GEORGIAN MEDICAL NEWS

ISSN 1512-0112

NO 2 (347) Февраль 2024

ТБИЛИСИ - NEW YORK

ЕЖЕМЕСЯЧНЫЙ НАУЧНЫЙ ЖУРНАЛ

Медицинские новости Грузии

საქართველოს სამედიცინო სიახლენი

GEORGIAN MEDICAL NEWS

Monthly Georgia-US joint scientific journal published both in electronic and paper formats of the Agency of Medical Information of the Georgian Association of Business Press. Published since 1994. Distributed in NIS, EU and USA.

GMN: Georgian Medical News is peer-reviewed, published monthly journal committed to promoting the science and art of medicine and the betterment of public health, published by the GMN Editorial Board since 1994. GMN carries original scientific articles on medicine, biology and pharmacy, which are of experimental, theoretical and practical character; publishes original research, reviews, commentaries, editorials, essays, medical news, and correspondence in English and Russian.

GMN is indexed in MEDLINE, SCOPUS, PubMed and VINITI Russian Academy of Sciences. The full text content is available through EBSCO databases.

GMN: Медицинские новости Грузии - ежемесячный рецензируемый научный журнал, издаётся Редакционной коллегией с 1994 года на русском и английском языках в целях поддержки медицинской науки и улучшения здравоохранения. В журнале публикуются оригинальные научные статьи в области медицины, биологии и фармации, статьи обзорного характера, научные сообщения, новости медицины и здравоохранения. Журнал индексируется в MEDLINE, отражён в базе данных SCOPUS, PubMed и ВИНИТИ РАН. Полнотекстовые статьи журнала доступны через БД EBSCO.

GMN: Georgian Medical News – საქართველოს სამედიცინო სიახლენი – არის ყოველთვიური სამეცნიერო სამედიცინო რეცენზირებადი ჟურნალი, გამოიცემა 1994 წლიდან, წარმოადგენს სარედაქციო კოლეგიისა და აშშ-ის მეცნიერების, განათლების, ინდუსტრიის, ხელოვნებისა და ბუნებისმეტყველების საერთაშორისო აკადემიის ერთობლივ გამოცემას. GMN-ში რუსულ და ინგლისურ ენებზე ქვეყნდება ექსპერიმენტული, თეორიული და პრაქტიკული ხასიათის ორიგინალური სამეცნიერო სტატიები მედიცინის, ბიოლოგიისა და ფარმაციის სფეროში, მიმოხილვითი ხასიათის სტატიები.

ჟურნალი ინდექსირებულია MEDLINE-ის საერთაშორისო სისტემაში, ასახულია SCOPUS-ის, PubMed-ის და ВИНИТИ РАН-ის მონაცემთა ბაზებში. სტატიების სრული ტექსტი ხელმისაწვდომია EBSCO-ს მონაცემთა ბაზებიდან.

WEBSITE

www.geomednews.com

К СВЕДЕНИЮ АВТОРОВ!

При направлении статьи в редакцию необходимо соблюдать следующие правила:

1. Статья должна быть представлена в двух экземплярах, на русском или английском языках, напечатанная через **полтора интервала на одной стороне стандартного листа с шириной левого поля в три сантиметра**. Используемый компьютерный шрифт для текста на русском и английском языках - **Times New Roman** (**Кириллица**), для текста на грузинском языке следует использовать **AcadNusx.** Размер шрифта - **12**. К рукописи, напечатанной на компьютере, должен быть приложен CD со статьей.

2. Размер статьи должен быть не менее десяти и не более двадцати страниц машинописи, включая указатель литературы и резюме на английском, русском и грузинском языках.

3. В статье должны быть освещены актуальность данного материала, методы и результаты исследования и их обсуждение.

При представлении в печать научных экспериментальных работ авторы должны указывать вид и количество экспериментальных животных, применявшиеся методы обезболивания и усыпления (в ходе острых опытов).

4. К статье должны быть приложены краткое (на полстраницы) резюме на английском, русском и грузинском языках (включающее следующие разделы: цель исследования, материал и методы, результаты и заключение) и список ключевых слов (key words).

5. Таблицы необходимо представлять в печатной форме. Фотокопии не принимаются. **Все цифровые, итоговые и процентные данные в таблицах должны соответствовать таковым в тексте статьи**. Таблицы и графики должны быть озаглавлены.

6. Фотографии должны быть контрастными, фотокопии с рентгенограмм - в позитивном изображении. Рисунки, чертежи и диаграммы следует озаглавить, пронумеровать и вставить в соответствующее место текста **в tiff формате**.

В подписях к микрофотографиям следует указывать степень увеличения через окуляр или объектив и метод окраски или импрегнации срезов.

7. Фамилии отечественных авторов приводятся в оригинальной транскрипции.

8. При оформлении и направлении статей в журнал МНГ просим авторов соблюдать правила, изложенные в «Единых требованиях к рукописям, представляемым в биомедицинские журналы», принятых Международным комитетом редакторов медицинских журналов - http://www.spinesurgery.ru/files/publish.pdf и http://www.nlm.nih.gov/bsd/uniform_requirements.html
В конце каждой оригинальной статьи приводится библиографический список. В список литературы включаются все материалы, на которые имеются ссылки в тексте. Список составляется в алфавитном порядке и нумеруется. Литературный источник приводится на языке оригинала. В списке литературы сначала приводятся работы, написанные знаками грузинского алфавита, затем кириллицей и латиницей. Ссылки на цитируемые работы в тексте статьи даются в квадратных скобках в виде номера, соответствующего номеру данной работы в списке литературы. Большинство цитированных источников должны быть за последние 5-7 лет.

9. Для получения права на публикацию статья должна иметь от руководителя работы или учреждения визу и сопроводительное отношение, написанные или напечатанные на бланке и заверенные подписью и печатью.

10. В конце статьи должны быть подписи всех авторов, полностью приведены их фамилии, имена и отчества, указаны служебный и домашний номера телефонов и адреса или иные координаты. Количество авторов (соавторов) не должно превышать пяти человек.

11. Редакция оставляет за собой право сокращать и исправлять статьи. Корректура авторам не высылается, вся работа и сверка проводится по авторскому оригиналу.

12. Недопустимо направление в редакцию работ, представленных к печати в иных издательствах или опубликованных в других изданиях.

При нарушении указанных правил статьи не рассматриваются.

REQUIREMENTS

Please note, materials submitted to the Editorial Office Staff are supposed to meet the following requirements:

1. Articles must be provided with a double copy, in English or Russian languages and typed or compu-ter-printed on a single side of standard typing paper, with the left margin of **3** centimeters width, and **1.5** spacing between the lines, typeface - **Times New Roman** (**Cyrillic**), print size - **12** (referring to Georgian and Russian materials). With computer-printed texts please enclose a CD carrying the same file titled with Latin symbols.

2. Size of the article, including index and resume in English, Russian and Georgian languages must be at least 10 pages and not exceed the limit of 20 pages of typed or computer-printed text.

3. Submitted material must include a coverage of a topical subject, research methods, results, and review.

Authors of the scientific-research works must indicate the number of experimental biological species drawn in, list the employed methods of anesthetization and soporific means used during acute tests.

4. Articles must have a short (half page) abstract in English, Russian and Georgian (including the following sections: aim of study, material and methods, results and conclusions) and a list of key words.

5. Tables must be presented in an original typed or computer-printed form, instead of a photocopied version. **Numbers, totals, percentile data on the tables must coincide with those in the texts of the articles.** Tables and graphs must be headed.

6. Photographs are required to be contrasted and must be submitted with doubles. Please number each photograph with a pencil on its back, indicate author's name, title of the article (short version), and mark out its top and bottom parts. Drawings must be accurate, drafts and diagrams drawn in Indian ink (or black ink). Photocopies of the X-ray photographs must be presented in a positive image in **tiff format**.

Accurately numbered subtitles for each illustration must be listed on a separate sheet of paper. In the subtitles for the microphotographs please indicate the ocular and objective lens magnification power, method of coloring or impregnation of the microscopic sections (preparations).

7. Please indicate last names, first and middle initials of the native authors, present names and initials of the foreign authors in the transcription of the original language, enclose in parenthesis corresponding number under which the author is listed in the reference materials.

8. Please follow guidance offered to authors by The International Committee of Medical Journal Editors guidance in its Uniform Requirements for Manuscripts Submitted to Biomedical Journals publication available online at: http://www.nlm.nih.gov/bsd/uniform_requirements.html
http://www.icmje.org/urm_full.pdf
In GMN style for each work cited in the text, a bibliographic reference is given, and this is located at the end of the article under the title "References". All references cited in the text must be listed. The list of references should be arranged alphabetically and then numbered. References are numbered in the text [numbers in square brackets] and in the reference list and numbers are repeated throughout the text as needed. The bibliographic description is given in the language of publication (citations in Georgian script are followed by Cyrillic and Latin).

9. To obtain the rights of publication articles must be accompanied by a visa from the project instructor or the establishment, where the work has been performed, and a reference letter, both written or typed on a special signed form, certified by a stamp or a seal.

10. Articles must be signed by all of the authors at the end, and they must be provided with a list of full names, office and home phone numbers and addresses or other non-office locations where the authors could be reached. The number of the authors (co-authors) must not exceed the limit of 5 people.

11. Editorial Staff reserves the rights to cut down in size and correct the articles. Proof-sheets are not sent out to the authors. The entire editorial and collation work is performed according to the author's original text.

12. Sending in the works that have already been assigned to the press by other Editorial Staffs or have been printed by other publishers is not permissible.

Articles that Fail to Meet the Aforementioned Requirements are not Assigned to be Reviewed.

ავტორთა საყურადღებოდ!

რედაქციაში სტატიის წარმოდგენისას საჭიროა დავიცვათ შემდეგი წესები:

1. სტატია უნდა წარმოადგინოთ 2 ცალად, რუსულ ან ინგლისურ ენებზე,დაბეჭდილი სტანდარტული ფურცლის 1 გვერდზე, 3 სმ სიგანის მარცხენა ველისა და სტრიქონებს შორის 1,5 ინტერვალის დაცვით. გამოყენებული კომპიუტერული შრიფტი რუსულ და ინგლისურენოვან ტექსტებში - **Times New Roman (Кириллица)**, ხოლო ქართულენოვან ტექსტში საჭიროა გამოვიყენოთ **AcadNusx.** შრიფტის ზომა – 12. სტატიას თან უნდა ახლდეს CD სტატიით.

2. სტატიის მოცულობა არ უნდა შეადგენდეს 10 გვერდზე ნაკლებს და 20 გვერდზე მეტს ლიტერატურის სიის და რეზიუმეების (ინგლისურ, რუსულ და ქართულ ენებზე) ჩათვლით.

3. სტატიაში საჭიროა გაშუქდეს: საკითხის აქტუალობა; კვლევის მიზანი; საკვლევი მასალა და გამოყენებული მეთოდები; მიღებული შედეგები და მათი განსჯა. ექსპერიმენტული ხასიათის სტატიების წარმოდგენისას ავტორებმა უნდა მიუთითონ საექსპერიმენტო ცხოველების სახეობა და რაოდენობა; გაუტკივარებისა და დაძინების მეთოდები (მწვავე ცდების პირობებში).

4. სტატიას თან უნდა ახლდეს რეზიუმე ინგლისურ, რუსულ და ქართულ ენებზე არანაკლებ ნახევარი გვერდის მოცულობისა (სათაურის, ავტორების, დაწესებულების მითითებით და უნდა შეიცავდეს შემდეგ განყოფილებებს: მიზანი, მასალა და მეთოდები, შედეგები და დასკვნები; ტექსტუალური ნაწილი არ უნდა იყოს 15 სტრიქონზე ნაკლები) და საკვანძო სიტყვების ჩამონათვალი (key words).

5. ცხრილები საჭიროა წარმოადგინოთ ნაბეჭდი სახით. ყველა ციფრული, შემაჯამებელი და პროცენტული მონაცემები უნდა შეესაბამებოდეს ტექსტში მოყვანილს.

6. ფოტოსურათები უნდა იყოს კონტრასტული; სურათები, ნახაზები, დიაგრამები - დასათაურებული, დანომრილი და სათანადო ადგილას ჩასმული. რენტგენოგრამების ფოტოასლები წარმოადგინეთ პოზიტიური გამოსახულებით **tiff** ფორმატში. მიკროფოტოსურათების წარწერებში საჭიროა მიუთითოთ ოკულარის ან ობიექტივის საშუალებით გადიდების ხარისხი, ანათალების შეღებვის ან იმპრეგნაციის მეთოდი და აღნიშნოთ სურათის ზედა და ქვედა ნაწილები.

7. სამამულო ავტორების გვარები სტატიაში აღინიშნება ინიციალების თანდართვით, უცხოურისა – უცხოური ტრანსკრიპციით.

8. სტატიას თან უნდა ახლდეს ავტორის მიერ გამოყენებული სამამულო და უცხოური შრომების ბიბლიოგრაფიული სია (ბოლო 5-8 წლის სიღრმით). ანბანური წყობით წარმოდგენილ ბიბლიოგრაფიულ სიაში მიუთითეთ ჯერ სამამულო, შემდეგ უცხოელი ავტორები (გვარი, ინიციალები, სტატიის სათაური, ჟურნალის დასახელება, გამოცემის ადგილი, წელი, ჟურნალის №, პირველი და ბოლო გვერდები). მონოგრაფიის შემთხვევაში მიუთითეთ გამოცემის წელი, ადგილი და გვერდების საერთო რაოდენობა. ტექსტში კვადრატულ ფჩხილებში უნდა მიუთითოთ ავტორის შესაბამისი N ლიტერატურის სიის მიხედვით. მიზანშეწონილია, რომ ციტირებული წყაროების უმეტესი ნაწილი იყოს 5-6 წლის სიღრმის.

9. სტატიას თან უნდა ახლდეს: ა) დაწესებულების ან სამეცნიერო ხელმძღვანელის წარდგინება, დამოწმებული ხელმოწერითა და ბეჭდით; ბ) დარგის სპეციალისტის დამოწმებული რეცენზია, რომელშიც მითითებული იქნება საკითხის აქტუალობა, მასალის საკმაობა, მეთოდის სანდოობა, შედეგების სამეცნიერო-პრაქტიკული მნიშვნელობა.

10. სტატიის ბოლოს საჭიროა ყველა ავტორის ხელმოწერა, რომელთა რაოდენობა არ უნდა აღემატებოდეს 5-ს.

11. რედაქცია იტოვებს უფლებას შეასწოროს სტატია. ტექსტზე მუშაობა და შეჯერება ხდება საავტორო ორიგინალის მიხედვით.

12. დაუშვებელია რედაქციაში ისეთი სტატიის წარდგენა, რომელიც დასაბეჭდად წარდგენილი იყო სხვა რედაქციაში ან გამოქვეყნებული იყო სხვა გამოცემებში.

აღნიშნული წესების დარღვევის შემთხვევაში სტატიები არ განიხილება.

GEORGIAN MEDICAL NEWS
No 2 (347) 2024

Содержание:

GEORGIAN MEDICAL NEWS
No 2 (347) 2024

PERIOCULAR HIGH RISK BCCS AFTER ADDITIONAL/PARALLEL INTAKE OF TORASEMIDE, MOXONIDINE AND MIRABEGRON: IMPORTANT LINKS TO SKIN CANCER RELATED (PHOTO-) NITROSOGENESIS IN THE CONTEXT OF PHARMACO-ONCOGENESIS

Tchernev G[1,2], Dimova D[3].

[1]*Onkoderma- Clinic for Dermatology, Venereology and Dermatologic Surgery, General Skobelev 26, 1606 Sofia, Bulgaria.*
[2]*Department of Dermatology and Venereology, Medical Institute of Ministry of Interior General Skobelev 79, 1606 Sofia, Bulgaria.*
[3]*Department of Ophtalmology, Medical Instittute of Ministry of Interior, General Skobelev 79 1606, Sofia, Bulgaria.*

Abstract.

The Nitrosogenesis of skin cancer is a modern newly introduced concept in medicine, mainly concerning melanoma, but also keratinocytic cancers such as basal cell carcinoma. The nitroso-contamination of more than 300 drugs worldwide and the permanent (relatively short-term) intake of mutagen-contaminated drugs could create serious prerequisites for the development of skin cancer. Retrospective but also prospective analyses following potentially contaminated polymedication with a heterogeneous type of nitrosamines in real patients are indicative of a causal connection rather than a sporadic association between 1) intake of a possibly nitrosamine-contaminated drug and 2) generation of keratinocytic skin cancer.

The pathogenesis of high-risk periocular localized basal cell carcinomas was until recently shrouded in mystery as it was mainly and until now associated with 1) intake of phototoxic drugs and 2) intense exposure to UV radiation (without intake of drugs), 3) congenital or acquired immunodeficiencies, and 4) Goltz Gorlin syndrome or 5) Xeroderma pigmentosum.

Nitrosamines/ NDSRIs within the framework of polycotaminated drug intake appear to be one reasonable additional explanation for the association between carcinogen intake and subsequent skin cancer development and progression, and a relatively short-term one at that. Recently published scientific data provide information on a new ability of some of the nitrosamines - namely that some of them are photocarcinogenic or genotoxic after activation with UVA radiation.

We present 4 patients who developed high-risk periocular localized basal cell carcinomas of the skin after/within the intake of potentially nitrosamine-contaminated drugs. The presented data are confirmatory with respect to previously published scientific observations on the carcinogenic effects of valsartan, candesartan, bisoprolol, metoprolol, perindopril, lisinopril and amlodipine. The contribution of newly validated data concerning potential/actual carcinogenic/genotoxic activity in the article is also due to the following newly announced nitroso preparations: torasemide, moxonidine and mirabegron.

The expansion of the ″bases of the pyramid″ determining the stability of drug related (Photo) Nitrosogenesis/ Carcinogenesis (in terms of skin cancer generation) is growing daily.

Exogenously/drug-induced Nitrosogenesis and the subsequently triggered carcinogenesis are a completely new explanatory concepts concerning the pathogenesis of skin tumors that remained unanalyzed and hidden for decades. Until now. The official lack of 1) availability, and of 2) precise concentrations regarding nitrosamines in medicinal preparations, are some of the most unexplained acts of irresponsibility to end-users and remain for the moment without a definitive answer from either regulators and manufacturers respectively. Polycontamination of polymedication in polymorbid patients remains highly problematic, at least as a cofactor in the development and progression of keratinocytic cancers, and this in the short term.

Recently published data but also data from the past are suggestive that nitrosamines in tobacco are pivotal in the development of acquired mutations in p53 and RAS oncogenes in humans and rodents. The same genes are also affected by mutations in keratinocytic cancer patients. The overlapping mutation patterns of UV radiation-induced mutations in target genes such as p53 and RAS with those caused by some nitrosamines is indicative of a synergism available in terms of gene toxicity or possibly photocarcinogenicity of the latter.

What leads the scientific community to believe that the nitrosamines in drugs, similar in composition and carcinogenic potency, act differently, is unclear. The link between drug intake, nitrosamine contamination, generation of some acquired mutations and subsequent cancer development becomes more than obvious and logically conditioned.

The thesis of the controlled spread of cancer sounds more than logical today because: whoever controls and regulates the spread of carcinogens/mutagens/nitrosamines is also able to control the occurrence and spread of skin cancer. The Pharmaco-oncogenesis of skin cancer is determined by exogenously mediated Nitrosogenesis or the permissive availability for certain nitrosamines in drugs worldwide.

Key words. Torasemide, mirabegron, moxonidine, candesartan, metoprolol, bisoprolol, Photo-Nitrosogenesis, candesartan, perindopril, Lisinopril, basal cell carcinoma, periocular tumours, high risk tumours.

Introduction.

It is the different perspective and approach that generally helps when standard practices do not lead to the desired results and the crisis deepens. The cancer pandemic, which concerns keratinocytic cancers in particular, does not seem to have found its solution so far. The incidence of keratinocytic cancers is rising at breakneck speed and prevention programmes aimed at its neutralisation are proving to be poorly effective. This should be seen by clinicians as an alarming sign regarding the thorough search, identification, and elimination of other, until now unknown etiological factors that may have carcinogenic/ mutagenic effects- nitrosamines [1].

Nitrosogenesis concerning keratinocytic cancers is not new as a concept for the academic community [1,2]. Polymedication and polymorbidity in the era of polycontamination with nitrosamines in all likelihood have a role regarding skin cancer carcinogenesis [1,2]. It is within this framework of polycontamination that the so-called daily allowable doses of certain carcinogens/nitrosamines/NDSRIs in a drug become difficult to conform to or comply with. Thus, patients' organisms are often exposed to a combined intake of multiple carcinogens with different carcinogenic potencies, defined by official FDA lists as between 1 and 5 [3].

Recent evidence has linked esophageal squamous cell carcinomas to human exposure to a type of nitrosamines known as tobacco-specific nitrosamines (NNN and N'-Nitrosoanatabine) [4]. It remains an open question: should it be surprising to the academic community that the intake of analogous nitrosamines (but via drugs) over prolonged periods of time and in possibly elevated concentrations, can cause keratinocyte cancer/squamous cell carcinoma, but this time affecting the skin?

Four patients taking different classes of drugs from the potentially contaminated group (according to the 2023 FDA list) are presented, focusing mainly on the role of nitrosamines as a cofactor in the occurrence of keratinocytic tumors in particular basal cell carcinomas with periocular localization.

Case series.

Case 1:

An 86-year-old female patient presented to the dermatology and dermatologic surgery outpatient clinic for a nonhealing wound under the left eyelid, the age of which is difficult to determine, but she reported that it occurred several years after starting antihypertensive therapy (2016).

Systemic therapy with Bisoprolol 2x5mg was started for arterial hypertension detected in 2016, and Torasemide 1x5mg and Perindopril 1x5mg were added to therapy in 2019. He has been taking the described medications until today.

During the dermatological status, an erosive lesion covered with yellowish crust and inflammatory infiltrate measuring about 1cm by 1.5cm was found in the left infraorbital area (Figure 1a).

Surgical excision under local anesthesia and subsequent lower eyelid reconstruction was performed (Figures 1b,c). The material was sent for histological verification, the result of which showed nodular basal cell carcinoma with superficial ulceration and clear resection lines, stage T1N0M0.

Case 2:

A 77-year-old female patient was admitted to the outpatient dermatology and dermatologic surgery clinic because of a suspected recurrence after surgery for metatypical basal cell carcinoma in the left infraorbital area 3 months previously.

The age of the primary lesion was about one year.

He reported arterial hypertension for 10 years as comorbidities, for which he started therapy with Valsartan 1x160mg, which he has been taking. Moxonidine 2x0.2 mg was added to it 3 years ago.

The dermatological status revealed erythemato-infiltrative plaque in the left infraorbital area (Figure 2a). Reexcision of

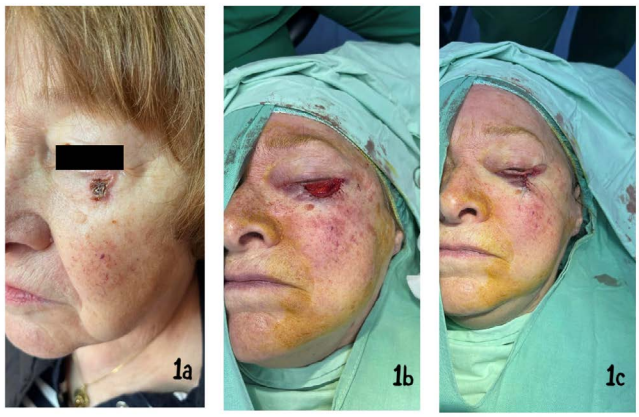

Figure 1. 1a: *Erosive lesion covered with yellowish crust and inflammatory infiltrate measuring about 1 cm by 1.5 cm in the left infraorbital area.*
1b: *Elliptical excision of the lesion.*
1c: *Postoperative photograph after lower eyelid reconstruction.*

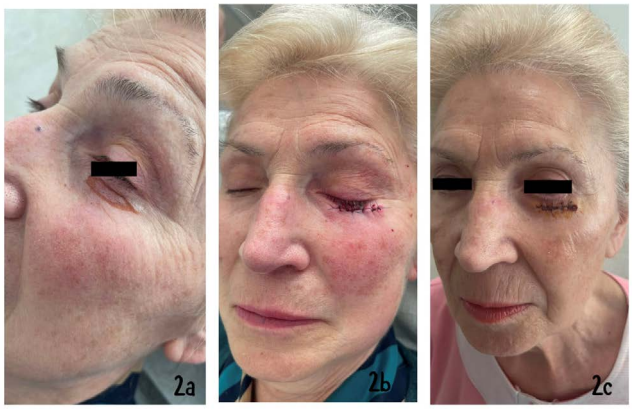

Figure 2. 2a: *Erythema infiltrative plaque in left infraorbital area several months after excision of BCC in the same location.*
2b: *Postoperative photograph.*
2c: *Postoperative day 7 photograph.*

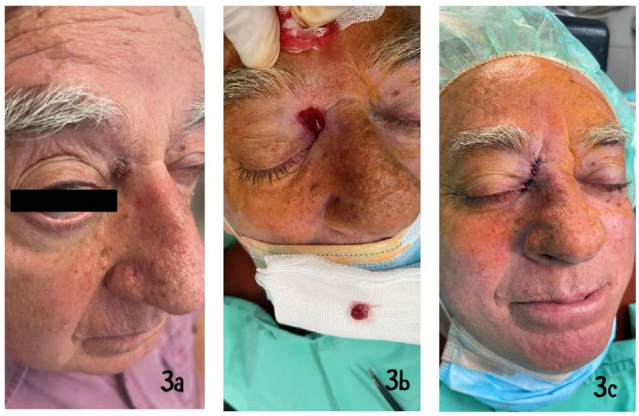

Figure 3. 3a: *Tumor-like mass with a pearly edge and superficial telangiectasias, measuring 1cm by 0.8cm medially in the upper right eyelid area.*
3b: *Photograph after removal of the lesion by elliptical excision.*
3c: *Postoperative photograph.*

the lesion was performed, the histology result of which showed metatypical basal cell carcinoma, clear resection lines, stage I, (T1N0M0) (Figures 2b,c).

Case 3:

A 78-year-old man reported a mass in the upper right eyelid medially, about 5-6 months old, which gradually grew. A biopsy was performed 10 days ago, and the result was basal cell carcinoma.

Due to established arterial hypertension she has been taking Amlodipine/Lisinopril 1x10/5mg, Moxonidine 1x0.2mg, Metoprolol 1x100mg for the past 5 years. He has been taking Mirabegron 1x50mg for 3 years for prostate hyperplasia.

During the dermatological status medial to the upper right eyelid, a tumor-like mass with a pearly edge and superficial telangiectasias, measuring 1cm by 0.8cm, was observed (Figure 3a). Oval excision of the lesion was performed. The defect was covered after mobilization of the subcutaneous tissue and subsequent adaptation of the wound edges. The result of histopathological examination of the material confirmed the diagnosis of basal cell carcinoma with infiltration of the lateral resection lines in 2 areas (T1N0M0R1), (Figure 3b,c).

The wound edges were refreshed and resected with fine surgical scissors after tumor removal. Active surveillance every 3 months and re-excision if necessary, as well as presentation to the regional cancer hospital was recommended.

Case 4:

A 52-year-old female patient reports a tumor-like formation in the medial corner of the left eye 10 years old.

The reason for her visit to the dermatology clinic was that she had noticed the lesion growing over the past 1 year.

Since one and a half year on the occasion of established arterial hypertension she started taking Candesartan 2x4mg and Bisoprolol 2x2.5mg.

During the dermatological status, a partially pigmented achromatous tumor-like formation, 2cm by 1.5cm in size, irregular in shape and clearly demarcated in the periphery, suggestive of BCC, was observed in the medial corner of the left eye (Figure 4a). The lesion was surgically removed by elliptical excision, and histological verification of the material was suggestive of nodular basal cell carcinoma, pure resection lines, (T1N0M0) (Figures 4b,c).

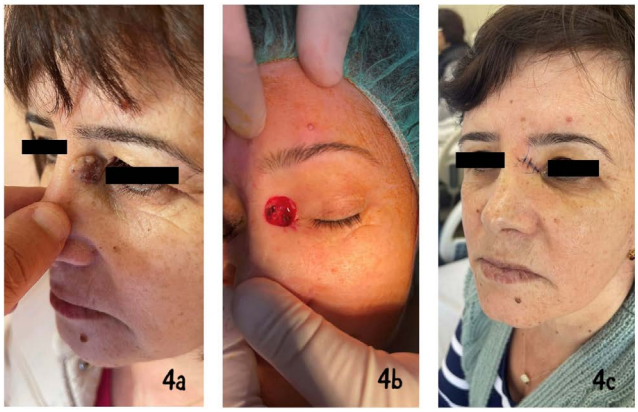

Figure 4. 4a: *Pigmented tumor-like formation measuring 2cm by 1.5cm with irregular shape and clearly demarcated peripheral skin borders.*
4b: *Elliptical excision of the lesion.*
4c: *Postoperative day 7 photograph.*

Discussion.

High-risk keratinocytic tumors of the periocular area are a problem from a pathogenetic and therapeutic point of view [1]. The reason is that it would be extremely difficult to determine the significance of individual factors in the occurrence of skin cancer on the basis of anamnestic data alone: whether it is 1) direct solar radiation [1], 2) the phototoxicity of some drugs such as beta blockers, thiazide diuretics and ACE inhibitors [5,6] or/and polycontamination with nitrosamines/NDSRIs in drug preparations [7,8]. The absence of any official data from regulators regarding the contamination of production, as well as the forced tolerance of nitrosamines in drugs, indirectly make the nitrosocomponent in the preparations a possible pathogenetic favourite.

Case analysis patient 1.

In the first patient we described, the combined administration of 3 potentially/really nitrosamine-contaminated drugs could have been pivotal with respect to the clinical presentation of high-risk basal cell carcinoma near the lower eyelid. Potentially/really contaminated bisoprolol has a carcinogenic potency of 4 (according to FDA), whereas torasemide and perindopril have a potency of 5 (according to FDA) [3]. Cumulative intake of these drugs over a period of 4 years could lead to the clinical manifestation of high-risk basal cell carcinoma.

The use of thiazide diuretics and ACE inhibitors is also associated with a significant risk of developing periocular keratinocyte cancer [9]. However, there were no objectifiable data at the time of diagnosis as to whether this was due to the phototoxicity of the two classes of medication or also to the potential presence of carcinogens in them. In addition to perindopril and torasemide, the patients we described were also taking bisoprolol, another phototoxic medication [6]. According to the most recent data from American, Canadian, and Japanese collectives, thiazide diuretics are associated with a significantly increased risk of developing keratinocytic cancer within even monomedication [10-12]. Even more interesting are the most recent data regarding the phototoxicity of hydrochlorothiazide, which could be completely absent within short-term intake [13]. What has been shared so far suggests that nitrosamines, within the framework of polymedication, could be identified (at the very least) as an important cofactor in the generation of keratinocytic cancer.

Case analysis patient 2.

In the second patient described, the periocular keratinocytic tumor developed after three years of concurrent valsartan and moxonidine therapy. While valsartan is known as of 2019 to be potentially contaminated with class 1 and 2 nitrosamines (strong carcinogenic potency) [14], moxonidine is currently only known to be available as nitroso-moxonidine [15,16]. Its categorization in the FDA list is probably yet to be done. The prevailing thesis in this case again concerns the intake of polycontaminated preparations within the framework of exogenously triggered nitrosogenesis and the subsequent development of basal cell carcinoma.

Case analysis patient 3.

The third patient presented developed basal cell carcinoma in the medial orbital angle area and was on systemic treatment with a combination agent containing amlodipine and perindopril, both of which are described in the FDA listings as having potential contamination with nitrosamines or NDSRIs [3]. Both preparations have been described as dangerous or risky to patients' health in terms of the development of keratinocytic skin cancer within the context of possible polycontamination [1,2]. Similar considerations have been made regarding concomitant administration of the beta blocker metoprolol [2,3] as well as the centrally acting sympatholytic moxonidine [15,16] (in the patient described).

Mirabegron has been taken for the past three years, and the drug has been described according to the FDA listings as possible for potential contamination with class 3 carcinogens [3].

In practice, the intake of 3 drugs ″officially declared″ as ″potentially contaminated″ with ″hypothetical carcinogens″/ nitrosamines/ NDSRIs in combination with nitroso-moxonidine could be cofactors or at least risk factors for the development of high-risk basal cell carcinoma of the periocular area. Formal regulatory checks for potential carcinogenic availability of nitrosamines in each drug batch are lacking.

And this is one of the main parameters on the basis of which the risk calculation could be conducted within the mono- and polycontamination of drugs.

It is because of this fact that the currently relevant data are mainly anamnestic data concerning the time intervals between the initiation of a particular intake and the development/ acceleration of growth of a particular form of skin cancer.

Case analysis patient 4.

The patient presented as number 4 had keratinocytic cancer with a lesion age of 10 years. Half a year after starting systemic treatment with bisoprolol in combination with candesartan, the lesion increased its growth rate significantly. Bisoprolol had a carcinogenic potency of 4, similar to the patient described in number 1. It has been repeatedly described as a drug at risk for the development of keratinocytic tumors in the context of polycontamination and polymedication [1,2]. Candesartan (carcinogenic potency 1 to 2) has been described as a possible trigger of both keratinocytic tumors within polymedication [2] and multiple melanomas within possible mono-contamination [17-21]. Short-term tumor progression after initiation of combination treatment with 2 antihypertensive drugs could also be considered as indicative of possible polycontamination within polymedication.

The clinical data presented to date are indicative of the development of cancer after intake of potentially nitrosamine-contaminated drugs that have been catalogued on the FDA list since 2023 [3].

A recent article from December 2023 focuses clinicians' attention on the impact of nitrosamines on key gene regulators of Carcinogenesis: p53 and RAS, and on the fact that it is the nitrosamines in tobacco that cause acquired mutations in these genes [22].

Based on the fact that, currently, drugs worldwide are affected by unprecedented (analogous) contamination with multiple nitrosamines/mutagens of similar (to the mentioned tobacco nitrosamines) carcinogenic potency [3], it should not be surprising to anyone that ″the modern trend″ is that it is ″these contaminants″ that cause acquired mutations and skin cancer. It's a matter of desire and time that the link: drug/type of nitrosamine/ type of mutation/ and type of cancer, be formally followed up and documented. Clinicians remain the priority, leading link in these relationships and their regulation. The trust in regulators and manufacturers remains largely lost. The data are suggestive that it is the moral of the researchers, without the support of the regulators and manufacturers, that has been able to overturn the vision of cancer generation and its incidence worldwide.

The need for a drastic reduction to a complete absence of nitrosamines in medical products is now becoming increasingly clear even to the manufacturers themselves [23]. It has been shown repeatedly under experimental/rodent conditions that (some) nitrosamines heterogeneous in type and carcinogenic potency are the basis of mutagenesis and carcinogenesis: 1) induction of p53 mutations by contact with N-butyl/N-(4-hydroxybutyl) nitrosamine, subsequently causing bladder tumors, and 2) of p53 mutations induced after administration of N-methyl/N-nitrosourea and leading to the development of colon tumors [24]. The relationship remains important: nitrosamines/mutations/different type of cancers [24].

Acquired RAS and p53 mutations could also be initiated after topical administration of nitrosamines/N-methyl-N-benzylnitrosamine under experimental conditions in rodents, and for a relatively short-term period/22 weeks [25].

The mutational pattern found in p53 and Ha-RAS in rodents resemble in many aspects the precancerous lesions found in the head and neck region in humans [25].

The observations in rodents under experimental conditions after administration of N-methyl N-nitrosourea remain similar to completely analogous: development of H-Ras mutations leading to generation of skin and mammary tumors [26].

Interestingly, mutations found in skin cancer patients also affect these two major genes: the tumor suppressor gene p53 and RAS oncogenes [27,28]. The p53 mutation occurs in basal cell carcinomas as well as in squamous cell skin cancer and melanoma [27], and until now no one has even thought in the direction of p53 mutations induced by the intake of nitrosamines in drugs. And these nitrosamines are inducers of precisely p53 mutations as well [24,25]. And they are distributed with the drugs [3], and- without being labelled on their packaging.

Increased expression of mutant p53 has been known in the past in patients with basal cell carcinomas of the head and neck [28], and these mutations have been previously defined as mainly UV-initiated/pathogenetically determined. However, any data regarding polymorbidity, polymedication, and polycontamination with nitrosamines are lacking in these patients groups. In support of the nitrosamine thesis, and against the generally accepted data on the incidence of keratinocytic skin cancer arising from direct exposure to solar radiation, the following could be mentioned: despite compliance with recommendations for protection from ultraviolet radiation (over the last 30 years/ worldwide), the incidence of basal cell carcinomas worldwide also remains difficult to determine

but is generally increasing [29-31]. The evidence regarding polycontamination with nitrosamines of the most commonly used drugs in clinical routine is also growing [3]. Poly- or monocontamination with nitrosamines in drugs also concerns periods going back at least 30-40 years.

RAS mutations, in addition to being induced by contact with nitrosamines [25,26] in rodents, have also been found in basal cell/spinocellular carcinomas in real patients [32]. Again, the aforementioned publication from as far back as 1990 lacks any data regarding polymedication, polycontamination, and polymorbidity in the patients described [32].

Recently published data by a German collective associated the use of ACE inhibitors and hydrochlorothiazide with a significantly increased risk of keratinocytic cancers in the head and neck region [33]. Despite focusing on these two classes of drugs, the authors do not comment on their possible polycontamination [33], which is, however, described in the 2023 FDA update: for all ACE inhibitors as well as for hydrochlorothiazide [3].

The thesis that whoever controls the availability/absence of carcinogens in pharmaceutical products also controls the cancer is proving to be more than consistent and scientifically justified.

The intake of drugs of different classes, officially declared as possibly contaminated with nitrosamines, causes, according to literature data, mutations and consequently skin cancer: both under experimental conditions in rodents and in real patients. The lack of 1) a cataloguing in general and of 2) a formalization of the carcinogens found in the drugs in the drug description so far, is highly indicative, that the problem is present and getting aggravated.

Last but not least, it should be noted that the role of academic criticism and different interpretation of the processes of Nitrosogenesis/ Carcinogenesis remains the leading link that effectively battles the increasing incidence of skin cancer. The starting point has been handed by regulators in the face of the FDA in 2018 and it could be seen as a ground-breaking start for those who are willing to analyse, monitor, officialise and fight for the truth in science.

But the fact that the active phase of this event is led by clinicians, in the name of end users and against globalisation processes worldwide, should not be overlooked. The need for a multi-polar model in science remains the only hope in trying to formalise the objective scientific truth and the real cause of the incidence of skin cancer and cancer in general.

The regulation of publishing content worldwide is more than critically modulated and directed in directions that can be safely defined as globalization-motivated, but also as fundamentally meaningless. These directions follow neither the path of academicism nor that of a general solution to the problem of cancer and objective truth.

In this respect, one of the most important data recently shared in the scientific literature should not be overlooked, namely that some of the nitrosamines are photo-carcinogens that are able to exert their genotoxic effects precisely after irradiation with UVA [34]. To this fact it would be appropriate to add the conclusion of another authors' collective postulating and proving that certain nitrosamines are already proven human mutagens [22].

Conclusion.

Clinical observations concerning the occurrence and progression of basal cell carcinomas in the periocular zone are indicative of the following:

1. The time intervals for the de novo manifestation of tumours, but also the progression of already existing ones within a certain (probably/ really contaminated) medication intake, are indicative of a potential relationship between nitrosamine intake and the generation/progression of skin cancer/basal cell carcinomas.

2. ″Contaminated drug intake″ has been officially described as possible and already repeatedly proven by regulators in the face of the EMA and the FDA. However, it is strange why none of the pharmaceutical companies are obliged by the regulators to officially announce the data of possible contamination of each affected batch and these batches are undisturbedly distributed in the drug market.

3. The formalization of the contaminated production (in future periods), even if the carcinogens are within the permissible doses for the day, does not solve the problem related to polymedication and contamination.

4. Contrary to the assertions of regulators and manufacturers, the clinical data are once again indicative of the following: relatively short-term intake of potentially/actually nitrosamine-contaminated drugs could lead to skin cancer or basal cell carcinomas development with periocular localization.

5. Supporting the thesis of the role of drug induced or exogenous Nitrosogenesis in skin cancer development is the identification of the following 3 new drugs: Torasemide and Mirabegron are available on the current FDA list of potentially/ really contaminated drugs as of 2023. However, moxonidine has been identified in the form of nitroso-moxonidine and its cataloguing is likely yet to be completed. The broad base of the pyramid of Nitrosogenesis is determined precisely by the continuous ″spectrum expansion″ of nitroso drugs, after the intake of which relatively uniform skin tumours develop. This is, and remains, one of the strongest indirect evidences for the role of nitrosogenesis in the pathogenesis/ carcinogenesis of keratinocytic tumors.

6. The article is once again confirmatory regarding the fact that the intake of bisoprolol/metoprolol, perindopril/lisinopril, valsartan/candesartan and amlodipine in the context of polymedication and polycontamination may be at least associated with the occurrence of keratinocytic cancer. Or paraphrased: the intake of hypothetical carcinogens/nitrosamines/NDSRIs could also be sometimes associated with the occurrence of real cutaneous tumours. Official concepts (created by regulators) such as ″potential contamination with hypothetical carcinogens″ continue to sound louder and more often like an ominous grotesque.

7. And while expert recommendations in the 21st century have directed public sentiment (regarding the importance of nitrosamines in drugs/carcinogenicity) toward in vivo testing in rodents, the data shared in this (but not only) publication are in fact indicative of the unauthorized conduct of prospective follow-up in patients. This is without their signed or even verbally taken informed consent. The only thing that could

justify to some extent the shared (hypo)thesis is - official regulators to permanently and transparently show controls for purity of drug production for each and every batch at every moment: for the benefit and interest of patients only. Even observations of intoxication with nitrosopreparations in humans as early as 1954 and subsequent in vivo tests in rodents in 1956/1962 are indicative of the identical action of carcinogens on the development of liver and kidney cancer.

8. Controlling the availability of certain carcinogens and their intake within the mono or polymedication (in certain geographic regions) , in practice, also means controlling the occurrence and spread of (skin) cancer.

9. Adequate prevention of skin cancer could only be accomplished by the gradual, but at the same time widespread, elimination of carcinogen-contaminated medical products. Full transparency of these processes would be the most important guarantor for gaining trust among end-users and the scientific community.

10. The propagation of a new thesis (or the (hypo)thesis of nitrosogenesis/ carcinogenesis) as an explanatory model on cancer pathogenesis is an innovative, provocative, and challenging, but also rapidly validable trend. A test of the validity and robustness of the data that has the sole purpose of leading to a dramatic decrease in skin cancer incidence. The necessity of its validation requires first of all its understanding / conceptualization, which in practice is also ″extremely simple″ and at the same time Genius or : simply genius. The stormy rejection (by certain circles) of this tendency of universal acceptability underline basically one thing : its strong presence and relevance with regard to the generation and progression of skin cancer, but also of cancer in general. And this globally, not locoregionally.

11. The control of skin cancer incidence / basal cell carcinomas / also consists in the control of the spread of carcinogens in drugs. It is the nitrosamines that are able to induce mutations of p53 / RAS oncogenes , and hence promote malignant cell clone development. The link between carcinogens officially declared by the FDA in drugs, the mutations known so far in keratinocytic tumors and the dose-dependent time intervals required for their occurrence and/or evolution should not be ignored once again.

12. The critical but still academic point of view, the different point of view, remains precisely the right, innovative or so-called new starting point that could guarantee a drastic decrease in skin cancer incidence, but not only. And this in the simplest or most elementary way: that of elimination. Or the one that follows the Hippocratic postulate: ″Primum non nocere!″.

References

1. Tchernev G. Nitrosogenesis Of Skin Cancer: The Nitrosamine Contamination In The Calcium Channel Blockers (Amlodipine), Beta Blockers (Bisoprolol), Sartans (Valsartan/Losartan), Ace Inhibitors (Perindopril/Enalapril), Tricyclic Antidepressants (Melitracen), Ssris (Paroxetine), Snris (Venlafaxine) And Metformin: The Most Probable Explanation For The Rising Skin Cancer Incidence. Georgian Med News. 2023;339:24-32.
2. Tchernev G. The Nitrosamine Contamination In Beta Blockers (Bisoprolol/Metoprolol), Ace Inhibitors (Lisinopril/Perindopril), Thiazides Diuretics (Hct), Calcium Channel Blockers (Amlodipine/Felodipine), Sartans (Candesartan) And The Subsequent Skin Cancer Development And Progression: Apocalypse Now. Georgian Med News. 2023;337:138-145.
3. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/updated-information-recommended-acceptable-intake-limits-nitrosamine-drug-substance-related
4. Etemadi A, Poustchi H, Chang CM, et al. Exposure to polycyclic aromatic hydrocarbons, volatile organic compounds, and tobacco-specific nitrosamines and incidence of esophageal cancer. J Natl Cancer Inst. 2023:djad218.
5. Furdova A, Kapitanova K, Kollarova A, et al. Periocular basal cell carcinoma - clinical perspectives. Oncol Rev. 2020;14:420.
6. Alrashidi A, Rhodes LE, Sharif JCH, et al. Systemic drug photosensitivity-Culprits, impact and investigation in 122 patients. Photodermatol Photoimmunol Photomed. 2020;36:441-451.
7. Tchernev G, Kordeva S. Nitrosogenesis Of Skin (Human) Cancer- The Hidden Truth Of A Neverending Story: Nitrosamine Contamination In Olmesartan, Valsartan And Hct As Main Risk Factor For The Development Of Keratinocyte Cancer. Georgian Med News. 2023;337:63-67.
8. Tchernev G, Kordeva S, Lozev I. Metatypical Bccs Of The Nose Treated Successfully Via Bilobed Transposition Flap: Nitrosamines In Aces (Enalapril), Arbs (Losartan) As Possible Skin Cancer Key Triggering Factor. Georgian Med News. 2023;335:22-25.
9. Mehlan J, Ueberschaar J, Hagenström K, et al. The use of HCT and/or ACE inhibitors significantly increases the risk of non-melanotic skin cancer in the periocular region. Graefes Arch Clin Exp Ophthalmol. 2022;260:2745-2751.
10. Nardone B, Majewski S, Kim AS, et al. Melanoma and Non-Melanoma Skin Cancer Associated with Angiotensin-Converting-Enzyme Inhibitors, Angiotensin-Receptor Blockers and Thiazides: A Matched Cohort Study. Drug Saf. 2017;40:249-255.
11. Azoulay L, St-Jean A, Dahl M, et al. Hydrochlorothiazide use and risk of keratinocyte carcinoma and melanoma: A multisite population-based cohort study. J Am Acad Dermatol. 2023;89:243-253.
12. Hashizume H, Nakatani E, Sasaki H, et al. Hydrochlorothiazide increases risk of nonmelanoma skin cancer in an elderly Japanese cohort with hypertension: The Shizuoka study. JAAD Int. 2023;12:49-57.
13. Götzinger F, Hohl M, Lauder L, et al. A randomized, placebo-controlled, trial to assess the photosensitizing, phototoxic and carcinogenic potential of hydrochlorothiazide in healthy volunteers. J Hypertens. 2023;41:1853-1862.
14. https://www.fda.gov/drugs/drug-safety-and-availability/fda-updates-and-press-announcements-angiotensin-ii-receptor-blocker-arb-recalls-valsartan-losartan
15. https://veeprho.com/impurities/n-nitroso-moxonidine-mononitroso/
16. https://www.agnitio.co.in/product/n-nitroso-moxonidine-impurity-1/
17. Tchernev G. Neighbouring Melanomas And Dysplastic Nevus Developing Simultaneously After Candesartan Intake:

Nitrosamine Contamination/ Availability As Main Cause For Skin Cancer Development And Progression. Georgian Med News. 2023;336:104-107.
18. https://www.chemistryworld.com/news/addressing-the-saga-of-nitrosamine-contamination-in-drugs/4018123.article
19. Barnes JM, Magee PN. Some toxic properties of dimethylnitrosamine. Br J Ind Med. 1954;11:167-74.
20. Magee PN, Barnes JM. The production of malignant primary hepatic tumours in the rat by feeding dimethylnitrosamine. Br J Cancer. 1956;10:114-22.
21. Magee PN, Barnes JM. Induction of kidney tumours in the rat with dimethylnitrosamine (N-nitrosodimethylamine). J Pathol Bacteriol. 1962;84:19-31.
22. Stanfill SB, Hecht SS, Joerger AC, et al. From cultivation to cancer: formation of N-nitrosamines and other carcinogens in smokeless tobacco and their mutagenic implications. Crit Rev Toxicol. 2023;53:658-701.
23. https://www.chemlink.co.uk/reducing-nitrosamines-in-pharmaceutical-formulations/
24. Min H, Kudo E, Hino A, et al. p53 gene mutation in N-butyl-N-(4-hydroxybutyl)nitrosamine-induced urinary bladder tumors and N-methyl-N-nitrosourea-induced colon tumors of rats. Cancer Lett. 1997;117:81-6.
25. Chang KW, Sarraj S, Lin SC, et al. P53 expression, p53 and Ha-ras mutation and telomerase activation during nitrosamine-mediated hamster pouch carcinogenesis. Carcinogenesis. 2000;21:1441-51.
26. Georgiadis P, Smith CA, Swann PF. Nitrosamine-induced cancer: selective repair and conformational differences between O6-methylguanine residues in different positions in and around codon 12 of rat H-ras. Cancer Res. 1991;51:5843-50.
27. Giglia-Mari G, Sarasin A. TP53 mutations in human skin cancers. Hum Mutat. 2003;21:217-28.
28. Shea CR, McNutt NS, Volkenandt M, et al. Overexpression of p53 protein in basal cell carcinomas of human skin. Am J Pathol. 1992;141:25-9.
29. Ibrahim N, Jovic M, Ali S, et al. The epidemiology, healthcare, and societal burden of basal cell carcinoma in Wales 2000-2018: a retrospective nationwide analysis. Br J Dermatol. 2023;188:380-389.
30. https://www.cancer.org/cancer/types/basal-and-squamous-cell-skin-cancer/about/key-statistics.html
31. Gangan R. Basal cell carcinoma: Epidemiology. J Skin Sex Transm Dis 2022;4:157-63.
32. van der Schroeff JG, Evers LM, Boot AJ, et al. Ras oncogene mutations in basal cell carcinomas and squamous cell carcinomas of human skin. J Invest Dermatol. 1990;94:423-5.
33. Mehlan J, Ueberschaar J, Hagenström K, et al. The use of HCT and/or ACE inhibitors significantly increases the risk of non-melanotic skin cancer in the periocular region. Graefes Arch Clin Exp Ophthalmol. 2022;260:2745-2751.
34. Mochizuki H, Nagazawa Y, Arimoto-Kobayashi S. Genotoxicity, and the stability of N-nitrosomorpholine activity following UVA irradiation. Mutat Res Genet Toxicol Environ Mutagen. 2024;893:503721.