

# Association of Non-Melanoma Skin Cancer with Temperament from the Perspective of Traditional Persian Medicine: A Case-Control Study

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## What's Known

- Non-melanoma skin cancer (NMSC) is the most common type of cancer in the world.
- Typical causes of NMSC are chronic skin ulcers, radiotherapy, and long-term exposure to sunlight.

## What's New

- Dry temperament, as a personality type, should be considered a risk factor for NMSC.
- Dry skin caused by radiotherapy or exposure to sunlight could be a major risk factor for NMSC.

## Abstract

**Background:** Non-melanoma skin cancer (NMSC) is the most common type of cancer in the world. In traditional Persian medicine (TPM), various types of temperament (*Mizaj*) are considered to diagnose, treat, and prevent a variety of illnesses. The present study aimed to evaluate the temperament of patients with NMSC in comparison with a control group.

**Methods:** A case-control study was conducted in 2018 at the Dermatology Clinic of Shahid Faghihi Hospital affiliated with Shiraz University of Medical Sciences (Shiraz, Iran). A total of 110 patients, aged  $\geq 20$  years with confirmed NMSC (case group), and 181 individuals without NMSC (control group) were enrolled in the study. The temperament of the participants in both groups was evaluated using Mojahedi's Mizaj questionnaire. The data were analyzed using SPSS software, and  $P < 0.05$  was considered statistically significant.

**Results:** The results showed that the odds ratio of developing NMSC was 2.62 (95%CI: 1.42-4.83,  $P = 0.002$ ) times higher in individuals with dry temperament than other types of temperament. Moreover, the odds ratio of patients with a history of chronic skin ulcers and other types of cancer was 35.7 (95%CI: 11.9-107.15,  $P < 0.001$ ) and 5.22 (95%CI: 1.43-19.06,  $P = 0.012$ ) times higher, respectively, than the control group.

**Conclusion:** Temperament is associated with NMSC, particularly the dry temperament type, and should be considered a risk factor.

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**Keywords** • Traditional • Skin neoplasms • Temperament • Persian medicine

## Introduction

Non-melanoma skin cancer (NMSC) is the most common type of cancer in the world. The two most prevalent types of NMSC are basal cell carcinoma (BCC) and squamous cell carcinoma (SCC). BCC is the least aggressive form of NMSC observed mainly on sun-exposed areas of the skin (e.g., scalp, face, neck). The reported risk factors for developing BCC are age, sex, exposure to ultraviolet (UV) radiation, Fitzpatrick skin types I and II, specific genetic diseases, long-term exposure to arsenic, and immunosuppression.<sup>1</sup> SCC, on the other hand, is an invasive tumor of epithelial keratinocytes, which is approximately three

times more common in men than in women.<sup>2</sup> The main risk factors for SCC are exposure to sunlight and UV radiation, outdoor occupations, Fitzpatrick skin types I and II, and inherited skin diseases such as xeroderma pigmentosum and human papillomavirus (HPV) infection (mostly types 16, 18, 31). It has been reported that of all cases, SCC is primarily observed on the scalp, face, and neck (55%) followed by extensor forearms and dorsal hands (18%).<sup>1</sup>

As an alternative to modern medicine in treating NMSC, traditional medicine has been suggested. According to the World Health Organization (WHO), traditional medicine is defined as “the total sum of knowledge, skill, and practices based on the beliefs, theories, and experiences indigenous to different cultures.” Traditional medicine, also referred to as complementary and alternative medicine, has been used to diagnose, treat, and prevent a variety of illnesses.<sup>3</sup> As one of the ancient medical disciplines, traditional Persian medicine (TPM) is based on religious beliefs.<sup>4,5</sup> It considers the human body as a single entity, such that disease in any part of the body is indicative of an imbalance of the entire body. TPM views each person to be unique with a specific temperament (*Mizaj*) that defines an individual's behavioral and physical characteristics. It considers temperament as the root cause of any illness and prescribes a natural remedy for each illness. TPM categorizes both our body and natural products to have one or a combination of the four qualities, namely hot, cold, wet, and dry.<sup>6</sup> Accordingly, the temperament of an individual is classified as moderate, hot, cold, dry, wet, hot-wet, hot-dry, cold-wet, and cold-dry. Any deviation of the whole body or any of its organs from these temperaments leads to disease.<sup>7</sup>

According to TPM, organs in the body are nourished with four types of bodily fluids, namely blood (*Dam*), phlegm (*Balgham*), yellow bile (*Safra*), and black bile (*Sauda*). These bodily fluid types are associated with the four types of temperament, namely sanguine (*Damaviy*, hot-wet), phlegmatic (*Balghamiy*, cold-wet), choleric (*Safraviy*, hot-dry), and melancholic (*Saudaviy*, cold-dry). Normal concentrations of these four elements are essential to have a healthy body and achieve balanced performance.<sup>8-10</sup> For example, cancer in TPM is described as “hard inflammatory lesions with tributaries filled with morbid melancholic fluid” and in Greek traditional medicine as “Warm-e-Sulb-Saudavi”.<sup>11-13</sup>

To the best of our knowledge, no previous studies have evaluated NMSC in the context of TPM and the four types of temperament.

Hence, the present study aimed to evaluate the temperament of patients with NMSC compared to a control group.

## Patients and Methods

A case-control study was conducted in 2018 at the Dermatology Clinic of Shahid Faghihi Hospital affiliated with Shiraz University of Medical Sciences (Shiraz, Iran). The target population was patients with confirmed NMSC (case group) and individuals without NMSC (control group). The sample size was calculated using the “power two proportions” module of the Stata software, version 14.2 (StataCorp LLC, College Station, Texas, USA). Based on the results of a pilot study, the prevalence of dry temperament in patients with NMSC (35%) and controls (20%) was used to calculate the sample size, as well as values for odds ratio (2.20), the control-case proportion using type I error (1.5), power (0.8), and alpha (0.05). Accordingly, the minimum sample size of 110 for the case group and 165 for the control group was computed. However, we decided to include 180 individuals in the control group. The inclusion criteria for the case group were patients aged >20 years, suffering from pathologically confirmed NMSC, and referred to the Dermatology Clinic of Shahid Faghihi Hospital. The exclusion criteria were patients suffering from other recurring diseases, pregnant and lactating women, and those unwilling to participate in the study.

Mojahedi's Mizaj Questionnaire was used to determine the temperament of the participants. This questionnaire includes 10 questions, in which questions 1-8 are related to hot and cold types of temperament and questions 9-10 to wet and dry types. The scoring system for the first set of questions is defined as the cut-off point values for the hot type:  $\geq 19$ , mild type: 15-18, and cold type:  $\leq 14$ . For the second set of questions, scores are defined as dry type:  $\geq 5$ , moderate type: 4, and wet type:  $\leq 3$ . The validity and reliability of the questionnaire were reported as acceptable (kappa coefficient: 0.4-0.82, Cronbach's  $\alpha$  coefficient: 0.71, content validity index of each item: 0.70-1.00).<sup>14</sup> Additional information obtained from the participants were history of exposure to mineral oils, tar, arsenic (agricultural, chemical, and industrial pesticides, and other types of poison), psoralen, ionizing radiation; cigarette smoking, history of HPV, genetic diseases (xeroderma pigmentosum, oculocutaneous albinism, epidermodysplasia verruciformis, epidermolysis bullosa); untreated wounds, history of systemic or cutaneous lupus, organ transplants, and other types of cancers.

### Statistical Analysis

The data were analyzed using SPSS software, version 18.0 (SPSS Inc., Chicago, IL, USA), and Stata software, version 14.20 (StataCorp LLC, College Station, Texas, USA). Data were reported as frequency, percentage, or mean±SD. An independent *t* test was used to compare quantitative data between the two groups and the Chi square test to compare qualitative data between the groups. Multiple logistic regression analysis was used to compute the odds ratio with a 95% confidence interval (CI) to detect significant risk factors by adjusting the confounders.  $P < 0.05$  was considered statistically significant.

### Ethical Considerations

The study was approved by the Ethics Committee of Shiraz University of Medical Sciences, Shiraz, Iran (IR.SUMS.MED.REC.1397.215). The participants were fully informed about the study procedure and confidentiality of any disclosed information was guaranteed. Written informed consent was obtained from the participants.

## Results

The case group (n=110) included 75 (68.2%)

patients with BCC and 35 (31.8%) with SCC of whom 103 (93.6%) individuals had scalp, face, and neck involvement. Demographic characteristics and type of temperament of the case and control groups are presented in table 1. The results showed a significant association between the groups in terms of demographic characteristics such as sex, education level, and duration of exposure to sunlight. However, age and ethnicity had no significant association. The percentage of men was higher in the case group, whereas in the control group women were overrepresented, and the difference was statistically significant. The age category  $\geq 60$  years had the highest frequency in both groups. There was a significant relationship between the groups in terms of wet-dry temperament ( $P=0.003$ ), however, the relationship for the hot-cold temperament was not significant ( $P=0.209$ ). Meaning that the percentage of dry temperament in people with NMSC was significantly higher than in the control group, but the percentage of moderate and wet temperament was higher in the control group.

The association of NMSC with exposure to risk factors and medical history of the participants is shown in table 2. Multiple logistic

**Table 1:** Demographic characteristics and type of temperament of patients with non-melanoma skin cancer (case group) versus individuals without non-melanoma skin cancer (control group)

Variables		Case (n=110)	Control (n=181)	P value <sup>*</sup>
Age (years)	20-39	7 (6.4)	20 (11)	0.096
	40-59	31 (28.2)	65 (35.6)	
	$\geq 60$	72 (65.5)	96 (53.6)	
Sex	Men	68 (61.8)	84 (46.4)	0.011
	Women	42 (38.2)	97 (53.6)	
Education level	Illiterate	46 (41.8)	18 (9.9)	<0.001
	Elementary and middle school	40 (36.4)	51 (28.2)	
	High school	21 (19.1)	49 (27.1)	
	University	3 (2.7)	63 (34.8)	
Occupation	Farmer and rancher	32 (29.1)	6 (3.3)	<0.001
	Employee	13 (11.8)	35 (19.3)	
	Retired	8 (7.3)	39 (21.5)	
	Self-employed	23 (20.9)	40 (22.1)	
	Housewife	34 (30.9)	61 (33.7)	
Ethnicity	Fars	80 (72.7)	155 (85.6)	0.059
	Turk	14 (12.7)	11 (6.1)	
	Lur	12 (10.9)	11 (6.1)	
	Others	4 (3.6)	4 (2.2)	
Duration of exposure to sunlight per day	<2 hours	22 (20)	123 (68)	<0.001
	2-6 hours	30 (27.3)	35 (19.3)	
	>2 hours	58 (52.7)	23 (12.7)	
Temperament (hot-cold)	Hot	30 (27.3)	54 (29.8)	0.209
	Moderate	43 (39.1)	83 (45.9)	
	Cold	37 (33.6)	44 (24.3)	
Temperament (wet-dry)	Dry	49 (44.5)	46 (25.4)	0.003
	Moderate	29 (26.4)	67 (37)	
	Wet	32 (29.1)	68 (37.6)	

\*Chi square test; Statistical significance:  $P < 0.05$ . Data are expressed as number and percentage.

**Table 2:** Presenting the association of non-melanoma skin cancer with exposure to risk factors and medical history of the participants in both groups

Variables		Case group (n=110)	Control group (n=181)	P value*
Exposure/contact	Mineral oil materials	7 (6.4)	13 (7.2)	0.789
	Tar	15 (13.6)	9 (5)	0.009
	Arsenic	2 (1.8)	7 (3.9)	0.334
	Psoralen	13 (11.8)	6 (3.3)	0.004
	Ionizing radiation	13 (11.8)	8 (4.4)	0.018
	History of cigarette smoking	27 (24.5)	24 (13.3)	0.014
Medical history	Human papillomavirus	3 (2.7)	4 (2.2)	0.780
	Xeroderma pigmentosum	0 (0)	3 (1.7)	0.175
	Oculocutaneous albinism	2 (1.8)	3 (1.7)	0.919
	Epidermodysplasia verruciformis	0 (0)	0 (0)	-
	Dystrophic epidermolysis bullosa	1 (0.9)	1 (0.6)	0.721
	Untreated wounds	46 (41.8)	4 (2.2)	<0.001
	Lupus	0 (0)	2 (1.1)	0.528
	Organ transplant	3 (2.7)	0 (0)	0.053
	Other types of cancer	12 (10.9)	5 (2.8)	0.004

\*Chi square test or Fisher's exact test; Statistical significance: P<0.05. Data are expressed as number and percentage.

regression analysis was performed to investigate the effect of all variables on NMSC. However, variables such as positive history of xeroderma pigmentosum disease, dystrophic epidermolysis bullosa, lupus, and organ transplant were excluded from the analysis due to low frequency. Moreover, variables with P>0.2 were excluded. The results of the multiple logistic regression analysis are shown in table 3. Compared with other variables, only dry temperament, a history of untreated wounds, and other types of cancer were significant. By moderating the effect of other variables, the odds ratio of developing NMSC was 2.41 times higher in those with dry than the wet temperament (P=0.015). Besides, the odds ratio for having a history of chronic ulcers or other types of cancer were 36.2 and 5.08 times higher, respectively, than those without such a history (P<0.001 and P=0.014, respectively).

To further analyze the data, the results of moderate/cold (based on hotness quality) and moderate/wet (based on wetness quality) temperaments were merged. The results showed

a significant relationship between NMSC and dry temperament (P=0.001), but no significant relationship was found between NMSC and hot/cold temperament (P=0.640). This means that the percentage of people with dry temperament was significantly higher in the case group than in the control group, whereas the percentage of people with moderate/wet temperament was higher in the control group.

After the integration of cold and moderate temperaments (based on hotness quality) and wet and moderate temperaments (based on wetness quality), the overall effect of the studied variables on NMSC was re-examined using multiple logistic regression (table 4). The results showed that only dry temperament, a history of untreated wounds, and other types of cancer were statistically significant in the presence of other variables in developing NMSC. After adjusting the effect of other variables, the odds ratio for developing NMSC was 2.62 times higher in those with dry temperament (95%CI: 1.42 to 4.83, P=0.002) than the other types of temperament.

**Table 3:** The results of multiple logistic regression analysis on the effect of variables on non-melanoma skin cancer

Variables		Odds ratio	95% confidence interval	P value*
Temperament (Hot-cold)	Cold	-	-	Reference
	Hot	1.03	0.46-2.27	0.94
	Moderate	0.74	0.35-1.54	0.42
Temperament (Wet-dry)	Wet	-	-	Reference
	Dry	2.41	1.18-4.88	0.015
	Moderate	0.83	0.38-1.79	0.63
Exposure/contact	Tar	2.59	0.94-7.15	0.06
	Psoralen	2.29	0.6-8.74	0.22
	Ionizing radiation	1.68	0.37-7.59	0.49
History of cigarette smoking		2.03	0.96-4.29	0.06
Untreated wounds		36.2	11.97-109.48	<0.001
Other types of cancer		5.08	1.39-18.52	0.014

\*Statistical significance: P<0.05



**Table 4:** Presenting the overall effect of variables on non-melanoma skin cancer using multiple logistic regression analysis by merging temperament categories

	Odds ratio	95% confidence interval	P value*
Temperament (hot/moderate, cold)	1.2	0.62-2.33	0.57
Temperament (dry/moderate, wet)	2.62	1.42-4.83	0.002
History of contact with tar	2.71	0.99-7.42	0.05
History of contact with psoralen	2.42	0.64-9.17	0.19
History of exposure to ionizing radiation	1.71	0.38-7.72	0.49
History of cigarette smoking	1.97	0.94-4.15	0.07
History of untreated wounds	35.7	11.9-107.15	<0.001
History of other types of cancer	5.22	1.43-19.06	0.012

\*Statistical significance: P<0.05

In addition, the odds ratio of patients with a history of chronic ulcers and other types of cancer was 35.7 (95%CI: 11.9-107.15, P<0.001) and 5.22 (95%CI: 1.43-19.06, P=0.012) times higher, respectively, than the control group.

## Discussion

The results showed that dry temperament, a history of untreated wounds, and other types of cancer were only significant in the presence of other variables. The odds ratio for developing NMSC was 2.62 times higher in those with dry temperament. In addition, dry skin was also found to be associated with NMSC and SCC. This finding was in line with a previous study on hereditary ichthyosis that reported mutations in the keratinization cells leading to a higher risk of skin cancer. In addition, dry skin is sometimes associated with increased keratinization and mitosis of squamous cells on the surface of the skin, which could potentially lead to unwanted mutations and an increased risk of malignancy in skin cells.<sup>15</sup>

The results showed that cold and dry temperaments were more frequent in patients with NMSC than the control group. Other studies have also stated the significance of different types of temperament in TPM as well as an association between cancer and cold/dry (simple and/or compound) temperament.<sup>16, 17</sup> It has been reported that increased concentrations of the black bile (*Saudā'*) in people with cold/dry temperament could be due to the types of food or exposure to sunlight or harmful substances.<sup>18, 19</sup> Moreover, a combination of intrinsic and inherent characteristics with environmental factors could make a person prone to such an imbalance.<sup>20</sup>

We found that the incidence of NMSC in patients with a history of chronic ulcers and other types of cancer was 35.7 and 5.22 times higher, respectively, than those without such a history. This finding was in line with previous studies on modern and traditional medicines. For instance, in modern medicine, Marjolin's

ulcer is described as an aggressive ulcerating SCC that can manifest itself in previously burned areas of the skin.<sup>21</sup> Furthermore, various types of cancer are associated with genetic issues or specific syndromes.<sup>22</sup> On the other hand, in traditional medicine, chronic ulcers (called *ghorouh-e-khabitkeh*) are suggested to develop due to a melancholic (*Saudaviy*, cold-dry) temperament.<sup>19, 23-25</sup>

The results of multiple logistic regression analysis showed that although cigarette smoking is a risk factor for NMSC, its effect was not statistically significant. This finding is in line with TPM suggesting that opium use and cigarette smoking could result in melancholic (*Saudaviy*) temperament and dry skin.<sup>10, 25</sup> In contrast, other studies have reported that cigarette smoking is associated with SCC, but not NMSC or BCC.<sup>26, 27</sup> The difference between the results could be due to genetic and ethnicity factors as well as the tobacco type, duration, and dosage of smoking. Further studies on this topic are recommended.

A relationship between temperament and conditions such as diabetes mellitus, geographic tongue, psychological disorders, and type of personality has been reported.<sup>8, 28-30</sup> It has been shown that geographic tongue is associated with dry and hot-dry types of temperament.<sup>30</sup> Besides, a relationship between hot temperament and the personality type neuroticism has been reported.<sup>8</sup> A previous study showed that people with cold temperaments are less happy.<sup>29</sup> Furthermore, it has been reported that the total mean scores of hot/cold and wet/dry temperaments in patients with type 1 diabetic mellitus were significantly higher than in healthy individuals.<sup>28</sup> However, to the best of our knowledge, no studies have shown an association between cancer and temperament.

As the main strengths of our study, for the first time, we evaluated an association between cancer, specifically skin cancer, and the various types of temperament. However, our study had three limitations. First, temperament is a qualitative characteristic and prone to bias, if

assessed quantitatively, as in our study. Secondly, although Mojahedi's Mizaj Questionnaire is well established, it is not comprehensive, as it lacks low priority factors associated with temperament. Thirdly, the single-center design of the study undermines the generalizability of our findings. Finally, individuals in the control group were mainly recruited from the caregivers of the patients. However, composition bias due to potential demographic heterogeneity was reduced by applying multiple logistic regression analyses. It is recommended to conduct further studies to include a multi-center design with a larger sample size and matched pair case-control study type.

### Conclusion

Temperament is associated with NMSC, particularly the dry type, and should be considered its risk factor. Further multi-center studies on the prophylactic effects of dry temperament on developing NMSC are recommended.

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### Authors' Contribution

M.M.P, M.G, N.S, and F.S.A: Contributed to Design of the work; M.M.P, M.G, F.S.A, Z.J, H.Z, M.K, and P.H: Contributed to data acquisition; M.M.P, N.S, and F.S.A: Contributed to Analysis; M.M.P, N.S, M.G, and F.S.A: Contributed to interpretation of data for the work; M.M.P, M.K, H.Z, P.H, and Z.J: Contributed to Drafting the work; F.S.A, N.S, M.M.P, and M.G: Contributed to revising it critically for important intellectual content; M.M.P, N.S, M.G, F.S.A, H.Z, Z.J, M.K, and P.H: Contributed to Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

### Conflict of Interest

Dr. Fatemeh Sari Aslani, as the Editorial Board Member, was not involved in any stage of handling this manuscript. A team of independent experts was formed by the Editorial Board to review the editor's article without her knowledge.

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