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Ionizing Radiation Exposure and Basal Cell Carcinoma Pathogenesis

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Abstract

This commentary summarizes studies showing risk of basal cell carcinoma (BCC) development in relationship to environmental, occupational and therapeutic exposure to ionizing radiation (IR). BCC, the most common type of human cancer, is driven by the aberrant activation of hedgehog (Hh) signaling. *Ptch*, a tumor suppressor gene of Hh signaling pathway, and Smoothened play a key role in the development of radiation-induced BCCs in animal models. Epidemiological studies provide evidence that humans exposed to radiation as observed among the long-term, large scale cohorts of atomic bomb survivors, bone marrow transplant recipients, patients with tinea capitis and radiologic workers enhances risk of BCCs. Overall, this risk is higher in Caucasians than other races. People who were exposed early in life develop more BCCs. The enhanced IR correlation with BCC and not other common cutaneous malignancies is intriguing. The mechanism underlying these observations remains undefined. Understanding interactions between radiation-induced signaling pathways and those which drive BCC development may be important in unraveling the mechanism associated with this enhanced risk. Recent studies showed that Vismodegib, a Smoothened inhibitor, is effective in treating radiation-induced BCCs in humans, suggesting that common strategies are required for the intervention of BCCs development irrespective of their etiology.

INTRODUCTION

This commentary focuses on epidemiological studies reporting exposure to ionizing radiation (IR), a known human carcinogen (1), in various populations and the relationship with basal cell carcinoma (BCC) development. Possible mechanism underlying the pathogenesis of radiation associated BCC development are also discussed, including, the effect of radiation on DNA damage and subsequent complex cellular responses, cell signaling pathways that are involved in the chronological progression of radiation-induced tumor lesions, and other factors that can modify susceptibility to radiation-induced BCCs.

Basal cell carcinoma of the skin, the most common type of human cancer, is characterized by mutations in *Ptch* and/or *Smoothened* genes permitting the aberrant activation of sonic hedgehog (Shh) signaling, a driver signaling pathway of neoplastic growth (2, 3). P53 mutations are also prevalent in human BCC (4, 5). The major risk factor for BCC

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development is chronic exposure to nonionizing solar radiation, specifically UVA and UVB (3). Fair skin and chronic immuno-suppression are important risk factors, particularly for UVB-induced carcinogenesis. Exposure to chemicals such as arsenic may also lead to BCC development (6). Patients with autosomal dominant genetic syndrome known as basal cell nevus syndrome (BCNS) or nevoid basal cell carcinoma syndrome (NBCCS) or Gorlin Syndrome have substantially augmented susceptibility to multiple BCCs, particularly for sun-exposed areas of the body, such as the head, neck, forearms, etc. These patients carry germline mutation in the tumor suppressor gene *PTCH* (2). It is known that one copy of the *PTCH* gene is mutated during the embryonic development and the other copy is lost during adulthood (7). Interestingly, genetic background seems to be another determining factor for both the susceptibility to BCC risk and other syndrome-associated phenotypes (8). Caucasians generally manifest the highest incidence of BCCs. There are estimates that one out of every three people born in the United States after 1994 will develop at least one BCC in their lifetime (3, 9). The U.S. alone records 2.8 million new diagnoses for BCCs every year (10). In addition to the factors stated above, exposure to radiation is another established risk factor for the development of BCC.

Epidemiological studies have substantially promoted the understanding of radiation-induced skin carcinogenesis (11). The first evidence for carcinogenic potential of ionizing radiation is based on a case report in 1902, which described development of non-melanoma skin cancers on the hands of radiation workers (12). Since then, an increased incidence of skin cancer associated with exposure to radiation has been reported in various populations, including atomic bomb survivors, uranium miners, radiologists, interventional cardiologists, and individuals treated with radiation in childhood for tinea capitis and malignant tumors (11, 13, 14) (Table 1). Nearly all of these reports indicate that exposure to radiation enhances the risk of BCC incidence, as opposed to melanoma or squamous cell carcinoma (SCC). The mechanism underlying differential responses of basal cells and squamous cells to radiation mediated malignant transformation still remains unclear (15–18).

BCCs in Atomic Bomb Survivors

The atomic bombs detonated over Hiroshima and Nagasaki exposed the population to both gamma rays and neutrons (19). Epidemiological studies among atomic bomb survivors residing in Hiroshima and Nagasaki have provided valuable data about the dose-response relationship between ionizing radiation and risk of skin cancer development (18). The incidence of BCCs among the population that received the highest dose was significantly elevated after 30 years, and remained so after 50 years, indicating a need for life-long follow-up for increased skin cancer occurrence in these atomic bomb survivors (18). These studies demonstrate that BCC development was correlated with radiation from atomic bomb exposure. However, the relative risk (RR) for other skin cancers such as SCC and melanoma remained largely unchanged (18). The BCC incidence rate shows a dose-response relationship decreasing significantly with distance from the hypocenter (20). There is an excess relative risk (ERR) per Gy of 0.48 for subjects receiving doses less than 1 Gy, whereas ERR climbs to 2.64 per Gy for those who absorbed greater than 1 Gy (21). Age at exposure was also found to be a significant modifier of response among atomic bomb survivors. The estimated ERR per Gy for age at exposure of 0–9, 10–19, and 20–39 years

were 15, 5.7, and 1.3, respectively. No apparent increased risk of BCC was observed for those aged 40 years or older at the time of detonation (17, 18). Importantly, the excess absolute risk (EAR) of BCC per unit skin surface area attributable to atomic bomb radiation is similar between UV-exposed and shielded parts of the body, indicating an additive radiation-related risk above the background BCC rate (22, 23).

Given the fact that Asians are at lower risk for BCCs compared with Caucasians, it is difficult to extend the relative risk for BCCs calculated for atomic bomb survivors to other exposed populations of the world. DNA damage response (DDR) was activated in the epidermis surrounding BCCs of exposed individuals. This suggests genomic instability as a molecular basis of radiation-induced BCCs (20). Genetic alterations in tumor suppressor genes including *Ptch* and *p53* have been correlated with atomic bomb exposure, and the frequency of *Ptch* and *p53* mutations increased with greater radiation dose (5). Recently, we observed in experimental animals that genetic background may alter the sensitivity to BCC induction (24). However, we lack a detailed mechanism explaining the effects of genetic background on radiation-induced carcinogenesis.

BCCs in Chernobyl Accident Populations

Other than the atomic bomb blasts in Hiroshima and Nagasaki, the explosions on April 26, 1986 at the Chernobyl No. 4 nuclear power plant resulted in the largest nuclear disaster in history (25). The radioactive cloud spread over Belarus, Ukraine, Russia and large parts of Europe. As a result, nearly 10 million people who lived in the most radio-contaminated areas have been chronically exposed to low levels of ionizing radiation. The risk from exposure is ongoing in these geographic areas (26, 27). The main radionuclides responsible for skin effects were ^{137}Cs, ^{134}Cs, ^{60}Co and ^{90}Sr (28). However, epidemiological studies focused on the most contaminated regions showed a sharp increase in the risk of thyroid cancer only, which was believed to be associated with the exposure to large amounts of iodine-131 (1, 19, 29). To date, no excess risk of cutaneous malignancies has been detected in those areas with large radiation exposures, despite such a large affected population (30). Gottlöber *et al.* followed 15 survivors of the Chernobyl accident with severe, localized exposure between 1991 and 2000. Two patients first presented in 1999 with BCCs on the nape of the neck and the right lower eyelid (25). In 2003, Steinert *et al.* evaluated 99 patients who had suffered from acute radiation sickness (ARS) and reported 22 out of 99 patients displayed radiation-induced cutaneous lesions. They also found 2 BCCs in 1 patient (28). In these two studies, common epidermal manifestations include epidermal atrophy, telangiectasia, pigment alterations and keratosis but no SCC development was reported (25, 28). These suggestive but inconclusive data indicate a requirement for large-scale, as well as long-term, follow-up after predominantly local radiation exposure (19, 28).

BCCs in Bone Marrow Transplant Recipients

For 40 years the use of hematopoietic cell transplantation has resulted in a large cohort of patients who have survived malignant or non-malignant diseases (12). However, increased rates of malignant neoplasms have been identified in these patients, the most frequent being BCCs (12). Although the majority of these patients survive, they suffer from multiple occurrences, disfigurement and increased expense for health care (31). In a systemic review

of 18 studies, the reported median interval to diagnosis after hematopoietic cell transplantation ranged from 7.3 to 9.4 years for BCC and the 20-year cumulative incidence was 6.5% (32). Many of these patients received preconditioning total-body irradiation (TBI) as a preparation for hematopoietic cell transplantation (33). Leisenring *et al.* reported that use of TBI conditioning regimen was a significant risk factor for BCCs but not for SCCs in a study involving 4,810 allogeneic hematopoietic cell transplantation survivors who received the treatment between 1969 and 2003 (12). A single or fractionated dose of ≥14 Gy significantly increased the incidence of BCC by more than 1.8-fold compared to non-TBI conditioning regimens (12). Schwartz *et al.* followed up with 6,306 patients who received hematopoietic cell transplantation treatment with or without TBI conditioning and reported that the overall relative risk of BCC development was 1.76 in TBI-treated patients who were exposed to prescribed radiation doses from 7.5 to 18.4 Gy (33). The ERR for BCC was highest for patients who were exposed at less than 10 years of age, but decreased by 10.9% per year above 10. There was no increased BCC risk associated with TBI conditioning for patients aged above 40 at hematopoietic cell transplantation (33). Surprisingly, the estimated ERR for BCCs in these hematopoietic cell transplantation patients are less than one tenth the risk reported among atomic bomb survivors (17, 18). Additionally, age, race and dose fractionation did not have a significant impact on relative risk for BCCs in these TBI-treated populations.

BCCs in Survivors of Childhood Cancer

In the Childhood Cancer Survivor Study (CCSS), Watt *et al.* reported that radiation therapy, either alone or in combination with chemotherapy, was associated with increased risk of BCCs compared to no chemotherapy or to radiation alone (31). This study identified a liner dose-response relationship showing an excess odds ratio (OR) of 1.09 per Gy. Patients who received a dose of ≥35 Gy had 39.8 times greater risk of developing BCC compared to survivors who had not received radiation therapy (31).

BCCs in Patients with Tinea Capitis

Ringworm of the scalp (tinea capitis) is a fungal infection common in children and has been a major public health problem in many countries (34). Before the introduction of antifungal medicine in the 1950s, X-ray irradiation has been widely employed for treating tinea capitis (35). It is estimated that approximately 200,000 children worldwide received X-ray treatment for this disease (36). The first study of long term effects of radiation epilation for tinea capitis was reported by Albert *et al.* in 1968, where among the 2,043 children treated at New York University Hospital, 14 cases of malignant tumors were identified, 7 of which were BCCs (37). A follow-up study of 2,215 patients published in 1976 confirmed that radiation treatment for children with tinea capitis infection was associated with increased rates of skin cancers (including BCCs), as well as malignancies of the brain, parotid, bone and thyroid (35). Several additional studies report similar incidence of radiation-induced scalp cancers in patients irradiated for tinea capitis (16, 38–43). In all follow-up studies, BCC was the primary type of skin cancer occurrence affected by therapeutic radiation, whereas the rates of SCCs and melanoma were not significantly altered. In these treated patients, a high prevalence of multiple BCCs was reported, most represented by the nodular histology type (42–45). Shore *et al.* reported that BCCs were found only in Caucasians in a

cohort of 2,200 irradiated children where 25% of these children were blacks suggesting that the susceptibility to UV radiation and ionizing radiation is similar in terms of BCC risk (16). It is suggested that excess risk of BCC development in the exposed population continues over a lifetime (42). Fifty years relative risk for BCC of the head and neck remains consistently high for a dose of about 4.8 Gy (16). Similar to reporting for atomic bomb survivors and hematopoietic cell transplantation, there is an inverse relationship between BCC risk and age at radiation exposure (16, 42, 43). Although BCC is generally characterized by slow growth, minimal soft tissue invasiveness and high cure rates, other studies showed that BCC developed in irradiated scalp skin tended to be more aggressive and more prone to recurrence (44, 46). Studies depicting the molecular mechanism underlying pathogenesis of aggressive radiation-induced BCCs are few. Recently, Boaventura *et al.* found that mitochondria D-Loop D310 mutation rate was associated with a higher radiation dose, although the role of this mutation in BCC from children is yet to be shown (47). Interestingly, genetic analysis of *p53* and *PTCH* genes in human BCCs revealed no differences between irradiated patients and nonirradiated patients (48).

BCCs in Medical Workers Exposed to Radiation

It is estimated that 7 million medical workers, including interventional cardiologists, are professionally exposed to ionizing radiation worldwide (49). In the past 20 years, radiation exposure to interventional cardiologists has dramatically increased, while the level of radiation protection has remained virtually unchanged (50). The occupational ionizing radiation exposure received by interventional cardiologists is 3 times higher than that of radiologists since they are working closer to the X-ray sources (49). Cardiologists using fluoroscopy-guided interventional procedures are exposed to the highest occupational doses of radiation (51). The current standard 0.5 mm lead apron offers less than complete protection, conferring as little as 60% coverage in complex situations (50). Therefore, interventional cardiologists are at increased risk of developing cancers, as well as other radiation-related diseases.

It is estimated that the most active and experienced interventional cardiologists were exposed to the equivalent of around 200–250 chest X rays (exposure from 1 chest X ray is about 0.1 mSv) (49), which is attributable to the excessive cancer risk of 1 in 400 according to the BEIR VII report published by the National Academy of Sciences (NAS) in 2006 (52). There are a few cohort studies estimating skin cancer risk associated with radiation exposures in interventional cardiologists. In 2010, Eagan *et al.* reported multiple BCC syndrome in an interventional cardiologist (50). This patient developed 41 skin lesions in total, 31 histologically confirmed to be BCCs, one recurrent, requiring wide surgical excision. After ruling out other major risk factors for this patient, multiple BCC syndrome was considered to be related to excess radiation doses received while performing high-volume, complex fluoroscopic procedures (50). Similarly, in a U.S. cohort of 65,304 white radiologic technologists, the relative risk for BCC, but not SCC, was elevated among those who started work before 1940 through the 1950s compared to those who began work after 1960. Since radiation doses were higher prior to 1960, these data suggest a dose-response relationship between radiation and BCC in lighter pigmented subjects (13). Wang *et al.* followed 27,011 diagnostic X-ray workers in China (radiologists and technicians), and

reported that their relative risk for all cancers was 4.1 among diagnostic X-ray workers compared to physicians who worked in the same hospitals. Those who worked for more than 15 years showed the highest relative risk for skin cancer (53, 54). The most recent follow-up study with the largest medical workers population, 65,719 Caucasian radiologic technologists, indicated that BCC risk was increased for radiation dose received before age 30 and before 1960 (55).

Increased reactive oxygen species, DNA damage, complex chromosome exchanges, immune responses and increased caspase-3 activity in human cells have been identified in studies of biological responses to radiation at the low doses associated with working in the catheterization procedures (49, 56–59). Nontarget effects, bystander effects and adaptive responses were also observed at low doses of radiation (56). However, further studies are needed to clarify whether these molecular changes are closely associated with the enhancement of skin cancer risks among these medical workers.

Other Occupational Radiation Exposure and Risk of BCC Development

Long-term exposure to occupational radiation in the workplace provides an opportunity to study the health effects of long-term exposure to low levels of external sources of radiation. Skin cancer related to occupational radiation exposure has been reported in aircrews, uranium miners, nuclear weapons test participants and nuclear industry workers (11).

Aircrews are mainly exposed to increased levels of cosmic radiation due to reduced protection from the atmosphere at high altitudes (60, 61). It is estimated that the cumulative dose at career-end for flight personnel could be as high as 75 mSv (61). A comprehensive review of studies conducted in the past 20 years on aircrew suggests an increased risk of melanoma (62, 63). However, interpretation of the data is complicated by disruption of day–night rhythm, which may influence the cancer risk (61, 64). Some studies provide mechanistic evidence for increased frequency of chromosome abnormalities, chromosomal translocations, and sensitivity to chromosomal damage in airline pilots with long-term flying history (64–66). On the other hand, it is possible that the risk of skin cancer among pilots is due to exposure to excess UVA radiation during flight operations. As described above, UV radiation from sun exposure is a major risk factor for skin cancers. Although most of the UVB radiation can be blocked by plastic and glass window shielding, up to 54% of UVA fluence can pass through; UVA radiation is 2 times higher at 9,000 m than on the ground (62, 67).

Hard-rock miners (uranium, iron, tin and gold) work in radon-rich environments (68–70). The majority of radiation emitted as a result of radon decay is as alpha particles, which can cause significant biological damage in exposed tissue due to their high relative biological effectiveness and mechanical tissue injury (71). There is ample evidence showing excessive risk of lung cancer in many groups of underground hard-rock miners due to inhalation of radon gas and its radioactive decay products (70, 72). However, the risk of non-melanoma skin cancers in radon-rich environments is not related to inhalation but to the contamination of radon progeny on the skin which exposes the epidermis to alpha particles from Po-218 and Po-214 (73). The dose received by the basal layer of the skin depends on the concentration of radioisotopes on the skin and the ability of alpha particles from Po-218 and

Po-214 to penetrate to the epidermis (71). Alpha emissions from Po-218 and Po-214 are capable of penetrating the epidermis as deep as 47 and 70 μm, respectively (71, 74). The nominal depth of basal cells, as described by the International Commission on Radiological Protection (ICRP), is 70 μm, which suggests that the radiation dose reaches to superficial cells only in the basal layer (73). However, large variations exist in the measurement of the depth of these cells on certain body sites, and some could be as low as 10 μm. Thus, basal layers on certain parts of the body may receive higher dose from α particles (73, 75, 76). Epidemiological studies describing the association between radon exposure and skin cancer risk among uranium miners are not very convincing (77). The only study showing an association between alpha radiation and skin cancer induction was reported for Czech uranium miners in 1978 (78, 79). BCCs were observed on the faces of miners after receiving an absorbed dose of 1 Gy over 10 or more years (78). A follow-up study with the same cohort by Sevcová found a significantly increased incidence of BCCs with an attributable annual risk of 1 per 10,000 workers per 1 Sv (79). Recent studies also showed an association between long-term residential radon exposure and an enhanced risk of BCC development (80, 81).

Mechanistic studies on radon-related carcinogenesis suggest that alpha particles produce complex biological responses. These include mutations, chromosome aberrations, generation of reactive oxygen species, modification of the cell cycle, alterations of cytokines, bystander effects, and carcinogenesis (71). Although most of the observed molecular changes may contribute to lung cancer, skin carcinogenesis may involve identical molecular alterations. Further studies are needed in this area to define the dose response from radon exposure among hard-rock miners to the risk of skin cancers as well as molecular mechanism underlying these effects.

Workers who participated in nuclear weapons testing were exposed, to some extent, to external radiation and radionuclides produced during the explosions. The world’s first atomic bomb was exploded at Alamogordo, New Mexico, on July 16, 1945. From 1945 to 1963, the U.S. conducted 235 atmospheric nuclear weapons tests. The epidemiological studies conducted by the UK and U.S. did not report increased risk of non-melanoma skin cancers among nuclear weapons test participants (82–84). A thorough search of the literature found two articles reporting multiple BCCs in atomic veterans. Morrissey *et al.* reported a case of an atomic veteran who developed 12 BCCs and 1 SCC at three to four decades after exposure to a 1952 atomic test in Nevada (85). Nelson and Randle reported another patient exposed to radiation after an aborted missile launch as part of atmospheric detonation testing (Starfish) had developed more than 300 BCCs over a period of 30 years. The majority of BCCs were papular-nodular type, a type usually associated with therapeutic radiation, and most of them occurred on sun-protected skin (86). In this study, it was noted that aside from the experience in that test, the patient had no family history of Gorlin Syndrome or other conditions associated with multiple skin cancers (86). The authors concluded that exposure to radiation during atomic weapons testing contributed to the excessive number and location of BCCs in this patient (86). There may be more atomic veterans carrying BCCs caused by radiation exposure, but low cancer-related mortality and underreporting complicate this determination. Moreover, the database of the National Association of Atomic Veterans (NAAV) does not specifically track the incidence of skin cancers among atomic veterans. A

large-scale long-term follow-up study could be helpful for determining whether exposure to occupational atomic radiation is the cause of skin cancers, including BCC, under these conditions.

Radiation Therapy for BCC

The gold standard treatment for BCC is surgical excision with histological control of excision margins, which has a 5 year recurrence rate of less than 3% on the face (87). However, surgical excision may not be the optimal treatment option for BCCs at anatomical sites where local surgery would require reconstruction or grafting. In such instances, radiotherapy becomes an alternative approach for the treatment of invasive or inoperable BCCs, with 5 year tumor control rates of 89–100% (87–89). Also, radiotherapy plays an important role in the therapeutic strategy of recurrent BCC (90, 91) or morphea-type basal cell carcinoma (MBCC), which is a rare form of BCC with lower response to treatment than other histologic types (92).

Basal cell carcinomas that recur after radiotherapy are often large, aggressive, invasive and very difficult to eradicate, with high recurrence rates after standard surgical excision or further radiotherapy (93). The mechanism underlying the malignant progression of these radiorecurrent BCCs is not clear.

Radiation Therapy for Patients with Basal Cell Nevus Syndrome

In addition to BCC, individuals with BCNS have a predisposition to an additional malignancy known as medulloblastoma, which comprises 20–30% of brain tumors in children (94). The standard radiation regimen has been a dose of 36 Gy followed by a total dose of 55 Gy to the entire craniospinal axis and the whole posterior fossa (95). However, radiotherapy has been found to accelerate the growth of BCCs or/and to promote the late-onset of tumors of other histology in BCNS patients (96–102). In several case reports, patients with BCNS were known to develop thousands of BCCs, some of which were even invasive and deadly, after radiotherapy for medulloblastoma (98, 103). Similarly, we recently reported that *Ptch*$^{+/-}$ mice on SKH-1 genetic background are highly sensitive to radiation in terms of BCC development (24) compared to mice of other susceptible genetic backgrounds (24, 99). Radiation-induced tumors in the exposed body area of BCNS patients include meningiomas (100), sinonasal cancer (101), schwannomas and liposarcomas (96). It is known that carcinogenesis is a multistage process in which both genetic and environmental factors contribute to tumor development (104). Therapeutic radiation expsoure may thus act as a second insult, leading to development of additional BCCs or other types of tumors in these patient populations (89, 105, 106). Therefore, radiation therapy in BCNS patient populations should be considered only with extreme caution (105).

Mechanisms of Radiation-induced BCCs and the Role of Pathways related to DNA Damage and Shh Signaling

The past 20 years of research into pathogenesis of radiation-induced carcinogenesis has generally focused on defining cellular and molecular mechanisms of radiation-induced alterations in mammalian cells. Each type of ionizing radiation can produce a variety of DNA damage with several potential outcomes (e.g., cell killing, chromosomal aberrations,

mutations, genomic instability, cell transformation, reactive oxygen species production and bystander effects) that ultimately contribute to carcinogenesis (106).

Extensive studies have demonstrated the role of aberrant Shh signaling activation in the pathogenesis of BCCs. Mutations in the tumor-suppressor gene *Ptch* and/or the G-protein–coupled receptor *Smoothened* drive activated Shh signaling. This is a key molecular mechanism in promoting oncogenic signaling of BCCs both in humans and experimental animals (2). However, the progression from basaloid hyperproliferation, leading to nodular then infiltrative BCC, involves the accumulation of multiple sequential genetic mutations (99). Ionizing radiation is known for its role in the induction of DNA damage. Cells have evolved mechanisms by which cell cycle halts until DNA damage is repaired. However, unrepaired DNA damage promotes apoptotic cell death or causes a threat to genetic integrity, and may give rise to mutations which are highly associated with carcinogenesis (107). Accumulating evidence shows that Shh signaling pathway modifies cellular responses to DNA damage. This may affect tumor initiation, promotion and progression in radiation-mediated carcinogenesis. *Ptch* heterozygous ($Ptch^{+/-}$) mice are known to be sensitive to radiation-induced tumorigenesis, including BCCs in the skin (9, 99). Whereas most of the studies were focused on the irradiated area, Mancuso *et al.* showed abscopal tumor induction of radiation-shielded skin in these mice, which might be mediated through constituent connexin 43 (C×43) status (108).

Activated Shh signaling promotes radio-resistance, which leads to impaired repair of DNA damage and genomic instability following IR (109, 110), whereas inhibition of Hh signaling significantly sensitizes tumors to radiotherapy (111, 112). Recently, Tripathi *et al.* established a novel connection between aberrant Gli1 and Bid in the survival of tumor cells by regulating the S-phase checkpoint (113). GLI transcription factors also facilitate propagation of skin keratinocytes with damaged DNA that give rise to early precursor tumor lesions (114). On the other hand, elevated Shh signaling promotes high levels of DNA damage, which increases the incidence of *Ptch* loss of heterozygosity, an important co-occurrence in the progression of Shh driven tumor (115). Taken together, a complex network regulating the cross-talk between Shh signaling and DNA damage pathway seems to be important in driving pathogenesis of BCCs under these experimental settings. However, exact molecular pathogenesis of these lesions remains to be defined.

Interestingly, a group of factors have been identified due to their ability to modify Hh pathway-associated BCCs developed in response to radiation exposure. For example, oncogenic Hh signaling can be suppressed by p53-mediated responses to DNA damage (116). Thus, p53 inactivating mutations may account for the enhancement or activation of Hh signaling in basal cells. Conversely, Hh signaling was found to override p53-mediated tumor suppression in BCCs, thus acting as a positive feedback loop in promoting oncogenesis (117, 118). In fact, in humans, high frequency and co-existence of genetic alterations in both *PTCH* and *p53* genes have been identified in BCCs from both normal population and atomic bomb survivors (119, 122). PARP-1 is another important protein found to cooperate with *Ptch* in the suppression of BCCs induced by radiation exposure (120). $Ptch^{+/-}$ mice with PARP-1 deletion were found to be highly susceptible to radiation-induced BCCs (120). Endogenous estrogen is also known to provide protection against

radition-mediated BCC development (121). Recently, Brennan-Crispi *et al.* showed that Desmoglein 2 (Dsg 2) may synergize with Hh signaling to promote chemical-induced BCC development (122). However, the role of Dsg 2 in pathogenesis of Radiation-induced BCCs remains unclear at this time.

In addition, we and other groups have demonstrated that genetic background contributes to the modification of *Ptch*-associated susceptibility to radiation-induced BCC development. Pazzaglia *et al.* revealed a striking difference of BCC penetrance in response to radiation in $Ptch^{+/-}$ mice between two different backgrounds that determine the susceptibility to carcinogenesis (8). We recently found that $Ptch^{+/-}$ mice with SKH-1 background manifested much shorter BCC latency and higher tumor multiplicity in response to either UVB or ionizing radiation (24). We also demonstrated that p50-Bcl3 regulated nuclear factor kappa B signaling is associated with pathogenesis of radiation-induced BCCs in a murine model (24). Moreover, BCC development in $Ptch^{+/-}$ mice was found to be hair cycle-dependent at the time of irradiation (123). BCCs with short latency and rapid growth were developed only in mice irradiated at early anagen phase of the hair cycle (123). This hair cycle-dependent response to radiation may be related to the fact that people who were exposed earlier in life have higher BCC rates than those exposed in late adulthood.

Therapeutic Intervention of Radiation-Induced BCCs

Accumulating evidence supports the idea that radiogenic or radiorecurrent BCCs tend to be more aggressive, difficult to eradicate by surgical excision and are often prone to recurrence (44, 45, 93). Thus, effective therapeutic intervention is needed for the management of these subtypes of BCC. Vismodegib (GDC-0449), an inhibitor of Smoothened, received FDA approval in 2012 for the treatment of recurrent, locally advanced or metastatic BCCs in BCNS patients (2). Interestingly, a recent study shows promise for this drug in treating multiple BCCs induced by radiotherapy (124). In this small clinical trial, 8 patients with a history of radiotherapy were recruited. 4 patients had partial response, 3 had stable disease and 1 was discontinued in follow-up at 34 weeks. A clinical trial incorporating large cohort size is needed to draw a firm conclusion. In addition, BCC recurrence, or resistance to Smoothened inhibitor treatment, was already reported in other non-radiation related BCC patients (125). Development of invasive keratoacanthomas in some patients is an additional dangerous side effect of this drug (126, 127). Clinical trials have shown their efficacy, and Smoothened antagonists such as sonidegib have already been approved by the FDA (128). Whether these new Smoothened targeting drugs are more or at least equally effective against radiation-induced BCCs remains to be seen.

Moreover, drugs that act by a mechanism distinct from these Smoothened antagonists showed promising inhibitory effects on the growth of BCCs. Itraconazole, an antifungal drug, has been employed in clinical trial as a potent antagonist of the Hh signaling pathway (129). Its role as either a chemopreventive or chemotherapeutic approach against BCC development, either alone or in combination with nonsteroidal anti-inflammatory drugs such as Sulindac, was supported by other recent animal studies (24, 130). It showed similar efficacy against radiation-induced BCCs in preclinical models. Itraconazole alone or in

combination with other small molecules may serve as a potent chemopreventive recipe for the management of radiation-induced BCCs.

CONCLUSION

The studies summarized in this commentary clearly indicate that human radiation exposure in environmental, occupational and therapeutic settings elevates risk of BCCs as opposed to any other skin cancer (Table 1). The exact cause of this specific human sensitivity to radiation remains unclear. However, based on data from radiation exposure to patients with Gorlin syndrome, it appears that abnormality in Hh signaling may contribute to enhanced radiation sensitivity. Our recent investigations also indicate that the murine model for Gorlin Syndrome is highly sensitive to ionizing radiation. This further strengthens the notion that activated Hh signaling may be an important determinant of augmented human sensitivity to radiation (24). Further mechanistic investigations are needed to clarify this phenomenon.

Ultraviolet B, which is known to induce both BCCs and SCCs in human skin and experimental animal models, differs from ionizing radiation in terms of inducing inflammatory responses. Although not very clear, there seems to be an apparent difference in acute erythema, sun burn, prostaglandin production etc. in the two treatments, at least in experimental animals. We observed that a dose of UVB (180 mJ/cm^2), which was used to induce BCC/SCC in our murine model, also caused severe inflammatory response in an acute setting. However, a single radiation dose (5 Gy), which is used to induce BCCs in our murine model, did not cause identical perceptible cutaneous inflammatory manifestations (24). Whether these differences in inflammatory signaling affect BCC sensitivity to radiation remains to be demonstrated. Important and interesting differences related to their cells of origin may govern radiation exposure-related risk for BCCs and not SCCs. For example, differences in basal cells versus squamous cells as they react to radiation could be an important factor. However, in the absence of solid evidence, this is all highly speculative at this time.

Disrupted tumor-suppressive pathways or aberrant activation of oncogenic signaling are the defined critical steps for the development of skin cancers. Those genes that play important roles in pathogenesis of BCC and/or SCC include *p53, Ptch* and *ras* among others. Mutations of tumor suppressor *p53* are common in both SCC and BCC while *Ptch* mutations drive pathogenesis of only BCCs (4). Both UV and ionizing radiation may induce mutations in these pathogenic genes. Therefore, the difference in the two types of radiation determining human BCC risk seems to be independent of the mutagenic potential of the radiation. However, some specific differences may occur in the overall cascade of signaling induced by the two radiation types down stream of mutations, which is not clearly defined so far.

In summary, studies are needed to understand molecular bases for the risk of induction of BCCs after radiation exposure. In the occupational setting, there is need to develop safe chemopreventive agents to reduce this radiation-associated skin carcinogenesis risk.

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TABLE 1

Summary of the Published Reports Showing Enhanced Risk of BCCs after Ionizing Radiation Exposure at Different Settings

Cohort	Size	Type of radiation	BCC no./cases	BCC risk (95% CI)	Year studied	BCC risk factors	Ref.
A-bomb survivors	79,972	Neutrons and γ rays	78	ERR_{1Sv}[a] = 1.0 (0.41–1.89)	1958–1987	dose, age at exposure	17
A-bomb survivors	80,158	Neutrons and γ rays	123	ERR_{1Gy} = 15 (4.2–43)/0–9 years; 5.7 (2.2–13)/10–19 years; 1.3 (0.35–2.9)/20–39 years; 0.19 (−0.32–1.2)/>40 years	1958–1996	dose, age at exposure	18
A-bomb survivors	105,427	Neutrons and γ rays	166	ERR_{1Gy} =0.57 (0.18–1.38) ERR/Gy[b] =0.48 (0.12–1.3)/<1 Gy; 2.64 (2.2–3)/>1 Gy	1958–1998	dose, age at exposure	21
A-bomb survivors	112,305	Neutrons and γ rays	106	ERR_{1Sv} = 1.9 (0.8–3.9)	1958–1987		22
A-bomb survivors	80,000	Neutrons and γ rays	80	ERR/Sv=21(4.1–7.3)/0–9 years; 6.7 (2.1–17)/10–19 years; 1.7 (0.5–3.8)/20–39 years; 0.7 (−0.05–2.2)/>40 years	1958–1987	dose, age at exposure	23
HCT recepients	4,810	Total body irradiation	158	Univariate hazard ratio = 1.8 (1.2–2.6)/≥14 Gy Cumulative incidence = 6.5% (5.3–7.7)/20 years	1969–2003	dose, race, age at exposure	12
HCT recepients	6,306	Total body irradiation	202	RR [c] = 1.76 (1.36–2.30)/all age combined ERR/Gy = 1.49 (0.64–3.17)/0–9 years; 0.55 (0.28–1.0)/10–19 years; 0.11 (0.06–0.18)/20–39 years; 0.02 (−0.01–0.06)/>40 years	1969–2006	age at exposure	33
Childhood cancer survivors	12,858	Radiotherapy	199	OR[d]/Gy = 1.09 (0.49–2.64)	1994–2003	dose	31
PatientTinea Capitis	10,834	X rays	41	RR = 4.9 (2.6–8.9)	1950–1980	dose, skin color, age at exposure	15
Patient with Tinea Capitis	2,215	X rays	11	Cumulative incidence = 22.6 (control = 2.6)/29 years	1968–1973	radiation	35
Patient with Tinea Capitis	2,200	X rays	80	RR = 3.8 (2.8–5.2)	1962–1979	skin color, Caucasian background	16
Patient with Tinea Capitis	2,224	X rays	328	RR = 3.6 (2.3–5.9)	50 years	North European ancestry, skin color, severe sunburn, age at exposure	42
Patient with Tinea Capitis	1,690	X rays	1553	RR = 2.3 (1.7–3.1)	4 years	age at exposure, years since first exposure, treatment for acne	43
Radiologic technologists	65,304	X rays	1,355	RR=2.16 (1.14–4.09)/before 1940; 2.04 (1.44–2.88)/1940s; 1.42 (1.12–1.80)/1950s;	1983–1998	dose, skin color	13
Radiologic technologists	65,719	X rays	3,615	ERR/Gy = 0.59 (−0.11–1.42)/<30 years; 2.92 (1.39–4.45)/before 1960	1983–2005	age at exposure	55
Residential radon exposed	51,445	Alpha particles	3,243	IRR[e]/100 Bq/m^3 = 1.14 (1.03–1.27)	1993–2011	dose, socio-economic status, living places	80

[a] Excess relative risk at 1 Sv

[b] excess relative risk per 1 Gy

[c] relative risk

[d] odds ratio

[e] incidence rate ratio.