ORIGINAL RESEARCH REPORT

Age, Sex, and Types of Occupation with Histopathological Types in Patients with Ocular Surface Squamous Neoplasia (OSSN) in a Tertiary Hospital in Surabaya, Indonesia

Stella Agatha Widjaja[1], **Delfitri Lutfi[2]***, **Linda Dewanti[3]**, **Alphania Rahniayu[4]**, **Fitria Kusumastuti[5]**

[1]Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia.
[2]Department of Ophthalmology, Faculty of Medicine, Universitas Airlangga; Dr. Soetomo General Academic Hospital, Surabaya, Indonesia.
[3]Department of Public Health and Preventive Medicine, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia.
[4]Department of Anatomy Pathology, Faculty of Medicine, Universitas Airlangga; Dr. Soetomo General Academic Hospital, Surabaya, Indonesia.
[5]East Java Community Eye Hospital, Surabaya, Indonesia.

Article Info	ABSTRACT
  Corresponding author: Delfitri Lutfi delfitri-l@fk.unair.ac.id	**Background**: Ocular Surface Squamous Neoplasia (OSSN) is a spectrum of tumors affecting the conjunctiva and cornea, in which a more invasive type of OSSN has a higher recurrence rate. As a tropical country, Indonesia is constantly exposed to intense ultraviolet (UV) radiation, the main risk factor for OSSN. Despite this, there are very few studies regarding OSSN in Indonesia. **Objective**: This study aimed to analyze the association between sociodemographic characteristics such as age, sex, and types of occupation (outdoor and indoor) and histopathological types of OSSN to fill the gap in research and contribute to early diagnostic strategies. **Material and Method**: Sociodemographic and histopathological data were extracted from the medical records of patients who were histopathologically diagnosed with OSSN at Dr. Soetomo General Hospital from 2017 to 2021. Data from 88 samples that met the inclusion and exclusion criteria were classified and analyzed with descriptive statistics and a two-sided Fisher's exact test using SPSS version 27.0 (IBM Corp., Armonk, N.Y., USA). **Result**: The exact test results of the two-sided Fisher's exact test revealed a statistically significant relationship between age ($p = 0.0004$) and occupation type ($p = 0.049$) with histopathological types of OSSN. However, no significant association was found between sex and histopathological types of OSSN ($p = 0.130$). **Conclusion**: Age and occupation were found to have a significant association with the histopathological types of OSSN, reinforcing the need for further exploration of their strength and nature to be considered by future researchers.

Highlights
1. The histopathological types of OSSN were significantly associated with age and occupation.
2. The study's findings enhance the understanding of OSSN in Indonesia and emphasize the importance of UV exposure, occupation, and age in its development.

BACKGROUND

Indonesia has a tropical environment and receives significant sunlight, resulting in high amounts of UV radiation. The UV index in Indonesia ranges from 9 to 11+, making it one of the countries with the highest UV indices worldwide (Istirohah, et al., 2018). Ocular Surface Squamous Neoplasia (OSSN) is a prevalent ocular surface tumor linked primarily to UV exposure, with additional risk factors including age, gender, immunosuppression, HPV infection, and insufficiency of vitamin A (Dandala, 2015; Höllhumer, et al., 2020; Gurnani & Kaur, 2023). However, OSSN demographics vary regionally, prompting a need for specific investigations in Indonesia (Höllhumer, et al., 2020).

Age, a key factor, is associated with increased OSSN risk, especially in individuals aged 40 and older (Dandala, 2015). Gender predispositions vary globally, with OSSN being predominantly male in some regions and predominantly female in others (Tananuvat, et al., 2022). Understanding OSSN's gender predisposition is crucial for assessing its impact in Indonesia.

Occupational exposure to solar radiation is a significant hazard for the approximately 40 million Indonesians working in agriculture, forestry, and fisheries (Statistics Indonesia, 2023). Studies reveal a higher OSSN incidence among outdoor occupations; however, the importance of the relationship varies (Dandala, 2015; Gichuhi, et al., 2016). The frequency of outdoor employment in Indonesia emphasizes the urgency of examining OSSN as a severe hazard.

Diagnosing OSSN based on clinical features alone is challenging. Hence, histopathology is required to confirm the diagnosis and determine the prognosis. OSSN includes dysplasia, carcinoma in situ, and invasive squamous cell carcinoma (Mishra, et al., 2022). Early detection and treatment are crucial for reducing recurrences, and understanding the association between demographic factors and histopathological types can contribute to a more effective diagnosis strategy (Cicinelli, et al., 2018).

Despite the substantial risk OSSN poses in Indonesia, there is a notable gap in research specifically addressing its association with histopathological types. This study aimed to fill this gap by analyzing medical records from a tertiary hospital of Dr. Soetomo General Academic Hospital, Surabaya, Indonesia, from 2017 to 2021, assessing the relationship between age, sex, occupation, and histopathological types of OSSN.

OBJECTIVE

The purpose of this study was to describe the distribution of histopathological types of OSSN among diagnosed patients, to investigate the distribution of age, biological sex, and occupation types within this patient group, and to conduct analyses to determine associations between age, biological sex, occupation type, and histopathological types among OSSN patients.

MATERIAL AND METHOD

This was an analytic cross-sectional study that examined the medical records of patients who were clinically diagnosed with Ocular Surface Squamous Neoplasia (OSSN) at the Department of Ocular Oncology of Dr. Soetomo General Academic Hospital, Surabaya, Indonesia, between January 2017 and December 2021. The study employed a whole population sample method, where all patients were included if they met the specified criteria. The inclusion criteria required patients to have histological data. In contrast, the exclusion criteria included those who previously had unrelated eye procedures, chronic eye disorders, recurrent OSSN, or incomplete records. Data were collected from July to August 2023, and 88 patients were examined. This study received ethical clearance from the Ethical Committee

of Dr. Soetomo General Academic Hospital, Surabaya, Indonesia (no. 2276/113/4/VII/2023) on 25-07-2023.

The retrieved characteristics included age, sex, occupation, and histological type. For analytical purposes, age was categorized as 0-39 and ≥40, occupation was classified as outdoor and indoor, and histopathological type was categorized as non-invasive (including mild-moderate dysplasia, moderate-severe dysplasia, severe dysplasia, and carcinoma in situ) and invasive (squamous cell carcinoma). The categorization of age groups and histological types was conducted based on a previous study by Dandala, (2015). The classification of occupations was performed by applying the methodology utilized in the study conducted by Cox-Ganser & Henneberger (2021). The classification was done by first matching the occupations as written in medical records to their equivalent Standard Occupational Classification (SOC) code(s) (U.S. Bureau of Labor Statistics, 2018). Afterward, the occupations were classified into outdoor and indoor work based on data extracted from the Occupational Information Network (O*NET) (Donsbach, et al., 2003). This data was the scored answer to the question: *How often does your current job require you to work outdoors, exposed to all weather conditions?* Occupations with an average score of ≥75 (once a week to every day) were categorized into outdoor work.

Table 1. Classification of patients into outdoor and indoor workers
(Donsbach, et al., 2003; U.S. Bureau of Labor Statistics, 2018).

Occupation	Occupation code(s)	Score	Occupation type	n
Farmer	45-2090	82.3	Outdoor	27
Fisher	45-3030	95	Outdoor	1
Military/Police Officer	33-3050	91	Outdoor	2
Driver	53-3030	91	Outdoor	1
Field employee	45-2090	82.3	Outdoor	2
Welder	51-4120	21	Indoor	2
Private employee	43-0000	13.6	Indoor	13
Civil servant	43-0000	13.6	Indoor	5
Teacher	25-1000, 25-2000	15.2	Indoor	2
Student	25-1000, 25-2000	15.2	Indoor	6
Housewife	39-9011.00, 39-9011.01, 35-9021.00, 37-1011.00, 37-2012.00, 35-2013.00, 21-1021.00	35.9	Indoor	19
Entrepreneur	11-1011.00, 11-1021.00, 13-1023.00, 13-1161.00, 41-1010	27.7	Indoor	6
Chef	35-1011	36	Indoor	1
Factory worker	11-3051	33	Indoor	1

Table 1 shows that farmers, soldiers or police officers, drivers, and field employees were classified as outdoor workers, while welders, private employees, civil servants, teachers, students, housewives, entrepreneurs, chefs, and factory workers were classified as indoor workers. As housewives did not have a SOC code, several occupations with similar activities were substituted. As students did not have a SOC code, we substituted them using data from teachers, as they shared identical activities at school.

The data were analyzed with descriptive statistics to determine the distribution of age, sex, occupation types, and histopathological types among patients with OSSN. The data were also analyzed using the two-sided Fisher's Exact test to determine the association between age, biological sex, occupation types, and the histopathological types of OSSN. The statistical analysis was performed using IBM SPSS Statistics for Windows, version 27.0 (IBM Corp., Armonk, N.Y., USA).

RESULT

Table 2 illustrates the distribution of age, sex, occupation type, and histopathological type. The mean age of patients is 52.7±19.1, with the majority falling into the 40 and older age group (75%), as categorized based on a previous study (Dandala, 2015). The study population was predominantly male, with 52 male patients (59.1%) compared to 36 female patients (40.9%). There were 55 indoor workers

(62.5%) and 33 outdoor workers (37.5%) among the patients. The most common histopathological type was conjunctival intraepithelial neoplasia (48.9%), followed by squamous cell carcinoma (46.6%) and carcinoma in situ (4.5%). For analytical purposes, we classified our population's histopathological types of OSSN into non-invasive and invasive OSSN. Non-invasive OSSN refers to conjunctival intraepithelial neoplasia and carcinoma in situ, while invasive OSSN refers to squamous cell carcinoma. This was done due to the low count of CIS, which hindered the application of Fisher's exact test. Most patients presented with a non-invasive OSSN (53.4%) rather than an invasive (46.6%).

Table 2. Distribution of age, sex, occupation type, and histopathological type. Processed from research data.

Variable	n = 88	%
Age		
0-39	22	25
≥40	66	75
Sex		
Male	52	59.1
Female	36	40.9
Occupation type		
Outdoor	33	37.5
Indoor	55	62.5
Histopathological type		
Non-invasive	47	53.4
Conjunctival Intraepithelial Neoplasia	43	48.9
Carcinoma in situ	4	4.5
Invasive	41	46.6
Squamous cell carcinoma		

We found a significant relationship between age (p = 0.0004) and occupation type (p = 0.049) with histopathological types of OSSN, as seen in Table 3. However, there was no significant association between sex and histopathological type (p = 0.130). Most patients with invasive OSSN are 40 years older (92.7%). Within 22 patients younger than 40, a majority (19) presented with non-invasive OSSN. Patients with non-invasive OSSN had an equal sex distribution, consisting of 24 males (51.1%) and 23 females (48.9%). Meanwhile, patients with invasive OSSN were predominantly male (68.3%). While most patients were indoor workers, we could observe that among outdoor workers, invasive OSSN was the most prevalent type (20 out of 33).

Table 3. Analysis result of two-sided fisher's exact test.

Parameter	Non-invasive	Invasive	p-value
Age			
0-39	19 (40.4%)	3 (7.3%)	0.0004
≥40	28 (59.6%)	38 (92.7%)	
Sex			
Male	24 (51.1%)	28 (68.3%)	0.130
Female	23 (48.9%)	13 (31.7%)	
Occupation type			0.049
Outdoor	13 (27.7%)	20 (48.8%)	
Indoor	34 (72.3%)	21 (51.2%)	

DISCUSSION

Distribution of age, sex, occupation type, and histopathological type

This study categorized the population into ages 0-39 and ≥40 to satisfy Fisher's Exact test conditions. A previous study conducted in India found 65 patients (57.5%) aged ≥40 and 48 patients (42.5%) aged

39 and younger (Dandala, 2015). When compared, there was a more significant proportion of middle-aged and older patients in this study (75%).

The ratio of males to females in patients with OSSN differs based on region. A systematic review revealed that most OSSN patients in temperate climates are older males, while OSSN patients in tropical climates, such as Eastern and Southern Africa, are typically young women (Gichuhi, et al., 2013). Based on Table 3, this study found more cases of OSSN in males (59.1%) rather than females (40.9%), aligning with other Indonesian studies where 62.5%-70% of OSSN patients are male (Ardjaja, 2017; Sandraningrum & Dahlan, 2019). Despite being a tropical country, Indonesia's OSSN gender distribution is different from the trend seen in Eastern and Southern Africa, where women make up 50%-70% of patients with OSSN. Africa's higher HIV rates in females might explain their higher OSSN incidence (Gichuhi, et al., 2014; Höllhumer, et al., 2023).

One likely explanation behind this discrepancy is the variation in HIV prevalence between the studies' populations. The prevalence of HIV in Eastern and Southern African countries is comparably higher than the prevalence of HIV in Indonesia (0.4%) (International Labour Organization, 2010). In Africa, HIV infection is more often found in females rather than males, which may explain why the sex predisposition in their studies lean towards females (Gichuhi, et al., 2014; Höllhumer, et al., 2023).

The most prominent risk factor for OSSN is exposure to UV light (Gichuhi, et al., 2016). Various factors affect a person's cumulative UV exposure, such as individual, environmental, and occupational factors (Modenese, et al., 2018). Some occupations involve more significant exposure to UV radiation due to the nature of their job requirements. Based on Table 1, most patients with OSSN are farmers, followed by housewives and private employees.

Farmers typically spend significant time outdoors, exposing them to direct sunlight for extended periods and during daylight hours when UV radiation is strongest. Their cumulative UV exposure is influenced by their duration of work, at what time they work, their environment's surface, and their sun-protective behavior (Modenese, et al., 2018).

A housewife is a woman whose job is to manage the household by doing tasks such as cooking, cleaning, and childcare and who does not have paid employment. There are 19 housewives (21.6%) found in this study, making it the second most common occupation among the study population. One plausible explanation is that many activities done by housewives require them to be outside, for example gardening, hanging the laundry, shopping in open-air markets, tending the yard, cleaning the exterior of the house, or they could be outside for transportation (Tesfai, et al., 2021). Other than that, they may also have a hobby requiring them to spend much time outside. There is also a possibility that they had a different occupation before their hospital visit, which was how they were exposed to UV. Nevertheless, as these were not specified in our analyzed medical records, we cannot confirm these possibilities.

Private employees are any people who work for a privately owned company. In this study, private employees were also found in great numbers compared to the total population, with 13 patients (14.8%). Initially, our database classified 20 patients classified as private employees. Upon manual inspection, we found that two patients worked as welders, one as a farmer, one as a chef, one as a factory worker, and two as field employees. This shows that the definition of private employee is comprehensive, therefore making it difficult to classify them as an indoor or outdoor occupation. Out of 20 private employees, only seven were described clearly, while 13 patients did not have a specific description of their occupation written in the medical records. There is a possibility that some of these 13 patients may have worked outdoors, and the lack of specificity is a limitation that we acknowledge.

Upon classification into outdoor and indoor occupations, as seen in Table 1, 62.5% of patients work indoors, while 37.5% work outdoors. Although classified by different methods, this study's finding was similar to a previous study where 70% were involved in indoor and 30% in outdoor occupations (Meel, et al., 2017). However, this distribution is not aligned with the fact that outdoor occupation has been recognized as a risk factor for OSSN in various studies (Gichuhi, et al., 2013; Dandala, 2015).

Among 88 patients histopathologically diagnosed with OSSN, most patients presented with CIN (48.9%), followed by SCC (46.6%) and CIS (4.5%). This corresponds with prior studies done in Bandung and Denpasar, where CIN (41.5%-50%) is the most common histopathological finding in patients with OSSN, followed very closely by SCC (39%-40%), then by CIS (10%-19.5%) (Ardjaja, 2017; Sandraningrum & Dahlan, 2019). These findings contrasted with studies in Nigeria and Kenya, where invasive SCC is the most frequently diagnosed lesion (58.8%-60.3%) (Gichuhi, et al., 2015;

Lomelí-Linares, et al., 2020). This variation suggests the influence of geographical factors such as climate, altitude, latitude, and ozone concentrations (Modenese, et al., 2018).

Another stark difference between Nigeria, Kenya, and Indonesia is the proportion of HIV-positive patients, with HIV being a predictive factor of higher-grade OSSN. The higher HIV prevalence in African countries could contribute to the observed histopathological variations, underscoring the multifactorial nature of OSSN (Rathi, et al., 2018; Suleiman, et al., 2022).

In this study, 53.4% of patients had a non-invasive OSSN, while 46.6% had an invasive OSSN. This study's population had a higher percentage of invasive OSSN cases compared to a previous study by Dandala (2015), where invasive OSSN only comprised 35.4% of the population.

Association between Age, Sex, and Types of Occupation with Histopathological Type of OSSN

This study investigated the association between age and the histopathological types of OSSN. While previous studies have yet to support a precise relationship between age and histopathological types, existing studies have proven that age plays a significant role in the development of OSSN (Dandala, 2015; Gurnani & Kaur, 2023).

This study found a significant association between age and histopathological type (p = 0.0004). Table 3 shows that adults aged 40 and older have a higher tendency to present with invasive OSSN compared to the younger group. Older adults have been exposed to UV light for longer, thus having higher cumulative UV exposure than younger groups. Older adults are also generally more susceptible to the development of malignancy due to the deterioration of their immune system (D'Orazio, et al., 2013). Meanwhile, many middle-aged adults were also found to have a more malignant type of OSSN, possibly because UV radiation has become more intense over time due to ozone depletion and the increasing occurrence of extreme climate events (Barnes, et al., 2023). Due to the increased intensity, the cumulative UV exposure in middle-aged adults may be comparable to older adults even though they have been exposed to UV for a shorter time.

Our study found no statistically significant association between biological sex and histopathological type (p = 0.130), aligning with a previous study which did not find any statistically significant association between sex and OSSN (Smith, et al., 2019). This study's findings also aligned with a study that found no statistically significant difference between females' and males' incidence of OSSN in Asia, even though a significant difference was found in other regions such as Central America, South America, North America, and Europe (Gichuhi, et al., 2013).

In contrast, a previous study done in Nigeria found that male sex is associated with higher-grade lesions of OSSN (p = 0.02). Several factors may contribute to the discrepancy between this study and the previous study. One possible explanation is the genetic and environmental differences in the studies' populations. While Nigeria and Indonesia share similar climates, geographical features, and certain sociodemographic factors, the study populations are composed differently. Nigeria, with its predominantly black African population, exhibits a different genetic constitution compared to the Asian population found in Indonesia. Genetic factors could potentially contribute to susceptibility to OSSN. However, there has not been any study that could prove a significant association between race and ocular surface squamous neoplasia as of date. Genetic factors' impact on gender-related variations in OSSN remains an area for further study (Suleiman, et al., 2022).

Additionally, the disparity observed in our study results may be attributed to an inherent selection bias, given that both studies were done in single institutes, the Dr. Soetomo General Academic Hospital, Surabaya, Indonesia, and Ahmadu Bello University Teaching Hospital, respectively. The difference in referral patterns and accessibility and the limited pool of patients in both institutions were some underlying reasons for selection bias in single-institution-based studies. As this study was the first to be done in Indonesia, there was limited basis for direct comparison to prior research.

Table 3 shows the distribution of outdoor and indoor workers across different histopathological types. Most outdoor workers (20 out of 33) have been diagnosed with invasive OSSN, while 34 out of 55 indoor workers are diagnosed with non-invasive OSSN. From this finding, we can observe that most patients who work outdoors have developed a more malignant lesion, possibly due to SCC's strong association with UV radiation as found in a study by Gichuhi, et al., (2013).

When the association between occupation types and histopathological types was analyzed, this study found a statistically significant relationship between the two variables (p = 0.049). This finding agrees with a previous study which found an association, albeit weak, between outdoor occupations and OSSN

(Gichuhi, et al., 2013).

Strength and limitations

This study was conducted first in Indonesia, a tropical country susceptible to OSSN. Its limitations include its reliance on medical records, which lacks data on potential confounding variables, such as HIV history, smoking habits, outdoor leisure activities, hobbies, and sun-protective habits, which poses a significant limitation. The use of BLS and O*NET for occupation classification also has limitations, with certain worker types not represented in the databases and potential discrepancies between American and Indonesian work environments.

To enhance research data quality, the hospital can improve its medical record system by incorporating additional patient information, including HIV status, smoking habits, detailed job descriptions, leisure activities, and sun-protective behaviors. Future researchers may also consider using a questionnaire to collect data for potential occupational hazards, protective habits, daily work duration, and job tenure. Collecting this information through patient questionnaires could contribute to a more comprehensive and reliable occupational classification system.

CONCLUSION

Most patients diagnosed with ocular surface squamous neoplasia (OSSN) at Dr. Soetomo General Hospital histopathologically exhibited non-invasive OSSN in males aged 40 and older, and worked indoors. Furthermore, we identified statistically significant associations between age and occupation with histopathological type of OSSN. Although these associations' specific direction and strength were not determined in this study, the higher prevalence of invasive types of OSSN observed among older individuals and outdoor workers suggests the need for targeted screening and preventive measures for these high-risk populations. These findings also reinforce the need for future researchers to further explore its strength and nature.

Conflict of Interest

All authors have no conflict of interest.

Ethic Consideration

This study received ethical clearance from the Ethical Committee of Dr. Soetomo General Academic Hospital, Surabaya, Indonesia (no. 2276/113/4/VII/2023) on 25-07-2023.

Author Contribution

SAW contributes to the conception and design, analysis and interpretation of the data, drafting of the article, and final approval. DL contributes to the conception and design, drafting of the article, critical revision of the article for important intellectual content, and final approval of the article. LD contributes to the conception and design, drafting of the article, critical revision of the article for important intellectual content, and final approval of the article. AR contributes to the conception and design, drafting of the article, critical revision of the article for important intellectual content, and final approval of the article. FK contributes to the conception and design, drafting of the article, critical revision of the article for important intellectual content, and final approval of the article.

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