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Original Article

A Nationwide Cohort Study of Actinic Keratosis in Taiwan☆

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SUMMARY

Background: Incidence of actinic keratosis (AKs) and nonmelanoma skin cancer appears to be increasing worldwide due to increasing levels of ultraviolet radiation, lifestyle changes, and an aging population. However, there is no population-based study focusing on AKs among Asian population. We aimed to investigate the incidence, the treatment pattern, the medical utilization and the risk of malignant neoplasm of the AKs patients in Taiwan.

Methods: We conducted a retrospective cohort study to investigate patients with AKs from 2003 to 2011 by using the National Health Insurance Research Database (NHIRD). The inclusion criteria were patients who had at least two outpatient visits or one hospital admission of AK identified by dermatologist from 2004 to 2011. There were 35,933 patients with AKs (elderly [aged ≥65 years]: n = 17,004; non-elderly [aged <65 years]:18,929 patients).

Results: We found the incidence rate for AKs among elderly patients was higher than non-elderly. We further found that there were 923 patients were identified skin malignant neoplasm after diagnosis of AKs, and the incidence rate among elderly patients was higher than non-elderly (122.66 vs. 13.80 per 10,000 patient-year).

Conclusions: The AKs incidence rate was low in general population but particular high in elderly population in Taiwan. Our findings warrants further investigation into the relationship between actinic keratosis and the nonmelanoma skin cancer (NMSC) in Asians and may affect the approach toward primary prevention of NMSC in Asians with AKs.

1. Introduction

Actinic keratosis (AKs) or solar keratosis is a cutaneous lesion that results from the proliferation of atypical epidermal keratinocytes and also represents a step in the development of squamous cell carcinoma (SCC)[1,2]. The diagnosis of AKs is more important for the geriatric population than young individuals because not only does the incidence of malignant skin lesions increase with age but diagnosis of AKs also places the patients in a high-risk group for a subsequent development of skin cancer[3].

Several reports provide estimates on the growing numbers of affected people and the economic burden of treatment[4]. In US, one study based on data from the National Ambulatory Medical Care Survey indicated that 5.2 million visits occurred annually for AK during the periods of 2000 through 2003[5]. A study in 2005 estimated that AK affects more than 58 million people[6]. In northern hemisphere populations, 11%–25% of adults have at least one AK, compared with 40%–60% of adult Australians[7,8]. The prevalence rate reported in England in 2000 was 15.4% in men and 5.9% in women older than 40 years[9]. These rates increased to 34.1% and 18.2%, respectively, at 70 years of age, when prevalence was most strongly related to 2 objective signs of sun exposure: solar elastosis and lentigines[9]. Although these studies clearly demonstrate the high prevalence of AK, there are no information focusing on the epidemiology of actinic keratosis regarding among Asian population. Updated investigation might be informative by providing a more contemporary prevalence estimate.

Moreover, prior studies had suggested the worldwide incidence of nonmelanoma skin cancer (basal cell carcinoma, and SCC) has increased by 4%–8% per year since 1960[10]. Meanwhile, a recent South Korean research also pointed to a 2.14 fold increase in the

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incidence of AKs in relation to the last decade of the last century[11]. The AKs resulted in the growing numbers of affected people and economic burden of treatment[1]. Early detection of skin cancer in the pre-SCC stage with proper management may suppress the rise in the incidence of SCC. In light of the above, AKs has become an important public health problem. However, much of the data on the epidemiology for AKs are derived from studies in light-skinned Caucasians, and there is no national population-based study focusing on AKs among a Chinese population.

We conducted a nationwide retrospective cohort study to investigate the frequency of AKs diagnosis, the type of AKs treatment, and the medical utilization of AKs patients in Taiwan. The risk of malignant neoplasm in AKs patients was also evaluated. Updated investigation in this study will be informative by providing a more contemporary incidence estimate.

2. Materials and methods

2.1. Data source

We used the National Health Insurance Research Database (NHIRD), which covered 99% of nearly 23 million people in Taiwan, to conduct a retrospective cohort study during 2003–2011. The NHIRD contained all the original claim data registration files and original claims data for reimbursement.

2.2. Study population and cohort entry/exit date

To conduct a retrospective cohort study with a 9-year observation period (2003–2011). The inclusion criteria was patients who had at least two outpatient visits or one hospital admission of AK International Classification of Disease-Clinical (ICD-9-CM) code (702.0) identified by dermatologist. We defined an individual's entry date as the date of first diagnosis of AK from 1 January 2004 to 31 December 2011. We excluded patients who developed skin malignant neoplasm (ICD-9 code: 173) before the entry date. An individual's cohort exit date would be the earlier of the first diagnosis of skin malignant neoplasm (ICD-9 code: 173), or end of the study period. A total of 35,933 patients with AKs were included in this analysis.

2.3. Actinic keratosis treatment and study outcomes

For all study patients, procedural treatment and medical treatment of AK during the whole period of follow-up after the entry date were used, including cryotherapy, electro cauterization, excision of skin (facial skin, skin), and 5-fluorouracil. All information on procedural and medical treatment used by individual patients was obtained from the NHIRD. The frequency of procedural treatment use was defined as number of outpatient visits within the whole follow-up years. The outcome of interest is skin malignant neoplasm (ICD-9 code: 173).

2.4. Statistical analysis

All statistical tests were two sided, with an alpha level of 0.05, and the confidence intervals (CIs) were 95%. Cox proportional hazards model was used to evaluate whether AK is an important risk factor for skin malignant neoplasm. We also adjusted for potential confounders in the multivariable Cox models, including patient demographics (age and gender), prior history of immunosuppressive drugs use, procedural and medical treatments during the follow-up period. Data management and statistical analyses were performed using SAS version 9.2 (SAS Institution Inc, Cary, North Carolina) and Microsoft Excel 2013 software.

3. Ethical approval

This study protocol was approved by Joint Institutional Review Board established by Medical Research Ethics Foundation.

4. Results

There were 36,858 patients who were admitted for the first time with a primary diagnosis of AKs between 2004 and 2010. After excluding 925 patients who had skin malignant neoplasm before entry date, a total of 35,933 patients were included in the analysis of procedural treatment of AKs and skin malignant neoplasm. The overall incidence rate for AKs from 2004 to 2011 ranged from 1.66 to 2.18 per ten thousand people. We found the incidence rate for AKs among elderly patients (range from 7.22 to 10.59) was higher than non-elderly (range from 0.87 to 1.13) (Figure 1). The trend of decreasing incidence of actinic keratosis in elderly patients was also found.

Of the 35,933 patients with AKs, 17,004 (47.3%) were elderly patients, and 18,929 were non-elderly patients. At the baseline, we found elderly patients had a higher proportion of male, lived in southern Taiwan and others area, diagnosed in medical center or regional or district hospital, used immunosuppressive drugs prior to entry date, underwent cryotherapy, excision of facial skin, and excision of skin (except face) surgery than non-elderly patients (Table 1).

Nine hundred and twenty-three patients were identified with skin malignant neoplasm after diagnosis of AKs, the overall incidence rate of skin malignant neoplasm was 67.07 per 10,000 patient-year (95%CI, 62.88–71.53). Ninety-seven of the 18,929 non-elderly patients and 826 of the 17,004 elderly patients were identified with skin malignant neoplasm after diagnosis of AKs (incidence rates: 13.80 [95%CI, 11.31–16.84], and 122.66 [95%CI, 114.58–131.32] per 10,000 patient-year, respectively) (Table 2).

In the multivariable-adjusted Cox proportional hazards model, we found the elderly (HR = 8.85, 95%CI = 7.06–11.08), female (HR = 1.26, 95%CI = 1.11–1.44), residence in central area (HR = 1.33, 95%CI = 1.08–1.64) or southern and others area (HR = 1.51, 95% CI = 1.29–1.78) were significant risk factors for skin malignant neoplasm. Patients receiving treatments of cryotherapy (HR = 0.82, 95%CI = 0.69–0.97) and electro cauterization (HR = 0.56, 95% CI = 0.39–0.78) for AKs was associated with decreased risk of skin malignant neoplasm (Table 3).

5. Discussion

The population-based estimates of the incidence of AKs are scanty, even for Caucasians. In 1986, Marks evaluated the incidence of AKs in 1040 Australian people aged more than 40 years and found 60% of patients with AKs at baseline developed new lesions during 12 months of follow-up, compared with only 19% of those who were lesion-free on the first examination[12]. Another study by Nestor et al. reported the incidence of treated AKs was 446 ~ 11,045 per 10,000 people per year in two health maintenance organization populations in South Florida, which many be the highest recorded incidences in the world[13]. However, growing evidence had showed precancerous and malignant skin alterations were relatively infrequent in Asians than Caucasians. A recent study of Japanese residents of Kauai, Hawaii, suggested that the average annual incidence of SCC among Caucasians was five times higher and that of BCC was 14 times higher than Japanese[14]. Suzuki et al. conducted a recent study evaluating 4867 Japanese residents of Hyogo and showed that the incidence of AKs was approximately 20 per 10,000 people per year. Compared with this study, the incidence of AKs in our study is even much lower (2.27 ~ 3.75 vs. 8.6 ~ 29.1 per 10,000 people per year)[14]. Although the direct comparison of these values