

## **Epidemiologic Pattern of Skin Malignancies in Semnan, Iran Between 1999 and 2007 and Comparing it with Meta-Analysis of Published Papers in World Between 2000 and 2008**

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**Abstract:** The skin is the body's largest organ. Melanoma and NMSC are now the most common types of cancer in white populations and both show an increasing incidence rate worldwide. The goal of this study was answering questions about skin malignancies epidemiologic pattern in Semnan. This study carried out in Semnan, Iran, from 1999-2007. Results of data from Semnan compared with meta-analysis results. Frequency of skin malignancies was 18.40%. Totally, the skin cancers were most prevalent malignancy. The most prevalent skin malignancies were BCC 65.1, SCC 28.5 and melanoma 1.07%. Male sex ratio was 61.87% for all cases, 56.9% for BCC and 72.2% for SCC cases ( $p = 0.02$ ). Mean age was 64.92 years for all skin malignancies, 65.74 in males and 63.74 years for females ( $p > 0.05$ ). This was 63.42 and 68.25 years for BCC and SCC, respectively ( $p = 0.026$ ). The most prevalent sites were nose or other parts of face with 40.21% and scalp and neck with 22.78%. The most prevalent site for BCC and SCC was nose or other parts of face to with 47.5 and 26.6%, respectively ( $p = 0.002$ ). Present results showed relatively constant trends by time for incidence of skin malignancies, including BCC and SCC and for sex and age. Epidemiologic pattern of skin cancers in Semnan was roughly comparable with the corresponding indexes in world and Iran especially for NMSC (BCC and SCC) comparing with other parts of Iran and Middle Asia, but the incidence of melanoma was lower.

**Key words:** Epidemiology, cancer, malignancy, skin, BCC, SCC, melanoma, meta-analysis

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### **INTRODUCTION**

The skin is the body's largest organ. The epidermis is made up of squamous cells, basal cells and contains melanocytes. Cancer may develop in any of the cell types: Squamous Cell Carcinoma (SCC), Basal Cell Carcinoma (BCC) and melanoma. Basal cell and squamous cell carcinomas are >10 times as common as melanoma but account for less morbidity and mortality. Nonmelanoma Skin Cancers (NMSC) are more prevalent in sun-exposed areas such as scalp, neck and face, old ages and mostly in male sex. Skin melanoma usually begins in a mole. It can occur on any skin surface in men, melanoma is often found on the trunk or the head and neck in women, it often develops on the lower legs (Johnson, 2004).

Melanoma and NMSC are now the most common types of cancer in white populations. Both tumor entities show an increasing incidence rate worldwide but a stable or decreasing mortality rate. Skin cancer is the most common form of cancer in the United States (Leiter and Garbe, 2008).

The rising incidence rates of NMSC are probably caused by a combination of increased sun exposure or

exposure to Ultraviolet (UV) light, increased outdoor activities, changes in clothing style, increased longevity, ozone depletion, genetics and in some cases, immune suppression. A dose-dependent increase in the risk of Squamous Cell Carcinoma (SCC) of the skin was found associated with exposure to Psoralen and UVA irradiation. An intensive UV exposure in childhood and adolescence was causative for the development of Basal Cell Carcinoma (BCC), whereas for the aetiology of SCC a chronic UV exposure in the earlier decades accused (Leiter and Garbe, 2008). Some experts say the rise in incidence (trend) of melanoma reflects a true increase in the disease, while others contend it is an artifact of more intensive recent surveillance. Others suggest that the rise in melanoma incidence may in part reflect longer life expectancy as well as efforts to detect melanoma earlier. The incidence of thin invasive lesions is increasing faster than that of thick ones, which reflects earlier detection by physicians and greater public awareness of warning signs of skin cancer. Among the reasons for these trends, increased exposure to UV radiation because of lifestyle changes is generally recognized as an important factor (Johnson, 2004).

In Iran and many underdeveloped or developing countries, including many Asian, African and other countries, well established registration systems, proper hard or soft databases and data validation and supervision don't exist, so many mistakes are seen in the data entry and output generation from these data. The aim of this study was correcting these data in Semnan pathology registration systems by pathology and database management experts, then creating valid outputs and corresponding world and Iran ASRs. The final goal was answering questions about skin malignancies epidemiologic pattern in Semnan (as a representative sample for Iranian population), for example trends in rate, changes in sex and age and many others; these questions in many instances previously answered based on incorrect data or personal nonscientific observations.

### MATERIALS AND METHODS

This study carried out in Semnan, Iran, from 1999-2007. All of the pathology reports of three pathology departments in this city during these years were collected (this data collected for Cancer Registry of Semnan or archived routinely). Data entered into the software specially designed for this purpose manually for years 1999-2001 and by converting electronic data from DBF (Fox pro) format to MDB (Access) format for other years; then all cases reviewed and corrected if necessary according to the ICD-O codes (International Classification of Diseases for Oncology) by two pathologists. Corrected data exported to SPSS format and used for statistical analysis.

**Analytical methods:** The software for entering data was designed by Access and VBA programming language (Microsoft Access, Microsoft Office 2007, Microsoft Corporation). Analytical tests performed with SPSS (release 11.5.0, ©SPSS Inc.) and EpiInfo (version 6.4, WHO and CDC) statistical packages. Calculating corresponding Age Standardized incidence Rates (ASR) and Standardized Incidence Ratios (SIR) for Iran and world done with software designed for this purpose by Excel and VBA (Microsoft Excel, Microsoft Office, 2007, Microsoft Corporation). Population data used for these calculations are shown in Table 1. Populations and age distribution data of years 1990, 1996 and 2007 for Semnan, Iran and world, respectively used as reference for calculating incidences and ASRs.

**Meta analysis methods:** We used Pubmed (<http://www.pubmed.com> or <http://www.ncbi.nlm.nih.gov/pubmed>) and SID (<http://www.sid.ir>) search engines for finding

Table 1: Population of Semnan, Iran and world used for calculating ASRs

Years	Semnan*	Iran*	World**
1999	154422	62736002	5948042000
2000	159249	63663942	6034542000
2001	164108	64528162	6122541000
2002	168937	65466600	6211579000
2003	173632	66365200	6301911000
2004	178527	67263800	6393556000
2005	183448	68162400	6486792000
2006	188211	69061000	6581126000
2007	193038	69959600	6676832000

\*<http://amar.sci.org.ir>; \*\*<http://www.ibiblio.org/lunarbin/worldpop>

relative researchers. Search keyword used for the Pubmed was skin and (cancer or cancers or malignancy or malignancies) and prevalence and incidence and registry (Title/Abstract) without any limitations that returned 687 results. All abstracts of these researchers reviewed and appropriate ones selected. For SID skin cancer and equivalent Persian search keywords used that returned 9 results. All results entered into database designed by SPSS and analyzed by it.

### RESULTS AND DISCUSSION

Totally, 1528 malignancies registered, 281 cases were skin malignancies (18.40 and CI95%: 16.51-20.39), 61.78% (CI95%: 56.05-67.44) of them were male and 38.12% (CI95%: 32.56-43.95) female with male/female sex ratio of 1.62 (CI95%: 1.46-1.85). Totally, the skin cancers were most prevalent malignancy. The stomach was the second prevalent site totally (13.48 and CI95%: 11.84-15.26).

The most prevalent skin malignancies were BCC 65.1% (CI95%: 59.41-70.53), SCC 28.5% (CI95%: 23.42-33.96) and melanoma 1.07% (CI95%: 0.27-2.88). Incidences and corresponding ASRs for Iran and world are shown in Table 2. As shown in Table 2, total incidence of skin malignancies is relatively constant by year but that of males is decreased and that of females is increased; of course no one of this trends are significant ( $p > 0.05$  by linear regression analysis). Prevalence of other morphologies and incidence of cases of BCC, SCC and melanoma are shown in Table 3.

Male sex ratio was 61.87% (CI95%: 56.05-67.44) for all cases, 56.9% for BCC and 72.2% for SCC cases ( $p = 0.02$ , Pearson Chi-square ( $\chi^2$ ) = 5.401). The trend for sex by time (year) showed no significant change ( $p > 0.05$  by linear and logistic regression analysis). This was true for BCC and SCC too.

Mean age was 64.92 years (SEM: 1.02, SD: 14.68) for all skin malignancies, 65.74 in males and 63.74 years for females ( $p > 0.05$  with t-test). This was 63.42 and 68.25 years for BCC and SCC, respectively ( $p = 0.026$ ,  $t = -2.241$ ). The trend for age by time (year) showed no significant change ( $p > 0.05$  by linear and logistic regression analysis). This was true for BCC and SCC too.

Table 2: Incidence and corresponding ASRs of skin malignancies according to year and sex in Semnan, Iran (1999-2007)

Years	Frequency	%	Incidence (100,000)			Iran ASR (100,000)			World ASR (100,000)		
			Male	Female	Total	Male	Female	Total	Male	Female	Total
1999	28	10.0	17.82	18.46	18.13	17.14	17.27	17.06	22.38	23.70	23.37
2000	27	9.6	24.68	8.95	16.95	23.75	8.37	15.86	31.01	11.49	22.18
2001	32	11.4	22.75	16.13	19.50	22.01	14.33	18.24	27.96	22.85	25.45
2002	39	13.9	37.23	8.44	23.09	35.72	7.89	21.41	47.24	10.83	30.79
2003	30	10.7	21.51	12.90	17.28	20.72	11.67	16.11	26.90	17.71	22.75
2004	31	11.0	14.31	20.53	17.36	13.66	18.18	15.91	18.54	29.28	23.80
2005	29	10.3	22.50	8.88	15.81	21.76	7.96	14.84	27.71	12.40	20.50
2006	30	10.7	15.66	16.23	15.94	15.09	14.64	14.87	19.57	22.38	20.99
2007	35	12.5	21.38	14.76	18.13	20.43	14.21	16.93	27.59	17.84	23.81
Total <sup>1</sup>	281	100.0	197.84	125.28	162.19	190.28	114.52	151.23	248.90	168.48	213.64
Mean	-	-	21.98	13.92	18.02	21.14	12.72	16.80	27.66	18.72	23.74
SEM	-	-	2.23	1.47	0.74	2.14	1.32	0.68	2.82	2.12	1.02
SIR <sup>2</sup>	-	-	-	-	-	0.96	0.91	0.92	1.26	1.34	1.32

ASR: Age Standardized incidence Rate, SIR: Standardized Incidence Ratio, <sup>1</sup>Total (sum) of all incidences and ASRs is a rough estimate of 9 years prevalence (cumulative incidence), <sup>2</sup>Calculated for mean of ASRs (Iran or world) relative to Semnan

The most prevalent sites were nose or other parts of face with 40.21% (CI95%: 34.59-46.03) and scalp and neck with 22.78% (CI95%: 18.16-27.95). The most prevalent site for BCC and SCC was nose or other parts of face too with 47.5 and 26.6%, respectively (p = 0.002, Pearson Chi-square ( $\chi^2$ ) = 10.004). The less prevalent site was skin of anus with 0.7% (2 cases of SCC). SCC was more prevalent in skin of lip (13.9%) and trunk-limbs (15.2%) relative to BCC (1.6 and 3.2%, respectively, p = 0.002 for lip and <0.001 for trunk-limbs with Chi-square ( $\chi^2$ ) test). Frequencies of other topographies are shown in Table 4.

**Meta-analysis results:** From 687 papers returned from the Pubmed search engine (with publication date between 1970 and 2008), 327 (47.6%) results were published between years 2000 and 2008 that 158 (48.32% of results between 2000 and 2008) of them selected and downloaded. After evaluating these papers, 73 papers (22.32% of results between 2000 and 2008) containing data about prevalence, incidence, ASR, or trends of skin cancers selected for meta-analysis (Schuz *et al.*, 2000; Plesko *et al.*, 2000; Holme *et al.*, 2000, 2001; Fidaner *et al.*, 2001; Kittler *et al.*, 2001; Garbe and Blum, 2001; Ocaña-Riola *et al.*, 2001; Ishihara *et al.*, 2001; Stang *et al.*, 2001, 2003, 2006; Wassberg *et al.*, 2001; Liao *et al.*, 2001; Hemminki *et al.*, 2001, 2003; Micheli *et al.*, 2002; Nola *et al.*, 2002; Verdecchia *et al.*, 2002; Crocetti *et al.*, 2002; Milan *et al.*, 2002; Lutz *et al.*, 2003; Forman *et al.*, 2003; Boi *et al.*, 2003, 2008; Sadjadi *et al.*, 2003; Barro-Traore *et al.*, 2003; Katalinic *et al.*, 2003; Al-Aboud *et al.*, 2003; Brisson *et al.*, 2003; Ulmer *et al.*, 2003; Martin *et al.*, 2004; Al-Maghrabi *et al.*, 2004; Uhoda *et al.*, 2004; De Vries *et al.*, 2004, 2005; Quatresooz *et al.*, 2004; San Sebastian and Hurtig, 2004; Asulin *et al.*, 2004; Andersen *et al.*, 2005; Paavilainen *et al.*, 2005; Vaktskjold *et al.*, 2005;

Babaei *et al.*, 2005; Bhurgri *et al.*, 2005; Stang *et al.*, 2006; Boniol *et al.*, 2006; Omari *et al.*, 2006; Lasithiotakis *et al.*, 2006a, 6; Downing *et al.*, 2006, 2008; AIRT Working Group, 2006; Jamal *et al.*, 2006; Piñeros *et al.*, 2006; El-Mistiri *et al.*, 2003; Hayes *et al.*, 2007; Hui *et al.*, 2007; Golger *et al.*, 2007; Brewster *et al.*, 2007; Hoey *et al.*, 2007; Brathwaite *et al.*, 2007; Youl *et al.*, 2007; Nasseri *et al.*, 2007; Valentin *et al.*, 2007; Maalej *et al.*, 2007; Noorbala and Kafaie, 2007; Moan *et al.*, 2008; Siesling *et al.*, 2008; Pellacani *et al.*, 2008; Dal *et al.*, 2008; Karim-Kos *et al.*, 2008; Zeb *et al.*, 2008; Soerjomataram *et al.*, 2008; Yavari *et al.*, 2008). From the 9 papers returned from the SID search engine, 6 papers (66.67%) selected for meta-analysis (Naimi, 2001; Golchai *et al.*, 2000; Tousi *et al.*, 2004; Shahbazi, 2006; Amouzgar *et al.*, 2006; Nour Bala, 2007).

**Pubmed results:** Year 2007 with 12 papers (16.4%) had the maximum frequency. Europe with 44 papers (60.3%) and Central America with one paper (1.4%) had the highest and lowest frequencies. Middle Asia had published 10 papers (13.7%). In Europe Germany and Italy with 6 (13.6) and 5 (11.4%) papers had the highest frequency. About melanoma, 26 papers published that Germany with 4 papers (15.4%) had the highest frequency. Four published papers (5.48%) from Iran listed in Pubmed that one of them was from Semnan. Sixteen papers (21.9) studied all skin cancers, 26 papers (35.6%) studied only melanoma and 3 papers (4.1%) studied only NMSC; other papers contained data about other cancers plus skin or studied BCC or SCC restrictively. The most common morphology was BCC (all of the papers) and the most common sites were nose or other parts of face in half the papers and scalp and neck in other half. The most common topography for melanoma was skin, lower limbs and hip totally and in females and skin, trunk for males in all papers.

Table 3: Prevalence and incidence of skin malignancies, Semnan city, Iran (1999-2007)

Malignancy	Frequency	%	Incidence* (100,000)			Iran ASR* (100,000)			World ASR* (100,000)		
			Male	Female	Total	Male	Female	Total	Male	Female	Total
BCC	183	65.10	12.22	10.55	10.88	11.71	10.23	10.25	15.56	12.51	13.98
SCC	80	28.50	10.18	4.22	7.25	9.71	3.98	6.68	13.21	5.34	9.83
Melanoma	3	1.07	1.02	2.11	1.55	1.00	1.89	1.47	1.17	2.95	1.97
MFH and DFSP	4	1.40	-	-	-	-	-	-	-	-	-
Vascular	2	0.80	-	-	-	-	-	-	-	-	-
Others	9	3.20	-	-	-	-	-	-	-	-	-

\*BCC and SCC for year 2007, melanoma for all years (due to low incidence)

Table 4: Topographies of skin malignancies, Semnan, Iran (1999-2007)

Site	Frequency	%
Skin, nose or other parts of face	113	40.2
Skin, scalp and neck	64	22.8
Skin, eyelid	20	7.1
Skin, lip	14	5.0
Skin, external ear	13	4.6
Skin, trunk	11	3.9
Skin, lower limbs and hip	8	2.8
Skin, upper limb and shoulder	5	1.8
Skin, anus	2	0.7
Skin, nose	31	11.0
Total	281	100.0

About 83.3% of papers that evaluated trends in incidence of skin cancers reported an increase in this trend; this was true for all papers about BCC and SCC too. In the case of melanoma, 80.9% of papers reported increase, 14.3% constant trend and 4.8% decrease in the trend.

Six papers published by countries of Middle East excluding Iran, 3 by Pakistan, 2 by Saudi Arabia and 1 by Jordan that the last two countries have hot and dry climate like Semnan and placed near or in the desert. Most common morphology was BCC, most common topography scalp and neck for all skin cancers and BCC, nose or other parts of face for SCC. In the case of melanoma, one paper reported skin, lower limbs and hip as the most common topography. Only one paper evaluated the trend of all skin cancers and reported increase of it.

**Papers from Iran (Pubmed or SID search engines):** Ten papers published from Iran (4 listed in Pubmed and other 6 listed in SID). Half of these papers reported skin cancers as the most prevalent malignancy of the body, all of them noted BCC as the most common skin cancer and nose or other parts of face as the most common topography in skin cancers.

Other data from all papers (Pubmed or SID search engines) are shown in Table 5. According to these results as shown in Table 5, epidemiologic pattern of skin cancers in Semnan is roughly comparable with the corresponding indexes in world and Iran, except that the incidence of melanoma was lower; this is especially, true for NMSC (BCC and SCC) comparing with other parts of Iran and Middle Asia. Relative frequency and incidence of skin

cancers in Semnan are relatively higher than world but similar to Middle Asia; this may be due to similar climates in Semnan and other middle Asia countries especially, Saudi Arabia and Jordan that have hot and dry climates. Similar clothing and body covering customs and social behaviors such as tanning, may be proposed as the cause for this equality. Totally, age and sex patterns are very similar in world, Middle Asia, Iran and Semnan. Relative frequencies of BCC and SCC in skin cancers, age and sex have relatively same distribution in world, Middle Asia and Iran in comparison with Semnan. Relative frequency and incidence of melanoma is significantly lower than world and Middle Asia in Semnan and this is more similar with Iran; different skin type, climates, genetic predisposition, life expectancy and screening-treatment programs may be the cause. This is in contrast with developed countries, notably those with fair-skinned populations (Stang *et al.*, 2001) that have more susceptible skin type and also better screening-treatment programs for skin and other cancers and so longer life expectancies. Clothing and skin type of the individual can play protective role (Al-Aboud *et al.*, 2003; Noorbala and Kafaie, 2007). Different exposure to UV radiation because of different lifestyles is an important factor too (Johnson, 2004). Both hereditary and environmental factors are implicated in the etiology of cutaneous neoplasms. Studies of twins suggests that environmental and not hereditary effects are most important in the causation of malignant skin cancers in a white population with low levels of sun exposure (Milan *et al.*, 2002) but we can't exclude it totally.

As seen in these results epidemiologic patterns for morphology and topography of skin cancers, including BCC, SCC and melanoma in Semnan show total similarity to world, Middle Asia and Iran patterns.

The results showed relatively constant trends by time for incidence of skin malignancies, including BCC and SCC and for sex and age. This is in contrast to nearly all results of other researches (Johnson, 2004; Stang *et al.*, 2001; Wassberg *et al.*, 2001; Nola *et al.*, 2002; Lutz *et al.*, 2003; Ulmer *et al.*, 2003; De Vries *et al.*, 2004, 2005; Quatresooz *et al.*, 2004; Downing *et al.*, 2006; Lasithiotakis *et al.*, 2006a, b; Hayes *et al.*, 2007).

Table 5: Results of meta-analysis data of skin cancers from published papers between years 2000 and 2008 in comparison with Semnan

Index*	World	Middle East**	Iran	Semnan
Relative Freq. (%)	14.58		19.58	18.4
Incidence (100,000)	13.50 (M: 12.4, F: 9.4)	16	11 (M: 12.4, F: 9.4)	18.02 (M: 21.98, F: 13.92)
World ASR (100,000)	07.80 (M: 6.7, F: 7.46)		M: 10.2, F: 7.46	23.74 (M: 27.66, F: 18.72)
Male relative Freq. (%)	63.82	65.39	61.47	61.87
Age (years)	75.00 (M: 61, F: 60)	75	64.49	64.92
BCC relative Freq. (%)	54.41	48.3	71.26	65.10
BCC world ASR (100,000)	31.70 (M: 35, F: 26.87)	M: 23.2, F: 19.7		13.98 (M: 15.56, F: 12.51)
BCC male relative Freq. (%)	57.98			56.90
SCC relative Freq. (%)	23.77		21.32	28.50
SCC world ASR (100,000)	04.40 (M: 10.7, F: 4.79)			9.83 (M: 13.21, F: 5.34)
SCC male relative Freq. (%)	71.83			72.20
Melanoma relative Freq. (%)	08.16	11.94	3.28	1.07
Melanoma incidence (100,000)	09.25 (M: 8.83, F: 9.95)			1.55 (M: 1.17, F: 2.95)
Melanoma male relative Freq. (%)	49.93	54.55	47.5	

\*Mean of values of all papers (empty cells are due to inadequate data), \*\*Excluding Iran, M: Value for males, F: Value for females

Incidence of cancer may vary within a country and over time because of previous differences in exposure to risk factors or interventions for early detection (screening) (Siesling *et al.*, 2008). This may reflect a true increase, or may be an artifact of more intensive recent surveillance. Longer life expectancy as well as efforts to earlier detection may be the cause too; for example, greater public awareness of warning signs of skin cancer (Johnson, 2004).

Increased exposure to UV radiation because of lifestyle changes (Johnson, 2004; Boniol *et al.*, 2006), increased accumulated sun exposure and increasing incidence among the elderly (Wassberg *et al.*, 2001; De Vries *et al.*, 2005), effectiveness of the health system on cancer control (Crocetti *et al.*, 2002), paradoxical effect of better treatments and thereby survival in well-developed economies (Lutz *et al.*, 2003) and belonging to white populations (Ulmer *et al.*, 2003) are generally recognized as important factors. Trend of the increase in incidence of melanoma is more impressive than that of SCC and BCC; this trend is particularly obvious for melanoma affecting young adults (Uhoda *et al.*, 2004). Incidence of BCC in the Netherlands is increasing rapidly, especially at body sites that are not chronically exposed to sunlight; the most likely explanation is an increased intermittent overexposure to UV radiation. More sensitive detection using the combination of clinical dermoscopy and laboratory immunohistochemistry are among these factors too (Quatresooz *et al.*, 2004). The relative increase of SCC of the trunk and upper limbs is a plausible reflection of intentional tanning (Dal *et al.*, 2008).

Small proportion of papers reported decrease in incidence or constant trend of skin cancers (Martin *et al.*, 2004; Boi *et al.*, 2008).

### CONCLUSION

In the end, comparison of the data with the only study that studied cancer prevalence in Semnan

(Babaei *et al.*, 2005) seems helpful. The study reported gastric cancer as the most prevalent malignancy (in contrast to this study that reported skin cancer as the most prevalent and gastric cancer as the second one), incidence rate of 12.4 for males and 9.4/100,000 for females (this study: 21.98 and 13.92, respectively) and world ASR of 10.2 for males and 7.46/100,000 for females (This study: 27.66 and 18.72, respectively). According to using same archive and electronic data from Cancer Registry of Semnan, this discrepancy can show the reason for the goal that mentioned in objectives: the aim of this study was correcting these data in Semnan pathology registration systems by pathology and database management experts, then creating valid outputs. We think different approaches in validation of data and role of experts in pathology and informatics can explain this difference.

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