3121 women who completed the health survey in the previous study[40] was assessed to allow for adjustment for known cancer risk factors Mortality rates of patients were compared with that of females in the USA **Statistical analyses:** Woman-years of follow-up began at the date of curvature diagnosis and ended at the date of death, date of last known vital status or 31 December 2004 Expected numbers of deaths, by cause, were calculated by multiplying the age- and calendar year-specific woman-years at risk, in 5-year intervals, by the corresponding mortality rates in the general population. SMRs were calculated by dividing the number of observed deaths by the number of deaths expected. Breast doses were lagged 10 years before cancer diagnosis for cases and study exit for non-cases to allow for latency	Radiation dose estimation: The total number of radiographs recorded was 137,711. The average number of radiographs taken per patient, that included exposure to the breast was 22.9 (range 0–553). The average estimated cumulative dose to the breast per patient was 10.9 cGy (maximum 170 cGy). The average estimated cumulative dose to the lung per patient was 4.1 cGy (maximum 67.6 cGy). The average estimated cumulative dose to the active bone marrow per patient was 1.0 cGy (maximum 16 cGy). The average estimated cumulative dose to the thyroid gland per patient was 7.4 cGy (maximum 137 cGy). The average estimated cumulative dose to the ovary per patient was 2.7 cGy (maximum 33.7 cGy) Cancer mortality rates: 1527/5513 patients (28%) were dead, 3614 (66%) were alive and 372 (7%) were lost to follow-up There was a statistically significant increase in the risk of dying of all causes for patients with curvature, compared with the general population (SMR 1.46, 95% CI 1.39 to 1.54) There were a total of 355 cancer deaths amongst the curvature patients, which was not significantly different to that of the general population (SMR 1.08, 95% CI 0.97 to 1.20) Breast cancer was the only cancer where there was a statistically significant increase in risk amongst curvature patients, compared with the general population (SMR 1.68, 95% CI 1.38 to 2.02). There were 112 deaths from breast cancer Other cancer sites where risk was increased (though not statistically significantly) were: ▪ Oral cavity SMR 1.93, 95% CI 0.77 to 3.98 ▪ Oesophagus SMR 1.42, 95% CI 0.38 to 3.63 ▪ Pancreas SMR 1.17, 95% CI 0.68 to 1.87 ▪ Bone SMR 1.91, 95% CI 0.21 to 6.90 ▪ Melanoma of skin SMR 1.29, 95% CI 0.47 to 2.81 ▪ Uterine corpus SMR 1.02, 95% CI 0.44 to 2.00	This was a very large cohort study, although numbers of patients dying from many of the cancers assessed were very low The estimate of cumulative radiation dose to the breast may be subject to error The authors acknowledge that breast cancer rates among scoliosis patients may be higher than the general population, owing to risk factors other than radiation exposure (such as reproductive characteristics) This study only assessed cancer mortality rates, not cancer incidence rates; other characteristics of curvature patients may affect their eligibility for/response to treatment, which may impact on survival rates. The authors acknowledge that by relying on cancer mortality data, it was not feasible to study cancers with low lethality, such as thyroid cancer

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		RRs for breast cancer mortality and lung cancer mortality according to spinal curvature history were estimated using a Cox proportional hazards model with age as the time scale. ERR per unit dose was calculated **Length of follow-up:** The mean length of follow-up was 46.9 years	Bladder SMR 1.34, 95% CI 0.36 to 3.42 Brain and CNS SMR 1.48, 95% CI 0.81 to 2.48 There were significantly fewer deaths from liver and cervical cancer among the curvature patients, compared with the general population (SMR 0.17, 95% CI 0.00 to 0.94 and SMR 0.31, 95% CI 0.06 to 0.92, respectively); however, these were based on very small numbers of deaths of these cancers (one and three, respectively). The number of patients dying of lung cancer was lower than the general population (57 patients, SMR 0.77, 95% CI 0.59 to 1.00), although this result was not statistically significant. The authors state that these types of cancer are smoking related **Subgroup analyses:** Risk of death from breast cancer did not vary significantly by age at curvature diagnosis, type of curvature, aetiology, maximum curve magnitude or number of spinal surgeries. However, there was an increase in risk of dying from breast cancer amongst patients who received ≥ 50 radiographs (involving exposure to the breasts), compared with those receiving < 25 radiographs (RR 2.7, 95% CI 1.3 to 5.5). Patients with a cumulative breast dose of ≥ 30 cGy had a statistically significantly higher risk of dying of breast cancer than those with a cumulative dose of 0–9 cGy (RR 2.4, 95% CI 1.2 to 4.8). *p*-value for trend = 0.001. ERR/Gy = 3.9 (95% CI 1.0 to 9.3)	

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			Among the subgroup of 3121 patients who responded to the health survey in the previous study,[40] 30 patients died of breast cancer and 17 patients died of lung cancer between 1993 and 2004. Results of subgroup analyses were broadly similar to results for the entire cohort. Risk of lung cancer was strongly associated with cigarette smoking and alcohol use, but not with scoliosis characteristics or with category of estimated lung dose **Authors' conclusions:** Women who were diagnosed with scoliosis before 1965 have increased risk of breast cancer, clearly related to radiation exposure from diagnostic radiographs during the period 1920–80, when doses were much higher than they are today. Mortality rates from cancers other than breast cancer were lower than expected	

CNS, central nervous system; mrad, milliradiation absorbed dose; NR, not reported; rad, radiation absorbed dose; SIR, standardised incidence ratio.

a Breslow NE, Lubin JH, Marek P, Langholz B. Multiplicative models and cohort analysis. *J Am Stat Assoc* 1983;**78**:1–12.