

# Risk of Skin Cancer and Actinic Keratosis in Patients with Rosacea: A Nationwide Population-based Cohort Study

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**The association between rosacea and skin cancer remains inconclusive, with conflicting reports. The aim of this nationwide population-based cohort study was to determine the risk of skin cancer in patients with rosacea. A rosacea cohort ( $n = 11,420$ ) was formulated and evaluated from 2010 to 2019. The incidence rate ratios of actinic keratosis, cutaneous melanoma, keratinocyte carcinoma and gastric, colorectal, and liver cancer were analysed in comparison with a matched control group, and multivariable stratified Cox proportional hazards model analysis was performed. The risk of actinic keratosis and keratinocyte carcinoma was increased in the rosacea group compared with the control group, with adjusted hazard ratios of 6.05 (95% confidence interval 3.63–10.09) and 2.66 (1.53–4.61), respectively. The risk of cutaneous melanoma and gastric, colorectal and liver cancer was not increased, with adjusted hazard ratios of 1.69 (0.25–11.37), 0.81 (0.59–1.10), 0.91 (0.69–1.18) and 1.32 (0.89–1.95), respectively. These results reveal an increased risk of actinic keratosis and keratinocyte carcinoma in patients with rosacea.**

**Key words:** rosacea; actinic keratosis; basal cell carcinoma; squamous cell carcinoma.

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Rosacea is a chronic skin disease characterized by transient or persistent facial erythema and may be exacerbated by conditions that induce chronic inflammation (1, 2). Recent studies have revealed an epidemiological association between rosacea and chronic inflammatory systemic conditions, including cardiovascular, gastrointestinal, and neurological disorders (3–6). Chronic inflammatory state is thought to be closely associated with the development and progression of multiple cancers, including skin cancer (7, 8). However, the association between rosacea, one of the most common chronic inflammatory skin disorders, and skin cancer remains unclear, with very few published studies. The aim of this study was to determine the risk of actinic keratosis and skin cancer in patients with rosacea.

## SIGNIFICANCE

Rosacea is a common skin disorder characterized by facial erythema. The exact cause of rosacea is unknown, but it is a disorder with persisting inflammation. Chronic inflammation is thought to be closely linked to cancer, but little is known about the association between rosacea and skin cancer. This nationwide study, using data from the National Health Insurance Sharing Service (NHIS) in South Korea to determine whether patients with rosacea are more prone to developing skin cancer, found that patients with rosacea are at greater risk of developing actinic keratosis, a precancerous skin lesion, and keratinocyte carcinoma. Close surveillance for skin cancer is recommended for patients with rosacea.

## MATERIALS AND METHODS

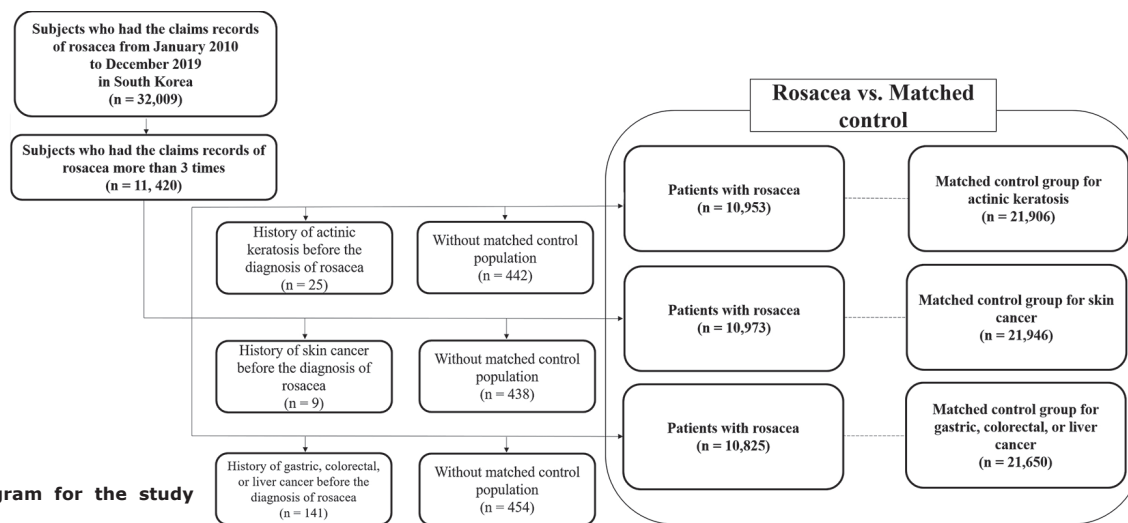
### *Study design and data sources*

This retrospective cohort study used data from the National Health Insurance Sharing Service (NHIS) in South Korea. The Korean National Health Insurance Service (KNHIS), mandatory social health insurance, covers approximately 97% of Korean residents, and the Medical Aid programme covers the rest of the population (9). NHIS provides the claims data covered by both insurance programmes, offering almost all medical claims records of the registered population in South Korea since 2002. The NHIS dataset contains records of diagnosis codes (International Statistical Classification of Diseases and Related Health Problems, 10<sup>th</sup> Revision (ICD-10) codes), prescription claims, procedure and surgery claims, as well as demographic information, such as birth year, sex, place of residence, and income (10).

The study was reviewed and approved by the Institutional Review Board of Seoul Metropolitan Government - Seoul National University Boramae Medical Center and NHIS (IRB number 07-2020-285 and NHIS-2021-1-352). All claims data provided by NHIS were deidentified.

### *Identification of study population and control group*

A rosacea cohort of people who made claims from January 2010 to December 2019 was established, based on the population dataset provided by NHIS. Patients aged between 30 and 89 years who had records of 3 or more principal diagnoses of rosacea with relevant ICD-10 code (L71.x; perioral dermatitis (L71.0) was excluded) from 2010 to 2019 were defined as the study population (11). The control group was defined as the patients without records of rosacea during the observation period. Patients who had diagnosis codes of disorders that can resemble rosacea: seborrhoeic dermatitis (L21), acne (L70), or lupus erythematosus (L93) from 2009 to 2019 (year 2009 was included as a 1-year washout-period) were excluded from the control groups.



**Fig. 1.** Flow diagram for the study population.

*Definition of study outcome*

New cases of actinic keratosis, skin cancer (including non-melanoma skin cancer, hereafter termed keratinocyte carcinoma (KC), cutaneous melanoma, gastric cancer, colorectal cancer, and liver cancer were defined based on having 1 or more relevant ICD-10 codes (actinic keratosis: L570; KC: C44, D04; melanoma: C43, D03; gastric cancer: C16; colorectal cancer: C18, C19, C20; and liver cancer: C22) from 2009 to 2019 (year 2009 was included as a washout-period). The diagnoses of all the target diseases, except for actinic keratosis, were further validated with the V193 code, a special registration code for cancer cases with histopathological confirmation in the KNHIS database (12). Gastric cancer, colorectal cancer, and liver cancer were selected in comparison with skin cancer as common cancers in South Korea with the most reliable claims data, as they are routinely screened in the general population of South Korea under the national cancer screening programme (13).

*Statistical analysis*

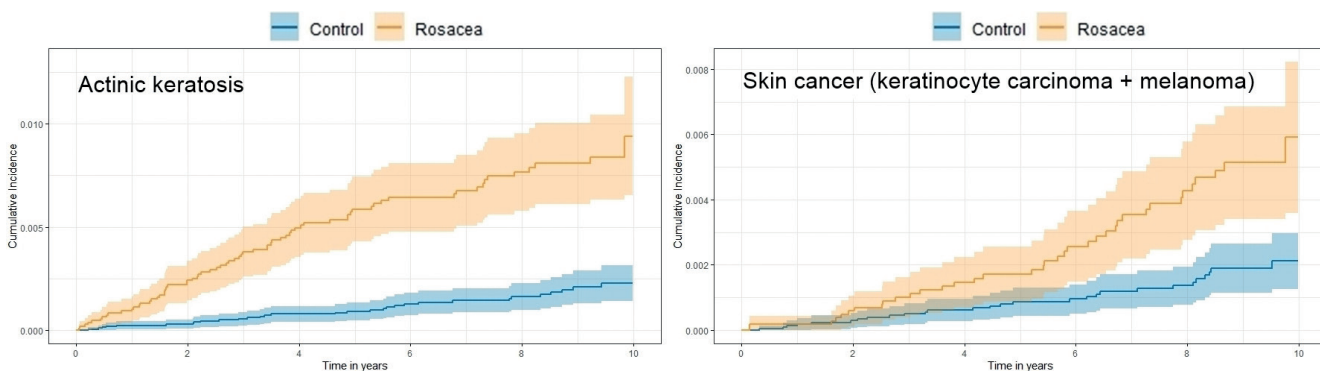
For risk analysis of each target disease, patients who had the principal diagnosis code of a target disease before the index date were excluded from the study population. Thereafter, the control

group was matched for sex, age, income, and residence at a ratio of 1 to 2 (data regarding income and residence is shown in Table SI). Study patients without matched controls, and matched control patients who had a principal diagnosis code of a target disease before the index date, were further excluded from the study and control groups, respectively. The index dates for the patients with rosacea were defined as the first date of diagnosis, and the index date for the control patient was assigned based on the index date of the matched rosacea patient. The endpoint was defined as the first day of diagnosis of a target disease. The observation period was up to 31 December 2019, and patients who died before the end date with no event (diagnosis of a target disease) were censored.

Pearson’s  $\chi^2$  test or Fisher’s exact test was used for categorical variables, and Student’s t-test was used for continuous variables. The incidence rate (IR) of each skin disease was calculated per 1,000 person-years, and the IR ratio (IRR) of each skin disease was calculated by comparing the IRs with the matched control group. Outcomes from a multivariable stratified Cox proportional hazards model analysis were shown as adjusted hazard ratio (aHR) with 95% confidence intervals (95% CIs); hazard ratios were adjusted for hypertension, diabetes, and dyslipidaemia. The proportional hazard assumption was confirmed via the supreme

**Table I.** General characteristics of the study population

Outcome	Actinic keratosis		Skin cancer		Gastric, colorectal, and liver cancer	
	Rosacea	Control	Rosacea	Control	Rosacea	Control
Number	10,953	21,906	10,973	21,946	10,825	21,650
Sex, n (%)						
Male	3,861 (35.3)	7,722 (35.3)	3,864 (35.2)	7,728 (35.2)	3,782 (34.9)	7,564 (34.9)
Female	7,092 (64.7)	14,184 (64.7)	7,109 (64.8)	14,218 (64.8)	7,043 (65.1)	14,086 (65.1)
Age, n (%)						
30–34 years	348 (3.2)	696 (3.2)	348 (3.2)	696 (3.2)	348 (3.2)	696 (3.2)
35–39 years	895 (8.2)	1,790 (8.2)	894 (8.1)	1,788 (8.1)	894 (8.3)	1,788 (8.3)
40–44 years	1,423 (13.0)	2,846 (13.0)	1,428 (13.0)	2,856 (13.0)	1,427 (13.2)	2,854 (13.2)
45–49 years	1,804 (16.5)	3,608 (16.5)	1,808 (16.5)	3,616 (16.5)	1,801 (16.6)	3,602 (16.6)
50–54 years	1,924 (17.6)	3,848 (17.6)	1,930 (17.6)	3,860 (17.6)	1,915 (17.7)	3,830 (17.7)
55–59 years	1,547 (14.1)	3,094 (14.1)	1,545 (14.1)	3,090 (14.1)	1,525 (14.1)	3,050 (14.1)
60–64 years	1,191 (10.9)	2,382 (10.9)	1,188 (10.8)	2,376 (10.8)	1,163 (10.7)	2,326 (10.7)
65–69 years	808 (7.4)	1,616 (7.4)	809 (7.4)	1,618 (7.4)	784 (7.2)	1,568 (7.2)
70–74 years	629 (5.7)	1,258 (5.7)	631 (5.8)	1,262 (5.8)	598 (5.5)	1,196 (5.5)
75–79 years	321 (2.9)	642 (2.9)	323 (2.9)	646 (2.9)	311 (2.9)	622 (2.9)
80–84 years	60 (0.5)	120 (0.5)	65 (0.6)	130 (0.6)	57 (0.5)	114 (0.5)
85–89 years	3 (0.0)	6 (0.0)	4 (0.0)	8 (0.0)	2 (0.0)	4 (0.0)
Comorbidities, n (%)						
Hypertension	3,326 (30.4)	6,308 (28.8)	3,330 (30.3)	6,321 (28.8)	3,271 (30.2)	6,230 (28.8)
Diabetes	1,685 (15.4)	2,904 (13.3)	1,683 (15.3)	2,898 (13.2)	1,654 (15.3)	2,837 (13.1)
Dyslipidaemia	1,799 (16.4)	2,636 (12.0)	1,803 (16.4)	2,645 (12.1)	1,778 (16.4)	2,598 (12.0)



**Fig. 2. Comparison of cumulative incidence of actinic keratosis and skin cancer in patients with rosacea with that in matched control group.** The shaded areas indicate the 95% confidence intervals.

test for proportional hazards assumption. Subgroup analysis was conducted for skin cancer (KC and melanoma). All statistical tests were performed with SAS Enterprise 7.15 (SAS Institute; Cary, NC, USA) or R statistical software version 3.63 (R Foundation for Statistical Computing, Vienna, Austria).

**RESULTS**

A total of 11,420 patients diagnosed with rosacea were identified during the study period. Thereafter, study patients without appropriate matched controls, and matched control patients with a principal diagnosis code of a target disease before the index date were excluded. The detailed study flow and general characteristics of the study population are described in detail in **Fig. 1** and **Table I**, respectively.

*Risk of actinic keratosis and skin cancer in patients with rosacea*

A total of 10,953 patients with rosacea were matched to a control group of 21,906 patients. Among the patients with rosacea, 64.7% ( $n=7,092$ ) were female and 61.2% ( $n=6,698$ ) were in the age range 40 and 59 years. The prevalence of hypertension, diabetes and dyslipidaemia in the rosacea group were 30.4%, 15.4% and 16.4%, respectively, and were meaningfully higher than those in the control group (28.8%, 13.3% and 12.0%, respectively). The IRR of actinic keratosis in patients with rosacea was statistically significant compared with the control

group at 4.48 (95% CI 2.94–6.84). The risk of actinic keratosis was increased in the study group compared with the control group after adjustment for comorbidities (aHR 6.05; 95% CI, 3.63–10.09) (**Fig. 2** and **Table II**).

For the analysis regarding skin cancer, a total of 10,973 patients with rosacea were identified and matched to the control group of 21,946 patients. The IRR of skin cancer in patients with rosacea was statistically significant, at 2.61 (95% CI 1.60–4.28). The risk of skin cancer was increased compared with the control group (aHR 2.41; 95% CI 1.45–4.02) (**Fig. 2** and **Table II**). Subgroup analysis revealed an increased risk of KC (aHR 2.66; 95% CI, 1.53–4.61), but not of melanoma (aHR 1.69; 95% CI, 0.25–11.37) (**Fig. 3** and **Table II**). The proportional hazard assumption was met for each analysis.

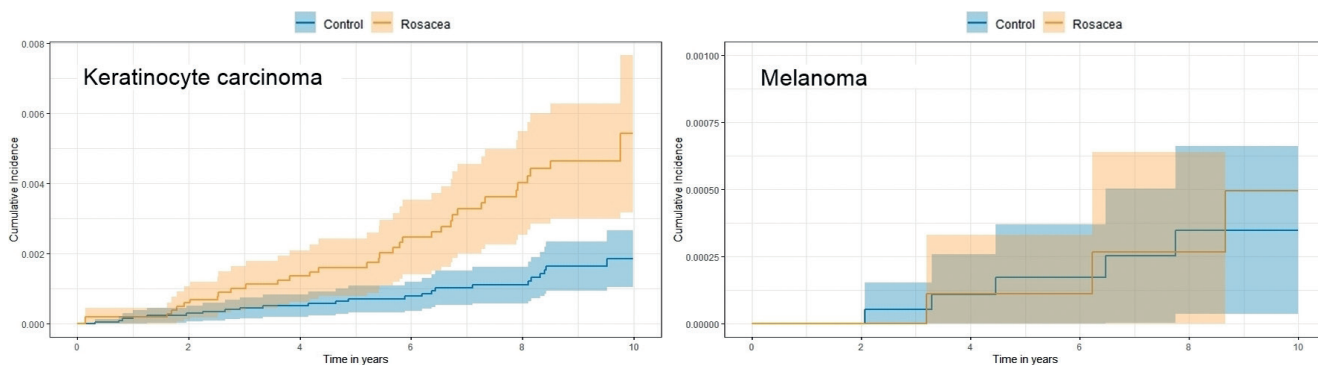
*Risk of gastric, colorectal and liver cancer in patients with rosacea*

For the analysis regarding gastric, colorectal, and liver cancer, a total of 10,825 patients with rosacea was identified and matched to the control group of 21,650 patients. There was no statistically significant increase in the risk of gastric, colorectal, or liver cancer in patients with rosacea compared with the control group (aHR 0.81, 95% CI 0.59–1.10; aHR 0.91, 95% CI 0.69–1.18; and aHR 1.32, 95% CI 0.89–1.95, respectively) (**Fig. S1** and **Table II**). Again, the proportional hazard assumption was met for each analysis.

**Table II. Risk of actinic keratosis, skin cancer (including melanoma and keratinocyte carcinoma) and gastric cancer, colorectal cancer and liver cancer in patients with rosacea and matched normal controls**

Outcome	Patients with rosacea			Matched normal controls			Absolute risk difference per 1,000 person-years (95% CI)	IRR (95% CI)	aHR (95% CI)
	Cases, n	Person-years	IR per 1,000 person-years (95% CI)	Cases, n	Person-years	IR per 1,000 person-years (95% CI)			
Actinic keratosis	70	72,266.4	0.97 (0.76–1.21)	31	143,417.3	0.22 (0.15–0.30)	0.75 (0.51–0.99)	4.48 (2.94–6.84)	6.05 (3.63–10.09)
Skin cancer	37	72,560.5	0.51 (0.36–0.69)	28	143,808.9	0.20 (0.13–0.28)	0.32 (0.14–0.50)	2.61 (1.60–4.28)	2.41 (1.45–4.02)
Melanoma	3	72,665.9	0.04 (0.01–0.11)	5	143,857.2	0.04 (0.01–0.08)	0.01 (–0.05–0.06)	1.19 (0.28–4.97)	1.69 (0.25–11.37)
Keratinocyte carcinoma	34	72,568.3	0.47 (0.33–0.64)	24	143,820.3	0.17 (0.11–0.24)	0.30 (0.13–0.47)	2.81 (1.67–4.74)	2.66 (1.53–4.61)
Gastric cancer	59	71,677.9	0.82 (0.63–1.05)	148	142,068.9	1.04 (0.88–1.22)	–0.22 (–0.49–0.05)	0.79 (0.58–1.07)	0.81 (0.59–1.10)
Colorectal cancer	81	71,604.6	1.13 (0.90–1.40)	174	141,912.7	1.23 (1.05–1.42)	–0.10 (–0.40–0.21)	0.92 (0.71–1.20)	0.91 (0.69–1.18)
Liver cancer	49	71,771.5	0.68 (0.51–0.89)	75	142,397.9	0.53 (0.42–0.66)	0.16 (–0.07–0.38)	1.30 (0.90–1.86)	1.32 (0.89–1.95)

aHR: adjusted hazard ratio; IR: incidence rate; IRR: incidence rate ratio.



**Fig. 3. Comparison of cumulative incidence of non-melanoma skin cancer (keratinocyte carcinoma) and malignant melanoma in patients with rosacea with that in matched control group.** The shaded areas indicate the 95% confidence intervals.

## DISCUSSION

This study revealed an increased risk of actinic keratosis and KC in patients with rosacea compared with the control group, whereas a statistically significant increase in the risk of melanoma and gastric, colorectal or liver cancer was not observed.

Recent findings suggest that rosacea is more than a localized facial skin disease implicated in multiple chronic inflammatory systemic disorders (14, 15). However, the association between rosacea and cancer, particularly skin cancer, has remained largely unclear. Regarding risk of skin cancer in patients with rosacea, 2 earlier studies showed similar results to the current study; a study conducted in the USA reported an increased risk of basal cell carcinoma, but not of melanoma (16), and a Danish study revealed an increased risk of KC, but not of melanoma in patients with rosacea (17). However, a population-based cohort study conducted in Taiwan reported no association between rosacea and any malignancies, including these forms of skin cancer (18). The results regarding other cancers in these studies were also inconsistent, as the risk of a particular type of cancer (breast, liver, or thyroid cancer) that was significant in one study was not significant in the others. Therefore, the findings of the current study are meaningful as they confirm the association between rosacea and KC, while the risk of melanoma or solid cancer was not increased.

Ultraviolet (UV) radiation, as well as chronic skin inflammation, is a possible common pathogenic factor that explains the association between rosacea and actinic keratosis, and rosacea and KC (19, 20). A previous study conducted in South Korea reported that approximately 95% of actinic keratosis, 91% of basal cell carcinoma and 71% of squamous cell carcinoma in the South Korean population occurred in the head and neck area, which supports the common role of UV exposure in rosacea and these target diseases (21). In addition, rosacea, actinic keratosis, and KC may share predisposing genetic factors; a recent genetic study highlighted *IRF4* as a gene that confers risk of rosacea (22), which is also implicated in actinic keratosis and KC (23, 24).

There are possible explanations for the lack of association found between rosacea and melanoma. First, while UV exposure is the common aetiological factor for both KC and melanoma, approximately half of all cases of melanoma are thought to be associated with UV radiation, whereas almost all cases of KC are associated with UV radiation (25, 26). Also, since acral malignant melanoma, which is not associated with UV radiation, is the most prevalent type of melanoma in South Korea (27), the effect of UV exposure on melanoma might not have been detected in the current study. Furthermore, the aforementioned 2 previous Western studies also reported no association between melanoma and rosacea (16, 17), which may indicate that rosacea simply might not share as many aetiological factors with melanoma as it does with KC.

This study has several strengths compared with the previous population-based studies regarding rosacea and cancer. First, it is a 10-year long, nationwide population-based study, whereas other studies had a shorter follow-up period (17) or a study group limited to a certain portion of the overall population (16). In addition, the current study included 3 common cancers that are routinely screened in South Korea in comparison with skin cancer to further ensure statistical validity. There has not been clear consensus regarding the association between rosacea and internal malignancy, and the current study also did not find any association between rosacea and gastric, colorectal, or liver cancer. Taken together, the systemic implication of rosacea may not be as influential as to cause internal malignancies.

Notably, this is the first study to analyse the risk of actinic keratosis in patients with rosacea. We were not able to analyse the subtypes of KC (basal cell carcinoma and squamous cell carcinoma) due to the single ICD-10 code. However, the higher aHR of actinic keratosis compared with that of KC found in the current study goes along with the progression of the spectrum disease, from premalignant to malignant skin tumour.

This study has a number of limitations. First, due to the retrospective insurance claims-based study setting,

the definition of rosacea had to be made based solely on diagnostic codes, and neither the anatomical location of the target diseases nor their subtype and severity could be identified. Similarly, skin phototype, family history, environmental factors, or genetic components could not be taken into account. Secondly, it should be noted that rosacea is often underdiagnosed in people with skin of colour compared with those with white skin (28), and that there are differences in melanoma subtypes in different ethnicities (27). The generalizability of these findings may be limited. Thirdly, despite the use of a 1-year washout-period, there is a possibility of a delayed diagnosis of rosacea or vice versa. However, the current study reduced both false-positive and false-negative cases by inserting strict inclusion criteria (rosacea patients with more than 3 records of the principal diagnosis code) and excluding subjects who had records of disorders that can mimic rosacea from the control group. In addition, a special cancer registration code was incorporated along with ICD-10 codes to include histologically confirmed cancer cases only.

This study conducted in South Korea found that patients with rosacea have a greater risk of developing actinic keratosis and KC, possibly because they share similar common pathogenic factors including UV radiation. The results of this study may lend further support to the importance of sun protection in rosacea patients. Further studies in different populations with detailed clinical data, genetic analysis, and a longer follow-up period are warranted to elucidate the shared pathogenic mechanisms and genetic factors between rosacea and skin cancer.

## ACKNOWLEDGEMENTS

This study was reviewed and approved by the Institutional Review Board of Seoul Metropolitan Government - Seoul National University Boramae Medical Center and National Health Insurance Sharing Service (NHIS) in South Korea (IRB number 07-2020-285 and NHIS-2021-1-352).

*The authors have no conflicts of interest to declare.*

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