

Radiotherapy in the Treatment of Hereditary Breast Cancer

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Hereditary breast cancer represents approximately 5% to 10% of breast cancers and a larger portion of patients with early-onset disease. Given the relatively recent identification of the BRCA1 and BRCA2 genes, the available literature with respect to outcomes related to radiation therapy has inherent limitations with relatively small patient numbers and a lack of prospective randomized trials. There is, however, a growing body of literature describing treatment and toxicity outcomes in patients undergoing radiation therapy after breast-conserving surgery and after mastectomy for breast cancer patients who have BRCA1 and BRCA2 mutations. Acknowledging the limitations in the available data, there does not appear to be any evidence of more severe normal tissue reactions or compromised long-term survival rates in women electing breast-conserving surgery and radiation. These studies are reviewed in this article. Outcomes related to radiation therapy in patients with variants in other breast cancer-related genes, such as p53, ATM, CHEK2, PALB2, and PTEN, are even less well documented because of the paucity of data. Available reports on radiation-related outcomes in these and single nucleotide polymorphisms in radiation repair and response genes are discussed.

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Hereditary breast cancer accounts for 5% to 10% of all breast cancers, with most cancers associated with germline BRCA1 and BRCA2 mutations.¹⁻³ Roughly 1 in 500 Americans are carriers of a deleterious BRCA1/2 mutation, and having a mutation places a woman at a 50% to 80% lifetime risk of a diagnosis of breast cancer and a 15% to 40% risk of ovarian cancer. Increased risks of other cancers have also been reported, including colon, prostate, pancreas, melanoma, stomach, and fallopian tube carcinomas. Male breast cancers are also observed in BRCA 2 families.

The hallmark of BRCA1/2-associated breast cancer is early onset disease, with cancer often diagnosed before age 50, particularly for cancers associated with BRCA1 mutations. The development of contralateral breast cancer is also increased in BRCA1/2 carriers, with bilateral cancers reported in up to 65% of BRCA1-associated breast cancers and up to 50% with BRCA2 mutations. In a review by the Breast Cancer Linkage Consortium of the pathology of familial breast cancer, BRCA 1-associated breast cancers were typically high grade with high mitotic

counts and less tubule formation compared with sporadic cases.⁴ Subsequent studies have also shown higher rates of p53 expression and the cancers to be associated with negative estrogen and progesterone receptors and lack of Her-2-neu over-expression.^{5,6} BRCA1-associated cancers are associated with the basal epithelial type. Medullary or atypical medullary cancers are more common among BRCA1-associated breast cancers compared with sporadic cases, whereas BRCA2-associated breast cancers have a similar frequency of medullary disease. BRCA2-associated cancers tend to be estrogen and progesterone receptor positive, and patients have survivals comparable to cancers associated with sporadic disease. Survival data are less clear with BRCA-1-associated breast cancer.⁷⁻¹¹

The BRCA1 and BRCA2 genes were identified and sequenced in 1994 and 1995, respectively, after analyses of families at high risk for breast and ovarian cancers.¹²⁻¹⁴ These genes appear to function as classic tumor suppressor genes in that only 1 defective copy in the germline confers cancer susceptibility but both copies are absent in malignant cells. These genes encode large proteins, with the BRCA1 protein consisting of 1863 aa and the BRCA2 protein 3418 aa. The exact functions of these proteins are unclear, but they appear to be intimately involved in DNA repair and recombination, cell cycle control, and the maintenance of genomic stability.¹⁵ Evidence is mounting that indicates a defective homologous recombination pathway, rerouting DNA repair through er-

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ror-prone pathways. Although a full discussion of the likely cellular alterations associated with BRCA1/2 mutations is beyond the scope of this article, the implications of radiation treatment that causes DNA damage must be considered both with respect to its effect upon normal tissue (with a single mutation) and upon the tumor (with 2 mutated genes). Both normal tissue toxicity and tumor control after radiotherapy are discussed.

Toxicity in BRCA1/2 Carriers Treated With Radiotherapy

Studies have been performed reporting complication rates in women with BRCA1/2-associated cancers and women with sporadic disease treated with radiotherapy.^{16,17} A retrospective cohort study from Pierce et al¹⁶ compared radiation-associated complications in 71 North American women with a BRCA1/2 mutation with early-stage breast cancer treated with breast-conserving surgery and radiotherapy with complications observed in 213 women with sporadic breast cancer. Complications recorded in the medical records at the time of treatment and during follow-up were collected and reported using the Radiation Oncology Group (RTOG) acute radiation morbidity scoring criteria. With a median follow-up of 5.3 years in the BRCA1/2 carriers and 4.6 years for women with sporadic disease, there was no difference in acute toxicity in skin and the lung in BRCA1/2 carriers compared with women with sporadic disease. Incidence of breast pain was also comparable between groups. The incidence of chronic adverse events at 5 years was reported using the RTOG/European Organization for Research and Treatment of Cancer late radiation morbidity scoring scheme. There were no significant differences in toxicity in the skin, subcutaneous tissue, lung, and bone between women with and without known BRCA1/2 mutations.

A second study by Shanley et al¹⁷ used a similar design and consisted of results in 55 BRCA1/2 mutation carriers from 4 centers across the United Kingdom who were matched with sporadic controls. Neither this study nor the study by Pierce et al¹⁶ required negative BRCA1/2 testing in patients in the control group. Both studies, however, excluded women from the control group with a family history of more than 1 postmenopausal relative with breast cancer or any family history of ovarian cancer. The likelihood of undetected BRCA mutations was thought to be 5% or less using these exclusion criteria. Most carriers (78%) in this study were treated with wide local excision and radiotherapy; a minority received mastectomy. The Shanley study used a 1:1 match rather than a 1:3 match as in the earlier study, and carriers were matched to controls using multiple variables including age at diagnosis, stage, type of surgery, radiation fields, fractionation schedule, use of chemotherapy, and length of follow-up. Although this study was retrospective, patients were interviewed in follow-up by 1 clinician, and photographs and examinations for late effects were performed by the lead author.

With a median follow-up of 6.75 years for BRCA1/2 carriers

and 7.75 years for controls, toxicities were comparable between groups. The rate of breast pain was increased in BRCA1/2 carriers ($P = .03$), but this was not accompanied by an increase in erythema as determined by patient recall or examination of the charts. The radiation course was interrupted because of skin reactions in only 1 patient in each group. Other measures of acute toxicity (breast erythema, moist desquamation, and fatigue) were not significantly different. Late effects (rib fractures, lung fibrosis, soft-tissue/bone necrosis, and cardiac fibrosis) were also not significantly different between carriers and controls. Thus, these 2 series show comparable acute and late effects in women known to have a deleterious BRCA1/2 mutation and sporadic controls. These data strongly suggest that radiation should not be withheld from germline BRCA1/2 carriers because of toxicity concerns for those who have indications for treatment.

Breast-Conserving Surgery and Radiotherapy in BRCA1/2 Carriers Diagnosed With Breast Cancer

Multiple randomized trials have proven the equivalence in survival between breast-conserving surgery with radiotherapy and mastectomy in early-stage disease. Given the older average age of trial participants, these trials most likely enrolled women with sporadic rather than hereditary breast cancer. Whether breast conservation is an appropriate option for women with known deleterious BRCA1/2 mutations is an area of active research. Because it is unlikely a randomized trial comparing mastectomy with breast-conserving therapy in BRCA1/2 carriers will be conducted in the near future, we must rely on retrospective reports to attempt to answer this question. However, results from retrospective series can be affected by factors such as small sample size, limited follow-up, and ascertainment bias or confounded by factors that affect local recurrence such as margin status, radiation dose, and so on. These limitations should be considered when interpreting results.

Despite these limitations, consistent findings between series have emerged (Table 1). Most of these studies suggest a greater increase over time in the risk of an in-breast recurrence in women known to have a BRCA1/2 mutation compared with sporadic controls. This was shown most clearly in the study by Haffty et al.²⁰ One hundred twenty-seven women diagnosed with breast cancer by 42 years of age agreed to undergo genetic testing, and 22 were found to have BRCA1/2 mutations. Women in the control group were tested and known to not have a germline BRCA1/2 mutation. Patients in the BRCA1/2 group were younger than the women in the control group. No patient received either tamoxifen or underwent oophorectomy.

With 12 years of follow-up, the genetic group had significantly higher rates of in-breast tumor events than the control group (49% vs 21%, $P = .007$). Rates of recurrence were

Table 1 Breast-Conserving Surgery and RT in BRCA 1/2 Carriers Compared With Controls

Author	Number of BRCA 1/2 Patients	Rates of Local Recurrence (%)			
		Genetic	Sporadic	P	Years
Garcia-Etienne ¹⁸ (Milan)	54	11 (crude)	2.5		4
		15	4	.03	5
Seynaeve ¹¹ (Rotterdam)	26 (87 HBC)	14	7		5
		30	16	.05	10
Robson ¹⁹ (MSK)	28	22	6.9	.25	10
Haffty ²⁰ (Yale)	22	49	21	.007	12
Kirova ²¹ (Curie)	27	36	33	0.42	13
Pierce ²² (Collaborative)	160	12	9	.19	10
		24	17		15

Abbreviation: HBC, hereditary breast cancer.

similar until approximately year 6, after which significantly more recurrences were observed in the genetic group. Nine of the 11 recurrences in the breast were in a different location or of a different histology than the original cancer, which is suggestive of the development of a new cancer rather than a true recurrence. Rates of contralateral events were also significantly higher in BRCA1/2 carriers compared with the sporadic controls (42% vs 9%, $P = .001$). Multivariate step-wise Cox regression analysis adjusted for age identified BRCA1/2 mutation status to be an independent predictor for both ipsilateral and contralateral breast events ($P = .003$). A recent study by Garcia-Etienne et al¹⁸ also showed a statistically significantly higher risk of local ipsilateral breast cancer events in 54 BRCA1/2 patients treated with breast-conserving surgery and radiation with a more limited follow-up. With a follow-up of 5 years, they reported a local relapse rates of 15% in BRCA1/2 carriers compared with 4% in sporadic controls ($P = .03$).¹⁸

Other studies have not shown BRCA1/2 status to be an independent predictor of ipsilateral breast tumor recurrence. A study by Robson et al¹⁹ comparing outcomes between carrier and noncarrier Ashkenazi women treated with breast-conserving therapy found nonsignificant increased rates of ipsilateral breast tumor recurrence in mutation carriers (ie, 22% and 6.9%, respectively, at 10 years, $P = .25$). Age was the only factor that independently predicted for in-breast tumor recurrence, with younger patients (<50 years at diagnosis) having a 2.5-fold relative risk of recurrence. Mutation status was, however, the only factor significant for contralateral breast events (relative risk [RR] = 3.5). Studies from the Institute Curie have not found BRCA1/2 carriers to be at significantly increased risk for local recurrence compared with women with sporadic breast cancer. With a median follow-up of 8.8 years, the crude rates of local breast tumor recurrence in 27 BRCA1/2 carriers and 261 women with sporadic breast cancer were 24% and 19% ($P = .47$).²³ Age was again identified as the most important factor for ipsilateral breast tumor recurrence. A recent update with a 13.4-year median follow-up reported rates of ipsilateral recurrence of 36% for 27 BRCA1/2 carriers and 33% for 261 controls ($P = .42$), with age as the only significant predictor of recurrence.²¹

Differences in modifiers of breast cancer risk may, in part,

explain the differences observed in the rates of in-breast tumor recurrence between series. With the significant reduction in risk for ovarian cancer after oophorectomy in the BRCA1/2 carrier population, oophorectomy is generally recommended. Oophorectomy has also been shown to reduce the risk of developing breast cancer in patients with BRCA1/2 germline mutations by approximately 50%,²⁴ with recent studies showing significant reductions in BRCA2-associated estrogen receptor-positive cancers.²⁵ Risk reduction with tamoxifen in BRCA1/2 carriers has also been shown although the reductions shown thus far are modest. A small subset analysis of the National Surgical Adjuvant Breast and Bowel Project P01 Breast Cancer Prevention Trial suggested a nonsignificant reduction in developing breast cancer with tamoxifen in BRCA2 carriers.²⁶

A collaborative analysis by Pierce et al²² of 160 mutation carriers identified by investigators at 11 institutions in the United States, Canada, and Israel was performed with results compared with outcomes in 445 women with sporadic disease.²² The median follow-up was 7.9 years for carriers and 6.7 years for control cases. Overall, there was no significant difference in rates of ipsilateral breast tumor recurrence at 10 and 15 years, with rates of 12% and 24% for carriers and 9% and 17% for controls ($P = .19$). Upon multivariate analysis, lack of chemotherapy use and young age were independent predictors of ipsilateral tumor recurrence; BRCA one-half status was not. However, when patients who had undergone oophorectomy were removed from the analysis, BRCA1/2 status was an independent predictor for recurrence, with rates of recurrence almost 2-fold higher in germline carriers compared with women with sporadic disease. Analyses of contralateral breast events were significantly higher for BRCA1/2 carriers at 10 and 15 years than controls, with estimates of 26% and 39% for carriers and 3% and 7% for sporadic controls ($P < .0001$). Multivariate analysis indicated BRCA1/2 status to be a powerful predictor for developing contralateral breast cancers regardless of oophorectomy, with a hazard ratio in excess of 10. Tamoxifen was associated with a significant reduction in contralateral breast cancer risk (hazard ratio = 0.31, $P = .05$). Thus, these results are consistent with the findings by Haffty et al²⁰ who observed increased rates of ipsilateral and contralateral breast events in the absence of oophorectomy and tamoxifen.

Mastectomy in BRCA1/2 Carriers With Breast Cancer

Although outcome after breast-conserving surgery and radiotherapy in BRCA1/2 carriers has been the focus of many reports, limited information is available on the rates of locoregional recurrence among patients with BRCA1/2-associated breast cancer treated with mastectomy. The risk reduction with prophylactic mastectomy in patients known to have a deleterious BRCA1/2 mutation, however, has been well documented. Hartmann et al²⁷ showed a 90% minimum reduction in developing breast cancer with prophylactic bilateral mastectomy in 18 BRCA1/2 carriers with over a 13-year median follow-up.

In a prospective series from Rotterdam, the Netherlands, by Meijers-Heijboer et al²⁸ of 76 BRCA1/2 mutation carriers who underwent prophylactic mastectomy, no cases of breast cancer were diagnosed with 2.9-year follow-up.²⁸ An expanded update of this series with 236 BRCA1/2 carriers and 4.5-years follow-up again indicated no primary breast cancers after prophylactic mastectomy and 1 patient diagnosed with metastatic breast cancer.²⁹ Rebbeck et al³⁰ reported outcomes in 483 BRCA1/2 carriers treated with and without bilateral prophylactic mastectomy and found a 1.9% incidence of breast cancer among those who underwent prophylactic mastectomy compared with a 49% incidence in matched controls. This was equal to a 90% reduction with prophylactic mastectomy only and a 95% reduction with mastectomy and oophorectomy.

Thus, it is clear that prophylactic mastectomy significantly reduces the risk of subsequent breast cancer in BRCA1/2 carriers without a diagnosis of breast cancer. However, in BRCA1/2 carriers with a breast cancer diagnosis, locoregional results from large studies are lacking. In a series from Columbia University by El-Tamer et al³¹ of 17 BRCA1, 13 BRCA2, and 216 sporadic breast cancer patients, rates of locoregional failure were not significantly different between the 3 groups, with estimates of 5.9% for BRCA1 carriers, 0% for BRCA2 carriers, and 3.7% for patients with sporadic disease with a 50-month median follow-up. Eccles et al³² from Southampton University, Southampton, United Kingdom, reported a 10.3% rate of loco-regional failure among 39 BRCA1/2 carriers compared with 16.5% among patients with a negative family history.

A study reporting the outcome of BRCA1/2-associated breast cancer in 655 carriers treated with either breast conservation or mastectomy was recently presented at the 2009 San Antonio Breast Cancer Symposium.³³ In this nonrandomized analysis, all patients were known to have a deleterious BRCA1/2 mutation; there were no sporadic controls. Three hundred two patients from 10 institutions in the United States, Israel, Spain, and Australia were treated with breast-conserving surgery and radiotherapy, and 353 were treated with mastectomy. Clinical data were abstracted from medical records or self-reported. The median follow-up of the breast-conservation patients was 8.2 and 8.9 years for mastectomy patients. Rates of local failure as first failure were

23.5% for the breast-conservation patients and 5.5% for patients treated with mastectomy at 15 years ($P < .0001$). Multivariate analysis found the choice of local therapy (breast conservation vs mastectomy) to be the single significant predictor of local recurrence, with patients treated with breast conservation at a 4.5-fold increased risk of local failure compared with mastectomy. Within the breast-conservation group, however, the use of chemotherapy was shown to significantly reduce the risk of local failure, with those patients not receiving adjuvant chemotherapy at a 5.4-fold increase in the risk of recurrence compared with those treated with chemotherapy. When breast cancer-specific and overall survivals were compared despite significant differences in local control, no differences were observed in overall survival. Although these results need to be confirmed, the similar survivals suggest the breast cancer events in the treated breast were more likely new cancers rather than true recurrences. Ideally, comparisons between patients treated with breast conservation and mastectomy should be randomized. However, in the absence of randomized data, retrospective comparisons are helpful but should be interpreted with caution.

Contralateral Breast Cancers

As previously noted, the risk of contralateral breast cancers in BRCA1/2 germline carriers is high, with bilateral breast cancer occurring in up to 65% of mutation carriers. Thus, it is important to study factors that could modify this risk. Hoonig et al³⁴ retrospectively studied the effect of radiotherapy, chemotherapy, and family history upon contralateral breast cancer risk in patients who were not known to be carriers but were young when diagnosed with breast cancer and thus at risk for having a germline mutation. Chemotherapy was associated with a nonsignificant reduction in the risk of contralateral breast cancer in the first 5 years. In the overall analysis, radiotherapy was not associated with a significant difference in risk of contralateral cancers. However, in a subset of patients younger than 45 years of age with a strong family history (defined as 3 or more relatives with breast cancer) treated with breast-conserving surgery and radiotherapy, the risk of contralateral breast cancer was significantly increased, suggesting an effect of scatter irradiation. An increase in contralateral breast cancers in BRCA1/2 carriers treated with radiotherapy was not shown, however, by Metcalfe et al.³⁵ Oophorectomy was associated with a significant reduction in contralateral breast cancer risk, and radiation was not associated with an increased risk. Univariate and multivariate analyses showed a nonsignificant reduction in contralateral breast cancers after radiotherapy, with hazard ratios of 0.77 and 0.86, respectively. In the recent collaborative, Pierce et al³³ did not find a significant difference in rates of contralateral breast cancers when using radiotherapy or at 15 years. However, continued follow-up of this issue is needed, and treatment planning techniques that minimize scatter to the opposite breast should be routinely applied for all patients.

Table 2 Genes Associated With Hereditary Breast Cancer: Outcomes With Radiation Therapy

Gene/Syndrome	Approximate Relative Breast Cancer Risk	Comments Relevant to Radiation Therapy
BRCA1/BRCA2	10-20 times relative risk	No evidence of increased complications/toxicity Risk of development of new primary tumors in conservatively treated breast may be elevated, but appears to be modified by oophorectomy, tamoxifen and chemotherapy.
P53-Li-Fraumeni	2-6 times relative risk	Anecdotal reports of increased risk of second malignancies in irradiated field. Laboratory evidence of increased radiation sensitivity.
PTEN Cowden	2-4 times risk	Conflicting reports regarding increased risk of fibrosis in some heterozygotes. Possible elevated risk of contralateral events in carriers who had previous radiation Homozygous affected individuals have significantly increased radiation sensitivity of normal tissues
STK11 Peutz-Jeghers	10-15 times risk	
ATM (ataxia-telangiectasia)	3-4 times risk	
CHEK2	2 times risk	Local control appears to be similar in carriers and noncarriers Possible higher risk of contralateral events in carriers who had previous radiation.
BRIP1–Fanconi’s anemia	2 times risk	Reports of adverse reactions and hypersensitivity to radiation
PALB2	2-3 times risk	

Summary of BRCA1/2 and Local-Regional Management of Breast Cancer

The decisions behind the choice of local treatment in women with BRCA1/2-associated breast cancer are complex. Although randomized trials comparing breast-conserving surgery and radiotherapy with mastectomy have shown comparable outcomes in women with sporadic breast cancer, randomized comparisons do not exist for women with germline mutations and are not likely to be conducted given the personal nature of the surgical decision-making process. Acknowledging the limitations of the available data, results to date suggest increased risks of in-breast tumor events over time in patients treated with conserving surgery and radiotherapy but no evidence of decreased long-term survival rates in women electing breast conservation compared with mastectomy. Furthermore, data suggest risk reductions in breast cancer events with chemotherapy and hormonal therapies in women treated conservatively. More study, however, is needed. Finally, studies do not suggest increased rates of toxicity in germline BRCA1/2 carriers treated with radiotherapy compared with women with sporadic disease. Radiotherapy should not be withheld when indicated for optimal cancer management.

Radiotherapy in Other Genetic Syndromes and Single Nucleotide Polymorphisms

There are limited data regarding the management of breast cancers in patients with other genetic syndromes or with polymorphisms and other genetic variants. Although BRCA1

and BRCA2 account for the majority of known hereditary breast cancer patients, there are several other genetic conditions that are associated with an increased breast cancer risk.³⁶ Fortunately, these genetic conditions are rare, and, therefore, there is a paucity of data regarding breast cancer management and specifically radiotherapeutic management in patients with these conditions. Table 2 lists a number of genetic syndromes known to be associated with an increased risk of breast cancer. Because many of the genes involved in these syndromes are associated with both increased breast cancer risk and potentially DNA repair and radiation response, there are potential concerns regarding radiation treatment. Fortunately, the syndromes are rare, and, overall, there are few reports of adverse outcomes with radiation treatment. There are, however, several reports showing concerns regarding radiation therapy in selected patients with these genetic syndromes.

Li-Fraumeni Syndrome

Li-Fraumeni syndrome, which is a result of a deleterious heterozygous mutation in the p53 gene, has been reported to be associated with increased risks of secondary malignancies within the irradiated field.³⁶ Limacher et al³⁷ reported 2 metachronous cancers in the irradiated field of a Li-Fraumeni patient. This observation is consistent with theoretic and laboratory data that support the hypothesis that germline p53 mutations lead to the impairment of p53 function and facilitate radiation-induced carcinogenesis.³⁸ Although the available clinical data remain anecdotal, this suggests that one should be extremely judicious when considering the risk/benefit ratio of radiation therapy in patients with Li-Fraumeni-associated breast cancers.

ATM

Patients who are homozygous for ATM mutations and phenotypically express the disease ataxia telangiectasia have been shown to be exquisitely radiation sensitive and clearly should avoid radiation treatment if possible.³⁹ Both clinical and laboratory data confirm exquisite radiation sensitivity in patients with ataxia telangiectasia.³⁹ There are mixed and inconsistent reports regarding patients who have heterozygous mutations in ATM.⁴⁰⁻⁴⁵ Although there have been reports of higher rates of fibrosis in these patients, these results have not been confirmed in other studies. Ho et al⁴⁰ reported that patients with a specific sequence variant in ATM may be associated with late radiation fibrosis. Edvardsen et al⁴³ also observed some associations with adverse normal tissue toxicities associated with ATM variants. No association with ATM variants was observed with local relapse in that study. Bremer et al⁴⁴ reported on 1,100 patients in whom 11 were heterozygous for a pathogenic mutation in ATM. No adverse radiation effects were observed in these patients compared with the control group without mutations.

In a recent study by Bernstein et al⁴⁵ of women enrolled in the WECARE study, there was a small but statistically significant elevated risk of contralateral breast cancers in women exposed to radiation for a first breast cancer who were heterozygous for deleterious mutations in ATM. Fortunately, these were in patients with known pathogenic mutations, which are rare. Further studies are needed to determine the clinical significance of polymorphisms in ATM and other genes as they relate to outcomes.

CHEK2

In a study of 150 early-stage breast cancer patients treated with breast-conserving surgery and radiation, Meyer et al⁴⁶ reported no increased risk of local relapse or complications in patients with a germline mutation in CHEK2. Of the 150 patients, 25 had germline mutations in 1 of the 3 CHEK2 genes. Local relapse rates in carriers and noncarriers were similar although distant metastasis was higher in the CHEK2 carriers.

Broeks et al⁴⁷ evaluated a specific mutation in CHEK2 (1100 delC) and reported an elevated risk of contralateral breast cancers in affected carriers of this gene. Of note, the excess risk was predominantly observed in the patients who had received radiation for their first breast cancer and suggested a potentially important interaction between CHEK2 mutation status and radiation treatment in the development of contralateral breast cancers.

There are limited data regarding breast cancer outcomes in patients with the other genetic syndromes (Table 2). Patients with known deleterious mutations in genes that are involved in DNA repair and radiation response, however, may be at an increased risk of complications and clearly require further study and careful consideration when weighing the risks and benefits of radiation treatment.³⁹

Single Nucleotide Polymorphisms in High-Frequency Low-Penetrance Genes

The mapping of the human genome has opened an entire new area of investigation regarding the genetic implications of cancer epidemiology, etiology, prognosis, and response to treatment.^{48,49} A broad spectrum of single nucleotide polymorphisms has been reported. Many of these polymorphisms result in amino acid changes in the protein products of these genes and may or may not have biological and/or clinical significance. These polymorphisms can be relatively common, affecting 10% to 30% of the population, and therefore may have significant implications. A recent example of this is the identification of polymorphisms in CPY2D6.⁵⁰ Up to 10% of the population is homozygous for a polymorphism that results in poor metabolism of tamoxifen and may not respond as well to the drug. Although the clinical implications of testing for this remain controversial, this is an example of the potential clinical implications of genetic analysis and how medicine is becoming increasingly personalized.

There are large numbers of genes that have been shown to directly relate to radiation response through DNA repair or other radiation response pathways. Genes in the p53 pathway, 53BP1, MDM2, ATM, TGF- β , Bcl-2, and others are all critical to radiation response.^{39,51-54} Known common polymorphisms in these and other genes have been identified that result in amino acid changes and may or may not be biologically and/or clinically significant. Researchers are only beginning to scratch the surface regarding the prognostic and therapeutic implications of these polymorphisms. However, there have already been reports of poorer survival rates, a poorer response rate, and increased complication rates in patients with selected polymorphisms in several of these genes.^{39,51-56}

There have been limited reports evaluating outcomes in patients after radiation therapy for breast cancer. In a pilot study, Haffty et al⁵⁷ recently showed slightly higher local relapse rates in patients homozygous for a polymorphism in 53BP1. Although this was significant in univariate analysis, it did not hold true in multivariate analysis, and further studies will be necessary to determine the clinical and biological significance of these findings. Furthermore, further basic science studies will be required to understand if and how these specific polymorphisms alter the biological response to radiation.

Summary of Non-BRCA1/2 Genetic Variants and Outcomes Related to Radiation

Given the rarity of non-BRCA1-BRCA2-associated hereditary breast cancer, there are limited data regarding the implications of radiation treatment. Despite the fact that many of the genes associated with these syndromes are involved in DNA repair and radiation response pathways, data on ad-

verse outcomes with the appropriate use of therapeutic radiation remain conflicting. Given the rarity of these conditions, it is likely that data will continue to be limited to anecdotal experiences and retrospective series as noted previously.

The potential radiotherapeutic implications of the more common low-penetrance but high-frequency polymorphisms, which can affect much larger segments of the population, will continue to unfold as we strive to link clinical data, including acute and chronic toxicities, local-regional control and secondary malignancies, to a broad range of genes involved in DNA repair and radiation response.

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