Metformin is associated with decreased risk of basal cell carcinoma: A whole-population case-control study from Iceland

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Background: Metformin has anticarcinogenic properties and is also known to inhibit the sonic hedgehog pathway, but population-based studies analyzing the potential protective effect for basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) are needed.

Objectives: To delineate the association between metformin use and invasive SCC, SCC in situ (SCCis), and BCC.

Methods: A population-based case-control study design was employed using all 6880 patients diagnosed in Iceland between 2003-2017 with first-time BCC, SCCis, or invasive SCC, and 69,620 population controls. Multivariate odds ratios (ORs) were calculated using conditional logistic regression.

Results: Metformin was associated with a lower risk of developing BCC (OR, 0.71; 95% confidence interval [CI], 0.61-0.83), even at low doses. No increased risk of developing SCC was observed. SCCis risk was mildly elevated in the 501-1500 daily dose unit category (OR, 1.40; 95% CI, 1.00-1.96).

Limitations: This study was retrospective in nature with the inability to adjust for ultraviolet exposure, Fitzpatrick skin type, and comorbidities.

Conclusion: Metformin is associated with decreased risk of BCC development, even at low doses. Metformin might have potential as a chemoprotective agent for patients at high risk of BCC, although this will need confirmation in future studies. (J Am Acad Dermatol 2021;85:56-61.)

Key words: basal cell carcinoma; keratinocyte carcinoma; metformin; squamous cell carcinoma; squamous cell carcinoma in situ.

INTRODUCTION

There is growing evidence to suggest that metformin may decrease the risk of several human malignancies, including those of the liver, pancreas, colon, and breast.[1] Metformin is thought to inhibit carcinogenesis through a number of

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mechanisms, including (1) inhibition of the mammalian target of rapamycin; (2) inhibition of protein synthesis and the cell cycle; (3) activation of p53 and p21, leading to cell apoptosis and autophagy; (4) activation of the immune system; (5) destruction of cancer stem cells; (6) inhibition of angiogenesis; and (7) reduction in blood lipid and insulin levels.[2] In addition to general anticarcinogenic effects, metformin has also been shown to directly inhibit the sonic hedgehog (Shh) pathway, a key pathway in basal cell carcinoma (BCC) pathogenesis.[3,4] This pathway is the target of vismodegib and sonidegib, which are highly effective for BCC prevention, but their broad use for BCC prophylaxis is limited due to numerous side effects.[5,6]

CAPSULE SUMMARY

- Metformin is known for its antiaging and anticarcinogenic effects.
- Metformin is associated with decreased risk of basal cell carcinoma and could have future potential as a chemoprotective agent in patients at increased risk for basal cell carcinoma.

The relationship between metformin and keratinocyte carcinoma has not been well-characterized but is of importance considering that metformin is a commonly prescribed medication.[7] To date, only 1 population-wide study from Taiwan has analyzed the impact of metformin on the development of keratinocyte carcinoma.[8] This retrospective cohort study found a significantly decreased risk of first-time keratinocyte carcinoma with metformin use, especially at higher cumulative doses, but it did not differentiate between BCC and squamous cell carcinoma (SCC).[8] Additionally, the Taiwanese population has a low baseline risk for keratinocyte carcinoma.[8] Another smaller retrospective cohort study of the Veterans Affairs population found no significant association between metformin and the development of a second keratinocyte carcinoma, but it was limited by the fact that BCC and SCC were not analyzed separately.[9]

Herein, we conducted a whole-population case-control study in the Icelandic population to better delineate the relationship between metformin and the development of BCC, in situ SCC (SCCis), and SCC. Iceland is unique compared with previously studied populations as it (1) has a largely White and genetically homogenous population[10]; (2) has a low level of ambient ultraviolet (UV) exposure given its high latitude[11]; (3) has minimal countrywide variation in UV exposure due to its small size; (4) keeps thorough records of skin cancer diagnoses with histologic verification in the Icelandic Cancer Registry (ICR)[12]; and (5) documents all electronic outpatient prescriptions in the Prescription Medicine Register.[13]

METHODS

A whole-population case-control study of the Icelandic population was performed using the ICR and Icelandic Prescription Medicine Register. The ICR records all keratinocyte carcinoma diagnoses with histologic verification.[12] The Prescription Medicine Register has documented all electronic outpatient prescriptions in Iceland since 2002.[13] All first-time diagnoses of SCCis, SCC, or BCC in the ICR between 2003 and 2017 were included as cases. Each case was matched with 10 randomly selected unaffected age- and gender-matched population controls. Unique personal identification numbers were used to identify all metformin prescriptions among cases and controls.

Individuals were considered exposed to metformin if they had filled at least 1 prescription of metformin more than 2 years before their diagnosis of keratinocyte carcinoma. To account for possible lag time, all medication prescriptions within 2 years of diagnosis were disregarded. Analyses were conducted using grams and daily dose units (DDUs) of metformin. A DDU of metformin, or its average daily maintenance dose when used for its primary indication, is 2 grams.[14]

Azathioprine, mycophenolate mofetil, and cyclosporine have been shown to increase the risk of keratinocyte carcinoma, thus individuals on these medications were excluded.[15] Multivariate odds ratios (ORs) were calculated with 95% confidence intervals (CIs) using conditional logistic regression analyses for the association between metformin and the risk of first-time SCCis, invasive SCC, and BCC. Analyses were adjusted for photosensitizing medications (tetracyclines and oral and topical retinoids), hydrochlorothiazide, statins, and tumor necrosis alpha inhibitors because these medications have been associated with increased risk of skin cancer.[15-18] Analyses were performed separately for SCCis, invasive SCC, and BCC with never-users of metformin serving as controls.

Cumulative dose-response analyses were conducted for each subtype of keratinocyte carcinoma using trend analysis. Weighted linear regression was used to calculate ORs based on the median dose of metformin for each category (1-500, 501-1500, and >1500 DDUs). For all analyses, $P < .05$ was considered statistically significant.

Abbreviations used:

BCC: basal cell carcinoma
DDU: daily dose unit
ICR: The Icelandic Cancer Registry
OR: odds ratio
SCC: squamous cell carcinoma
SCCis: squamous cell carcinoma in situ
Shh: sonic hedgehog
T2DM: type 2 diabetes mellitus

RESULTS

During this study, 4700 individuals with BCC, 1167 with SCCis, and 1013 with invasive SCC were identified and matched with 47,293, 11,961, and 10,367 controls, respectively (Table I).

The relationship between metformin use and keratinocyte carcinoma risk is summarized in Table II. Of the individuals with BCC, 4.0% were exposed to metformin, as compared to 5.3% of controls. Lower risk of BCC was significantly associated with metformin use as compared to nonuse (adjusted OR, 0.71; 95% CI, 0.61-0.83).

Additionally, 7.5% of individuals with SCCis and 6.2% of controls were exposed to metformin. Metformin use was not significantly associated with SCCis (adjusted OR, 1.06; 95% CI, 0.84-0.35).

Similarly, 7.2% of individuals with invasive SCC and 6.6% of controls were exposed to metformin. Metformin use was not significantly associated with invasive SCC (adjusted OR, 1.01; 95% CI, 0.78-1.30). Dose-response relationships were not statistically significant for BCC, SCCis, or invasive SCC (P = .87, .94, and .88, respectively).

Subgroup analysis was conducted and shown in Table III. Metformin use was associated with a lower risk of BCC in both males and females (adjusted OR, 0.71; 95% CI, 0.57-0.88 and adjusted OR, 0.72; 95% CI, 0.57-0.90, respectively). Similarly, individuals older than 60 years had a decreased risk of BCC with metformin exposure (adjusted OR, 0.69; 95% CI, 0.59-0.82).

DISCUSSION

This population-based study shows an association between decreased risk of BCC and metformin use in a low-UV environment. By using a nested case-control design and linking nationwide health registries, the risks of having a nonrepresentative control group or information bias were eliminated. These are drawbacks typical for most case-control studies. The Icelandic unique personal identification numbers provided high-quality record linkage and ensured that virtually no loss to follow-up occurred during the study's 15-year span. Fitzpatrick skin type is a risk factor for skin cancer development at a population level. The majority of the Icelandic population is White,[14] which contributes to the study's internal validity. Although background UV is low in Iceland, it is important to note that tanning bed use and foreign travel are commonplace.[16] These 2 factors likely play a relatively recent and important role in the exposure of this population to UV radiation.

Metformin is an oral medication used mostly for type 2 diabetes mellitus (T2DM). It has been shown to have potential when it comes to inhibiting cancer cell proliferation in animal models and, to a limited extent, has been linked with a lower risk of certain types of cancer in humans, such as breast, pancreatic, and colon cancer.[19-21] Metformin's main antitumor properties are thought to be due to AMP-kinase inhibition, leading to the inhibition of the mammalian target of rapamycin.[19] In addition, metformin can directly inhibit the Shh signaling pathway,[3,4] which is an important pathway for cell growth in BCC. Specifically, it has been shown that metformin inhibits expression of the Shh ligand, thereby reducing activation of this pathway, a finding that is clinically relevant, as demonstrated by direct inhibition of the Shh pathway in breast cancer cells and cancer stem cells.[19]

Decreased BCC risk seen with metformin administration was similar for all dose categories. It is unclear why this is. It could be that we have a

Table I. Characteristics of individuals with BCC, SCCis, and SCC and age- and gender-matched controls

	BCC		In-situ SCC		SCC	
Characteristic	Case (n = 4700)	Control (n = 47,293)	Case (n = 1167)	Control (n = 11,961)	Case (n = 1013)	Control (n = 10,367)
Age, Median (IQR)	69 (56-79)	69 (56-79)	77 (67-84)	77 (67-84)	79 (71-85)	79 (70-85)
Gender						
Male	1988 (42.30%)	20,023 (42.34%)	425 (36.42%)	4368 (36.52%)	521 (51.43%)	5309 (51.21%)
Female	2712 (57.70%)	27,270 (57.66%)	742 (63.58%)	7593 (63.48%)	492 (48.57%)	5058 (48.79%)
Metformin Use						
Ever	189 (4.02%)	2500 (5.29%)	87 (7.46%)	740 (6.19%)	73 (7.21%)	687 (6.63%)
Never	4511 (95.98%)	44,793 (94.71%)	1080 (92.54%)	11,221 (93.81%)	940 (92.79%)	9680 (93.37%)

BCC, Basal cell carcinoma; *IQR,* interquartile range; *SCC,* squamous cell carcinoma; *SCCis,* squamous cell carcinoma in situ.

Table II. Association between metformin and BCC, SCCis, and SCC

	Cases	Controls	OR (95% CI)	Adjusted OR (95% CI)*	Adjusted OR (95% CI)†	Adjusted OR (95% CI)‡	Adjusted OR (95% CI)§	Adjusted OR (95% CI)‖
BCC								
Never use	4511	44,793	1.0	1.0	1.0	1.0	1.0	1.0
Ever use	189	2500	0.75 (0.64-0.87)	0.74 (0.63-0.86)	0.73 (0.63-0.85)	0.71 (0.61-0.83)	0.71 (0.61-0.83)	0.72 (0.61-0.85)
Cumulative dose								
1-500 DDUs	79	1041	0.75 (0.60-0.95)	0.75 (0.59-0.94)	0.74 (0.58-0.93)	0.72 (0.57-0.91)	0.72 (0.57-0.91)	0.76 (0.59-0.97)
501-1500 DDUs	60	816	0.73 (0.56-0.95)	0.72 (0.54-0.93)	0.71 (0.54-0.93)	0.69 (0.53-0.90)	0.69 (0.53-0.90)	0.69 (0.53-0.90)
>1500 DDUs	50	643	0.77 (0.57-1.03)	0.76 (0.57-1.01)	0.75 (0.56-1.00)	0.73 (0.54-0.98)	0.73 (0.54-0.98)	0.73 (0.54-0.97)
Continuous trend test		$P = .87$						
In situ SCC								
Never use	1080	11,221	1.0	1.0	1.0	1.0	1.0	1.0
Ever use	87	740	1.22 (0.97-1.54)	1.20 (0.95-1.52)	1.20 (0.95-1.51)	1.06 (0.84-1.35)	1.06 (0.84-1.35)	1.05 (0.82-1.34)
Cumulative dose								
1-500 DDUs	25	281	0.92 (0.61-1.40)	0.91 (0.60-1.38)	0.91 (0.60-1.37)	0.83 (0.55-1.27)	0.84 (0.55-1.27)	0.74 (0.46-1.21)
501-1500 DDUs	43	273	1.64 (1.18-2.27)	1.61 (1.16-2.24)	1.59 (1.15-2.22)	1.40 (1.00-1.96)	1.40 (1.00-1.96)	1.38 (0.99-1.93)
>1500 DDUs	19	186	1.06 (0.65-1.71)	1.05 (0.65-1.69)	1.05 (0.65-1.71)	0.91 (0.56-1.48)	0.90 (0.56-1.47)	0.91 (0.56-1.49)
Continuous trend test		$P = .94$						
SCC								
Never use	940	9680	1.0	1.0	1.0	1.0	1.0	1.0
Ever use	73	687	1.10 (0.85-1.42)	1.10 (0.85-1.42)	1.09 (0.85-1.41)	1.01 (0.78-1.30)	1.01 (0.78-1.30)	1.05 (0.80-1.37)
Cumulative dose								
1-500 DDUs	24	267	0.93 (0.61-1.42)	0.93 (0.60-1.42)	0.92 (0.60-1.40)	0.86 (0.56-1.32)	0.86 (0.56-1.32)	0.95 (0.60-1.51)
501-1500 DDUs	33	234	1.47 (1.01-2.14)	1.47 (1.01-2.14)	1.47 (1.01-2.14)	1.35 (0.92-1.97)	1.35 (0.92-1.97)	1.35 (0.92-1.97)
>1500 DDUs	16	186	0.89 (0.53-1.50)	0.89 (0.53-1.50)	0.89 (0.53-1.50)	0.79 (0.47-1.34)	0.79 (0.47-1.34)	0.79 (0.47-1.34)
Continuous trend test		$P = .88$						

BCC, Basal cell carcinoma; *CI,* confidence interval; *DDU,* daily dose units; *OR,* odds ratio; *SCC,* squamous cell carcinoma; *SCCis,* squamous cell carcinoma in situ.
1-500 DDUs equivalent to 2-1000 g; 501-1500 DDUs equivalent to 1002-3000g; >1500 DDUs equivalent to >3000 g.
*Adjusted for hydrochlorothiazide.
†Adjusted for hydrochlorothiazide and photosensitizing medications.
‡Adjusted for hydrochlorothiazide, photosensitizing medications, and statins.
§Adjusted for hydrochlorothiazide, photosensitizing medications, statins, and tumor necrosis alpha inhibitors.
‖Excludes patients on voriconazole and those with <2 filled metformin prescriptions; adjusted for hydrochlorothiazide, photosensitizing medications, statins, and tumor necrosis alpha inhibitors.

Table III. Subgroup analysis by age and gender

Subgroup	Case patients (exposed/unexposed)	Controls (exposed/unexposed)	OR (95% CI)	Adjusted OR (95% CI)*
BCC				
Male	100/1888	1314/18,709	0.75 (0.61-0.93)	0.71 (0.57-0.88)
Female	89/2623	1186/26,084	0.75 (0.60-0.93)	0.72 (0.57-0.90)
<60 years	27/1398	309/14,074	0.88 (0.59-1.31)	0.86 (0.57-1.30)
≥60 years	162/3113	2191/30,719	0.73 (0.62-0.86)	0.69 (0.59-0.82)
In situ SCC				
Male	39/386	345/4023	1.18 (0.83-1.68)	1.06 (0.74-1.52)
Female	48/694	395/7198	1.25 (0.92-1.71)	1.06 (0.77-1.47)
<60 years	4/138	32/1508	1.34 (0.46-3.88)	1.04 (0.34-3.21)
≥60 years	83/942	708/9713	1.21 (0.96-1.54)	1.06 (0.83-1.36)
SCC				
Male	50/471	435/4874	1.12 (0.88-1.64)	1.12 (0.81-1.54)
Female	23/469	252/4806	0.94 (0.61-1.46)	0.83 (0.53-1.30)
<60 years	2/93	23/1005	1.17 (0.27-5.177)	1.10 (0.23-5.35)
≥60 years	71/847	664/8675	1.10 (0.85-1.42)	1.01 (0.77-1.31)

BCC, Basal cell carcinoma; *CI,* confidence interval; *OR,* odds ratio; *SCC,* squamous cell carcinoma.
*Adjusted for hydrochlorothiazide, photosensitizing medications, statins, and tumor-necrosis alpha inhibitors.

confounder that is unaccounted for in the analysis. It could also be that metformin's BCC risk-lowering effect is immediate, with only a low dose being needed to see a clinical benefit. Notably, the OR continued to decrease when adjusted for hydrochlorothiazide and statins, but not TNF-alpha inhibitors, which have been associated with increased risk of keratinocyte cancer in this population. This decreased risk of BCC was seen in all subanalyses, except for the younger than 60 years category. This might signify that metformin has less of a protective effect in younger individuals, but we might also have lacked power in this category. Looking at SCCis, we saw no decrease in risk; on the contrary, for the 501-1500 DDU dose category, we observed an adjusted OR of 1.40 (95% CI, 1.00-1.96), showing a possible increased risk of SCCis. This was not seen in any of the subanalyses or the other dose categories. A decrease or increase in risk was not observed for SCC formation with metformin exposure. However, similar to what we saw with SCCis, there was a significantly higher risk of SCC in the 501-1500 DDU category (OR, 1.47; 95% CI, 1.01-2.14), but this was not significant after adjusting for the use of other medication (OR, 1.35; 95% CI, 0.92-.97).

This study has several important limitations. We did not have information on patient comorbidities (eg, T2DM), photodynamic therapy utilization, tanning bed use, UV exposure habits, smoking status, socioeconomic status, or all potential confounding medications patients were taking.[18] The relationship between metformin and lower BCC risk raises the possibility of diabetes or other diabetic medication being possible confounders. It is unclear whether T2DM truly affects the risk of keratinocyte carcinoma, with some studies reporting an increased risk of skin cancer[22] and others reporting a decreased risk.[23,24] A study based in the United Kingdom observed that patients diagnosed with BCC had T2DM less often.[23] They speculated that differences in lifestyle of diabetic patients might account for the association they observed.[23] This reason is unlikely to explain this study's findings, as decreased risk of SCC in addition to BCC would be expected. In addition, it has been reported that there might be a possible protective role of insulin-like growth factor 1 receptor in keratinocytes, with activation protecting keratinocytes from UVB-induced carcinogenesis.[24] However, if this were the case, a decreased risk of SCC in addition to BCC would be expected. Thus, we speculate that metformin's selective inhibition of the Shh pathway is the main mechanism that decreased the observed risk of BCC in exposed Icelanders. It might be that T2DM increases the overall risk of SCC, as some studies have shown[22] with metformin selectively decreasing the risk of BCC rather than SCC. Optimally, a control group taking a separate diabetic medication, such as insulin, should have been included in this study. However, we lacked sufficient power to assess this variable.

BCC chemoprophylaxis options are lacking. Nicotinamide and acitretin have shown effectiveness in reducing SCC and actinic keratoses counts, but the benefit for BCC prophylaxis is less clear.[25,26] Vismodegib was the first Shh pathway inhibitor to gain Food and Drug Administration approval for the treatment of BCC,[5] followed by sonidegib.[6] These agents work as antagonists to the smoothened receptor, directly inhibiting activation of the Shh pathway.[5] However, their use is limited by side effects, which affect most patients, such as muscle spasms, alopecia, and dysgeusia.[5] Metformin's most

common side effects are diarrhea and nausea, which are present in up to 50% of patients. These effects are usually mild and can be minimized by taking metformin at mealtimes or by lowering the dose.[27] As mentioned earlier, our results suggest that metformin's BCC risk reduction might be idiosyncratic, with only small doses required to be effective, thereby lowering the risk of side effects. Limiting the potential of Shh inhibitors is the possibility of increased SCC risk.[28] This might also be the case with metformin, as we saw a borderline significant increase of in situ SCC risk with moderate doses. This observed risk increase might be due to an inability to adjust for all possible confounders, such as organ transplant status and all potential immunosuppressive medication.

While this study does not imply causation, it does suggest an association between metformin use and lower rates of first-time BCC. Furthermore, randomized prospective trials are required to fully understand the effect metformin has on BCC and SCC risk.

Conflicts of interest

None disclosed.

REFERENCES

1. Zhang P, Li H, Tan X, Chen L, Wang S. Association of metformin use with cancer incidence and mortality: a meta-analysis. *Cancer Epidemiol*. 2013;37(3):207-218.
2. Saraei P, Asadi I, Kakar MA, Moradi-Kor N. The beneficial effects of metformin on cancer prevention and therapy: a comprehensive review of recent advances. *Cancer Manag Res*. 2019;11:3295-3313.
3. Niu C, Chen Z, Kim KT, et al. Metformin alleviates hyperglycemia-induced endothelial impairment by downregulating autophagy via the Hedgehog pathway. *Autophagy*. 2019;15(5):843-870.
4. Song Z, Wei B, Lu C, Huang X, Li P, Chen L. Metformin suppresses the expression of Sonic hedgehog in gastric cancer cells. *Mol Med Rep*. 2017;15(4):1909-1915.
5. Aditya S, Rattan A. Vismodegib: a smoothened inhibitor for the treatment of advanced basal cell carcinoma. *Indian Dermatol Online J*. 2013;4(4):365-368.
6. Lear JT, Migden MR, Lewis KD, et al. Long-term efficacy and safety of sonidegib in patients with locally advanced and metastatic basal cell carcinoma: 30-month analysis of the randomized phase 2 BOLT study. *J Eur Acad Dermatol Venereol*. 2018;32(3):372-381.
7. Marshall SM. 60 years of metformin use: a glance at the past and a look to the future. *Diabetologia*. 2017;60(9):1561-1565.
8. Tseng CH. Metformin is associated with decreased skin cancer risk in Taiwanese patients with type 2 diabetes. *J Am Acad Dermatol*. 2018;78(4):694-700.
9. Ravishankar A, Zhang T, Lindgren BR, Farah RS, Dong Z, Goldfarb NI. The effect of metformin on the risk of recurrent nonmelanoma skin cancers. *Int J Dermatol*. 2020;59(8):e303-e305.
10. Helgason A, Nicholson G, Stefánsson K, Donnelly P. A reassessment of genetic diversity in Icelanders: strong evidence from multiple loci for relative homogeneity caused by genetic drift. *Ann Hum Genet*. 2003;67(4):281-297.
11. Adalsteinsson JA, Ratner D, Olafsdóttir E, et al. Basal cell carcinoma: an emerging epidemic in women in Iceland. *Br J Dermatol*. 2020;183(5):847-856.
12. Sigurdardottir LG, Jonasson JG, Stefansdottir S, et al. Data quality at the Icelandic Cancer Registry: comparability, validity, timeliness and completeness. *Acta Oncol*. 2012;51(7):880-889.
13. The Icelandic Directorate of Health Web site. 2020. Accessed October 1, 2020. Available at: https://www.landlaeknir.is/english
14. World Health Organization. Biguanides. Accessed October 1, 2020. Available at: https://www.whocc.no/atc_ddd_index/?code=A10BA02
15. Didona D. Non melanoma skin cancer pathogenesis overview. *Biomedicines*. 2018;6(1):6.
16. Adalsteinsson JA, Muzumdar S, Waldman R, et al. Association between hydrochlorothiazide and the risk of in situ and invasive squamous cell skin carcinoma and basal cell carcinoma: a population-based case-control study. *J Am Acad Dermatol*. 2021;84(3):669-675.
17. Wang JL, Yin WJ, Zhou LY, et al. Risk of non-melanoma skin cancer for rheumatoid arthritis patients receiving TNF antagonist: a systematic review and meta-analysis. *Clin Rheumatol*. 2020;39(3):769-778.
18. Yang K, Marley A, Tang H, Song Y, Tang JY, Han J. Statin use and non-melanoma skin cancer risk: a meta-analysis of randomized controlled trials and observational studies. *Oncotarget*. 2017;8(43):75411-75417.
19. Fan C, Wang Y, Liu Z, et al. Metformin exerts anticancer effects through the inhibition of the Sonic hedgehog signaling pathway in breast cancer. *Int J Mol Med*. 2015;36(1):204-214.
20. Kisfalvi K, Eibl G, Sinnett-Smith J, Rozengurt E. Metformin disrupts crosstalk between G protein-coupled receptor and insulin receptor signaling systems and inhibits pancreatic cancer growth. *Cancer Res*. 2009;69(16):6539-6545.
21. Hosono K, Endo H, Takahashi H, et al. Metformin suppresses colorectal aberrant crypt foci in a short-term clinical trial. *Cancer Prev Res*. 2010;3(9):1077-1083.
22. Tseng HW, Shiue YL, Tsai KW, Huang WC, Tang PL, Lam HC. Risk of skin cancer in patients with diabetes mellitus. *Medicine (Baltimore)*. 2016;95(26):e4070.
23. Reinau D, Surber C, Jick SS, Meier CR. Epidemiology of basal cell carcinoma in the United Kingdom: incidence, lifestyle factors, and comorbidities. *Br J Cancer*. 2014;111(1):203-206.
24. Chuang TY, Lewis DA, Spandau DF. Decreased incidence of nonmelanoma skin cancer in patients with type 2 diabetes mellitus using insulin: a pilot study. *Br J Dermatol*. 2005;153(3):552-557.
25. Snaidr VA, Damian DL, Halliday GM. Nicotinamide for photoprotection and skin cancer chemoprevention: a review of efficacy and safety. *Exp Dermatol*. 2019;28:15-22.
26. Kadakia KC, Barton DL, Loprinzi CL, et al. Randomized controlled trial of acitretin versus placebo in patients at high-risk for basal cell or squamous cell carcinoma of the skin (North Central Cancer Treatment Group Study 969251). *Cancer*. 2012;118(8):2128-2137.
27. Siavash M, Tabbakhian M, Sabzghabaee A, Razavi N. Severity of gastrointestinal side effects of metformin tablet compared to metformin capsule in type 2 diabetes mellitus patients. *J Res Pharm Pract*. 2017;6(2):73-76.
28. Bhutani T, Abrouk M, Sima CS, et al. Risk of cutaneous squamous cell carcinoma after treatment of basal cell carcinoma with vismodegib. *J Am Acad Dermatol*. 2017;77(4):713-718.