

Małgorzata Drobnicka-Stępień<sup>1</sup>, Joanna Narbutt<sup>2</sup>, Irmína Olejniczak<sup>2</sup>,  
Anna Sysa-Jędrzejowska<sup>2</sup>, \*Aleksandra Lesiak<sup>2</sup>

## Low folic acid serum concentration as one of the factors leading to basal cell carcinoma development\*\*

### Niskie stężenie kwasu foliowego jako jeden z czynników predysponujących do rozwoju raków podstawnocomórkowych skóry

<sup>1</sup>Infectious and Liver Diseases Ward, Bieganski Hospital, Łódź  
Head of Department: prof. Zbigniew Deroń, MD, PhD

<sup>2</sup>Department of Dermatology, Medical University of Łódź  
Head of Department: prof. Anna Sysa-Jędrzejowska, MD, PhD

#### Summary

Basal cell carcinoma (BCC) is the most common neoplasm in Caucasian population, it represents over 80% of newly diagnosed tumors. Folic acid insufficiency has been recently considered as a risk factor for several cancers.

**Aim.** To assess the contribution of folic acid metabolism in the process of carcinogenesis in patients with BCC by determining the concentration of folic acid in the serum of patients with BCC and in control group.

**Material and methods.** Study group included 125 Caucasian subjects, 79 persons (41 women, 38 men, median age – 60.2 years, phototype: I/II – 20, III – 52, IV – 7) with BCC diagnosed on the basis of histopathological examination and 46 healthy volunteers (21 women, 25 men, median age – 58.4 years, phototype: I/II – 10, III – 28, IV – 8). In all patients serum folic acid concentration was measured with the use of Vitamin Folic Acid Test (DRG Vitamin Folic Acid, Mountainside, USA).

**Results.** Folic acid concentration was significantly higher in a control group than in BCC patients (median 16.5  $\mu\text{g/l}$  vs. median 9.6  $\mu\text{g/l}$ ; respectively;  $p < 0.001$ ). In most of the subjects both from control group and with BCC folic acid serum concentration was within normal limit.

**Conclusions.** Based on the obtained results and literature data we may conclude that the folic acid is involved in BCC development and its insufficiency may be concerned as one of the risk factors leading to skin cancerogenesis.

Key words: folic acid, basal cell carcinoma, cancerogenesis

#### Streszczenie

Rak podstawnocomórkowy skóry jest najczęściej występującym nowotworem wśród ludzi rasy białej, stanowi 80% nowo zdiagnozowanych guzów. Niedobór kwasu foliowego został ostatnio uznany za czynnik ryzyka w przypadku kilku nowotworów złośliwych.

**Cel.** Ocena roli metabolizmu kwasu foliowego w procesie karcynogenezy u pacjentów z rakiem podstawnocomórkowym skóry poprzez oznaczenie stężenia kwasu foliowego w surowicy pacjentów chorych na raka podstawnocomórkowego i w grupie kontrolnej.

**Materiały i metody.** Grupa doświadczalna liczyła 125 pacjentów rasy białej, 79 osób (41 kobiet i 38 mężczyzn, średnia wieku – 60,2 lata, fototyp I/II – 20, III – 52, IV – 7) ze zdiagnozowanym na podstawie badania histopatologicznego rakiem podstawnocomórkowym skóry oraz 46 zdrowych ochotników (21 kobiet, 25 mężczyzn, średnia wieku – 58,4 lata, fototyp I/II – 10, III – 28, IV – 8). U wszystkich pacjentów pomiar stężenia kwasu foliowego w surowicy został przeprowadzony za pomocą Vitamin Folic Acid Test (DRG Vitamin Folic Acid, Mountainside, USA).

**Wyniki.** Stężenie kwasu foliowego było znacząco wyższe w grupie kontrolnej niż w grupie pacjentów z rakiem podstawnocomórkowym skóry (odpowiednio: mediana 16,5  $\mu\text{g/l}$  vs. mediana 9,6  $\mu\text{g/l}$ ;  $p < 0,001$ ). U większości badanych zarówno z grupy kontrolnej, jak i z grupy chorych na raka podstawnocomórkowego skóry stężenie kwasu foliowego w surowicy mieściło się w normalnych granicach.

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**Wnioski.** Na podstawie otrzymanych wyników i danych zawartych w literaturze możemy stwierdzić, że kwas foliowy bierze udział w rozwoju raka podstawnocomórkowego skóry i jego niedobór może być uznany za jeden z czynników zwiększających ryzyko wystąpienia karcynogenezy skóry.

Słowa kluczowe: kwas foliowy, rak podstawnocomórkowy skóry, karcynogeneza

Recently increase in frequency of non-melanoma skin cancers (NMSC) which include basal cell carcinomas (BCC) and squamous cell carcinomas (SCC) has been observed (1-3). Basal cell carcinoma is the most common neoplasm in Caucasians and in Australian population and it represents over 80% of newly diagnosed cancers (4). In white race its frequency estimates between 18 and 40% (5, 6).

Despite of low mortality, NMSC, as the most common tumors in USA, Europe and Australia, are the major medical, social and economic problem (5, 7, 8).

Folic acid is a complex of folates, among which pteroil-1glutamic acid is the most stable form, therefore it is used in diet supplements, while it is rarely found in nature. Folates are sensible to high temperature, sun radiation and low pH. The active folates in the organism that act as coenzymes in many metabolic reactions are 5-tetrahydrofolate derivatives. They transfer one-carbon units in synthesis of purine and pyrimidine nucleotides, are involved in the synthesis of deoxyribonucleic acid (DNA) and therefore are essential for the correct cell division. They also play an important role in the metabolism of amino acids. One of the major reaction is the methylation of homocysteine to methionine – an amino acid which is an important substrate

for the methylation reactions (9). Methionine derived from food undergoes remethylation into homocysteine. Disconnected methyl group is used for methylation of various compounds such as phospholipids, proteins, DNA and RNA. Approximately 50% of homocysteine is converted with the participation of vitamin B6, to cysteine. The remaining 50% is remethylated to methionine. 5-methylenetetrahydrofolate and vitamin B12 are necessary for this reaction (10) (fig. 1).

The active form of folic acid (5-methylenetetrahydrofolate) is involved in the synthesis of purines, pyrimidines and DNA synthesis, amino acid metabolism and in the synthesis and transformation of formates. It also plays an important role in tissues with high rates of cell division, especially in the hematopoietic system, gastrointestinal tract epithelia and fetal tissues. In addition, it is important in the process of myelination of nerve fibers. During pregnancy it prevents neural tube birth defects in the fetus (11, 12).

The role of folate in preventing the development of cancer is not fully elucidated. Epidemiological studies suggest an inverse relationship between folate intake and the occurrence of cancer of the colon, lung, pancreas, esophagus, stomach, cervix, prostate, ovarian, breast cancer and leukemia (13, 16).

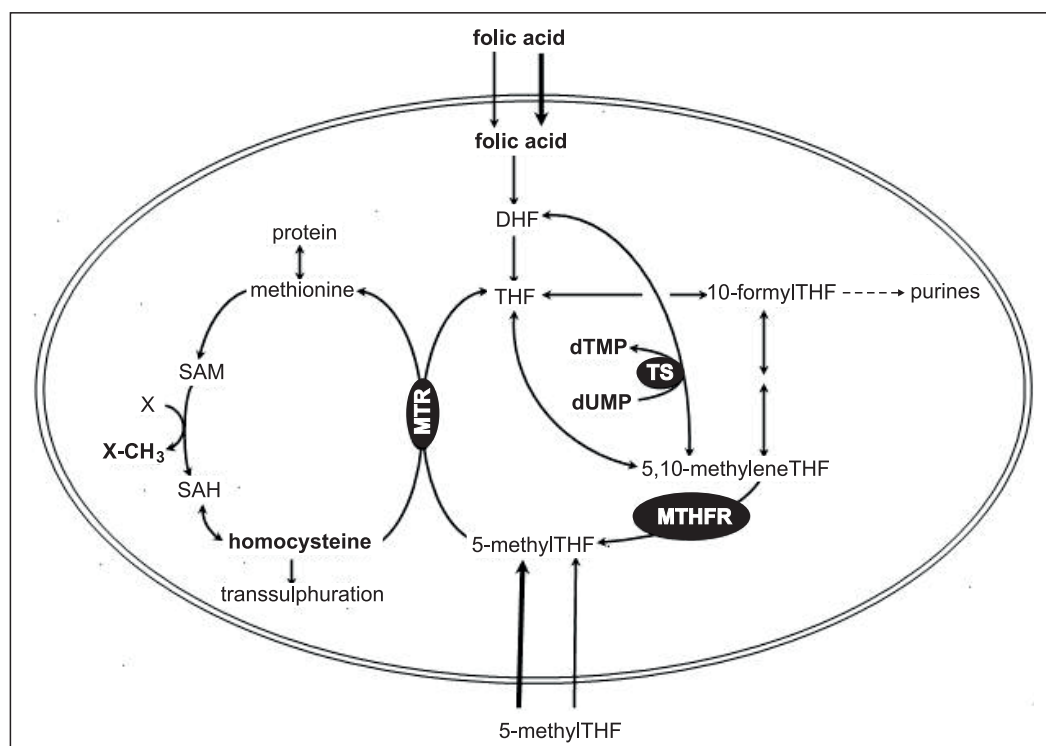


Fig. 1. Folate metabolic pathway (9).

Most of data concerns the role of folic acid in preventing colon cancer. Recent studies showed an inverse relationship between folate intake or blood folate levels and risk of colorectal cancer. The postulated link between folate deficiency and carcinogenesis is likely due to the participation of this vitamin in the synthesis of DNA. Folate deficiency is responsible for impairment of DNA methylation, increased chromosome fragility and decreased ability to repair damaged DNA fragments, which contributes to mutagenesis (15, 17-19).

There are only scarce data on the role of folate insufficiency in BCC development. Thus, the aim of the study was to assess the contribution of folic acid metabolism in the process of carcinogenesis in patients with BCC by determining the concentration of folic acid in the serum of patients with BCC and in control group.

**MATERIAL AND METHODS**

Study group consisted of 125 Caucasian subjects, including 79 (41 women, 38 men, median age – 60.2 years, phototype: I/II – 20, III – 52, IV – 7) persons with BCC diagnosed on the basis of histopathological examination and 46 healthy volunteers (21 women, 25 men, median age – 58.4 years, phototype: I/II – 10, III – 28, IV – 8). The control group was randomly selected (tab. 1). The inclusion criterion was negative history for any neoplasms. Exclusion criteria were the use of tanning bath or increased exposure to sunlight within two months prior the study. Patients with BCC were treated in Outpatient Clinic of Dermatology and Venereology Medical University of Łódź between 2005 and 2008. None of the them was transplant recipient, was treated with immunosupresants, nor suffered from internal organs neoplasm. In all the subjects risk factors for BCC development were evaluated. They included lesion localization, chronic sunlight exposure, using of sunbeds, past history of sunburn, smoking, alcohol abuse. The patients' skin types were defined according to the Fitzpatrick classification (1988). From all patients blood samples in order to determine serum folic acid concentration, were taken. Sampled sera were stored at -25°C until the measurement. Measurement of the total folic acid serum level was performed with the use of Vitamin Folic Acid Test (DRG Vitamin Folic Acid, Mountainside, USA). This assay is a microtiter plate test kit based on a microbiological assay. Serum samples were diluted with a buffer solution. The diluted samples were added into the microtiter plate wells [coated with *Lactobacillus rhamnosus* which metabolizes folic acid]. The addition of folic acid in either standards or samples gave a folic acid-dependent growth response until it was consumed. After incubation at 37°C for 48 h, the growth of *Lactobacillus rhamnosus* was measured turbidimetrically at 610-630 nm (alternative at 540-550 nm) in an ELISA-reader and a standard curve was generated from the dilution series. The amount of folic acid was directly proportional to the turbidity. The reference values of folate concentrations in this method were 3.8-23.2 ug/l. The obtained results were statistically evaluated with the use of STATISTICA 6.0 Software (Statsoft, Tulusa, USA).

Table 1. Clinical characteristic of BCC patients and control group.

	Group 1 BCC	Group 2 control
n	79	46
Female/Male [n]	41/38	21/25
Age [years]	60.2	58.4
Hair	Fair 47, dark 32	Fair 29, dark 17
Eyes	Fair 44, dark 35	Fair 24, dark 22
Skin phototype	I/II n = 20 III n = 52 IV n = 7	I/II n = 10 III n = 28 IV n = 8

**RESULTS**

In most cases (n = 67, 84.8%) basal cell carcinomas were located on the body areas exposed to sunlight (face, neck, dorsal side of hands), only in 12 (15.2%) cases tumor was located on unexposed surfaces (back, lower limbs). In 47 patients (59.5%) there was significant medical history concerning sunburn, in 68 subjects (86.1%) – erythema after sun exposure. In analyzed BCC-group 49 patients (62.0%) suffered had at least 1 incidence of sunburn, while 30 (38.0%) did not notice this side effect after sunlight exposure. 53.2% of patients (n = 42) were smoking.

Family history of cancers was positive in 40 patients (50.6%). Family incidence of cancer has been confirmed by 41 patients (51.9%), while 38 (48.1%) had a negative family history in terms of skin cancer. 42 respondents (53.1%) work in the open-air, while 37 patients (46.8%) practiced indoor.

Folic acid serum concentration was significantly higher in a control group than in BCC patients (median 16.5 µg/l (min 4.6 µg/l – max 70.6 µg/l) vs median 9.6 µg/l (min 3.4 µg/ml – max 30.6 µg/l; p < 0.001) (fig. 2). In most of the subjects both from control group and with BCC folic acid serum concentration was within normal limits. We found no correlation between folic acid serum level and phenotypic features such as sex, age, skin phototype, hair and eyes colour (p > 0.05 for all comparison).

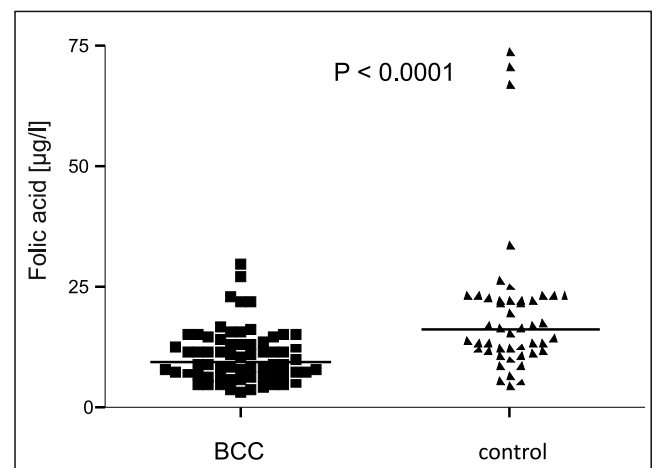


Fig. 2. Folic acid serum concentration in BCC patients and in healthy control.

## DISCUSSION

Recently dynamic increase in skin cancers occurrence has been observed. They account for about 10% of all cancers in men, 90% of them are NMSC skin cancers, most of which are basal cell carcinomas (approx. 80%) (20).

Based on studies conducted between 1973-2000 in several countries an increase in BCC incidence in both men and women was noted (from 40 to 92 cases of BCC per 100 000 men and from 34 to 79 cases per 100 000 women) (21).

The fact of dynamic increase in BCC incidence in recent decades has contributed to conducting of numerous studies aimed at understanding the phenomena underlying the pathogenesis of cutaneous photocarcinogenesis, as well as interactions between environmental factors and molecular genetics.

Clinical observations indicate that some factors may predispose to the development of BCC. These include, among others, age, gender, occupation and environmental factors. It seems that their individual participation may vary by region of the world and as it may change over the years.

In the group of patients there was no difference between the incidence of BCC and gender, which is in agreement with literature data, indicating that the difference between the occurrence of cancer in each sex is no longer significant. The confirmation of these findings are the results of studies conducted in European, Australian, and Asian populations (22-24). Previous studies have indicated a higher incidence of BCC in men. Nowadays, an increasing number of new cases in the female has been observed (25-28). This may be due to more frequent use of sunbeds by women and even, in some cases, addiction to artificial light sources (21, 29). It is widely recognized that there is a higher prevalence of BCC in people between seven and eight decade of life (30). However, recently decrease in average age of onset of BCC, from 56 to 30-39 years, has been noted (31). It is probably caused by observed also in our country, change of lifestyle, more frequent sun exposure and the usage of artificial radiation sources (31, 32). One of the proofs for the participation of tanning in sunbeds is in BCC development is its increase of the localization in the body area normally not exposed to sunlight, for example on the trunk (21, 29). However in our own study, in most cases ( $n = 67$ , 84.8%) BCC were located on the skin exposed to the sun (face, neck, dorsal side of hands) and in only 12 (15.2%) of patients had tumor in not exposed areas (trunk, lower limbs).

Literature data also show that the majority of cases of BCC localize on the scalp and neck (80%), and only 15% of them on the body (33). Scrivener al. (2002) analysed 13 457 cases of BCC, most of which occurred on the skin of the head (89.6%), while significantly fewer cases were found on the rest of the body (34).

Analyzing the dependence of the incidence of BCC on the race it has been shown that the Caucasian race is particularly predisposed to skin cancerogenesis because of fair skin and low skin phototype. These are the features that promote development of cutaneous

photocarcinogenesis and explain an increased risk of skin cancers among Caucasians (35-37).

In most BCC patients (80%) low skin phototype (light hair and eye color, tendency to sunburn) was noted. Most of the subjects, 49 (62.0%) reported the occurrence of sunburn in the past, while 30 (38.0%) persons did not notice this side effect after exposure to solar radiation.

Over half of the patients gave the history of frequent sunbath, and almost 90% of them confirmed the presence of erythema after exposure to UVR. These data confirm that ultraviolet radiation is one of the most important environmental factors involved in skin carcinogenesis (38, 39).

**Normal serum folate concentration is essential in physiological conditions to repair DNA damage caused by ultraviolet radiation.** Thus, folates and their metabolites are vital for normal cell proliferation and DNA repair in rapidly dividing cells which include keratinocytes. Folates are precursors of S-adenosylmethionine, which is essential in de novo synthesis of substrates involved in the processes of DNA replication and repair. The most common epigenetic phenomenon in the process of carcinogenesis is incorrect DNA methylation (40, 41). DNA methylation is an important process for normal cell division and development. The impairment of the process occurs with aging and in the course of cancerogenesis.

The process of methylation plays also a key role in regulating gene expression and maintaining genome integrity. Decreased concentrations of folic acid cause disruption in the availability of nucleotides, incorrect incorporation of uracil in the DNA what in a consequence leads to impaired replication and DNA strand break (42, 47).

Thus, folate insufficiency is associated with the development of some cancers, which contributed to the hypothesis that folic acid supplementation may be a preventive approach to their development (48). Confirmation of this hypothesis are the study results obtained by Zhang (49) and Hussien et al. (50) who showed that folic acid supplementation significantly reduces the risk of developing breast cancer, especially in alcohol abuse women.

In a recently published study, Liang et al. (51) showed the presence of DNA hypomethylation in skin squamous cell carcinomas, what indirectly justifies the prophylactic use of folate supplementation.

Our results and literature data confirm the participation of folate metabolism in the pathogenesis of cutaneous cancerogenesis.

To our best knowledge there is no other data on folic acid serum level in BCC patients. Our study showed significantly lower folic acid concentrations in patients with BCC (9.6  $\mu\text{g/l}$ ) compared to the control group (16.5  $\mu\text{g/l}$ ), although in all cases they were within normal limits.

Based on the obtained results and literature data we can not clearly define the role of folic acid in the development of basal cell carcinoma, although there are some strong proofs for its significant participation in the process of skin cancerogenesis.



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Address/adres:

\*Aleksandra Lesiak

Department of Dermatology

Medical University of Łódź

ul. Krzemieniecka 5, 94-014 Łódź

tel.: +48 (42) 686-79-81

e-mail: [aleksandra.lesiak@umed.lodz.pl](mailto:aleksandra.lesiak@umed.lodz.pl)