1. **Doody2000**: Breast Cancer Mortality After Diagnostic Radiography
   * Retrospective cohort study to examine breast cancer mortality among women with scoliosis, exploring the potential risks arising from radiographic medical imaging.
   * Reviewed medical records tabulate radiographic imaging exposure counts, and use them with the context of the dates under consideration and likely machine configurations to estimate and tabulate cumulative radiation doses to the patients’ breasts. In estimating the radiation dose, they also took the location of the scan on the patients’ bodies into account.
   * Where information was insufficient to estimate a patient’s total radiation dose, they used averages doses from other exposures the patient had or average doses from patients of similar ages, calendar years, and medical centers, as necessary.
   * The expected number of deaths in a given group of patients (whether grouped by age, calendar year, age of diagnosis, scoliosis variety, or other classification characteristics) was determined from the rate observed in the general American population.
   * The expected number of deaths was compared with the observed number of deaths to compute standardized mortality ratios (SRMs).
   * Patients with scoliosis were significantly (P < 0.05) more likely to die from breast cancer than the general population. The scoliosis patients had an SRM of 1.69.
   * The risk of breast cancer increased relative to the general population with both the number of radiographic exposures (Ptrend = 0.0006) and with the radiation dose   
     (Ptrend = 0.001).
   * The fact that the SMR for all causes of death was 1.71 for the scoliosis patient population caused the authors concern that SMR values might be overestimated. They say this overestimation could come from more complete collection of death records than living follow-ups.
   * Other potentially confounding factors are relationships between other breast cancer risks such as reproductive history, and disease severity.
2. **Ronckers2010**: Cancer Mortality among Women Frequently Exposed to Radiographic Examinations for Spinal Disorders
   * Retrospective cohort study examining the relationship between diagnostic X-ray exposure and risk of death due to breast cancer and other cancers
   * This study refers to [Doody2000] for details on the experimental procedure and apparently uses the same patients.
   * They differentiate this work by evaluating other cancer risks and potentially confounding factors.
   * They observe a statistically significant increase in breast cancer death risk, SMR = 1.68 (P < 0.05), and a non-significant decrease in the collective risk from other cancer types, SMR = 0.93. The total cancer SMR was 1.08, not significantly elevated.
   * There was a significant dose-response relationship between cumulative radiation dose and excess relative risk (ERR), 3.9ERR/Gy (P = 0.001).
   * The PEANUTS (Epicure) Cox proportional hazards models (used to compute the ERRs) for the full cohort were not adjusted for scoliosis characteristics as they did not significantly improve the model fit. The model for follow-up survey participants was adjusted for age of diagnosis, number of live births, age at menopause, and family history of breast cancer.
   * They list the higher overall mortality of scoliosis patients as a reason why the general population might not be entirely comparable to the study population.
   * The observed lower incidence of lung cancer deaths among the study population may be due to the possibility of severely scoliotic patients smoking less (while the general population smoked only slightly more that the study population), due to respiratory problems which often accompany severe scoliosis.
   * The observed lower incidence of cervical cancer deaths may be due to a decreased likelihood of contracting HPV, in turn caused by decreased sexual activity.
3. **Himmetoglu2015**: DNA damage in children with scoliosis following X-ray exposure
   * This study explored the relationship between radiographs performed on scoliotic patients, and biochemical factors indicating DNA damage.
   * They compared 8-OHdG (a reactive oxidized base), p53 tumor suppressor gene protein, and SOD and G-Px (two antioxidant enzymes) serum levels between scoliotic patients and healthy patients of similar ages.
   * Blood samples were collected within 3 hours of radiographs performed on the scoliotic patients.
   * Serum levels of 8-OHdG were about 2.5 times higher in scoliotic patients than the control group (P < 00.001), p53 levels were about 2 times the levels of the control group (P < 0.01), SOD levels were less than half that of the control group (p < 0.001), and there was no significant different in G-Px levels.
   * While the 8-OHdG levels indicates DNA damage, it also indicates that DNA repair mechanisms are engaged, accounting for the presence of the species in the serum, outside of cells.
   * The increase in p53 levels also indicates the activation of DNA repair mechanisms.
   * The decrease in SOD levels may be due to exhaustion of the species due to increased reactive oxide species levels.
   * The changes in serum levels of these chemical species may not correspond to an increased cancer risk. While increased levels of reactive oxide species and decreased antioxidant levels may suggest an increased risk, the activation of DNA repair mechanisms indicated by p53 levels may offset or outweigh the risks.
   * This study did not measure serum levels before radiographs to assess individual changes; it only used the control group.
   * The carcinogenic effects of these biochemical species should be investigated by measuring their serum levels through time.
4. **Law2016**: Cumulative radiation exposure and associated cancer risk estimates for scoliosis patients: Impact of repetitive full spine radiography
   * They present a method for obtaining cumulative effective radiation doses, and their resulting cancer risks, caused by scoliosis monitoring with X-ray imaging.
   * They used PCXMC, a Monte Carlo program, to simulate the radiation received by the organs of a mathematical phantom during imaging.
   * Normalized effective doses were computed by dividing patient doses by the product of the X-ray tube potential, the product of tube current and exposure time, and the number of projections.
   * PCXMC was also used to calculate the lifetime attributable risk (LAR). They used a dose-to-risk conversion factor of one cancer expected per 100,000 patients receiving 100mSv effective radiation doses. This factor comes from the National Research Council’s seventh Biological Effects of Ionizing Radiation (BEIR VII) report.
   * Functions were fitted to the normalized effective dose and LAR data, as they related to patient age. This allowed calculation of risk as patients received X-rays throughout monitoring.
   * It was assumed that patients had their first X-ray at 5 years old, followed by 1 annually until the age of 30.
   * Their results indicate a LAR of 0.17% for Western females by the age of 30 (1 possible cancer induction per 588 patients), and a LAR of 0.09% for Western males by the age of 30 (1 cancer in 1111 patients).
   * While their results indicate some cancer risk from scoliosis monitoring, the risk is lower than that arrived at by Ronckers2010. Monitoring the disease, from 5 to 30 years of age, exposes patients to about the equivalent of 7 years of background radiation.
5. **Faria2013**: The EOS 2D/3D X-ray imaging system: A cost-effectiveness analysis quantifying the health benefits from reduced radiation exposure
   * Compared EOS imaging to computed radiography (CR) and digital radiography (DR) using a cost-benefit economic analysis.
   * Various orthopaedic diseases were considered, including several varieties of scoliosis. Financial costs were evaluated from the perspective of the UK National Health Service (NHS) in terms of UK pound sterling (2011). Health costs and benefits were expressed in terms of quality-adjusted life years (QALY).
   * Disease monitoring procedures were obtained from expert advice and radiation doses were obtained from a report by the Health Protection Agency (HPA).
   * Radiation reduction from using EOS was estimated from the ratio of EOS entrance surface dose, rather than effective radiation doses. Entrance surface doses were taken from literature.
   * No evidence for benefits in patient health outcome was found from using EOS over CR or DR.
   * The HPA report was used to compute cancer risks resulting from the radiation doses for the various orthopaedic diseases.
   * QALY losses for several cancer types, given the patient’s age at diagnosis, were retrieved from literature. They were averaged to obtain a QALY loss for all types of cancer.
   * Imaging system costs took into account set-up costs including training and installation, maintenance costs, and other recurring costs, for two available EOS contracts, and both CR and DR imaging.
   * The costs were annuitized over 10 years at rate of 3.5% per annum. The results were per-scan costs of £3.42 and £6.16 for CR and DR, respectively. The per-scan cost of EOS was £14.54 assuming no change in patient throughput from 30 per day, or £9.09 assuming an average of 48 patients per day, rather than 30.
   * They compared the cost per additional QALY gained for each imaging modality. DR was more expensive than CR without conveying any benefits, and so was not considered further.
   * Values used by the National Institute for Health and Clinical Excellence (NICE) for cost-effectiveness thresholds were £20,000 – £30,000 per QALY gained.
   * They found that maximum health losses from a standard CR image and EOS image were 0.001 and 0.00015 QALYs, respectively. This difference corresponds to a lifetime cancer risk reduction of about 1 patient in 100,000. With the increase in cost per image being £10.66 to £224.47, depending on the disease under consideration, and the throughput assumptions used, the incremental cost-effectiveness ratios (ICERs) were below NICE’s cost-effectiveness threshold.
   * The EOS would need much more use than X-ray to achieve cost effectiveness; between 60 and 106 patients per day for an ICER of £30,000 and between 71 and 110 patients per day for an ICER of £20,000.
6. **McKenna2012**: EOS 2D/3D X-ray imaging system: a systematic review and economic evaluation
   * A review of studies to determine the clinical and cost effectiveness of using EOS to evaluate and monitor scoliosis and other orthopaedic conditions.
   * Presents a narrative synthesis, rather than a formal meta-analysis, due to the heterogeneity of the studies included in the review.
   * They reviewed multiple aspects of the research area: The clinical effectiveness of EOS, adverse effects of diagnostic radiation, and economic evaluations of EOS.
   * 3 studies met the criteria for inclusion in their clinical effectiveness review: Kalifa1998, Le Bras (unpublished), and Deschenes2010. The criteria were that the studies compare EOS to computed radiography (CR) or digital radiography (DR), the studies include patients with orthopaedic conditions assessed by EOS. Studies focused on patient health outcomes were of primiary interest. Ones investigating “surrogate outcomes” like image quality or radiation reduction were of secondary interest.
   * The studies reported considerable reduction in radiation exposure per imaging session by using EOS versus CR or DR, often an order of magnitude.
   * EOS demonstrated image quality comparable or superior to CR and DR.
   * Patient outcomes were not reported, preventing assessment of health benefits.
   * They establish the cancer risks associated with radiography primarily from four information sources: The BEIR VII Phase 2 report[[1]](#footnote-1), the 2007 recommendations International Commission on Radiological Protection (ICRP), the United Nations Scientific Committee on the Effects of Atomic Radiation, and a personal communication with Paul Shrimpton of the Health Protection Agency.
   * These sources establish the increased risk in lifetime cancer incidence as a function of ionizing radiation exposure.
   * Their primary information sources do not focus on orthopaedic imaging risks, so they complement their information with references to several works including [Doody2000] and [Ronckers2010].
   * They found no studies meeting their criteria for economic evaluation of EOS. However they obtained the recommendation of the Committee for the Evaluation and Diffusion of Innovative Technologies (CREDIT), files from the manufacturer, and 3 costing analyses.
   * They did not use these economic assessment sources either for not assessing potential health benefits, or being related to billing procedures irrelevant to the UK healthcare system.
   * Instead, they propose a decision-analytic model to assess the cost-effectiveness of EOS for monitoring various orthopaedic conditions.
   * This model relates expected radiation doses from to the conditions’ monitoring protocols to obtain expected cumulative radiation doses for the various conditions.
   * They related the radiation doses to cancer risks from their four main sources on radiation risks. They related the risks of cancer to expected financial and quality adjusted life-years (QALYs).
   * They compared EOS incremental cost-effectiveness ratios (ICERs) in £/QALY to threshold values used by the National Institute for Health and Clinical Excellence (NICE), £20,000 - £30,000 / QALY.
   * EOS’ ICERs were higher for all indicated diseases than the thresholds used by NICE. Furthermore, given the limited prevalence of the indicated diseases, increased economic viability from increased patient throughput is unlikely.

1. <https://www.nap.edu/catalog/11340/health-risks-from-exposure-to-low-levels-of-ionizing-radiation> [↑](#footnote-ref-1)