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RESEARCH REVIEW

New Concepts for Basal Cell Carcinoma. Demographic, Clinical, Histological Risk Factors, and Biomarkers. A Systematic Review of Evidence Regarding Risk for Tumor Development, Susceptibility for Second Primary and Recurrence

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Basal cell carcinoma (BCC) is the commonest cancer in Caucasians and its incidence is increasing. Whilst ultraviolet radiation (UVR) is recognized as the main etiological factor, the relationship between exposure and host phenotype is still unclear. We systematically searched Medline, Embase, and the Cochrane databases for studies assessing the genetic basis of host response to UVR DNA damage, the effect of UVR on generation of reactive oxygen species (ROS), and their detoxification, UVR induced skin immunity modifications, and the role of genomic instability with a focus on the potential use of these biomarkers to the surgical treatment planning and prognosis of BCC patients. Data suggest that risk for BCC development is likely to result from the combined effect of many genes, each with a relatively weak individual contribution. Certain genomic alterations have been associated with increased or reduced risk for BCC development, with a second primary BCC or with recurrence of BCC. However, use of these biomarkers in everyday practice should be supported by further studies, mainly for its cost-effectiveness. In addition, not enough information exists on the prognostic value of existing demographic and clinical risk predictors for BCC regarding development of second primary or recurrent tumors. Information reviewed suggests that these predictors are of higher predictive value compared with biomarkers whilst they are indisputably cheaper and easier to monitor even in developing countries. Conclusively, we suggest that further studies aimed in investigating second primary or recurrent BCC are needed to provide better information on the predictive value of certain demographic, clinical and histological factors.

Key Words: **basal cell; carcinoma; skin; epidemiology; histology; second primary; multiple tumor; recurrence; tumor site; risk factor; clinical; demographic; gene.**

INTRODUCTION

Basal cell carcinoma (BCC) is the most common cancer in Caucasians and its incidence is increasing [1, 2]. Whilst ultraviolet radiation (UVR) is recognized as the main etiological agent, the relationship between exposure and host phenotype is still unclear [3].

In recent years, cancer research and BCC research more specifically are focusing on finding new biomarkers of potential prognostic value and on better understanding the pathophysiological processes of the disease, so as to improve current therapies or introduce novel treatment approaches [4]. Human cells, in order to transform to cancer cells, need to (1) provide growth signals–obtain growth self-sufficiency, (2) ignore growth inhibitory signals, (3) avoid apoptosis, (4) replicate without limit, (5) sustain angiogenesis, and (6) invade and proliferate [4]. While these are true for most cancers, in BCC it is rather unlikely that the last two conditions occur. Proof for that is the low to nonexistent metastatic

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potential of BCC [5] and the fact that the majority of tumors ulcerate in the center, thereby suggesting a limited ability to provoke and sustain angiogenetic molecular signaling [5].

In this systematic review, we concentrate on recent work to investigate whether new discoveries in the molecular pathology of BCC could have implications on the surgical treatment. Moreover, we describe currently available clinical prognostic factors and attempt a hypothetical comparison between future biomarkers and currently available risk indicators.

METHODS

We systematically searched Medline, Embase, and the Cochrane databases for studies assessing the genetic basis of host response to UVR-induced DNA damage, the effect of UVR on generation of reactive oxygen species (ROS) and their detoxification, UVR-induced skin immunity modifications, and the role of genomic instability with a focus on the potential use of these biomarkers in the treatment and prognosis of BCC patients. The search included articles published from January 1996 through July 2008. The Medline search strategy included any of the following medical subject headings (MeSH) terms: "basal cell," "carcinoma," and "skin." These terms then were combined with the secondary terms "epidemiology," "histology," "second primary," "multiple tumor," "recurrence," "tumor site," "risk factor," "clinical," "demographic," and "gene". Articles were excluded if they were letters to the editor, case reports, or reviews, if the article focused only on treatment or diagnosis, or if the article did not report on BCC cases. Articles published in languages other than English were evaluated from their English abstract when available. Data about patient age, gender, tumors, risk factors, and potential follow-up were abstracted. To be eligible, a published study must have explicitly stated the probability of developing a certain outcome under the influence of one or more risk factors. Only studies conferring statistically significant results were selected for tabular presentation.

RESULTS

The initial Medline search strategy resulted in 9423 articles that included the basal cell carcinoma term. This number was reduced to 264 when combined with the secondary terms. The article abstracts were reviewed, and 73 articles that matched the search criteria were reviewed. An additional 10 articles were identified within the citations of articles reviewed.

Defective Host Response to Ultraviolet Radiation

DNA Repair

Exposure to UVR, especially UVB, induces covalent bonds in DNA between adjacent pyrimidines, generating photoproducts such as cyclodipyrimidine dimers (TT) and pyrimidine lesions, which are mutagenic if not repaired. Polymorphisms in the melanocortin 1 receptor (MC1R, locus 16q24.3) have been shown to be strongly associated with skin type [6 ,7]. Variant alleles have also been found to be strongly associated with red hair and experimentally assessed UVR sensitivity. A large study suggested that MC1R gene variants were an important independent risk factor for nonmelanoma skin cancer (NMSC) [7]. Information on MC1R status is reported to contribute up to 3.3-fold increase in BCC risk (Table 1) [6, 8]. CpG sites are regions of DNA where a cytosine (C) nucleotide occurs next to a guanine (G) nucleotide in the linear sequence of bases along its length. Cytosine (C) to Thymidine (T) transitions at CpG sites adjacent to pyrimidine-pyrimidine (PyPy) sequences were reported to be more prevalent in tumors from UV-exposed than UV-shielded body areas [9]. CpG-mutations at non-PyPy sequences were reported to be more prevalent in tumors that received cumulative irradiation dose higher than 1 Gy compared with those who received cumulative dose lower than 0.2 Gy [9]. These data could be of potential value to determine the risk for BCC development among different subjects or different body sites of a subject when exposed to irradiation.

A haplotype near agouti signaling protein (ASIP, locus 20q11.2) known to affect a similar spectrum of pigmentation traits as the MC1R variants was recently found to confer significant risk of BCC (odds ratio = 1.33, $P < 0.001$) [10] (Table 1). However other authors reported the ASIP polymorphism not to be associated with BCC [8]. The results concerning MC1R and ASIP polymorphisms were reported to be independent of the subjects' pigmentation characteristics [8], thus adding value to their potential use as biomarkers. Another polymorphism in tyrosinase (TYR, 11q14-q21) encoding the R402Q amino acid substitution, which was previously shown to affect eye color and tanning response, was also found to confer risk of BCC (odds ratio = 1.14, $P < 0.001$) [10].

DNA repair capacity (DRC) was measured in peripheral blood lymphocytes by using a host-cell reactivation assay that measures cellular activation of a reporter gene irradiated with UV light [3]. Elderly BCC patients were reported to demonstrate a higher DRC compared with younger BCC patients and non-BCC controls [11]. Hall et *al.* reported that effects of age, family history of skin cancer, and current sun exposure may confound results [11] and, therefore, DRC measurement is unlikely to become a useful routine predictor.

Nucleotide excision repair (NER) is instrumental in removing DNA lesions caused by ultraviolet (UV) radiation, the dominant risk factor for BCC. Studies have examined polymorphisms in genes associated with DNA repair and identified significant association with both xeroderma pigmentosum complementation group D (XPD, locus 19q13.2-3, also known as ERCC2) [12], and X-ray complementing defective in Chinese hamster 3 genes (XRCC3, locus 14q32.3) [13], but not with any of five common haplotypes of excision repair complementing defective in Chinese hamster 1 (XRCC1, locus 19q13.2-q13.3) gene [14, 15]. The variant allele for susceptibility to breast cancer T241M (C > T)