# An Overview of Basal Cell Carcinoma

Nathaniel Peterson

Robert Pietruszka

BI-231

24 September 2012

Basal cell carcinoma (BCC) is a slow-growing neoplasm that originates in the germinating layer of the epidermis (Wells 2008). Metastasis of BCC is exceptionally rare, occurring in no more than 0.1% of reported cases (Khan et al. 2010). Although BCC is not prone to metastasis, it is the most common form of cancer among fair-skinned individuals (Moore and Bennett 2012), whose lifetime risk of developing the cancer is 30% (Lesiak et al. 2010). In addition, BCC accounts for approximately 75% of all non-melanoma skin cancers (Nakayama et al. 2011). Furthermore, incidence of BCC in the general human population has been increasing by approximately 10% each year (Raasch 2009). These alarming details make BCC a significant personal and public healthcare issue. Here we will briefly cover several important topics associated with this common cancer including diagnosis, risk factors, treatment, and prevention.

Noninvasive diagnostic procedures are available to confirm the existence of BCC including techniques such as dermatoscopy, high-frequency ultrasound, optical coherence tomography, and reflectance confocal microscopy (Altamura et al. 2010). Shave or punch biopsies may be used with these procedures to acquire tissue samples (Scope et al. 2010). Three main histological subtypes of BCC may be diagnosed including noduplar, superficial, and infiltrative (Raasch 2009). However, many other non-distinct histological subtypes exist (Yoneta et al. 2011) and more than one subtype may be present in a single tumor (Ro et al. 2011). Tumors appear most frequently on sun-exposed surfaces of the body (Sarma et al. 2011). Axillary and anogenital regions are the rarest sites of occurrence while the head and neck are the most common, comprising 80-85% of reported cases (Park et al. 2011; Sarma et al. 2011). An individual's risk for developing BCC depends on several broad criteria including genetic disposition, environmental phenomena, and immune status (Goppner and Leverkus 2011).

Fair-skinned individuals are more prone to develop BCC than genetically darker-skinned individuals (Samarasinghe and Madan 2012). This increased vulnerability is attributed to decreased activity of melanocytes, epidermal cells that produce melanin, a natural pigment that shields the integument and inferior tissues from ultraviolet (UV) radiation (Martini et al. 2012). Blue or green eyes

and blonde or red hair are also traits correlated to an increased risk of developing the cancer (Goppner and Leverkus 2011). According to one article, a gender-risk disparity of more than 2:1 exists between males and females, respectively (Chung 2012). Other genetically-determined risk factors may include some inherited skin disorders, such as basal cell nevus syndrome (Gorlin syndrome), xeroderma pigmentosa, epidermodysplasia verruciformis, and albinism (Amini et al. 2010).

Some somatic cellular gene mutations may lead to signaling pathway disruptions that are responsible for the uncontrolled proliferation of BCC (Li et al. 2011). Its carcinogenesis has been attributed to mutations in several genes including PTCH, smoothened (Smo), cytochrome 450, glutathione S-transferase, p53, and CDKN2A (O'Bryan and Ratner 2011; Samarasinghe and Madan 2012; Torti et al. 2011). PTCH encodes a receptor associated with Hedgehog signaling, a critical pathway that is partly responsible for cell proliferation and differentiation (Torti et al. 2011). Mutations in PTCH or Smo may result in activation of the Hedgehog signaling pathway, a common etiology for many BCCs (Frey et al. 2011). Therapies directed at suppressing the Hedgehog pathway are among the most relevant clinical applications currently being researched (Eberl et al. 2012).

The primary environmental contributor to the development of BCC is excessive exposure to UV radiation (Actis and Actis 2011; Amini et al. 2010; Sonkoly et al. 2012; Rangwala and Tsai 2011). Other environmental risk factors may include subjection to radiation therapy (Park et al. 2011), exposure to chemicals such as arsenic, aromatic hydrocarbons, anthracene, creosote oil (Dim-Jamora and Perone 2008), and psoralen (Goppner and Leverkus 2011). Physical traumas such as burns, chronic ulcers, and chronic dermatitis may additionally contribute to the development of BCC ( Goppner and Leverkus 2011; Samarasinghe and Madan 2012). Organ transplant recipients run a very high risk of developing non-melanoma skin cancers in general (Ericson et al. 2008). Some sexually-transmitted diseases may also play a role in the development of BCC (Park et al. 2011).

Although tumor regression is rare, there is significant evidence indicating that the body's innate and adaptive immune responses play a part in this process (Fujimura 2012). Tumor-infiltrating

lymphocytes including helper T-cells have been associated with tumor regression in one case report (Fujimura 2012). The immune system may utilize antibodies, certain dendritic cells, cytotoxic T-cells, and macrophages in initiating an anti-tumor response (Rangwala and Tsai 2011). Risk of developing certain cancers, including BCC, has been shown to increase among immunosuppressed individuals, including those who are HIV-positive and those who have undergone solid organ transplants (Lanoy et al. 2010). The elderly are among the most likely individuals to develop BCC (Gupta et al. 2011).

Surgical excision has been a longstanding treatment for BCC (Lien and Sondak 2011) and offers relatively high cure rates (Zeichner et al. 2011). Three common surgical modalities exist including standard excision (SE), curettage and electrodesiccation (CE), and Mohs micrographic surgery (Chung 2012). SE is the most common treatment option and involves tumor removal with 3-4mm margins (Smith and Walton 2011). Curettage and electrodesiccation (CE) is a common treatment for BCC, and as its name suggests, involves a two-step process to completely remove cancerous growths (Nakayama 2011). It is used primarily to treat superficial BCC (Pariser et al. 2009). The tumor is first excised using a curette and then the removal site is desiccated to control bleeding and destroy any remaining cancerous tissue (Smith and Walton 2011). CE is a relatively straightforward and inexpensive procedure that offers very high cure rates when performed by experienced physicians (Rodriguez-Vigil et al. 2007). However, the technique has been known in some cases to result in hypertrophic scarring (Nakayama 2011; Zeichner 2011) and hypopigmentation (Nakayama 2011). Mohs micrographic surgery (MMS) has been considered the most confident method of removing BCC (Chung 2012). MMS may be considered superior to SE because it involves marginal analysis to ensure thorough tumor removal ( Samarasinghe and Madan 2012). Studies of five-year cure rates for both primary and recurrent tumors excised using MMS were 90% or more according to one review (Smith and Walton 2011). Some non-surgical treatment options include photodynamic therapy and imiquimod (Zhao and He 2010).

Photodynamic therapy (PDT) is a treatment modality with purportedly superior cosmetic results than surgical alternatives (Hsiao et al. 2011). PDT works by applying a photosensitizing agent such as

aminolevulanic acid to the area of treatment prior to exposure to specific wavelengths of light (Raasch 2009). The therapy destroys target cells by producing reactive oxygen species (Kabingu 2009). Alone, PDT is relatively ineffective at treating thick skin tumors, however, curettage prior to PDT can provide excellent treatment outcomes (Christensen et al. 2011).

Imiquimod is a topical medication commonly formulated as a 5% or 3.75% cream (Zeichner et al. 2011). Imiquimod's effectiveness is derived from its ability to stimulate innate and cell-mediated immune responses (Raasch 2009). As a stand-alone therapy, imiquimod treatment is best-suited for superficial BCC or for circumstances in which SE is not ideal (Smith and Walton 2011). Many imiquimod trials have reported local inflammation, itching, burning, and in rare cases, ulceration in some individuals during treatment, yet it has proven effective in treating BCC (Lee et al. 2011; Raasch 2009; Zeichner 2011). Imiquimod may be combined with other treatments such as SE and CE while providing better results than isolating either (Brightman et al. 2011; Zeichner et al. 2011).

Successful treatments for skin cancers like BCC are valuable assets, yet prevention and early intervention is potentially a much more powerful course of action. Routine full self-examination of the skin is critical to ensuring early detection of pre-cancerous growths (Leffell 2000). Some warning signs include appearance of new moles, changes in mole color, shape, or texture, and sores that fail to heal (Leffell 2000). The most effective way to minimize risk of developing skin cancers of all types is to moderate sun exposure by avoiding long-term or intense periods of direct sunlight (Green et al. 1999). At the same time, however, sunlight appears to be crucial for synthesizing in vivo cholecalciferol, a steroid hormone more commonly known as vitamin D (Bertone-Johnson et al. 2011). Vitamin D is produced in the skin when exposed to UVB radiation (Kennel et al. 2010). The vitamin D metabolic pathway plays many vital roles in the human body, including tumor-suppression (Vuolo et al. 2012). Several reports indicate that deficient vitamin D levels are associated with a higher risk of developing many types of cancers, including those of the skin (Kennel et al. 2010; Trump et al. 2011; Zhang and Naughton 2010). Vitamin D tends to inhibit the Hedgehog pathway, thereby preventing and slowing tumor progression by

limiting proliferation (Tang et al. 2011). Lastly, among our most modern prevention and treatment therapies currently being researched include DNA-repairing proteins synthesized from engineered viruses (Cafardi et al. 2011).

Skin cancer is a significant matter to public health (Moore and Bennett 2012; Nakayama 2011; Raasch 2010). In particular, BCC represents a pertinent healthcare issue due to the substantial distress and economic strain that it causes (Elmets et al. 2010). Lifetime skin cancer risk is higher than all other cancers combined (Athar and Kopelovich 2011). Proceeding from these observations is the obligation to take care of our skin. Given the exceptionally high risk of developing cancers like BCC and the relatively uncomplicated process of preventing them, there is no reason to ignore the warning signs.

Literature Cited

Actis, A. & Actis, G. 2011. Reconstruction of the Upper Eyelid with Flaps and Free Grafts after Excision of Basal Cell Carcinoma. *Case Reports in Opthalmology*, 2011; 2: 347-353.

Altamura, D., Menzies, S., Argenziano, G., Zalaudek, I., Soyer, P., Sera, F., Avramidis, M., DeAmbrosis, K., Fargnoli, M. & Peris, K. 2010. Dermatoscopy of basal cell carcinoma: Morphologic variability of global and local features and accuracy of diagnosis. *Journal of the American Academy of Dermatology*, 62(1): 67-75.

Amini, S., Viera, M., Valins, W. & Berman, B. 2010. Nonsurgical Innovations in the Treatment of Nonmelanoma Skin Cancer. *The Journal of Clinical and Aesthetic Dermatology*, 3(6): 20-34.

Athar, M. & Kopelovich, L. 2011. Rapamycin and mTORC1 Inhibition in the Mouse: Skin Cancer Prevention. *Cancer Prevention Research*, 4(7): 957-961.

Bertone-Johnson, E., Powers, S., Spangler, L., Brunner, R., Michael, Y., Larson, J., Millen, A., Bueche, M., Salmoirago-Blotcher, E., Liu, S., Wassertheil-Smoller, S., Ockene, J., Ockene, I. & Manson, J. 2011. Vitamin D intake from foods and supplements and depressive symptoms in a diverse population of older women. *American Journal of Clinical Nutrition*, 2011; 94: 1104–12.

Brightman, L., Warycha, M., Anolik, R. & Geronemus, R. 2011. Do Lasers or Topicals Really Work for Nonmelanoma Skin Cancers? *Seminars in Cutaneous Medicine and Surgery*, 2011; 30: 14-25.

Cafardi, J., Shafi, R., Athar, M. & Elmets, C. 2011. Prospects for Skin Cancer Treatment and Prevention: the Potential Contribution of an Engineered Virus. *Journal of Investigative Dermatology*, 131(3): 559-561.

Christensen, E., Mork, C. & Foss, O. 2011. Pre-Treatment Deep Curettage Can Significantly Reduce Tumour Thickness in Thick Basal Cell Carcinoma While Maintaining a Favourable Cosmetic Outcome When Used in Combination with Topical Photodynamic Therapy. *Journal of Skin Cancer*, 2011: 240340. Published online 15 November 2011.

Chung, S. 2012. Basal Cell Carcinoma. *Archives of Plastic Surgery*, 2012; 39: 166-170.

Dim-Jamora, K. & Perone, J. 2008. Management of Cutaneous Tumors with Mohs Micrographic Surgery. *Seminars in Plastic Surgery*, 22(4): 247-256.

Eberl, M., Klingler, S., Mangelberger, D., Loipetzberger, A., Damhofer, H., Zoidl, K., Schnidar, H., Hache, H., Bauer, H., Solca, F., Hauser-Kronberger, C., Ermilov, A., Verhaegen, M., Bichakjian, C., Dlugosz, A., Nietfeld, W., Sibilia, M., Lehrach, H., Wierling, C. & Aberger, F. 2012. Hedgehog-EGFR cooperation response genes determine the oncogenic phenotype of basal cell carcinoma and tumour-initiating pancreatic cancer cells. *EMBO Molecular Medicine*, 2012; 4: 218-233.

Elmets, C., Viner, J., Pentland, A., Cantrell, W., Lin, H., Bailey, H., Kang, S., Linden, K., Heffernan, M., Duvic, M., Richmond, E., Elewski, B., Umar, A., Bell, W. & Gordon, G. 2010. Chemoprevention of Nonmelanoma Skin Cancer With Celecoxib: A Randomized, Double-Blind, Placebo-Controlled Trial. *Journal of the National Cancer Institute*, 102(24): 1835-1844.

Ericson, M., Wennberg, A. & Larko, O. 2008. Review of photodynamic therapy in actinic keratosis and basal cell carcinoma. *Therapeutics and Clinical Risk Management*, 4(1): 1-9.

Frey, L., Houben, R. & Brocker, E. 2011. Pigmentation, Melanocyte Colonization, and p53 Status in Basal Cell Carcinoma. *Journal of Skin Cancer*, 2011: 349726. Published online 29 September 2010.

Fujimura, T., Kakizaki, A., Kambayashi, Y. & Aiba, G. 2012. Basal Cell Carcinoma with Spontaneous Regression: A Case Report and Immunohistochemical Study. *Case Reports in Dermatology*, 2012; 4: 125-132.

Goppner, D., & Leverkus, M. 2011. Basal Cell Carcinoma: From the Molecular Understanding of the Pathogenesis to Targeted Therapy of Progressive Disease. *Journal of Skin Cancer*, 2011: 650258. Published online 29 December 2010.

Green, A., Williams, G., Neale, R., Hart, V., Leslie, D., Parsons, P., Marks, G., Gaffney, P., Battistutta, D., Frost, C., Lang, C. & Russell, A. 1999. Daily sunscreen application and betacarotene

supplementation in prevention of basal-cell and squamous-cell carcinomas of the skin: a randomised controlled trial. *The Lancet*, 1999; 354: 723-729.

Gupta, N., Kapoor, R. & Sharma, S. 2011. Colon Carcinoma Presenting with a Synchronous Oesophageal Carcinoma and Basal Cell Carcinoma of the Skin. *ISRN Oncology*, 2011: 107970. Published online 3 May 2011.

Hsiao, Y., Tseng, F., Yang, C. Chiu, C. 2011. Successful treatment of superficial basal cell carcinoma in the central face by photodynamic therapy in an Asian woman with dermoscopic diagnosis and a serial follow-up. *Dermatologica Sinica*, 2011; 29: 91-93.

Moore, M. & Bennett, R. 2012. Basal Cell Carcinoma in Asians: A Retrospective Analysis of Ten Patients. *Journal of Skin Cancer*, 2012: 741397. Published online 5 July 2012.

Kabingu, D., Oseroff, A., Wilding, G. & Gollnick, S. 2009. Enhanced Systemic Immune Reactivity to a Basal Cell Carcinoma Associated Antigen Following Photodynamic Therapy. *Clinical Cancer Research*, 15(13): 4460–4466.

Kennel, K., Drake, M. & Hurley, D. 2010. Vitamin D Deficiency in Adults: When to Test and How to Treat. *Mayo Clinic Proceedings*, 85(8): 752-758.

Khan, M., Powell, S., Cox, N., Robson, A. & Murrant, N. 2010. Cervical in-transit metastasis from a truncal basal cell carcinoma. *BMJ Case Reports*, 2010: bcr0920092281. Published online 22 July 2010.

Kabingu, E., Oseroff, A., Wilding, G. & Gollnick, S. 2009. Enhanced Systemic Immune Reactivity to a Basal Cell Carcinoma Associated Antigen Following Photodynamic Therapy. *Clinical Cancer Research*, 15(13): 4460-4466.

Lanoy, E., Costagliola, D. & Engels, E. 2010. Skin cancers associated with HIV infection and solid organ transplant among elderly adults. *International Journal of Cancer*, 126(7): 1724.

Lee, M., Varigos, G., Foley, P. & Ross, G. 2011. Photodynamic Therapy for Basal Cell Carcinoma in Recessive Dystrophic Epidermolysis Bullosa. *ISRN Dermatology*, 2011: 346754. Published

online 27 April 2011.

Leffell, D. 2000. *Total Skin: The Definitive Guide to Whole Skin Care for Life*. New York, NY: Hyperion.

Lesiak, A., Slowik-Rylska, M., Rogowski-Tylman, M., Sysa-Jedrzejowska, A., Norval, M., Narbutt, J. 2010. Risk factors in Central Poland for the development of superficial and nodular basal cell carcinomas. *Archives of Medical Science*, 2010(2): 270-275.

Lien, M. & Sondak, V. 2011. Nonsurgical Treatment Options for Basal Cell Carcinoma. *Journal of Skin Cancer*, 2011: 571734. Published online 9 January 2011.

Li, C., Chi, S. & Xie, J. 2011. Hedgehog signaling in skin cancers. *Cellular Signaling*, 23(8): 1235-1243.

Martini, F., Nath, J. & Bartholomew, E. 2012. *Fundamentals of Anatomy & Physiology, ninth edition*. San Francisco, CA: Pearson Education, Inc.

Nakayama, M., Tabuchi, K., Nakamura, Y. & Hara, A. 2011. Basal Cell Carcinoma of the Head and Neck. *Journal of Skin Cancer*, 2011: 496910. Published online 15 December 2010.

O'Bryan, K. & Ratner, D. 2011. The Role of Targeted Molecular Inhibitors in the Management of Advanced Nonmelanoma Skin Cancer. *Seminars in Cutaneous Medicine and Surgery*, 2011; 30: 57-61.

Pariser, D., Spencer, J., Berman, B., Suzanne, B., Parr, L., & Gross, K. 2009. Using a Hydroquinone/Tretinoin-based Skin Care System Before and After Electrodesiccation and Curettage of Superficial Truncal Basal Cell Carcinoma. *The Journal of Clinical and Aesthetic Dermatology*, 2(5): 38-43.

Raasch, B. 2009. Management of superficial basal cell carcinoma: focus on imiquimod. *Clinical, Cosmetic and Investigational Dermatology*, 2009; 2: 65-75.

Rangwala, S. & Tsai, K. 2011. Roles of the Immune System in Skin Cancer. *British Journal of Dermatology*, 165(5): 953-965.

Rodriguez-Vigil, T., Vazquez-Lopez, F. & Perez-Oliva, N. 2007. Efficacy of Curettage-Electrodesiccation for Basal Cell Carcinoma in Medium- and High-Risk Areas. *Actas Dermosifiliograficas*, 2011;

102: 634-635.

Samarasinghe, V. & Madan, V. 2012. Nonmelanoma Skin Cancer. *Journal of Cutaneous and Aesthetic Surgery*, 5(1): 3-10.

Sarma, D., Olson, D., Olivella, J., Harbert, T., Wang, B. & Ortman, S. 2011. Clear Cell Basal Cell Carcinoma. *Pathological Research International*, 2011: 386921. Published online 20 April 2011.

Scope, A., Mahmood, U., Gareau, D., Kenkre, M., Lieb, J., Nehal, K. & Rajadhyaksha, M. 2010. In vivo reflectance confocal microscopy of shave biopsy wounds: feasibility of intra-operative mapping of cancer margins. *British Journal of Dermatology*, 163(6): 1218-1228.

Smith, V. & Walton, S. 2011. Treatment of Facial Basal Cell Carcinoma: A Review. *Journal of Skin Cancer*, 2011: 380371. Published online 27 April 2011.

Sonkoly, E., Love, J., Xu, N., Meisgen, F., Wei1, T., Brodin, P., Jaks, V., Kasper, M., Shimokawa, T., Harada, M., Heilborn, J., Hedblad, M., Hippe, A., Grande, D., Homey, B., Zaphiropoulos, P., Arsenian-Henriksson, M., Stahle, M. & Pivarcsi, A. 2012. MicroRNA-203 functions as a tumor suppressor in basal cell carcinoma. *Oncogenesis*, 1(3): e3. Published online 12 March 2012.

Tang, J., Xiao, T., Oda, Y., Chang, K., Shpall, E., Wu, A., So, P., Hebert, J., Bikle, D. & Epstein Jr., E. 2011. Vitamin D3 Inhibits Hedgehog Signaling and Proliferation in Murine Basal Cell Carcinomas. *Cancer Prevention Research*, 4(5): 744-751.

Torti, D., Christensen, B., Storm, C., Fortuny, J., Perry, A., Zens, M., Stukel, T., Spencer, S., Nelson, H. & Karagas, M. 2011. Analgesic and Non Steroidal Anti-Inflammatory Use in Relation to Non Melanoma Skin Cancer: A Population-Based Case- Control Study. *Journal of the American Academy of Dermatology*, 65(2): 304-312.

Park, J., Cho, Y., Song, K., Lee, J., Yun, S. & Kim, H. 2011. Basal Cell Carcinoma on the Pubic Area: Report of a Case and Review of 19 Korean Cases of BCC from Non-sun-exposed Areas. *Annals of Dermatology*, 23(3): 405-408.

Trump, D., Deeb, K. & Johnson, C. 2011. Vitamin D: Considerations in the Continued Development as an

Agent for Cancer Prevention and Therapy. *Cancer Journal*, 16(1): 1-9

Vuolo, L., Di Somma, C., Faggiano, A. & Colao, A. 2012. Vitamin D and cancer. *Frontiers in Endocrinology*, 2012; (3): 00058. Published online 23 April 2012.

Wells, G. 2008. Basal Cell Carcinoma. *Merck Manuals*. Retrieved 1 November 2012 from: http://www.merckmanuals.com/professional/print/dermatologic_disorders/cancers_of_the_skin/basal_cell_carcinoma.html

Ro, K., Seo, S., Son, S. & I. Kim. 2011. Subclinical Infiltration of Basal Cell Carcinoma in Asian Patients: Assessment after Mohs Micrographic Surgery. *Annals of Dermatology*, 23(3): 276-281.

Yoneta, A., Horimoto, K., Nakahashi, K., Mori, S., Maeda, K. & Yamashita, T. 2011. A Case of Cystic Basal Cell Carcinoma Which Shows a Homogenous Blue/Black Area under Dermatoscopy. *Journal of Skin Cancer*, 2011: 450472. Published 23 September 2010.

Zeichner, J., Patel, R., Birge M. 2011. Treatment of Basal Cell Carcinoma with Curettage Followed by Imiquimod 3.75% Cream. *The Journal of Clinical and Aesthetic Dermatology*, 4(5): 39-43.

Zhang, R., Naughton, D. 2010. Vitamin D in health and disease: Current perspectives. *Nutrition Journal*, 2010; 9: 65.

Zhao, B. & He, Y. 2010. Recent advances in the prevention and treatment of skin cancer using photodynamic therapy. Expert Review of Anticancer Therapy, 10(11): 1797-1809.