Ionizing Radiation and Breast Cancer

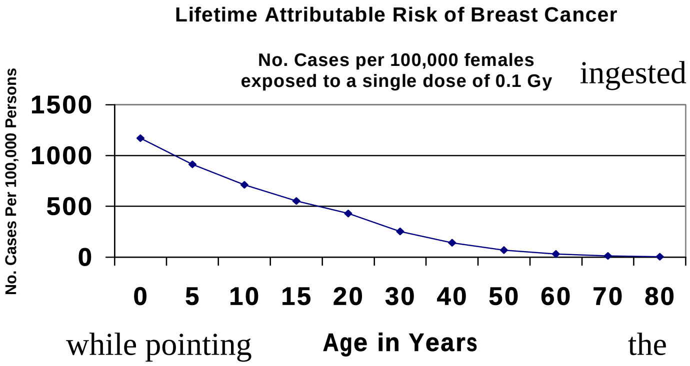
Definition and Sources of Exposure

Radiation is energy that travels in the form of high-speed particles or waves. When radiation has enough energy to break chemical bonds in molecules or remove tightly bound electrons from atoms it is referred to as "ionizing" radiation. Ionizing radiation takes the form of energized sub-atomic particles such as protons, neutrons, beta particles (electrons), and alpha particles, and electromagnetic radiation in the form of x-rays and gamma rays. The types of ionizing radiation differ in their ability to penetrate the body. Most medical x-rays, gamma rays and neutrons are highly penetrating. In contrast, electrons and alpha particles are relatively non-penetrating and can affect internal organs only if the radiation source is inhaled, ingested, injected, or otherwise able to enter the body.

Exposure to ionizing radiation results from: (1) background sources, i.e., cosmic radiation from our sun and distant stars, and terrestrial radiation emitted during the decay of radioactive elements in rocks, soil, water, and the atmosphere; and (2) human-made sources, i.e., radioactive materials used in medicine, research, nuclear weapons, nuclear power, and other industries.

Estimates made as recently as 2006 attributed about 82% of total radiation exposure in the United States to background sources.[1] The largest background source of exposure to radiation is to alpha particle radiation from inhaled radon gas that collects in mines and poorly ventilated basements. However, a study by the National Council on Radiation Protection to be released in 2008 reportedly calculates that diagnostic imaging procedures have now displaced natural background radiation as the leading source of human exposure.[2] The per-capita dose of ionizing radiation from clinical imaging exams in the United States increased almost 600 percent from 1980 to 2006.[2] Consumer products, such as tobacco, certain building materials, television and computer screens, and smoke detectors, occupational exposure, nuclear fallout, and the nuclear fuel cycle are also human made sources of radiation that contribute to population exposure. However, exposures are not distributed uniformly over the population. An individual's exposure can vary above relative population averages, for example, due to increased use of radiation for medical purposes, smoking, working near ionizing radiation such as in medicine, mining, milling, nuclear power, or nuclear weapons industries; living in areas affected by weapons testing or planned or accidental releases from nuclear power plants or other nuclear facilities; and/or being a veteran exposed directly at a distance to nuclear weapons testing.[1]

The type of radiation affecting breast tissue is almost entirely by gamma rays and (to a lesser extent) neutrons from cosmic rays and terrestrial sources, and, in the case of the survivors of the nuclear weapons dropped on Hiroshima and Nagasaki, from those bombs, and from medical x-rays. However, the possibility that alpha particles can reach and therefore be emitted within breast tissue is not well described but cannot be dismissed. Historical exposures to alpha radiation among radium dial painters, who ingested radium in the course of using their lips to bring their brush tips to a point, resulted in the development of bone sarcomas from radium in bone surfaces and bone matrix. The excess of breast cancer risk among radium dial painters has been ascribed to the penetrating gamma rays given off by the radium paint pot in front of the painters, not to the radium ingested while pointing the brush tips.[3] However, as radium is chemically similar to calcium, there is the potential that ingested or injected radium might end up in lactating breast tissue. The possibility that alpha radiation could impact breast cancer is also supported by the finding of a dose-related excess of breast cancer among German patients with tuberculosis of the bone who were treated by injection of Ra-224.[4]



Source: National Academy of Sciences, National Research Council Committee to AssessHealth Risks from Exposure to Low Levels of Ionizing Radiation. Health risks from exposure to low levels of ionizing radiation: BEIR VII – Phase 2. Washington, D.C.: National Academies Press, 2006: Table 12 D-1 p. 311

Biologic Plausibility

Mechanism

Ionizing radiation is harmful to human health because it has sufficient energy to remove electrons from atoms and disrupt molecular bonds, for example in DNA. During the last decade, major advances have led to increased understanding of the molecular and cellular responses to ionizing radiation and of the nature of the relationship between radiation exposure and the types of damage that underlie adverse health outcomes.[1] The main effects of ionizing radiation on DNA are mediated by secondary electrons energized by interactions with gamma rays, x-rays, and neutrons (also possibly by any alpha particles emitted within breast tissue). The resulting DNA damage is handled by cellular repair mechanisms that are error-prone, often resulting in mutations. A single electron track can induce complex damage[5] and the number of electron tracks in a small amount of tissue is roughly proportional to the dose to that tissue. Additional mechanisms by which radiation may influence breast cancer risk include the creation of genomic instability and bystander effects on neighboring cells that are not directly exposed.[6] However, there is currently insufficient knowledge of adaptive responses, genomic instability, and bystander signaling among cells to incorporate these potential mechanisms in a meaningful way into modeling cancer risk.[1]

Radiation Dose and Cancer Risk

Radiation dose is measured in units called grays (Gy) or sieverts (Sv), which, when describing exposures from x-rays and gamma rays, are equivalent measures of the amount of energy deposited in living tissue. In 2006, The National Academy of Sciences (NAS), National Research Council's Committee on the Biological Effects of Ionizing Radiation (BEIR VII) updated the estimated relationship between exposure to low levels of ionizing radiation and harmful health effects.[1] The NAS/BEIR VII report reaffirmed the prevailing model used for radiation risk estimates, that every exposure to radiation produces a corresponding increase in cancer risk. Excess cancer risk is well quantified for a given exposed population by a linear dose response over the range 200–2000 mSv. Continuing the linear dose-response down to zero dose fits the data well, but dose-response data are, for statistical reasons, increasingly uninformative about excess risk per unit dose at very low doses.[1, 5, 7] In a review of the evidence for what is the lowest dose of x- or gamma-radiation for which good evidence exists of increased cancer risks in humans, Brenner et al concluded the epidemiological data suggest that it is approximately 10–50 mSv for an acute exposure and 50–100 mSv for a protracted exposure.[8]

Radiation exposures during infancy, childhood, and adolescence appear to confer the greatest increased breast cancer risks (Figure 1).[1, 9, 10] Breast tissue may proliferate from stem cells during adolescence and if some cells have previously been damaged by radiation there may be more chance for carcinogenesis to occur.[9]

The levels of radiation needed to induce human carcinogenesis may vary by whether the exposure is acute or chronic. There may be more time for DNA repair to occur when the exposure is given over a longer period.[11] There is also some evidence, based on very small numbers, that radiation exposure received during pregnancy may also convey highly increased risk to the exposed mother.[12] Pregnancy represents a highly estrogenic and proliferative stage of development. Postmenopausal breast tissue does not proliferate to the same extent, which may be why there is a smaller increased breast cancer risk with postmenopausal radiation.[9]

Genetic factors may also influence radiation-related cancer risk. Subgroups of women appear genetically susceptible to radiation-induced breast cancer. Certain genes, including BRCA-1, BRCA-2, ataxia-telangiectasia mutated gene (ATM) and CHEK2, are associated with increased breast cancer risk, and they appear to decrease the efficiency of DNA repair.[13-16] Women who are carriers of these genes exhibit increased breast cancer risk with exposure to diagnostic x-rays, especially to the chest, which may be due to the decreased ability to repair DNA damage following radiation exposures.[14-16] There are no published direct measures of the prevalence of clinically important BRCA-1 or BRCA-2 mutations in the general non-Jewish U.S. population; models have estimated the population prevalence to be less than one-half percent.[17]

Ataxia-telangiectasia (A-T) is a rare genetic disease that causes a hypersensitivity to radiation.[18] The ATM gene encodes a protein that plays a key role in the detection and repair of DNA double strand breaks.[19] An estimated one percent of the U.S. population, about two and a half million people, may be carriers for A-T (carriers have one normal and one mutated copy of the gene and usually do not know that they are carriers).[20] Some studies suggest that mutations on the ATM gene may be associated with greatly increased risk of breast cancer, however not all studies are consistent in this finding.[18]

The risk of exposure to ionizing radiation may also be modified by exposure to chemical agents.[21-24] The synergistic relationship between exposure to tobacco smoke and ionizing radiation is a well studied, albeit complex, example of how co-exposure to chemicals and radiation increases risk beyond additive effects.[21] Mineral dusts and fibers, including asbestos show supra-additive interaction with radiation at historical workplace exposure levels.[21] The interaction between radiation and chemical exposures is leveraged by cancer therapies that irradiate tumors in combination with drugs that inhibit cellular repair of radiation damage.[21]

A 2000 review of the combined effects of radiation and other agents by the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) describes many other chemicals present in the human environment that interact with radiation, and these examples and the limitations of the existing data are summarized in Table 1. In general, interactions between exposure to ionizing radiation and a wide range of agents having a variety of mechanisms of action have been demonstrated at high levels of exposure; it is difficult to infer the nature of potential interactions at levels of exposure encountered in the workplace and ambient environment from the existing data.

There is no guidance for conducting risk assessment for two agents with different mechanisms of action (i.e., energy deposition from ionizing radiation versus DNA interactions with chemicals) but similar biological endpoints (i.e., chromosomal aberrations, mutations, and cancer).[24] Of potentially greatest concern are interactions that are multi-step mechanisms for which two different agents would promote different steps that normally have low probability of occurrence, such as radon (initiation) and smoking (promotion).[23] UNSCEAR recommends that substantial evidence that hormones modify cancer risk be incorporated into radiation risk analyses.[21] In general, assessing the cumulative health risks from aggregate exposures to ionizing radiation and chemicals is an important area of future research.[24] As a supra-additive relationship between endocrine disrupting chemicals and radiation is biologically plausible, this interaction may be an untapped and productive avenue for breast cancer research.

Incidence and Etiology

Exposure to Nuclear Weapons

More is known about the relationship between radiation dose and cancer risk than any other human carcinogen, and female breast cancer is the most accurately quantified radiation-related cancer, according to Charles Land, Co-Chair of the National Action Plan on Breast Cancer's 1997 Workshop on Medical Ionizing Radiation. Much is known about the effects of radiation and cancer risk due to long-term studies of the survivors of exposure to nuclear weapons in Hiroshima and Nagasaki, Japan. For breast cancer in these women, the strength of the radiation dose response and the generally low level of population risk in the absence of radiation exposure provide a clear description of excess risk and its variation by age at exposure and over time following exposure.[25] The female survivors in this cohort had higher breast cancer risk that was strongly associated with dose,[26] and risk was highest in women who were less than 20 years old at the time of the bombings.[10, 26] Male atomic bomb survivors also exhibited a statistically significant association between ionizing radiation and breast cancer.[27]

Exposure to Ionizing Radiation in the Workplace and Community Environment

Further, albeit much weaker, evidence for an association between exposure to ionizing radiation and breast cancer comes from studies of workers who incur on-the-job exposure and community members living near nuclear power and weapons facilities. There are many limitations to the interpretation of these studies (Table 2). Whereas increased incidence of breast cancer has been demonstrated among radium dial workers,[3] flight attendants[28-30] and radiologic technicians,[31] studies of (mostly male) nuclear workers have shown a weak or no association between exposure to radiation and breast cancer risk.[32-34] Moreover, it is important to note that Pukkala et al. state that the estimated cumulative cosmic radiation dose (15–20 mSv) to flight attendants would be expected to barely affect the relative risk at all (RR = 1.01) based on a linear low dose extrapolation from the A-bomb data and therefore conclude that cosmic radiation does not account for the excess risk in female flight attendants. Studies of populations living near nuclear weapons and power facilities exposed to radiation from unintentional and routine releases into the environment are also plagued by methodological limitations, and have demonstrated an impact on breast cancer risk in some (Chernobyl),[35] but not all (Hanford, Washington; Pennsylvania) communities that have been studied.[36, 37]

Exposure to Ionizing Radiation in Medical Diagnostic and Therapeutic Procedures

The use of ionizing radiation in medicine produces health benefits and also causes extra cases of cancer. Exposure to ionizing radiation for disease therapy and diagnosis has been linked to increased breast cancer risk across a variety of patient populations. Radiation-related treatments for tuberculosis in the 1930s and 1940s,[9] scoliosis, enlarged thymus glands, skin hemangiomas, and Hodgkin disease,[9, 47-49] and primary breast cancer[9] have all been linked to increased breast cancer risk. Radiation therapy for breast cancer has also been linked to the creation of angiosarcomas within the chest wall.[50] John et al. found increased risks for breast cancer among women who had radiotherapy for a previous cancer (OR = 3.55, CI = 1.47–8.54) and diagnostic chest x-rays for tuberculosis (OR = 2.49, CI = 1.82–3.40) or pneumonia (OR = 2.19, CI = 1.38–3.47). Risks were highest for women with a large number of exposures at a young age or exposed in earlier calendar years.[51]

Cancer risk in the general population due to routine use of medical x-rays has not been well studied.[15] One estimate is that in the United States 5,695 cancer cases (all types) annually are attributable to medical x-rays (cumulative risk up to age 75 years).[52] Computed tomography (CT) scans screen the whole body in a series of x-rays and result in more exposure than a single diagnostic x-ray. The estimated effective radiation dose from a CT scan is 12 mSv,[1] although the dose to breast tissue may be higher for certain procedures, (i.e. 20 mGy during pulmonary CT angiograms,[53] and there is the potential for high cumulative doses (i.e., ranging from 19 to 153 mSv in a six-year period among patients being treated for renal colic.[54] While CT use has increased substantially in the past decades, little is known about the possible long-term effects, and most physicians are unaware of the radiation risks associated with CT scans.[55]

Much more is known about the risks and benefits of using ionizing radiation for breast screening, although key questions of much practical importance remain unanswered. Whereas the average annual background dose to breast tissue is about 1 mSv, almost all of it from gamma rays with a relatively small contribution from neutrons, the average breast dose of radiation per single screening mammogram is about 3 mSv.[8] Lower energy photons, like the softer x-rays s used for mammography, have a greater effect per unit dose than higher-energy x-rays, like those used for chest x-rays, or the gamma rays from the use of nuclear weapons in Japan.[56]

Generally, the numbers of lives saved by mammography is presumed to outweigh the harm. Whereas mortality reductions from detected breast cancer appear to be greater than the radiation risks in women 50 years and over,[57] the risk/benefit for women below age 50 is not fully characterized, and this issue remains a source of debate.[58]

Reasons why the risk/benefit analysis of mammography is less clear for women age 40 to 49 include that breast tissue in younger women is denser making mammograms less effective,[59] and it is also more sensitive to radiation. Many studies have examined the efficacy of mammography screening in women under age 50 years. In a meta-analysis the summary relative risk was 0.85, showing a reduction in mortality.[57] However, a randomized screening trial of mammography conducted in Canada did not find that annual mammograms reduced breast cancer mortality in women age 40 to 49 years.[60] Another large observational study, however, also from Canada, found a relative risk of death of 0.6 for women having a first mammogram between 40 and 49; this study followed about 600,000 women in British Columbia from 1988 to 2003.[61] A recent analysis of the radiation risks compared to the decreased breast cancer mortality benefits in the United Kingdom determined that a relative risk of 0.8 (a 20% reduction in mortality) would be needed to outweigh the increased risks in this age group.[59]

The risk/benefit ratio for mammography may also be different for women under age 50 years who have a family history of breast cancer. Current consensus advises earlier mammograms for these women.[62] The benefits from mammography may be greater in these women, because of the greater probability of detecting life-threatening disease. However, the risks of mammography may also be greater for these women, some of whom may have inherited genetic factors that might make them more sensitive to radiation-induced breast cancer. Those women who are at most risk for breast cancer are precisely those who are often screened the most intensely and thereby exposed to the highest amount of ionizing radiation through early and frequent screening. There have been no randomized controlled trials of screening mammography specifically in younger women with a family history of the disease.[62]

Another factor that may modify the risk-benefit equation of mammography is reproductive status. Women who give birth at older ages, women who have never given birth, premenopausal women, and women with a history of benign breast disease may represent radiation susceptible subgroups.[12] Women who have never given birth are at higher risk of breast cancer, but their breasts are also physiologically more susceptible to radiation damage. A case-control study of breast cancer among atomic bomb survivors found that interactions between reproductive history and radiation exposure (nulliparity, age at 1st full-term pregnancy, cumulative lactation, number of births) were consistent with a multiplicative interaction but not with an additive model.[25, 63] For example, an early age at 1st full-term pregnancy was protective against both baseline and radiation-related breast cancer risk, whether the pregnancy occurred before or after the exposure. On the other hand, the fact of being American (high baseline risk) or Japanese (low baseline risk) interacted additively with radiation dose (the increment in breast cancer rate per unit dose was approximately equivalent for high-risk Americans and low-risk Japanese).[64] The US-Japan difference in baseline rates is not genetic – Americans of Japanese descent tend to have rates comparable to those of other Americans – but whatever it is that is responsible for the difference appears to interact additively with radiation dose.

Regarding the interaction of dose with reproductive history, Russo et al found evidence suggesting that differentiated breast cells are less susceptible to chemical carcinogens,[65] and experimental studies have concluded that mammary cells differentiated for milk secretion are less susceptible to radiation carcinogenesis.[66, 67] The risks and benefits of irradiating lactating breasts is a matter of great interest and debate within the lactation community as well as the breast cancer community.

There are factors other than radiation to consider when evaluating mammography risks such as false positives and unnecessary biopsies.[57] Because it is difficult to quantify all of the potential risks and benefits of mammograms in women under age 50, various government and medical groups disagree upon the recommended age and frequency for early mammograms. The U.S. Preventive Services Task Force, the American Medical Association and the American Cancer Society support guidelines advising mammograms every one to two years for all women starting at age 40.[57] However, the Canadian Task Force on Preventive Health Care and the American Academy of Family Physicians recommend beginning mammography at age 50 and counseling women ages 40 to 49 about the risks and benefits.[57] The American College of Physicians recently recommended that for women between the ages of 40 to 49 years, physicians should periodically perform an individualized assessment of breast cancer risk, inform women of the risks and benefits of mammography, and base screening mammography decisions on the risks and benefits as well as a women's preferences and breast cancer risk profile.[68] In the United Kingdom women are offered mammograms every three years between ages 50 and 70.[59]

Summary and Research Directions

Ionizing radiation is a well-established, extensively studied carcinogen.[69] The prevailing model used for radiation risk estimates is that every exposure to radiation produces a corresponding increase in cancer risk, and exposures during infancy, childhood, and adolescence confer the greatest risks. The relationship between exposure to ionizing radiation and breast cancer risk has been clearly demonstrated in studies of the survivors of the nuclear weapons dropped on Hiroshima and Nagasaki. Further evidence comes from studies of individuals exposed to ionizing radiation at work, as a result of living near a nuclear facility, or due to the use of radiation in medical diagnostic and therapeutic procedures.

The use of ionizing radiation for breast cancer screening and treatment and for other medical procedures produces health benefits and also causes extra cases of cancer. Cancer risk in the general population due to routine use of medical x-rays has not been well studied, and while CT use has increased substantially in the past decades, little is known about the possible long-term effects, and most physicians are unaware of the radiation risks associated with CT scans.Generally, the numbers of lives saved by mammography outweigh the harm; however the risk/benefit for women below age 50 is not fully characterized, and this issue remains a source of debate. Moreover, subgroups of women appear to be more susceptible to the harmful effects of radiation, for example due to inherited genes or reproductive status, and all together, these represent a large subset of the total number of women receiving annual mammograms.

Therefore, research is needed to improve our understanding of the relationship between low-dose exposure to ionizing radiation and breast cancer, and to identify, implement, and monitor policies and practices that ensure the benefits of the use ionizing radiation outweigh the harm. A key area of research is related to the possibility that genetic factors may modify radiation-related cancer risk. The National Research Council has recommended further study of gene mutations and functional polymorphisms that are involved in the body’s response to radiation and cancer risk in order to better understand the DNA repair capacity, especially for the double strand and multiple stand breaks at low doses of radiation.[1] In addition, research is needed to assess the cumulative health risks from aggregate exposures to ionizing radiation and chemicals.[24] Because of the complexity of this problem, future research on breast cancer and radiation should involve a diverse group of scientists with expertise in molecular and clinical genetics, radiation biology, physics, medicine, and epidemiology.[18]

Increased understanding of the risks of low-dose radiation is also of much importance in that exposures are prevalent across issues as varied as screening tests for cancer, the future of nuclear power, nuclear weapons, occupational radiation exposure, and air travel. Epidemiologic studies of exposed occupational and community-based populations such as nuclear industry workers, radiologic technicians, and exposed community members near Chernobyl are needed and should include improved dose measurements to gain more insights into risks associated with low dose exposures.[1]

Research is also needed to identify and implement steps to reduce occupational exposure to ionizing radiation. Ionizing radiation is used extensively in a wide range of industries and while its use has grown significantly in recent years, for example in the use of x-rays in security screening, the U.S. Occupational Health and Safety Administration (OSHA) workplace exposure limits for ionizing radiation have not been updated since they were promulgated in 1971. Workers covered by the current OSHA regulations are permitted to incur annual exposures of 50 mSv (29 CFR 1910.1926), a level of exposure that corresponds to a cancer risk of 1 in 200.

Finally, many questions related to the use of ionizing radiation for medical diagnostic and therapeutic procedures remain unanswered. The use of radiation in breast cancer screening and treatment for subpopulations of women with increased susceptibilities to its harmful effects should be evaluated. Breast cancer advocates have called for alternative screening tools that do not expose the breast to a known carcinogen. There is also the related need to investigate the impact of exposure among people receiving CT scans and other x-rays, especially children.[1] The U.S. Food and Drug Administration (FDA) classifies medical x-rays as a known carcinogen although the agency does not monitor clinical practices other than mammography. The FDA should closely regulate all radiologic medical devices and create guidelines for maximum acceptable doses, acute and cumulative, especially for CT scans[55] Research is needed to identify ways to reduce the dose of radiation from CT scans,[55] minimize exposure to x-rays to girls' and young women's breasts,[9] include measured doses of radiation in patient medical records and calculate dose through the lifetime of each individual, quantify the exposure to the general population over time, and educate physicians about radiation risks.[55]

References

1. National Research Council (NRC), Committee to Assess Health Risks from Exposure to Low Level of Ionizing Radiation. Health risks from exposure to low levels of ionizing radiation: BEIR VII Phase 2. 1st Ed. Washington, DC, USA: National Academies Press, 2006. (ISBN: 9780309091565)

2. Rabin RC. With rise in radiation exposure, experts urge caution on tests [newspaper article]. In: The New York Times. New York, NY, USA: The New York Times Company, 2007 Jun 19. Available at http://www.nytimes.com/2007/06/19/health/19cons.html?ex=1187236800&en=bc2ce2878414ad49&ei=5070.

3. Stebbings JH. Health risks from radium in workplaces: an unfinished story. Occup Med. 2001, 16(2):259-70.

4. Nekolla EA, Kellerer AM, Kuse-Isingschulte M, Eder E, Spiess H. Malignancies in patients treated with high doses of radium-224. Radiat Res. 1999, 152(6 Suppl):S3-7.

5. Valentin J. Low-dose extrapolation of radiation-related cancer risk. Ann ICRP. 2005, 35(4):1-140.

6. Goldberg Z, Lehnert BE. Radiation-induced effects in unirradiated cells: a review and implications in cancer. Int J Oncol . 2002, 21(2):337-49.

7. Land CE. Estimating cancer risks from low doses of ionizing radiation. Science. 1980, 209(4462):1197-203.

8. Brenner DJ, Doll R, Goodhead DT, Hall EJ, Land CE, Little JB, Lubin JH, Preston DL, Preston RJ, Puskin JS, Ron E, Sachs RK, Samet JM, Setlow RB, Zaider M. Cancer risks attributable to low doses of ionizing radiation: assessing what we really know. Proc Natl Acad Sci U S A. 2003, 100(24):13761-6.

9. Boice JD Jr. Radiation and breast carcinogenesis. Med Pediatr Oncol. 2001, 36(5):508-13.

10. Land CE, Tokunaga M, Koyama K, Soda M, Preston DL, Nishimori I, Tokuoka S. Incidence of female breast cancer among atomic bomb survivors, Hiroshima and Nagasaki, 1950-1990. Radiat Res. 2003, 160(6):707-17.

11. Doody MM, Freedman DM, Alexander BH, Hauptmann M, Miller JS, Rao RS, Mabuchi K, Ron E, Sigurdson AJ, Linet MS. Breast cancer incidence in U.S. radiologic technologists. Cancer. 2006, 106(12):2707-15.

12. Ronckers CM, Erdmann CA, Land CE. Radiation and breast cancer: a review of current evidence. Breast Cancer Res. 2005, 7(1):21-32.

13. Gutierrez-Enriquez S, Fernet M, Dork T, Bremer M, Lauge A, Stoppa-Lyonnet D, Moullan N, Angele S, Hall J. Functional consequences of ATM sequence variants for chromosomal radiosensitivity. Genes Chromosomes Cancer. 2004, 40(2):109-19.

14. Bernstein JL, Teraoka SN, John EM, Andrulis IL, Knight JA, Lapinski R, Olson ER, Wolitzer AL, Seminara D, Whittemore AS, Concannon P. The CHEK2*1100delC allelic variant and risk of breast cancer: screening results from the Breast Cancer Family Registry. Cancer Epidemiol Biomarkers Prev. 2006, 15(2):348-52.

15. Andrieu N, Easton DF, Chang-Claude J, Rookus MA, Brohet R, Cardis E, Antoniou AC, Wagner T, Simard J, Evans G, Peock S, Fricker JP, Nogues C, Van't Veer L, Van Leeuwen FE, Goldgar DE. Effect of chest X-rays on the risk of breast cancer among BRCA1/2 mutation carriers in the international BRCA1/2 carrier cohort study: a report from the EMBRACE, GENEPSO, GEO-HEBON, and IBCCS Collaborators' Group. J Clin Oncol. 2006, 24(21):3361-6.

16. Millikan RC, Player JS, Decotret AR, Tse CK, Keku T. Polymorphisms in DNA repair genes, medical exposure to ionizing radiation, and breast cancer risk. Cancer Epidemiol Biomarkers Prev. 2005, 14(10):2326-34.

17. U.S. Preventive Services Task Force. Genetic risk assessment and BRCA mutation testing for breast and ovarian cancer susceptibility: recommendation statement. Ann Intern Med. 2005, 143(5):355-61.

18. Bernstein JL, Seminara D, Borresen-Dale AL. Workshop on The Epidemiology of the ATM Gene: Impact on Breast Cancer Risk and Treatment, Present Status and Future Focus, Lillehammer, Norway, 29 June 2002. Breast Cancer Res. 2002, 4(6):249-52.

19. Angele S, Romestaing P, Moullan N, Vuillaume M, Chapot B, Friesen M, Jongmans W, Cox DG, Pisani P, Gerard JP, Hall J. ATM haplotypes and cellular response to DNA damage: association with breast cancer risk and clinical radiosensitivity. Cancer Res. 2003, 63(24):8717-25.

20. National Cancer Institute (NCI). Ataxia Telangiectasia: Fact Sheet. Washington, DC, USA: National Cancer Institute (NCI), 2006. Available at http://www.nci.nih.gov/cancertopics/factsheet/ataxiaqa.

21. United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR). Combined effects of radiation and other agents. In: United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR). Sources and Effects of Ionizing Radiation, Vol. II: Effects. Vienna, Austria: UNSCEAR, 2000. Available at http://www.unscear.org/docs/reports/annexh.pdf.

22. Ullrich RL. Interactions of radiation and chemical carcinogens. Carcinog Compr Surv. 1980, 5:169-84.

23. OECD Nuclear Energy Agency, Committee on Radiation Protection and Public Health, Working Group on Scientific and Technology Affecting Radiation Protection Sub-Group on Radiation Health Sciences (WGST-RHS). Developments in Radiation Health Science and Their Impact on Radiation Protection. Paris, France: OECD, 1998. Available at http://www.nea.fr/html/rp/reports/1998/devrad.pdf.

24. Chen WC, McKone TE. Chronic health risks from aggregate exposures to ionizing radiation and chemicals: scientific basis for an assessment framework. Risk Anal. 2001, 21(1):25-42.

25. Land CE. Studies of cancer and radiation dose among atomic bomb survivors. The example of breast cancer. JAMA. 1995, 274(5):402-7.

26. Tokunaga M, Land CE, Tokuoka S, Nishimori I, Soda M, Akiba S. Incidence of female breast cancer among atomic bomb survivors, 1950-1985. Radiat Res. 1994, 138(2):209-23.

27. Ron E, Ikeda T, Preston DL, Tokuoka S. Male breast cancer incidence among atomic bomb survivors. J Natl Cancer Inst. 2005, 97(8):603-5.

28. Pukkala E, Auvinen A, Wahlberg G. Incidence of cancer among Finnish airline cabin attendants, 1967-92. BMJ. 1995, 311(7006):649-52.

29. Reynolds P, Cone J, Layefsky M, Goldberg DE, Hurley S. Cancer incidence in California flight attendants (United States). Cancer Causes Control. 2002, 13(4):317-24.

30. Rafnsson V, Sulem P, Tulinius H, Hrafnkelsson J. Breast cancer risk in airline cabin attendants: a nested case-control study in Iceland. Occup Environ Med. 2003 , 60(11):807-9.

31. Sigurdson AJ, Doody MM, Rao RS, Freedman DM, Alexander BH, Hauptmann M, Mohan AK, Yoshinaga S, Hill DA, Tarone R, Mabuchi K, Ron E, Linet MS. Cancer incidence in the US radiologic technologists health study, 1983-1998. Cancer. 2003, 97(12):3080-9.

32. Omar RZ, Barber JA, Smith PG. Cancer mortality and morbidity among plutonium workers at the Sellafield plant of British Nuclear Fuels. Br J Cancer. 1999, 79(7-8):1288-301.

33. Telle-Lamberton M, Bergot D, Gagneau M, Samson E, Giraud JM, Neron MO, Hubert P. Cancer mortality among French Atomic Energy Commission workers. Am J Ind Med. 2004, 45(1):34-44.

34. Reynolds P, Austin DF. Cancer incidence among employees of the Lawrence Livermore National Laboratory, 1969-1980. West J Med. 1985, 142(2):214-8.

35. Pukkala E, Kesminiene A, Poliakov S, Ryzhov A, Drozdovitch V, Kovgan L, Kyyronen P, Malakhova IV, Gulak L, Cardis E. Breast cancer in Belarus and Ukraine after the Chernobyl accident. Int J Cancer. 2006, 119(3):651-8.

36. Boice JD Jr, Bigbee WL, Mumma MT, Blot WJ. Cancer incidence in municipalities near two former nuclear materials processing facilities in Pennsylvania. Health Phys. 2003, 85(6):678-90.

37. Boice JD Jr, Mumma MT, Blot WJ. Cancer mortality among populations residing in counties near the Hanford site, 1950-2000. Health Phys. 2006, 90(5):431-45.

38. Buja A, Mastrangelo G, Perissinotto E, Grigoletto F, Frigo AC, Rausa G, Marin V, Canova C, Dominici F. Cancer incidence among female flight attendants: a meta-analysis of published data. Womens Health (Larchmt). 2006, 15(1):98-105.

39. Haldorsen T, Reitan JB, Tveten U. Cancer incidence among Norwegian airline cabin attendants. Int J Epidemiol. 2001, 30(4):825-30.

40. Blettner M, Zeeb H, Langner I, Hammer GP, Schafft T. Mortality from cancer and other causes among airline cabin attendants in Germany, 1960-1997. Am J Epidemiol. 2002, 156(6):556-65.

41. Zeeb H, Blettner M, Langner I, Hammer GP, Ballard TJ, Santaquilani M, Gundestrup M, Storm H, Haldorsen T, Tveten U, Hammar N, Linnersjo A, Velonakis E, Tzonou A, Auvinen A, Pukkala E, Rafnsson V, Hrafnkelsson J. Mortality from cancer and other causes among airline cabin attendants in Europe: a collaborative cohort study in eight countries. Am J Epidemiol. 2003, 158(1):35-46.

42. Fogelholm R. Cancer among airline cabin attendants. Risk due to active and passive smoking should have been mentioned. BMJ. 1996, 312(7022):53; author reply 53-4.

43. Kojo K, Pukkala E, Auvinen A. Breast cancer risk among Finnish cabin attendants: a nested case-control study. Occup Environ Med. 2005, 62(7):488-93.

44. Wang JX, Zhang LA, Li BX, Zhao YC, Wang ZQ, Zhang JY, Aoyama T. Cancer incidence and risk estimation among medical x-ray workers in China, 1950-1995. Health Phys. 2002, 82(4):455-66.

45. Zielinski JM, Garner MJ, Krewski D, Ashmore JP, Band PR, Fair ME, Jiang H, Letourneau EG, Semenciw R, Sont WN. Decreases in occupational exposure to ionizing radiation among Canadian dental workers. J Can Dent Assoc. 2005, 71(1):29-33.

46. Sont WN, Zielinski JM, Ashmore JP, Jiang H, Krewski D, Fair ME, Band PR, Letourneau EG. First analysis of cancer incidence and occupational radiation exposure based on the National Dose Registry of Canada. Am J Epidemiol. 2001, 153(4):309-18.

47. Travis LB, Hill DA, Dores GM, Gospodarowicz M, van Leeuwen FE, Holowaty E, Glimelius B, Andersson M, Wiklund T, Lynch CF, Van't Veer MB, Glimelius I, Storm H, Pukkala E, Stovall M, Curtis R, Boice JD Jr, Gilbert E. Breast cancer following radiotherapy and chemotherapy among young women with Hodgkin disease. JAMA. 2003, 290(4):465-75.

48. Travis LB, Hill D, Dores GM, Gospodarowicz M, van Leeuwen FE, Holowaty E, Glimelius B, Andersson M, Pukkala E, Lynch CF, Pee D, Smith SA, Van't Veer MB, Joensuu T, Storm H, Stovall M, Boice JD Jr, Gilbert E, Gail MH. Cumulative absolute breast cancer risk for young women treated for Hodgkin lymphoma. J Natl Cancer Inst. 2005, 97(19):1428-37.

49. Van Leeuwen FE, Klokman WJ, Stovall M, Dahler EC, van't Veer MB, Noordijk EM, Crommelin MA, Aleman BM, Broeks A, Gospodarowicz M, Travis LB, Russell NS. Roles of radiation dose, chemotherapy, and hormonal factors in breast cancer following Hodgkin's disease. J Natl Cancer Inst. 2003, 95(13):971-80.

50. Huang J, Mackillop WJ. Increased risk of soft tissue sarcoma after radiotherapy in women with breast carcinoma. Cancer. 2001, 92(1):172-80.

51. John EM, Phipps AI, Knight JA, Milne RL, Dite GS, Hopper JL, Andrulis IL, Southey M, Giles GG, West DW, Whittemore AS. Medical radiation exposure and breast cancer risk: Findings from the Breast Cancer Family Registry. Int J Cancer. 2007, 121(2):386-94.

52. Berrington de Gonzalez A, Darby S. Risk of cancer from diagnostic X-rays: estimates for the UK and 14 other countries. Lancet. 2004, 363(9406):345-51.

53. Parker MS, Hui FK, Camacho MA, Chung JK, Broga DW, Sethi NN. Female breast radiation exposure during CT pulmonary angiography. AJR Am J Roentgenol. 2005, 185(5):1228-33.

54. Katz SI, Saluja S, Brink JA, Forman HP. Radiation dose associated with unenhanced CT for suspected renal colic: impact of repetitive studies. AJR Am J Roentgenol. 2006, 186(4):1120-4.

55. Martin DR, Semelka RC. Health effects of ionising radiation from diagnostic CT. Lancet. 2006, 367(9524):1712-4.

56. Brenner DJ, Sawant SG, Hande MP, Miller RC, Elliston CD, Fu Z, Randers-Pehrson G, Marino SA. Routine screening mammography: how important is the radiation-risk side of the benefit-risk equation? Int J Radiat Biol. 2002, 78(12):1065-7.

57. Humphrey LL, Helfand M, Chan BK, Woolf SH. Breast cancer screening: a summary of the evidence for the U.S. Preventive Services Task Force. Ann Intern Med. 2002, 137(5 Part 1):347-60.

58. Moss S. Should women under 50 be screened for breast cancer? Br J Cancer. 2004 , 91(3):413-7.

59. Berrington de Gonzalez A, Reeves G. Mammographic screening before age 50 years in the UK: comparison of the radiation risks with the mortality benefits. Br J Cancer. 2005, 93(5):590-6.

60. Miller AB, To T, Baines CJ, Wall C. The Canadian National Breast Screening Study-1: breast cancer mortality after 11 to 16 years of follow-up. A randomized screening trial of mammography in women age 40 to 49 years. Ann Intern Med. 2002, 137(5 Part 1):305-12.

61. Coldman A, Phillips N, Warren L, Kan L. Breast cancer mortality after screening mammography in British Columbia women. Int J Cancer. 2007, 120(5):1076-80.

62. Lucassen A, Watson E, Eccles D. Evidence based case report: Advice about mammography for a young woman with a family history of breast cancer. BMJ. 2001, 322(7293):1040-2.

63. Land CE, Hayakawa N, Machado SG, Yamada Y, Pike MC, Akiba S, Tokunaga M. A case-control interview study of breast cancer among Japanese A-bomb survivors. II. Interactions with radiation dose. Cancer Causes Control. 1994, 5(2):167-76.

64. Preston DL, Mattsson A, Holmberg E, Shore R, Hildreth NG, Boice JD Jr. Radiation effects on breast cancer risk: a pooled analysis of eight cohorts. Radiat Res. 2002, 158(2):220-35.

65. Russo J, Gusterson BA, Rogers AE, Russo IH, Wellings SR, van Zwieten MJ. Comparative study of human and rat mammary tumorigenesis. Lab Invest. 1990, 62(3):244-78.

66. Clifton KH, Sridharan BN, Douple EB. Mammary carcinogenesis-enhancing effect of adrenalectomy in irradiated rats with pituitary tumor MtT-F4. J Natl Cancer Inst. 1975, 55(2):485-7.

67. Clifton KH, Crowley JJ. Effects of radiation type and dose and the role of glucocorticoids, gonadectomy, and thyroidectomy in mammary tumor induction in mammotropin-secreting pituitary tumor-grafted rats. Cancer Res. 1978, 38(6):1507-13.

68. Qaseem A, Snow V, Sherif K, Aronson M, Weiss KB, Owens DK. Screening mammography for women 40 to 49 years of age: a clinical practice guideline from the American College of Physicians. Ann Intern Med. 2007, 146(7):511-5.

69. Wakeford R. The cancer epidemiology of radiation. Oncogene. 2004, 23(38):6404-28

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