Original Article

Radiation Therapy and Breast Cancer Risk

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Abstract
Exposure to ionizing radiation has clearly been established as one of the risk factors for the development of breast cancer. Much data on the relationship between radiation exposures and subsequent breast cancer are derived from atomic bomb survivors and women who received medical exposures either for diagnostic or therapeutic purposes. Although these populations differ in background breast cancer risks and the dose, quality, and timing of radiation, consistent findings include an increased risk with younger age at exposure, long latency to breast cancer development, and increasing risk with increasing radiation dose. Although therapeutic radiation is rarely used to treat benign conditions, it remains an important and effective treatment modality for a wide range of cancers. Increased knowledge of radiation-related breast cancer and modifying influences plays an important role in guiding the initial treatment approach for young women and optimizing long-term follow-up care. (*JNCCN* 2009;7:1121–1128)

Female breast cancer is a well-documented late effect of exposure to doses of ionizing radiation as low as 0.1 to 0.5 Sievert (Sv).[1] Sievert is the unit dose equivalent and the product of the absorbed dose in gray and quality factors; in this article, Sv will be used interchangeably with Gray (Gy), the unit of absorbed dose, kerma, and specific energy imparted.

Ample data are available on radiation-associated breast cancer based on epidemiologic studies of atomic bomb survivors,[1–9] and cohorts of women who underwent repeated diagnostic exposure,[10–13] or therapeutic radiation to treat either benign conditions[14–24] or cancer.[25–40] Although the radiation administered to these populations varied in terms of quality, dose rate, fractionation, and cumulative amount, and the patients differed in terms of age at exposure and background risk, consistent findings between studies have emerged. These observations include a diminishing risk for breast cancer with increasing age at radiation exposure, and a significant relationship between increasing radiation dose and increasing breast cancer risk, although the precise shape of the dose–response curve can vary.

Preston et al.[41] reviewed 8 cohorts of irradiated women, including atomic bomb survivors and 7 other groups who received medical exposures. Results from this pooled analysis suggested that radiation exposure at any age was associated with an increased risk for breast cancer. Although breast cancer excesses decreased with increasing age at exposure, significantly elevated risks persisted throughout life, with the largest excess rates occurring late in life, as background rates increase. Although a cell-killing effect for high dose-rate exposures totaling several Gy or more was suggested, the pooled analysis showed no evidence contrary to a linear dose response in the low-dose region. In subsequent studies that focused on Hodgkin lymphoma (HL) survivors who underwent radiation in therapeutic dose ranges, there was also no evidence of a downturn in risk, even in the highest dose ranges.[34,35]

A thorough understanding of the relation between radiation exposure and subsequent breast cancer excesses can facilitate the development of radiobiologic risk models for estimating risks in various settings. Furthermore, this information can then provide the foundation for patient counseling, and also guide recommendations for optimal breast cancer screening and prevention strategies in exposed women.

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Risk in Atomic Bomb Survivors

Epidemiologic studies on atomic bomb survivors represent a major source of data on cancer risk after small doses of radiation. The Radiation Effects Research Foundation's (RERF) extended Life Span Study (LSS) on the health effects of exposure to atomic bomb radiation published a series of reports on female breast cancer,[2–5,7,42,43] with an estimated overall excess relative risk per Sv (ERR_{1Sv}) of 1.56.[3]

An analysis of breast cancer mortality reported that women who received average doses of 0.09, 0.75, and 1.99 Sv experienced 1.05-, 2.14-, and 2.47-fold increased risks for mortality, respectively, compared with women who received zero mean doses.[10] The estimated ERR_{1Sv} declined with increasing age at exposure. Among survivors exposed before 20 years of age, the ERR_{1Sv} ranged from 2.65 to 3.94, whereas among those exposed after this age, the ERR_{1Sv} ranged from 0.54 to 1.33.[2] The higher dose-specific ERR among women exposed before 20 years of age could reflect the lower susceptibility to radiation carcinogenesis of terminally differentiated breast cells. In addition, older women may be more likely to have experienced a full-term pregnancy before exposure, thus reducing their breast cancer risk. A case-control study found that younger age at full-term pregnancy, multiple births, and a prolonged cumulative period of breastfeeding were protective against subsequent breast cancer among the atomic bomb survivors, whereas age at menarche and menopause did not significantly influence risk.[5]

A pathologic review of breast cancer in atomic bomb survivors showed that the distribution of histologic types was similar to that of de novo breast cancer in Japanese women, and did not seem dependent on dose.[8] In a recent immunohistopathologic study, however, Miura et al.[44] found a higher histologic grade, including larger nuclear size and higher mitotic count for breast cancers in survivors exposed to atomic bomb radiation at a closer distance. In addition, a higher incidence of both *HER2* and *c-myc* amplification in invasive ductal carcinomas was reported among these women.

Risk After Diagnostic Radiation Exposures

The risk for breast cancer among women who underwent multiple fluoroscopic examinations during artificially induced pneumothorax to treat tuberculosis has been described in multiple studies. Patients were typically exposed to hundreds of these examinations regularly over 3 to 5 years, with an estimated dose to the breast of 0.01 to 0.1 Gy per fluoroscopy.[12]

In a study comparing breast cancer incidence in the Massachusetts tuberculosis fluoroscopy cohort and among atomic bomb survivors,[12] the ERR_{1Sv} of breast cancer was significantly lower in the fluoroscopy cohort (0.58 vs. 1.55, $P = .04$). This finding was partly attributed to the low background risk for breast cancer among Japanese women. The excess absolute risk for breast cancer, however, was not significantly different between the cohorts (5.48 vs. 4.95 per 10,000 person-years per Sv; $P = .32$). Howe and McLaughlin[10] described a significant effect of radiation dose on the risk for breast cancer mortality in the Canadian fluoroscopy cohort study. Women exposed to the highest mean dose category of 13.27 Sv had a 27.9-fold increased risk for breast cancer mortality compared with those who received zero mean doses.

Patients with scoliosis were historically exposed to frequent diagnostic radiographs. In the U.S. Scoliosis Cohort Study,[45] the mean estimated cumulative radiation dose to the breast in exposed women was 0.12 Gy and mean age at exposure was 10.6 years. At an average follow-up of 40 years, the relative risk for breast cancer mortality was 1.7 (95% CI, 1.3–2.1). The risk increased with increasing cumulative radiation dose. Patients who received breast doses of greater than 0.20 Gy had a standardized mortality ratio (SMR) of 3.36 (P-trend, .001). Among women who received at least one radiographic examination, the estimated ERR_{1Sv} was 2.7. Age at exposure was also significantly associated with breast cancer mortality. The risk was largest among patients first exposed at 10 or 11 years of age, with an SMR of 3.4 compared with 1.4 to 1.9 for younger and older ages. The dose–response relation, however, did not differ by age at first radiographic examination.

A recent study suggested that family history of breast cancer could enhance the carcinogenic effect of radiation.[13] In this investigation, the overall ERR_{1Sv} was 2.86, but was significantly higher (8.37; $P = .03$) among women who reported a family history of breast cancer in first- or second-degree relatives.

Mammographic screening has been shown to reduce breast cancer mortality, although its role in women aged 40 to 49 years is less clear.[46,47] Current-

ly, the U.S. Preventive Services Task Force recommends screening mammography, with or without clinical breast examination, every 1 to 2 years for women aged 40 years and older. The mean radiation dose of screening mammogram to breast has been estimated to be 2.25 mGy per view.[48] No study has yet addressed whether any association exists between this type of very low-level radiation exposure and subsequent excess breast cancers. Current estimates are largely extrapolated from populations exposed to higher doses of radiation.

In a study comparing the number of detected breast cancers with those possibly induced by mammographic screening,[49] the detected/induced ratio increased with increasing age of screening. The ratios ranged from 0.47 to 2.6 among women aged 30 to 34 years, depending on radiation dose, whereas for those aged 60 to 64 years, the ratios ranged from 3.7 to 20. Women with a family history of breast cancer, as expected, were estimated to have higher, more favorable detected/induced ratios. Based on the findings, the authors concluded that some measure of caution may be required in annual mammographic screening of women younger than 35 years.

The risk for radiation-induced breast cancer from screening mammography may be especially relevant in carriers of BRCA-1 and -2 mutations because of the young age at which examinations are initiated, combined with concerns regarding the higher risk for radiation-induced malignancy in these patients.[50,51]

In a recent study by Berrington de Gonzalez et al.,[52] the lifetime risk for radiation-induced breast cancer caused by 5 annual mammographic screenings in *BRCA* mutation carriers aged 40 years or younger was estimated to be 26, 20, and 13 per 10,000 women for screening examinations at ages 25 to 29, 30 to 34, and 35 to 39 years, respectively. The breast cancer mortality reduction needed to outweigh the risk associated with screening in these 3 age groups was greater than 45%, greater than 12%, and greater than 4%, respectively. Assuming a mortality reduction from mammography of 15% to 25%, the results suggested that women would derive no net benefit from annual mammographic screening at 25 to 29 years of age, a small benefit at 30 to 34 years, and some net benefit at older than 35 years.

Risk After Therapeutic Radiation for Benign Conditions

Low-dose ionizing radiation has been used to treat benign conditions, including skin hemangioma and thymic enlargement during infancy or childhood, acute postpartum mastitis, and benign breast disease. Hildreth et al.[14] compared the incidence of breast cancer in a cohort of 1201 women administered radiation during infancy to treat an enlarged thymus gland with 2469 nonirradiated sisters.[14] The estimated mean absorbed dose of radiation to the breast was 0.69 Gy. After a mean follow-up of 36 years, exposed women had a significantly increased 3.6-fold risk for developing breast cancer compared with siblings. A significant linear dose–response relationship was observed.

Similarly, increased risk for developing breast cancer was shown in women irradiated for skin hemangiomas during infancy. In a cohort study in Sweden including 17,202 women, the median absorbed breast dose was 0.05 Gy (average dose, 0.29 Gy; range, 0–35.8 Gy).[17] Compared with the normal matched population, the relative risk for developing breast cancer was 1.2 (95% CI, 1.09–1.36) and the ERR_{1Sv} was estimated at 0.35, which is lower than that observed in most other studies on radiation-related cancer. In the pooled analysis by Preston et al.,[41] a lower excess risk in the hemangioma cohorts was similarly observed, suggesting a possible ameliorating dose-rate effect for protracted low dose-rate exposure in women irradiated for skin hemangiomas, which was typically administered with radium-226 applicators.

One study showed that 601 women who underwent radiation therapy to treat acute postpartum mastitis had a significantly increased 3.2-fold risk for developing breast cancer at a mean follow-up of 29 years compared with control subjects who did not receive radiation therapy.[20] The risk increased with increasing radiation dose in a linear fashion. Unlike other studies on radiation-related breast cancer, however, age at exposure did not significantly influence breast cancer risk. This observation was hypothesized to reflect the increased susceptibility to radiation of proliferating breast tissues stimulated by hormones during pregnancy and lactation regardless of age at treatment. Similarly, an increased risk for breast cancer was observed in women who were irradiated for benign breast disease.

In a cohort study of 1216 women with benign breast disease treated with radiation therapy,[23] the relative risk for breast cancer was significantly increased at 3.26 compared with the normal matched population. The relative risk was higher in women younger than 40 years at exposure than in those 40 years or older (relative risk, 3.92 vs. 2.54). A radiation dose–response relationship was also observed, although it was significant only among women younger than 25 years of age at exposure.[24]

Risk After Therapeutic Radiation to Treat Cancer

Many data on breast cancer risk after radiotherapy derive from women given chest irradiation to treat HL during childhood or young adulthood.[34–40] Increasing literature also exists on the risk for contralateral breast cancer after either breast-conserving therapy with lumpectomy and radiation therapy or postmastectomy chest wall irradiation.[25–27,29–33] As in breast cancer after exposure to low doses of radiation, breast cancer after high-dose therapeutic radiation therapy is characterized by a higher risk with younger age at exposure, a long latency period, and a significant radiation dose–response relationship.

Breast Cancer After Radiation Therapy for HL and Childhood Cancer

Breast cancer is one of the most common second primary tumors in childhood cancer survivors whose treatment included chest radiation therapy. In a study of survivors of childhood HL conducted by the Late Effects Study Group,[40] the relative risk of breast cancer was 56.7 (95% CI, 40.5–77.3) with a median latency of 18.1 years (range, 4.3–28.3 years). In another multi-institutional follow-up study of HL survivors,[53] the relative risk for breast cancer was 37.2 (95% CI, 25.0–53.6) and the absolute excess risk was 18.6 per 10,000 person-years. In addition, 34% of patients were diagnosed with bilateral disease. The mean time to development of breast cancer after HL was 18.7 years; among women who developed bilateral breast cancer, the average interval between the first and second cancer was 23 months.

Based on data from the Childhood Cancer Survivor Study (CCSS), Kenney et al.[38] described the risk for breast cancer in 6068 female patients. Ninety-five women (68% of whom were survivors of pediatric HL) were diagnosed with 111 confirmed cases of breast cancer. Girls who were treated between ages 5 and 9 years did not subsequently experience a significantly increased risk for breast cancer, whereas significant excesses were observed among girls treated at 10 years of age or older. The authors suggested that, in contrast to prepubertal breast tissues, proliferating and developing breast tissues may be more sensitive to the tumorigenic effects of radiation.

In studies focused largely on survivors of adult HL, second primary breast cancer also emerged as one of the most common solid tumors. Studies have consistently shown that younger age at radiation treatment is associated with a significantly larger risk for breast cancer.[36,54–56] In a population-based cohort study, Hodgson et al.[55] reported that the absolute risks for breast cancer in women diagnosed with HL at ages 15 to 25 years were 34 to 47 per 10,000 person years at 10 years, which was higher than the absolute risks among women in the general population between ages 50 and 54 years, a standard age when mammographic screening is recommended. Given this considerable risk for breast cancer, informed counseling for long-term survivors of HL is critical.

Travis et al.[37] developed estimates of the cumulative absolute risk for breast cancer, taking into account age and calendar year of HL diagnosis, age at counseling, baseline breast cancer incidence rates, radiation dose and chemotherapy, and competing causes of mortality. For example, for an HL survivor who received a chest radiation dose of 40 Gy or greater at 25 years of age without undergoing alkylating agent therapy, the cumulative absolute risk for breast cancer was estimated to be 1.4% after 10 years, 11% after 20 years, and 29% after 30 years.

Several case-control studies have clearly documented a convincing radiation dose–response relation for breast cancer after HL. In a large international case-control study of HL survivors, including 105 cases of breast cancer and 266 matched controls, Travis et al.[35] estimated radiation dose to the area of the breast where the tumor developed (and a comparable area in matched controls) for each case-control set. Breast cancer risk increased significantly with increasing radiation dose, reaching 8-fold for the highest category (median dose, 42 Gy) compared with the lowest dose group (< 4 Gy; P trend for dose, < .001). A separate Dutch study[34] similarly showed a significant radiation dose–response relationship, with most patients also included in the international

investigation. The CCSS recently published a case-control study of 120 cases of breast cancer (65% in survivors of HL) matched with 464 controls according to age and time since initial cancer diagnosis.[57] Again, a significant linear radiation dose–response was observed (*P* trend, < .0001), with an estimated relative risk for breast cancer of 6.4 at 20 Gy and 11.8 at 40 Gy.

Early menopause seems to have a protective effect on radiation-associated breast cancer, because of either alkylating agent chemotherapy or radiation dose greater than 5 Gy administered to the ovaries.[34,35] The Dutch study specifically showed that the breast cancer risk reduction associated with chemotherapy was secondary to the high number of women who developed premature menopause.[34] This case-control study showed that women who experienced menopause at 19 to 35 years of age had a significantly decreased risk for developing breast cancer compared with women who did not undergo premature menopause (relative risk, 0.06; 95% CI, 0.01–0.45).[34] Results suggest that ovarian hormones play an important role in promoting tumorigenesis once an initiating event is produced by radiation. However, alkylating chemotherapy's protective effect against breast cancer is less evident in survivors of childhood HL,[38,57] which may be related to the larger reserve of oocytes and follicles in girls, and perhaps differences in types of alkylating agents and doses between pediatric and adult patients.

The data on breast cancer risk after radiotherapy for HL were based on patients treated in an era during which large treatment fields and very high radiation doses were used. In contrast, radiation treatment fields are significantly smaller, with the current standard of involved-field radiation therapy given as part of combined modality therapy. Moreover, current studies are also exploring the effect of further reductions in radiation treatment dose for HL, and a trend exists toward the application of involved-node radiation therapy, both of which will result in additional reductions in the exposure of normal tissue to radiation.[58] Therefore, patients with HL who undergo radiotherapy in the modern treatment era will probably incur a lower risk for breast cancer.

For survivors of HL, NCCN recommends mammogram/breast MRI screening 8 to 10 years after irradiation or by 40 years of age. The American Cancer Society currently recommends yearly breast MRI imaging as an adjunct to mammography in women who underwent chest radiation between 10 and 30 years of age.[59] Prospective trials evaluating the role of breast MRI screening in women who underwent mantle or mediastinal radiotherapy for HL are ongoing at the Dana-Farber Cancer Institute and M. D. Anderson Cancer Center.

Contralateral Breast Cancer After Radiation Therapy

In an overview of randomized trials on surgery with or without radiotherapy for early-stage breast cancer, the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) showed that improvement in locoregional control with the addition of radiation therapy resulted in a significant reduction in 15-year breast cancer–specific and overall mortality.[60] Therefore, radiation therapy is expected to continue to play an important role in the curative treatment for breast cancer, either as part of breast conserving therapy or given as postmastectomy chest wall irradiation in high-risk patients.

One long-term effect of radiation therapy is an increased risk for second malignancy, including risk for contralateral breast cancer, which accounts for 40% of all second tumors among women with breast cancer, with a 25-year cumulative risk of 6.9%.[61] Although these excesses are largely related to preexisting breast cancer risk factors, prior radiation therapy, especially treatment at a young age, may contribute to the increased risk.[28–30,62]

In early case-control studies by Storm et al.[33] and Boice et al.,[62] the overall relative risk for contralateral breast cancer was not significantly increased after radiation therapy (relative risk, 1.2; 95% CI, 0.94, 1.2). However, among women younger than 45 years at irradiation, Boice et al.[62] showed that the relative risk for breast cancer was significantly elevated at 1.6 (95% CI, 1.1–2.4).

A recent Dutch study[32] assessed the long-term risk for contralateral breast cancer in 7425 survivors of breast cancer. Similar to the earlier studies, the overall relative risk for contralateral breast cancer for those who underwent radiation therapy was not significantly elevated compared with those who did not (after adjusting for family and smoking histories). However, in patients who underwent radiation therapy before 35 years of age, the hazard ratio for contralateral breast cancer was 1.78 (95% CI, 0.85–3.72), and decreased to 1.09 (95% CI, 0.82–1.45)

among women irradiated at 45 years or age or older.

Stovall et al.[25] conducted a multi-institutional case-control study of 708 women with contralateral breast cancer, matched with 1399 controls. Among women younger than 40 years, those who received more than 1 Gy of radiation had a 2.5-fold (95% CI, 1.4–4.5) greater risk than unexposed women, whereas no excess risk was observed for women older than 40 years treated with radiotherapy. In contrast, the EBCTCG study[60] found a significantly increased risk for contralateral breast cancer after radiotherapy (relative risk, 1.4; $P = .00001$), and remained statistically significant among women older than 50 years at treatment (relative risk, 1.3; $P = .002$).

Studies have also shown that the risk for contralateral breast cancer in breast cancer survivors is significantly associated with radiation dose, although the association was mainly limited to younger women. In the case-control study by Stovall et al.,[25] women younger than 40 years had an excess relative risk of 0.6 per Gy (95% CI, 0.1–1.5), and those younger than 40 years who had at least a 5-year latency had an excess relative risk of 1 per Gy (95% CI, 0.1–3.0). In the Dutch study,[32] among women younger than 45 years at irradiation, a significant dose–response relationship was also observed, with a linear excess relative risk of 0.21 per Gy increase (P trend, .03). The relationship was stronger for risk of medially located contralateral breast cancer, with a linear excess relative risk of 0.37 per Gy (P-trend, .01). In addition, women treated with postlumpectomy radiation (which was associated with higher doses to the contralateral breast) had a significantly 1.5-fold increased risk for contralateral breast cancer compared with patients treated with postmastectomy radiation therapy.

Conclusions

Epidemiologic data on historical cohorts of women exposed to various forms of ionizing radiation have provided a valuable foundation on the relationship between radiation exposure and subsequent breast cancer risk. Although radiation therapy is now rarely used to treat benign conditions, it remains a key modality in the management of many patients with cancer, including children and young adults. The cumulative risk for subsequent breast cancer in these patients[37] should be taken into consideration both during initial treatment decisions and implementation of follow-up strategies. Future directions include the development of radiation techniques and treatment strategies to minimize dose to breast tissue, and the identification of underlying susceptibility factors[50–52] and modifying influences.[5,13,16,34,35,63] Moreover, the molecular and pathologic features[44,64] of radiation-associated breast cancer should continue to be characterized. Furthermore, in this era of rapidly advancing molecular technologies, which include genome-wide association studies and next-generation sequencing, application of these techniques might help identify women at highest risk for radiation-associated cancer. In the interim, breast cancer screening and prevention programs should be implemented for long-term cancer survivors who undergo chest radiotherapy, along with efforts directed toward educating patients and health care providers.[65]

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