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Original Article

The effectiveness of chemopreventive therapies in reducing non-melanoma skin cancer

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Abstract

Introduction: Non-melanoma skin cancer (NMSC) is the most common type of skin cancer and has a significant impact on patient quality of life. Effective prevention of NMSC is essential to reduce the incidence of skin cancer. One approach that has been developed is chemopreventive therapy, which uses pharmacological agents to inhibit or delay the development of cancer.
Objective: To assess the effectiveness of various chemopreventive therapies, such as nonsteroidal anti-inflammatory drugs (NSAID), difluoromethylornithine (DFMO), vitamin D3, nicotinamide, and acitretin, in reducing the incidence of NMSC.
Methods: Systematic literature review with a search for articles in the PubMed and Google Scholar databases, using the keywords "chemopreventive" and "non melanoma skin cancer". The inclusion criteria were that articles had the same objectives and results as the objectives of this study. Five articles that met the inclusion criteria were used in this analysis.
Results: This study showed that NSAIDs, DFMO, vitamin D3, nicotinamide, and acitretin significantly reduced the incidence of NMSC. The use of NSAIDs reduced the risk of BCC, DFMO showed a decrease in the incidence of new NMSC, vitamin D3 reduced BCC recurrence, nicotinamide reduced the incidence of new NMSC, and acitretin was effective in preventing invasive SCC.
Conclusion: Chemopreventive therapy can be an effective strategy in reducing the incidence of non-melanoma skin cancer.

Keywords: *basal cell carcinoma, chemopreventive, non-melanoma skin cancer, squamous cell carcinoma.*

Abstrak

Pendahuluan: Kanker kulit non-melanoma merupakan jenis kanker kulit yang paling sering ditemukan dan memiliki dampak signifikan terhadap kualitas hidup pasien. Upaya pencegahan yang efektif sangat penting untuk menurunkan insidens kanker kulit. Salah satu pendekatan yang telah dikembangkan adalah terapi kemopreventif, yaitu penggunaan agen farmakologis untuk menghambat atau menunda perkembangan kanker.
Tujuan: Menilai efektivitas berbagai terapi kemopreventif, seperti NSAID, DFMO, vitamin D3, nikotinamid, dan asitretin, dalam menurunkan insidens kanker kulit non-melanoma.
Metode: Tinjauan pustaka sistematis dengan penelusuran artikel pada basis data PubMed dan Google Scholar menggunakan kata kunci *"chemopreventive"* dan *"non melanoma skin cancer"*. Kriteria inklusi meliputi artikel yang memiliki tujuan dan luaran yang sesuai dengan tujuan penelitian ini. Sebanyak lima artikel yang memenuhi kriteria inklusi dianalisis dalam penelitian ini.
Hasil: Hasil penelitian menunjukkan bahwa NSAID, DFMO, vitamin D3, nikotinamid, dan asitretin secara signifikan menurunkan insidens kanker kulit non-melanoma. Penggunaan NSAID menurunkan risiko terjadinya BCC, DFMO menunjukkan penurunan insidens NMSC baru, vitamin D3 menurunkan kekambuhan BCC, nikotinamid menurunkan insidens NMSC baru, serta asitretin efektif dalam mencegah terjadinya SCC invasif.
Kesimpulan: Terapi kemopreventif dapat menjadi strategi yang efektif dalam menurunkan insidens kanker kulit non-melanoma.

Keywords: *kanker kulit non-melanoma, karsinoma sel basal, karsinoma sel skuamosa, kemopreventif*

Background

Cancer Non-melanoma skin cancer or Non-Melanoma Skin Cancer (NMSC) is the most commonly diagnosed type of malignant skin tumor throughout the world. This disease is mostly caused by exposure to ultraviolet (UV) radiation.[1] More than 95% of NMSC cases appear in the head and neck area, such as the nose, ears, eyelids, and lips. NMSC consists of two main types, namely squamous cell carcinoma (SCC) and basal cell carcinoma (BCC).[2]

According to the Surveillance, Epidemiology, and End Results (SEER) program, NMSC, although it does not have a significant impact on the number of cancer deaths, its incidence continues to increase with age.[2] As of 2019, it was found that globally there were more than 6 million new cases of NMSC, of which 4 million were BCC and the rest were SCC.[3,4] Based on other data from the Global Cancer Observatory (GLOBOCAN), the highest incidence of NMSC is in North America (49%) and the highest mortality is in Asia (43.6%).[2]

In Indonesia, there has not been much research on the prevalence of skin cancer, but according to one researcher at Dr. Cipto Mangunkusumo General Hospital, of the 263 cases of skin cancer studied, the most common skin cancer was BCC 66.9%, followed by SCC 27.4% and malignant melanoma 5.7%.[5] Therefore, an effective prevention strategy is needed to reduce the incidence of skin cancer. One approach developed in the prevention of skin cancer is chemopreventive therapy, namely the use of pharmacological agents to inhibit, delay or fight the development of cancer cells.[6,7]

Some chemopreventive agents that have been studied include non-steroidal anti-inflammatory drugs (NSAIDs), difluoromethylornithine (DFMO), vitamin D3, nicotinamide, and vitamin A.[8,9] Some chemopreventive agents work by inhibiting the development of precancerous enzymes in cells, inhibiting inflammation, cancer cell proliferation, and increasing apoptosis so that they can suppress the development of NMSC.[1,10] However, no recent studies have been found that examine all of these chemopreventive therapies. Therefore, this systematic review was conducted with the aim of evaluating the effectiveness of various chemo-preventive therapies in reducing the incidence of non-melanoma skin cancer. This study also examines scientific evidence related to the role of chemopreventive in suppressing the rate of NMSC development and its implications in clinical practice.

Methods

The search for this article is a systematic literature review to determine the benefits of chemopre-ventive in reducing cases of non-melanoma skin cancer. The literature search was conducted on the electronic databases PubMed and Google Scholar using the keywords "chemopreventive" and "non-melanoma skin cancer". With the inclusion criteria, namely articles that have the same objectives and results as the objectives of this study, articles are available in full text for free, articles are written in English with a publication time of the last 15 years. Exclusion criteria were articles with quantitative data that were not included, and literature that was not fully accessible or duplicated.

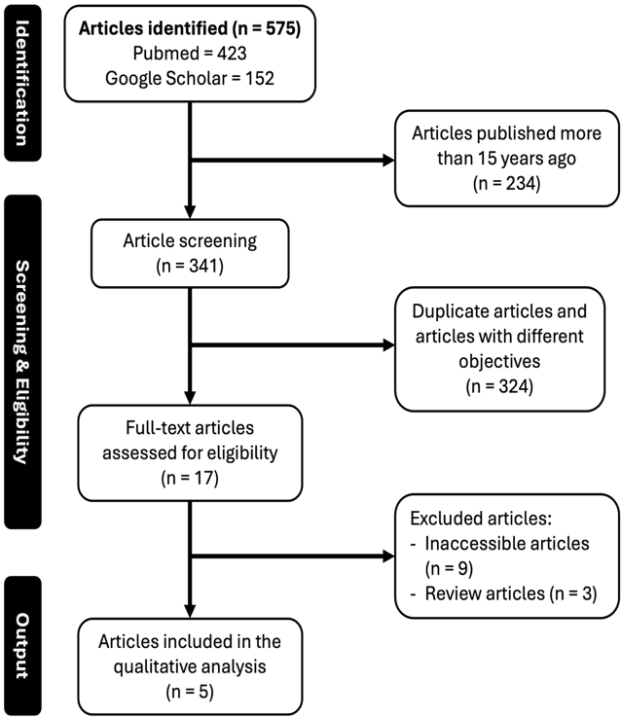

Figure 1. Systematic review extraction scheme.

Results

A total of 5 articles were used in this study. These articles have met the specified criteria. The following are the extraction results of the 5 articles used in this study:

Table 1. Characteristics of research studies

Author	Study Design	Chemopreventive Agent	Average Age (years)	Number of Subjects	Study Duration
Reinau D, et al. 2014.[7]	Case Control	NSAID	66	73,262	19 years
Kreul, et al. 2012.[11]	RCT	DMFO	61	291	5 years
Ince B, et al. 2019.[12]	Prospective Cohort	Vitamin D	69	496	3 years
Chen AC, et al. 2015.[13]	RCT	Nicotinamide	66	386	1 year
Bhullar S, et al. 2023.[14]	Retrospective Cohort	Vitamin A	71	34	2 years

Table 2. Summary of extracted articles

Author	Study Subjects	Results
Reinau D, et al. 2014.[7]	65,398 cases of BCC and 7,864 cases of SCC with NSAID use	The risk of BCC with long-term ibuprofen use decreased (OR: 0.61, 95% CI: 0.48-0.78). The reduction in SCC risk was statistically significant only for naproxen use (OR: 0.84, 95% CI: 0.70-0.99).
Kreul, et al. 2012.[11]	291 patients with a history of NMSC, divided into intervention with 500 mg/day DFMO (144 participants) vs. placebo (147 participants)	The incidence of new NMSC during the study was lower in the DFMO intervention group compared to placebo (0.444 vs. 0.701, p = 0.012). The incidence of new BCC was also lower in the DFMO group compared to placebo (0.294 vs. 0.466, p = 0.014).
Ince B, et al. 2019.[12]	A total of 496 BCC patients: 239 in the first stage, 114 in the second stage, and 143 in the third stage. In the third stage, 50,000 IU oral vitamin D3 was administered weekly for 6 weeks.	The average serum 25-OH vitamin D3 level after replacement therapy was 40.1 ng/mL, and recurrence rates dropped to 3.49%. Recurrence rates in stage 2 were statistically higher than in stage 3 (P < 0.05).
Chen AC, et al. 2015.[13]	386 non-melanoma patients receiving 500 mg of nicotinamide twice daily for 12 months	The incidence of new non-melanoma skin cancer was 23% lower (95% CI, 4 to 38) in the nicotinamide group compared to placebo (P = 0.02). The incidence of new BCC (20% lower [95% CI, -6 to 39], P = 0.12) and new SCC (30% lower [95% CI, 0 to 51], P = 0.05).
Bhullar S, et al. 2023.[14]	34 SCC patients: 20 immunocompetent, 9 immunosuppressed, and 5 immunodeficient, treated with 14.1 mg/day acitretin for 1.8 years	A 68% reduction in invasive SCC incidents during acitretin therapy compared to no therapy (P < 0.0001). SOTR and immunocompetent patients showed reductions of 73% and 76% in invasive SCC incidents with acitretin therapy, respectively.

Discussion

Based on the research results that we obtained from 5 articles that met our inclusion criteria, there are several chemopreventive agents that can significantly reduce the incidence of NMSC.
According to Sari M, et al, several studies have shown that UV exposure is associated with increased expression of cyclooxygenase-2 (COX-2) in human skin. COX-2 is found in actinic keratosis (AK), SCC, and is expressed in the parenchyma and stroma of BCC tissue. Increased expression of COX-2 triggers the production of prostaglandins (PG) and vascular epidermal growth factor (VEGF), which accelerate tumor proliferation.[15,16]

According to Janicka N, et al, parenteral administration of naproxen (nonselective COX) to mice at a dose of 1 mg in 100 µL phosphate-buffered saline (PBS) increases apoptosis and inhibits tumor growth, which has potential therapeutic implications.[17] Literature review conducted by Sari, et al. stated a cohort study of 92,125 Caucasian women found that aspirin or ibuprofen use was associated with a lower risk of SCC tumors that were positive for p53 (by immunohistochemistry or TP53 mutation analysis) or with PTCH loss.[15]

A study by Taznin T, et al. in the lightest Caucasians often had lower vitamin D levels than other races.[18] This is partly due to their increased photosensitivity. Vitamin D insufficiency contributes to tumorigenesis, more specifically a worse prognosis related to drug resistance. Vitamin D3 hydroxyderivatives can suppress the development of skin cancers induced by ultraviolet B or chemical exposure.[19] In addition, vitamin D3 can also inhibit the hedgehog signaling pathway associated with several types of cancer, making it a target for research into skin cancer treatments, including SCC and BCC.[2]

In a study by Lappe J, et al. Among 2303 women with a mean age of 65 years, the mean baseline serum 25-hydroxyvitamin D level was 32.8 ng/ml. At year 1, serum 25-hydroxyvitamin D levels were 43.9 ng/ml in the vitamin D3 + calcium group versus 31.6 ng/ml in the placebo group. A new cancer diagnosis was confirmed in 109 participants, 45 (3.89%) in the vitamin D3 + calcium group and 64 (5.58%) in the placebo group (difference, 1.69% [95% CI, -0.06% - 3.46%]; P=0.06).[20] A literature review by Gorgojo AM, et al, suggested that taking 1500 IU of vitamin D3 daily may reduce the risk of cancer death in men in the United States by 30%. This suggests that adequate vitamin D intake may have a protective effect against cancer.[21]

Based on a literature review by Russomanno K, et al, the risk of developing SCC and BCC in the solid organ transplant recipient (SOTR) population is estimated to be 40–250 and 5–10 times higher than the general population, respectively. Systemic retinoid administration can reduce the risk of developing SCC and BCC.[22] A study by Kadakia C, et al, involving 70 non-SOTR patients who took acitretin 25 mg orally for five days a week showed an equivalent level of effectiveness in preventing NMSC.[23]

A randomized control trial (RCT) study, conducted by Bailey, et al, showed that oral DFMO administration at a dose of 500 mg/day for 5 years was safe and well tolerated and resulted in significant inhibition of Ornithine decarboxylase (ODC) activity.[24] There was a significant decrease in the incidence of NMSC developing into BCC in patients taking DFMO compared to placebo. A total of 69 subjects taking DFMO developed 163 new BCCs compared to 77 subjects taking placebo who developed 245 new BCCs. The incidence of BCC in the placebo group (0.40 events/patient-year) was significantly greater (P=0.03) than the rate in subjects taking DFMO (0.28 events/patient-year).[24]

In accordance with research conducted by Schneider, et al, conducted a survey of 50 skin cancer patients undergoing Moh's surgery in 2019 who consumed nicotinamide 2x500 mg compared to sunscreen on the perceived risk reduction of skin cancer. In the subgroup of respondents who consumed nicotinamide had a significantly higher risk reduction of 41.2% in BCC and 38.3% in SCC ($p<0.05$) and was positively correlated with nicotinamide use. In addition, 15.6% of respondents believed that nicotinamide was more effective than sunscreen in preventing skin cancer.[25]

Limitations

This study has several limitations. One of them is that although the data collection aimed to gather relevant studies from databases, some references included are older than five years. Furthermore, the inclusion and exclusion criteria for this systematic review only considered sources written in English and excluded studies published in other languages, which could potentially lead to bias. The small

number of articles included in analysis potentially leads to overestimation of results.

Conclusion

This study demonstrates that chemopreventive agents such as NSAIDs (particularly ibuprofen and naproxen), DFMO, vitamin D3, nicotinamide, and acitretin can reduce the incidence of NMSC, including BCC and SCC. Various studies highlight the protective effects of these agents through mechanisms such as the inhibition of inflammation, suppression of cancer cell proliferation, and enhancement of apoptosis. High-risk populations, such as organ transplant recipients, exhibit higher incidences, making chemopreventive interventions highly relevant. While the efficacy of these agents is significant, further research is needed to confirm their long-term benefits and determine optimal dosages, positioning chemoprevention as a promising adjunct strategy in NMSC prevention.

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