



## Pharmacist-Physician Collaboration for the Prevention and Treatment of Eyelid Basal Cell Carcinoma

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### Abstract

**Background:** This proof of concept (PoC) study employs a multifaceted approach and focuses on collaboration's impact in preventing basal cell carcinoma (BCC), a predominant form of skin tumors occurring in the eyelid. **Methods:** The first phase includes a literature review spanning 2010-2023, where relevant data from PubMed and Web of Science are collected and analyzed. Specific criteria are applied to filter articles, aiming to identify trends, and gaps in existing research. The second phase focuses on clinical data analysis at Centro Hospitalar de Setúbal, Portugal (CHSP), involving the retrieval and analysis of diagnostic records of suspicious eyelid malignant lesions. The third phase entails a community perception survey on self-care and prevention, employing anonymous surveys distributed via Quick Response codes (QR codes) and Google Forms to hospital visitors and patients. Targeted interventions and educational programs, including ABCDE rule criteria for distinguishing malignant lesions, guide physicians and pharmacists in the early detection of eyelid BCC.

**Results:** Among the 350 initially screened articles, a total of 55 articles were selected, aligning with our objectives. Within this subset, a correlation was found between eyelid BCCs and Portugal (n = 1) and Ophthalmology (n = 10). Regarding self-care and prevention strategies by analyzing responses from 201 patients. Lastly, results showed that the implemented the Clinical "ABCDE" Rule for Pharmacist-Physician Collaboration, aiming to guide patients towards early detection and treatment is a valuable assessment technique for identifying suggestive tumor lesions and optimizing patient care.

**Conclusion:** Overall, the coordinated efforts of the three study phases provide promising insights into collaborative strategies and actively facilitate pharmacist-physician collaboration in promptly identifying malignant indicators for effective eyelid BCC prevention.

**Keywords:** ABCDE Rule; Basal Cell Carcinoma; Eyelid Basal Cell Carcinoma; Ophthalmology; Pharmacist; Skin Cancer

## Introduction

Preventing cancer is crucial to achieving the Millennium Goals by 2030, aiming to reduce incidents and mortality rates [1]. Basal cell carcinoma (BCC) is experiencing a significant global increase in incidence rates, with projections indicating a substantial rise in diagnoses in the coming decades [2,3]. However, comprehensive documentation of the incidence and mortality of non-melanoma skin tumors (NMSTs), including BCC, is lacking due to underreporting [4]. According to GLOBOCAN 2020, new skin cancer cases exceeded one million, with BCC being among the most prevalent oncological conditions [4]. Mortality statistics also included BCC, with reported numbers exceeding 60,000 [4]. Despite these alarming numbers, cases of eyelid BCC are often underreported in several regions, leading to misdiagnoses due to infrequent biopsies and potentially inaccurate diagnostic statistics [5,6].

Ultraviolet (UV) exposure, particularly in the eyelids, critically contributes to BCC development [7]. BCC primarily originating from basal cells in the epidermis and ocular conjunctiva constitutes over 90% of malignant eyelid tumors [7-10]. The incidence of BCC is notably higher in the lower eyelid compared to the upper eyelid, with tumors commonly found in the medial canthal region [7,8,11].

UV rays penetrate the skin, causing DNA damage and genetic mutations [12]. TP53 gene mutations, often found in eyelid BCC cases, are triggered by repeated UVB exposure [12,13]. Chronic UVB exposure can compromise the local immune system of the skin, hindering its ability to eliminate cancer cells [12,13]. Meanwhile, UVA radiation deeply affects the epidermal layers, inducing actinic degeneration, particularly in lower eyelid fibroblasts, leading to DNA impairment, a hallmark of invasive BCC [14].

Given the increasing incidence rates and the looming specter of underreporting and misdiagnosis in eyelid BCC, effective prevention, early detection strategies, coupled with improved reporting and diagnostic practices, are essential for reducing its burden and associated morbidity and mortality [5,6,15-18]. Additionally, BCC can frequently involve multiple periocular areas [19,20], with early detection crucial in preventing severe consequences such as functional impairment, aggressive local growth, and eyelid deformities [6,19], and the potential misdiagnosis of tumoral lesions as benign [21].

The management of patients with eyelid lesions requires a multidisciplinary healthcare team, with effective communication and timely referrals among specialists being imperative to optimize patient outcomes [22-24]. In many countries, incomplete records on eyelid BCC make it challenging to accurately determine the prevalence rates [6]. To address the high-cost preventive services, there is growing interest in utilizing interprofessional teams focused on prevention practices and improving access to healthcare services [25]. Pharmacists play a crucial role in promoting awareness of tumor risk, especially among high-risk groups [22,26], and integrate into multidisciplinary teams to improve health outcomes, particularly in primary healthcare settings [16,26].

Fernandez-Llimos, *et al.* (2023) characterized pharmacy practice as “the scientific discipline that examines various aspects of the practice of pharmacy, assessing its impact on healthcare systems, medication usage, and patient care” [27]. Studies in pharmacy practice aim to explore various aspects of pharmaceutical care and its impact on patient outcomes, including patient adherence, healthcare disparities, patient education, and the social determinants of health [27,28]. Therefore, this study investigates the impact of pharmacist-physician collaboration on the prevention and treatment of eyelid BCC, aiming to contribute to public health outcomes and achieving the Millennium Goals.

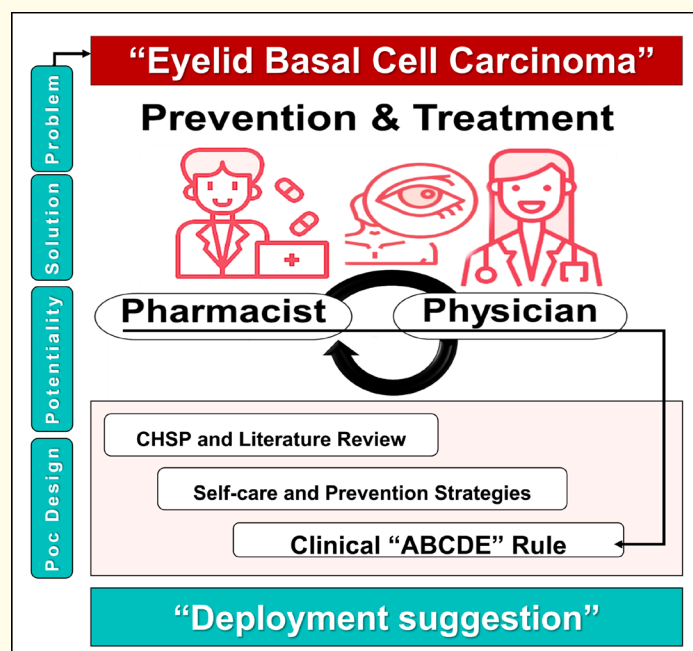
## Methods

### PoC Designing

In this prospective Proof of Concept (PoC) study, we have developed a comprehensive methodology that emphasizes the collaborative efforts between pharmacists and physicians to improve primary healthcare outcomes through the implementation of collaborative practices among pharmacists (Figure 1). This PoC examines the possible impact of collaboration between pharmacists and physicians on the prevention and treatment of eyelid BCC. Consequently, identifying potential challenges and solutions in preventing and treating these malignant tumors is essential. The methodology is organized into three stages.

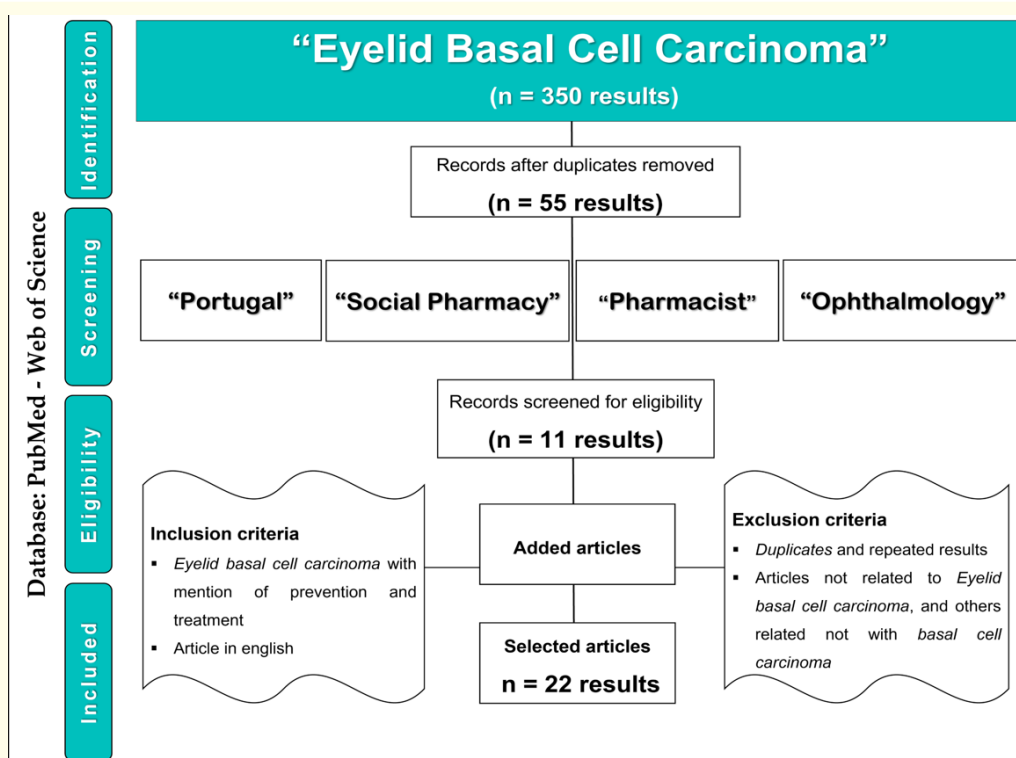
### Stage 1: CHSP Database and Literature Review

- **Sub-stage 1.1:** Identification of suspected cases of eyelid lesions in a hospital setting was based on a preliminary study of the incidence of eyelid tumors referred to the oculoplastic department between 2015 and 2021 [7,22]. Ethical approval was obtained from the institutional committee (Ethics Committee Id.46).



**Figure 1:** PoC design methodology for pharmacist-physician collaboration. Abbreviation: CHSP- Centro Hospitalar de Setúbal, Portugal; ABCDE Rule Meaning - Asymmetry, Border, Color, Diameter and Evolving.

- Sub-stage 1.2:** Searches were conducted on PubMed and Web of Science using the term “Eyelid Basal Cell Carcinoma.” The term was combined with “Portugal,” “Social Pharmacy,” “Pharmacist,” and “Ophthalmology.” All data are limited to articles published in the English language between 2010 and 2023 and screened following specific criteria (Figure 2).



**Figure 2:** Flowchart illustrating the data collection process and search criteria.

### Stage 2: Self-care and prevention strategies

Evaluation of self-care and prevention strategies involved asking a semi-structured anonymous question to CHSP visitors/patients during a specific day through Quick Response codes and Google Forms about eyelid BCCs. It included the question “Did your pharmacist advise you to use sunscreen as UVA/B protection? (Yes/No),” aiming to identify professional counseling and implement improvements in pharmacist-physician collaboration.

### Stage 3: Clinical “ABCDE” rule for pharmacist-physician collaboration

To provide direct and accurate information on the prevention and treatment of eyelid BCCs, the clinical “ABCDE” rule (Table 1) was utilized as a guideline for conducting visual examinations to differentiate between benign and malignant tumors. Educational intervention was directed at physicians and pharmacists, both in hospital settings and primary care services, including community pharmacies. This intervention was supported by the results and the clinical characteristics in oncology considering the “ABCDE” rule a significant breakthrough in understanding the clinical morphology of eyelid skin tumors [29,30].

**Table 1:** ABCE rule indicating malignancy lesions.

Letter	Meaning	Malignant clinical features
A	Asymmetry	Asymmetry lesion
B	Border	Border irregularity
C	Color	Color variegation
D	Diameter	Diameter > 6 mm
E	Evolving	Evolution in lesion changes

During the training, the effectiveness of the clinical rule was evaluated qualitatively and quantitatively, considering the following criteria: False Positives (lesions initially considered malignant but found benign) and False Negatives (lesions initially considered benign but found malignant):

- **Malignant Lesion Detection Rate:** This metric served as a direct quantitative measure of the rule’s effectiveness in successfully identifying malignant lesions compared to the total lesions evaluated by a specific number of trainees (pharmacists and physicians).

- **Assessment of False Positives and Negatives:** This analysis was crucial for quantitatively assessing the number of incorrect outcomes, which included false positives (lesions initially considered malignant but found benign) and false negatives (lesions initially considered benign but found malignant).

### Statistical analysis

Statistical analyses were performed using the statistical software GraphPad Prism 5.0 and an independent-samples t-test (SPSS Statistics, version 28.0.1.0, 2021, IBM, Armonk, NY, USA). A p-value of less than 0.05 was considered to indicate statistical significance.

### Results

#### Stage 1: CHSP database and literature review

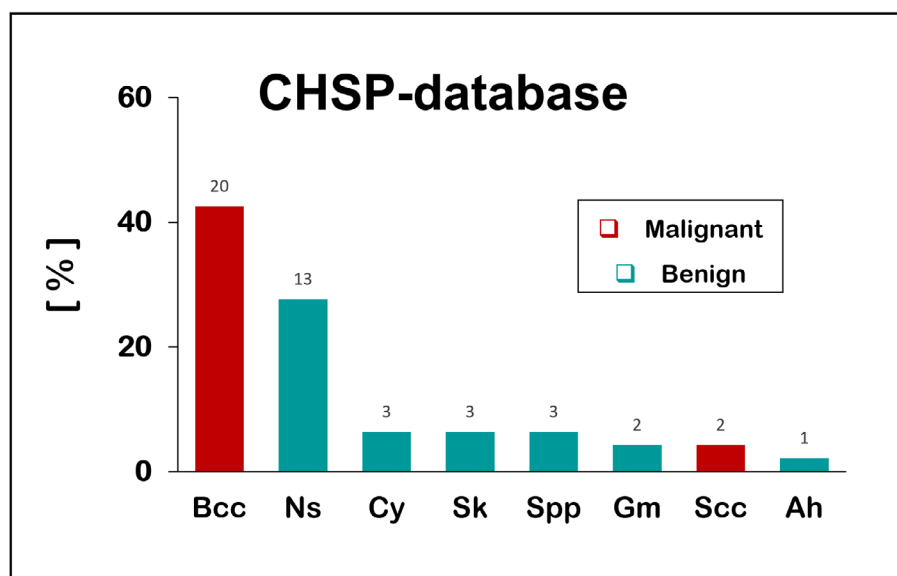
Figure 3 summarizes the main clinical types of patient cases with histopathologically proven eyelid tumors. Of the total cases referred, 46.8% were malignant tumors, occurring in patients over 50 years old from the Setúbal region. None of these patients had a documented history of previous phototherapy treatment. Additionally, more than 50% of benign lesions were also diagnosed through biopsy.

In the studied literature (2010-2023), an initial search using the term “Eyelid Basal Cell Carcinoma,” yielded a broad pool of 350 articles. Upon meticulous refinement, eliminating duplicates and ensuring alignment with predefined objectives, we narrowed down our selection to 55 articles of particular relevance.

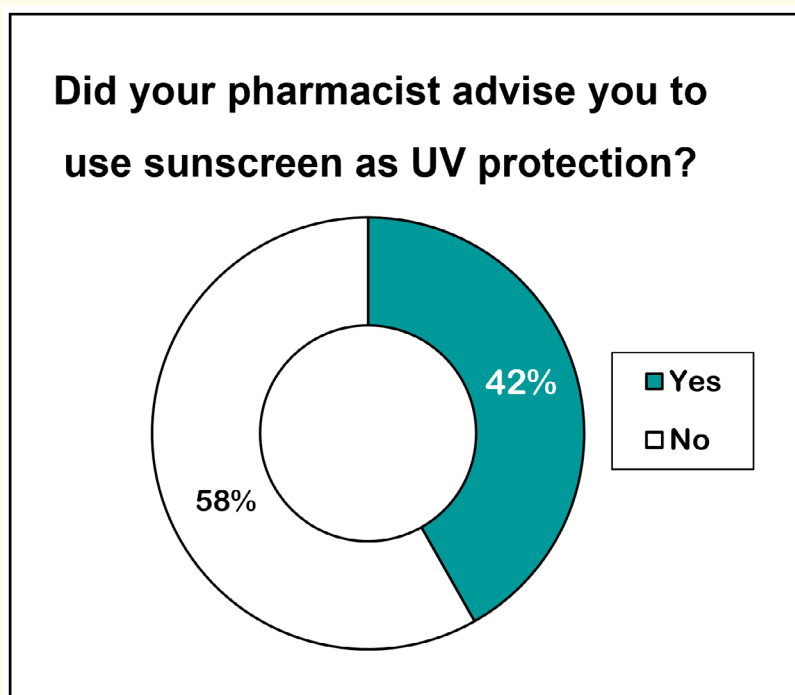
Within this subset, we identified a correlation between eyelid BCCs and “Portugal” (n = 1) and “Ophthalmology” (n = 10). Notably, no correlation was found between eyelid BCCs and “Social pharmacy” and “Ophthalmology”.

#### Stage 2: Self-care and prevention strategies

Regarding patients’ answers (n = 201) to the PoC question, 42% responded that pharmacists advised the use of sunscreen as UV A/B protection (Figure 4). Among the patients who answered affirmatively, 81% were female, 18% were male, and 1% chose not to disclose their gender, with participants ranging in age from 16 to 86 years (mean age =  $43.0 \pm 13.2$  years old).



**Figure 3:** Histopathological types of eyelid tumors. Abbreviations: Ah, apocrine hidrocystoma; BCC, basal cell carcinoma; Cy, cyst; Gm, granulomatous inflammation; Ns, nevus; Sk, seborrheic keratosis; SCC, squamous cell carcinoma; Spp, squamous papilloma.



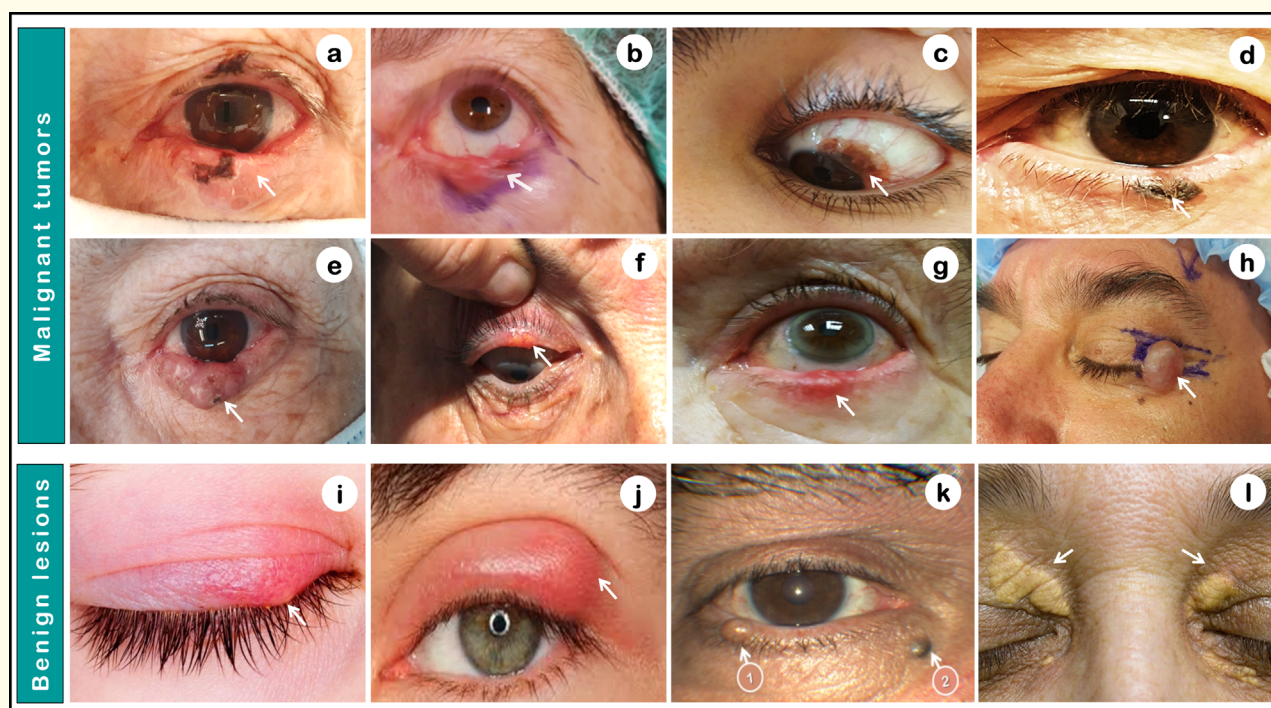
**Figure 4:** PoC answers from anonymous survey for hospital visitors/patients.

### Stage 3: Clinical “ABCDE” rule for pharmacist-physician collaboration

To draw an analogy with simple questions aimed at guiding patients regarding self-care and to establish an objective methodology beneficial for the collaboration between pharmacists and physicians during the prevention and screening of eyelid BCCs, the authors presented the histopathological results and potential clinical

characteristics based on the “ABCDE” rule (A-E). This approach serves as an important assessment tool for identifying early signs of suggestive tumors and prioritizing patient treatment.

For instance, each letter of the rule represents a critical characteristic indicative of potential malignancy (Figure 5).



**Figure 5:** Malignant tumors: asymmetric BCC (a); BCC with irregular border (b); melanoma (c); pigmented BCC (d); ulcerative BCC (e); superficial BCC (f-g); nodular BCC (h). Benign lesions: hemangioma (i); chalazion (j); arteriovenous hemangioma (k-a); intradermal melanocytic nevus (k-b); xanthelasma (l) [30].

The letter A means “asymmetry” observed in malignant lesions (Figure 5-a), the letter B, “irregular border”, signifies typical irregularities along the contour edges; distinctly marked during clinical evaluation (Figure 5-b).

The letter C indicates “irregular coloration” observed if the lesion presents a pigmented lesion with multiple shades, a hallmark of malignant tumors (Figure 5-c) [29]. Pigmented BCCs (Figure 5-d) may exhibit various morphologies overlapping with recognized subtypes such as superficial, nodular, and morpheaform. The letter D refers to “diameter” of the lesion, specifically lesions exceeding six millimeters in size, including those with central necrosis (Figure 5-e).

Lastly, the letter E, stands for “evolving”, indicating changes over time in size, color, and shape of the lesion. For example, Figure 5-f illustrates a lesion initially resembling a hordeolum that failed to respond to treatment and was later diagnosed as BCC. Eyelash loss is also characteristic of BCC evolution (Figure 5-g). In the literature, apocrine hidrocystoma tumors have been reported to have this characteristic; however, in some severe cases, there was no eyelash involvement [31].

This comprehensive characterization underscores the utility of the “ABCDE” rule in enhancing diagnostic accuracy and guiding timely intervention strategies.

Nodular or nodular-ulcerative BCC (Figure 5-h) represents classic basal cell carcinoma, characterized by a shiny, firm, indurated nodule with dilated blood vessels, which can resemble non-cancerous, chalazion-like lesions.

Benign eyelid lesions, such as infectious or inflammatory conditions, can sometimes present clinically indistinguishable features. A hordeolum, an acute bacterial infection of an eyelid gland typically caused by *Staphylococcus aureus* (Figure 5-i), and a chalazion, caused by obstructive inflammation of the meibomian gland's secretion ducts (Figure 5-j) [32], fall into this category. Chronic chalazions resistant to treatment should prompt referral by pharmacists for medical evaluation and potential biopsy.

Arteriovenous hemangioma (Figure 5-k1) has a highly characteristic vascular appearance, sometimes necessitating surgical excision. Intradermal melanocytic nevi (Figure 5-k2) are composed of red-brown nevi or melanocytes that can be mistaken for melanoma (a malignant tumor). It is important to highlight that these benign tumors, especially melanocytic nevi, require close examination regarding their evolution and/or modified appearance to prevent misdiagnosis as benign when they may in fact be malignant tumors.

Xanthelasma (Figure 5-l), a lesion characterized by cholesterol deposition, is typically associated with dyslipidemias but rarely with tumors. In most cases, there is no need for removal.

The evaluation results revealed a success rate exceeding 80% in identifying malignant lesions using the "ABCDE" rule. Additionally, approximately 10-15% of lesions were initially misclassified, highlighting areas for improvement in the rule's application.

Importantly, during clinical interventions, pharmacists are recognized as valuable resources for both prevention and ensuring compliance with therapeutic treatments, as well as for identifying complications in post-surgical cases. In addition, they are trained to identify other dermatological problems that may coexist with eyelid lesions.

## Discussion

The research indicates a gap in understanding the connection between eyelid BCCs, Portugal, and ophthalmology. To address this gap, there's a need for focused studies on pharmacist-physician collaboration within health systems. This collaboration is crucial for effective prevention of eyelid BCCs.

Eyelids lesions, including BCCs, can be mistaken for benign conditions, underscoring the importance of training healthcare professionals to accurately identify them. Figure 3 provides a comprehensive overview of the main clinical types of patient cases with histopathological proven eyelid tumors and highlights the importance of histopathological examination in accurately diagnosing eyelid tumors. This underscores the necessity for clinicians to maintain a high index of suspicion, to ensure appropriate treatment and management.

A systematic approach and integration of the clinical "ABCDE" rule into educational interventions directed at physicians and pharmacists underscores its utility in assessing these lesions characteristics, in enhancing the early detection of malignant lesions, preventing misdiagnosis or oversight [21] and referral to prevent tissue disfigurement [16,33].

While most eyelid lesions are benign, applying the "ABCDE" rule systematically, along with considering the patient's medical history, aids in accurate diagnosis [21,34]. Pharmacists, often the first point of contact for patients, play an important role in early detection due to their accessibility [21,34]. Expansion of training programs based on PoC results is necessary to improve diagnosis and management, contributing to databases in central cancer registries. Additionally, the pharmacist's involvement in patient education about the use of sunscreen contributes to preventive measures.

Effective prevention of eyelid BCCs involves avoiding excessive UV radiation exposure and early detection through educational campaigns and screenings. Pharmacies serve as key points for patient educations and referrals for ophthalmic consultations in cases of suspicious lesions [16,35]. Despite advances in topical and systemic therapies, surgery remains the cornerstone of BCC treatment [36]. Pharmacist-physician teamwork is fundamental to improve the care provided to patients affected by BCCs, especially in their control and recurrence. Although pharmacists are not included in most health programs, their level of preparedness for providing both minor and major support in public healthcare is increasing and critical in ensuring the notification of cases and particularly to BCC guidelines [26,37].

Pharmacists hold a comprehensive understanding of the drug therapies for treating BCCs, enabling them to tailor therapeutic care to individual patient's needs. They collaborate closely with

medical professionals to ensure treatment aligns with medical recommendations. Additionally, pharmacists play an important role in managing potential adverse effects associated with treatments, such as hyperemia, conjunctivitis, and burning, commonly caused by medications like Imiquimod [16,38-40].

Patients who have had BCC require counseling regarding the risk of developing new primary skin cancers. In this context, health professionals particularly pharmacists, provide guidance on self-screening and emphasize the importance of habitual sunscreen use [16,36]. Furthermore, pharmacists address concerns about inappropriate use of dietary supplements, ensuring patients receive proper education and care to maintain their health [41,42]. Understanding that topical and oral retinoids are not recommended for reducing BCC risk in patients with a history of BCC, pharmacists monitor and control the dispensing of such drugs. They provide patients with guidance on their appropriate use based on medical indications and ensure necessary precautions are taken [43].

BCCs pose a significant global health challenge, and there remain gaps in understanding and clarifying specific treatments. Therefore, the management of eyelid BCCs must be personalized to meet individual needs [1,16,36]. Early detection is crucial for promptly referral of patients with suspicious lesions, as BCCs can occur not only on the eyelids.

While evidence supports pharmacists' roles in managing various chronic diseases, their involvement in ophthalmological contexts, specifically regarding BCCs remains relatively unexplored [44,45]. In our department, this approach had not been thoroughly investigated.

Given the complexity of preventing and treating BCCs, pharmacists, in both community and hospital settings play central roles in identification, referral, preventive guidance (sunscreens), medication, counseling and care. Their ability to identify complications during the postoperative period of eyelid BCCs excision highlights the importance of collaborative efforts between pharmacists and physicians in ensuring optimal patient outcomes and advancing public health.

#### Deployment Suggestion: Pharmacist-physician collaboration

This study takes an observational approach rather than a randomized controlled trial. It focuses on implementing the "ABCDE" rule through interventions led by pharmacists to evaluate patients with eyelid lesions.

The study's inclusion criteria target individuals seeking consultation or guidance for eyelid skin lesions from pharmacists or healthcare professionals in Setúbal, Portugal.

Clinical and diagnostic follow-ups will depend on the study protocol, typically after the initial consultation and evaluation by pharmacists. The specific timeline for these follow-ups will be determined by the study design.

The main goal of the study is to assess the accuracy of detecting and referring malignant eyelid tumors by pharmacists' using the "ABCDE" rule and to observe any improvements in patient outcomes.

During patient assessment, pharmacists will conduct anamnesis, accessing family history and predisposing risk factors if authorized by the patient through informed consent and within their professional scope and local regulations. Access to sensitive patient information will be granted based on need-to-know and patient consent.

The ethical and professional conduct of pharmacists in achieving the study objectives depends on adherence to a Code of Ethics, which undergoes regular updates and adaptation to social and legal standards. The Order of Pharmacists grants self-regulatory power, emphasizing the importance of ethical guidance [46].

To broaden access to healthcare services, the study includes virtual consultations for individuals seeking online assistance. Healthcare professionals or pharmacists will guide patients in self-screening using the "ABCDE" rule, evaluate their observations, and provide recommendations for further evaluation and care. This approach extends the scope of the study to a broader patient population.

#### Conclusions

The findings from this PoC study highlight the significant burden of malignant eyelid tumors, the essential role of histopathological diagnosis, allowed us to evaluate the effectiveness of the collaborative care model in improving the relationship between pharmacist and physician, thereby enhancing the prompt identification and treatment of malignant indicators for effective eyelid BCC prevention. The percentage improvement provides a measurable outcome indicating the degree of success achieved in fostering better collaboration, communication, and teamwork among these groups. Ultimately, this benefits patient care and outcomes within

the broader context of health, contributing to the Millennium Goal of “health as a universal right”.

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## Conflicts of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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