

BASAL CELL CARCINOMA: REVIEW OF EPIDEMIOLOGY AND RISK FACTORS

CARCINOMUL BAZOCELULAR - EPIDEMIOLOGIE ȘI FACTORI DE RISC - REVIEW

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Abstract

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Basal cell carcinoma (BCC) is a malignant tumor with slow extension and local malignancy, with an exceptionally rare metastatic potential. BCC incidence is continuously increasing and there are geographical variations, the highest values being reported in Australia. The following are involved in BCC pathogenesis: actinic radiation, ionizing radiation, genetic factor, chemical carcinogens, immunosuppression, smoking etc. Actinic radiation is the main etiologic factor. There are multiple mechanisms of photocarcinogenesis, without being fully elucidated yet. Changing the attitudes towards the sun (tanning fashion), increased life expectancy and the presence of immunosuppression (organ transplant, HIV / AIDS) are factors that will further contribute to the increased incidence of BCC.

Rezumat

Cuvinte-cheie:

carcinom bazocelular,
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Carcinomul bazocelular (CBC) este o tumoră cu extensie lentă și malignitate locală, având potențial excepțional de rar de metastazare. Incidența CBC este în continuă creștere și există variații geografice, cele mai mari valori raportându-se în Australia. În etiopatogenia CBC sunt implicați următorii factori: radiațiile actinice, radiațiile ionizante, factori genetici, carcinogeni chimici, imunodepresia, fumatul etc. Radiațiile actinice reprezintă principalul factor etiologic. Mecanismele intime ale fotocarcinogenezei sunt multiple, fără a fi încă elucidate. Modificarea atitudinii față de soare (moda bronzării), creșterea speranței de viață și circumstanțele prezenței imunodepresiei (transplant de organe, infecția HIV/SIDA) sunt factori care vor contribui în continuare la creșterea incidenței CBC.

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Figure 1. Pearl-like BCC with central ulceration (Prof. dr. Pătrașcu personal photo archive)

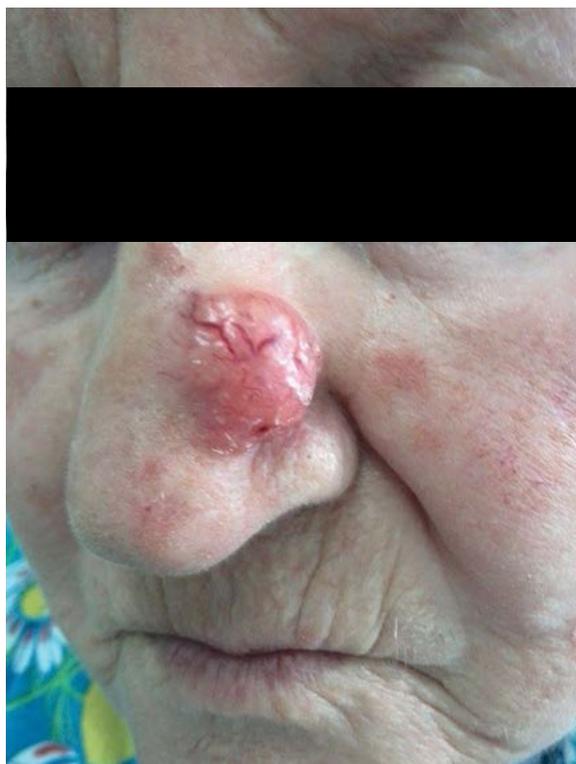


Figure 2. Nodular BCC (Prof. dr. Pătrașcu personal photo archive)

Basal cell carcinoma (BCC) is a slow growing malignant tumor with local extension that develops in the basal cells of the skin or its annexes^[1].

BCC was first described in 1824 by Arthur Jacob as "ulcus rodens" and in 1951, Thackray had correlated histopathologic data about the specific growth pattern of the tumor with clinical aspect^[2,3].

Basal cell carcinoma is characterized by slow extension and invasion (in years), and its frequency of metastasis is exceptionally rare (0.0028)^[4-6]. The clinical evaluation of BCC lesions has revealed a clinical polymorphism (Figure 1-4). Despite this relatively benign behavior, some tumors grow aggressively and may cause extensive tissue damage. The concepts of "low risk" and "high risk" factors for BCC recurrence have been described. Nodular and superficial types fall into the "low risk" category, while the morpheaform type belongs to the "high risk" category^[7]. BCC is found in both sexes (sex ratio B / F-1.5-2: 1), with a maximum incidence after 50 years old^[8].

Recently, an increased incidence of BCC among young population has been noticed (under 40 years) especially at women. The increased incidence of BCC is a result of the action of multiple factors: increased exposure to UV radiation, the depletion of the ozone layer, increasing life expectancy and taking over by developing countries of some habits from industrialized countries (smoking, changing clothing style, sedentarism)^[9]. There are significant geographical variations in the incidence of basal cell carcinoma: the highest values are reported in Australia, where there are over 1000 cases /100 000 inhabitants / year. Minimum

values are found in Africa, where there are less than 1 /100 000 person-years. In Germany, Canada, Italy, Finland, Switzerland, Scotland, Ireland, UK intermediate values have been reported (49-128 / 100,000 inhabitants)^[10-13].

The worldwide incidence of BCC is increasing rapidly. It is estimated that approximately 2.8 million new cases of BCC are diagnosed each year in USA, the annual growth rate ranging between 3% and 7%^[14,15].

BCC represents 80% of non-melanoma skin cancers and is the most common cancer among Caucasians^[16, 17]. Bauer et al. showed an increased frequency of BCC in people with occupations involving excessive sun exposure (farm laborers, fishermen, sailors, builders, pilots of aircraft)^[18].

Up to 80% of all the lesions are found on the head and neck (30% nose, cheek 22%, 15% forehead, periorbital 5%, 4% scalp, neck 4%, etc.)^[19]

The pathogenesis of basal cell carcinomas involves the following factors:

Ultraviolet Light

The ground solar spectrum comprises wavelengths between 290 and 3000 nm. The solar energy received at the Earth's surface is divided as follows: 50% is infrared radiation, visible radiation 40%, 10% is UV (8% UVA and 2% UVB). It still depends on the altitude, latitude, season and is influenced by a number of factors: water vapor content in the troposphere, ozone layer, air masses, molecules and atmospheric particles, the presence of reflective surfaces, etc.



Figure 3. Cicatricial basal cell carcinoma, effects of sun damage with solar elastosis and cutis rhomboidalis nuchae (Prof. dr. Pătrașcu personal photo archive)

As the earth's protective ozone layer thins continuously, increases in the incidence of skin cancer must be anticipated.

The first experimental evidence on the causal relationship between UV radiation and skin cancer are known from the period 1920-1930^[20].

There are many arguments advocating for the role of solar radiation in the pathogenesis of skin cancer^[21]. About 80% of all skin carcinomas are located on the face.

Also in terms of epidemiological aspect, we mention the increased incidence of skin cancer as we approach the Equator.

International Agency for Research on Cancer has classified UV radiation - regardless of its source (solar or artificial) - in Group 1 of risk^[22].

Several studies have shown that one exposure to artificial tanning increases the risk of BCC with 29% and 6 sessions of artificial tanning increases the risk by 73% [23-25].

In a meta-analysis of 12 studies on 9328 patients with non-melanoma skin cancers, Wehner et al. have found that artificial tanning is associated with an increased risk of developing basal cell carcinoma and squamous cell carcinoma. The risk was higher among users of tanning beds, under the age of 25 years^[26].

A higher incidence of BCC was reported in people who had frequent or severe sunburns in childhood. Thus, it is considered that adolescence and childhood are critical periods for determining an increased risk of BCC and implicitly of other skin

disorders in adulthood^[27]. Carcinogenesis is considered a multistadial process which comprises the following steps: initiation, promotion and neoplastic progression. Ultraviolet radiation can act as initiator, promoter or both of them. Although the mechanisms of photocarcinogenesis are not fully elucidated, it is known that together with the photons action on DNA, UV may intervene through the following:

- increased ornithine decarboxylase activity (the enzyme ornithine decarboxylase is involved in the synthesis of the following polyamines - putrescine, spermine and spermidine;
- pheomelanin irradiation produces superoxide ions and other free radicals, highly cancerigen;
- the action of oxygenated sterols, particularly α 1 - dehydrocholesterol produced by UV irradiation of the cholesterol. This, product is powerful carcinogenic and also an immunosuppressive agent;
- depression of cellular immunity.

Studies have shown that the repair of UV-induced damage at DNA level is possible due to the action of the p53 protein (encoded by the p53 gene that belongs to the family of tumor suppressor genes). This stops cell proliferation, and after repair, the cells resume their cycle. If damages are very important, then p53 leads to programmed death (apoptosis) by inducing the Bax gene and decreasing the Bcl2 gene expression (bax protein has antagonistic action with Bcl2). Mutations in this gene enable the developing of skin carcinomas or others cancers. It has been found that the p53 gene is inactive in 20-50% of cases of skin cancers.

Interestingly, mutations in the p53 gene were found in precancerous lesions and in chronically UV-irradiated skin, data that can be viewed as a warning for the accumulated solar energy which is already dangerous.

Hras mutations were found as well in cutaneous carcinomas, but less frequently^[28].

UVB radiation represents the most harmful portion of the solar spectrum for the skin, due to photocarcinogenesis by a continuous and cumulative process^[29].

Recent studies, certify the involvement of UVA radiation in skin carcinogenesis^[30]. After these studies, in cutaneous carcinogenesis would participate with 65% UVB and UVA with 35%.

We mention that phototherapy (PUVA= psoralen + UVA) can cause in long term, skin cancers. The incidence of basal cell carcinoma among patients with psoriasis has been proved to be dependent on the irradiation dose and the number of PUVA sessions^[31,32].

Regarding the carcinogenesis, the following mechanisms may be involved:

- the decrease of immune response, both cutaneous and systemic. The decrease of epidermal Langerhans cells was observed.- the intervention of psoralen on DNA;
- the interventions of HPV virus type 16 and 18, capable of inactivate the p53 gene by forming inactive complexes between the E6 protein (encoded



Figure 4.

Pearl-like basal cell carcinoma
(Prof. dr. Pătrașcu personal photo archive)

by the virus), and the p53 protein. The presence of HPV in skin lesions suggest that immunosuppression induced by PUVA may have an important role in photocarcinogenesis.

Risk factors for skin cancers in people who underwent PUVA - therapy are:

- skin phototypes I and II;
- intense and repeated sun exposure;
- previous history of skin cancer;
- existence of precancerous lesions;
- previous treatment with arsenic, ionizing radiation, UVB, methotrexate, cyclosporine.

Ionizing Radiation

Ionizing radiation are ionizing particles in different forms: α (helium nucleus consisting of two protons and two neutrons), β (electrons, protons), electromagnetic ionizing radiation (X-rays, gamma rays, cosmic rays).

In 1895 Wilhelm Conrad Röntgen discovered X-rays, and a few years later had established their role in the pathogenesis of skin cancers [33].

The effects of ionizing radiations on tissues and cells are:

- determines rapid cell death by apoptosis (may be induced by the overexpression of p53 molecule because of the important alterations in the DNA), or cause delayed cell death (by inhibiting mitosis);
- causes mutations and chromosome aberrations: the alteration of tumor suppressor genes or proto-oncogenes causes cancer. The Study of radiation-induced skin cancer on rats revealed the fact that the activation of C-myc oncogene occurs, gene heavily involved in different stages of cancer;
- neoplastic transformation through sublethal alterations and mutations in irradiated cells.

The cutaneous cellular targets of radiation-induced carcinogenesis are mainly, in basal layer and superjacent cells. The other cells, located in the upper epidermis, are more resistant.

Skin carcinogenesis is measured in terms of the years order, the latency depending on irradiation dose. We emphasize that human skin has a medium sensitivity to ionizing radiation and there is no safe minimum dose. The risk of developing skin cancer increases if along with irradiation the pa-

tient will be exposed to ultraviolet radiation, chemical carcinogens or oncogenic viruses.

Radiation-induced basal-cell carcinoma is rare. BCC appears on chronic radiodermatitis 40-50 years after irradiation with low doses, especially in the lumbar region (radiodiagnostic) or on the scalp after roentgen epilation in patients with pilomycosis (method now abandoned).

In a study conducted on a sample of 2224 children treated by roentgen epilation for tinea capitis the risk of developing CBC in the cephalic region was 3.6. We have also noted an increased incidence of CBC in the irradiation field after the treatment of angiomias, Hodgkin's disease or after accidental exposure^[34].

Genetic factors

In this context we mention the importance of individual sensitivity to sunlight.

Epidemiological studies have revealed significant differences in the incidence of skin carcinomas according to skin pigmentation^[35]. Regarding the skin response to ultraviolet radiation (presence or not of burns and susceptibility to sunburn) there are 6 skin phototypes.

The risk of developing skin carcinomas is maximum in phototype I and minimum in phototype VI [36]. In the USA, it is estimated that the frequency of skin cancers is 7-8 times higher in whites compared with african-americans (phototype VI)^[37].

It is known that in some genetic disorders (Gorlin-Goltz syndrome, Xeroderma pigmentosum) skin carcinomas occur early and are multiple [38, 39].

Chemical carcinogens

More frequently cause carcinomas and rarely sarcomas or lymphomas. The target cells for chemical carcinogens have mechanisms of detoxification (Selenium-dependent glutathione peroxidase protein, superoxide dismutase, etc.) which, for a time, succeed to neutralize the effect of these substances. The following substances are considered chemicals carcinogens:

- Arsenic: only mineral trivalent arsenic is a human carcinogen^[40]. It causes skin cancers but also upper aerodigestive tract, lung, bone and liver can-

cers. Latency period is 25-30 years. Tseng et al. have found a dose-dependent relation between the arsenic levels in drinking water and the prevalence of skin cancer^[41];

- Coal tar: the carcinogen agents found in coal tars are polycyclic aromatic hydrocarbons (PAHs). The main PAHs are benzo (a) pyrene, benzofenanthracen, dibenzanthracen, actually the same substance involved in smoking-induced malignancies. Regarding the carcinogenetic mechanisms the occurrence of mutations in the p53 gene and in the proto-oncogene H-ras are currently discussed. Also, the generation of free radicals, the inhibition of Langerhans cell antigen-presenting function and reducing the T cell response are mechanisms brought into discussion;

- Local cytostatic agents: caryolysine, BCNU (carmustine);

- Other chemical carcinogens: phorbol esters, pesticides, insecticides, fungicides, benzoyl peroxide.

Immunosuppression

Immune status appears to be a fundamental parameter in promotion and progression of photo-induced skin cancers. The risk of skin cancer is increased in patients treated with immunosuppressants (transplant patients) or those with AIDS. In these categories of patients, skin cancers appear earlier and often are more aggressive.

The risk of developing BCC in patients with organ transplant is 10 times higher than the general population^[42, 43].

Risk factors include - skin phototype I-II, cumulative sun exposure, age at transplantation, the degree of immunosuppression.

Smoking

The oncogenic effect of smoking is the result of thermal and chemical action. After almost half a century of research for identifying toxic and carcinogenic substances (over 480) contained in cigarette smoke, the list remains open. Recent researches revealed the association of smoking with mutations in the p53 gene (tumor suppressor), which reveals another way of smoking involvement in the process of carcinogenesis. Boyd et al. found that BCC appearance in young women is related

to smoking. Smith and Randle have described an increased prevalence of BCC with a diameter greater than 1 cm in smokers [44,45].

Other factors

Repeated micro traumatisms [46], chronic skin infections, ulcers with chronic evolution, chronic alcoholism, a high dietary fat intake diet [47], etc.

As regards the cancers developed on burn scar, it was noted that the latency period is approximately 35 years (7-62 years), although cases in children have been described. Squamous cell carcinoma appears predominantly but basal cell carcinoma and melanoma can develop. Approximately 2% of burn scars, may degenerate.

Although the role of actinic radiation seems preponderantly in the pathogenesis of skin cancers, in many cases, cancer is the result of a complex of factors (external and internal), which makes the assessment of the rate of participation of each of them difficult.

However, identifying the mentioned risk factors and limiting their action on the skin, can promote the prevention of BCC. Thus, the BCC prevention include: knowledge of risk factors, early diagnosis and adoption of preventive measures, especially in susceptible populations (light phototypes, unprotected professional exposure to UV rays)

Conclusions

BCC is often the consequence of the action of several etiological factors, whose share of contribution is difficult to assess.

Changing attitudes regarding sun exposure (tanning fashion), increasing life expectancy and the presence of immunosuppression (organ transplant, HIV / AIDS) are factors that will continue to contribute to the increased incidence of BCC.

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