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# Incidence of cutaneous malignant melanoma in Iranian provinces and American states matched on ultraviolet radiation exposure: an ecologic study☆

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ABSTRACT

*Objectives:* Ultraviolet radiation (UVR), with UVB and UVA as the relevant components, is a risk factor for melanoma. Complete ascertainment and registration of melanoma in Iran was conducted in five provinces (Ardabil, Golestan, Mazandaran, Gilan and Kerman) during 1996–2000. The aim of our study was to compare population-based incidence data from these provinces with rates in the United States (US) while standardizing ambient UVR.

*Methods:* Population-based rates representing all incident cases of melanoma (1996–2000) across the five Iranian provinces were compared to rates of melanoma among white non-Hispanics in the US. Overall age-standardized rates (ASR) for Iran and the US (per 100,000 person-years adjusted to 2000 world population) and standardized rate ratios (SRR) were calculated.

We measured erythemally-weighted average solar UVR exposures (with contributions from both UVB and UVA range) of the five Iranian provinces using data from NASA's Total Ozone Mapping Spectrometer and selected five US states (Kentucky, Utah, Texas, Oklahoma, and Hawaii) with matching UVR exposure to each province. Incidence rates of melanoma during 1996–2000 in each Iranian province were compared to rates among white non-Hispanics in its UVR-matched US state.

*Results:* The overall male and female ASRs of melanoma were 0.60 (95%CI: 0.56–0.64) and 0.46 (95%CI: 0.42–0.49), respectively, for Iran and 22.78 (95%CI: 22.42–23.14) and 16.61 (95%CI: 16.30–16.92) for the US. SRRs of melanoma comparing US to Iran were 37.97 (95%CI: 35.78–40.29) for males and 36.11 (95%CI: 33.69–38.70) for females, indicating significantly higher incidence in the US. ASRs and age-specific rates of melanoma for both genders were significantly lower in each Iranian province compared to its UVR-matched US state.

*Conclusion:* The markedly lower incidence rates of melanoma in Iranian provinces with similar UVR exposures to US states underscore the need for additional comparative studies to decipher the influence of other extrinsic and intrinsic factors on the risk of this malignancy.



## 1. Background

Incidence of malignant melanoma has been rising worldwide in the past several decades with consistent and dramatic increases noted for developed countries in Europe (Grange, 2005) and North America (Ward et al., 2006) since the 1950's. Recent trends indicate a global increase of 56% in melanoma incidence from 2005 to 2015 (Fitzmaurice et al., 2016). In the United States (US), melanoma is the fifth most common cancer among men and the seventh most common among women. There will be an estimated 52,170 new cases of melanoma among men and 34,940 cases among women in the US in 2017 (ACS, 2017). The sharp increase in melanoma incidence in the US has been reported for children as well as adults 50 and older (Jemal et al., 2011) with projected lifetime risk of

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developing melanoma for American men and women approaching 1 in 33 and 1 in 52, respectively (ACS, 2017). Although five-year relative survival is high at 91%, an estimated 65% of all skin cancer deaths are attributed to melanoma (Cummins et al., 2006). There will be an estimated 9730 deaths from melanoma among both sexes in the US in 2017 (ACS, 2017).

Reliable data on incidence rates of melanoma in developing countries are scarce. Studies on limited hospital and regional data from countries in Asia and Africa have suggested lower incidence but higher case fatality rates for melanoma in comparison to European and North American countries (Stubblefield and Kelly, 2014). The underlying causes of observed trends in melanoma in most countries are not known, although a number of host and environmental agents have been implicated as contributing factors (Ward et al., 2006; Rastrelli et al., 2014a; Liu et al., 2015; Cho et al., 2005). Exposure to ultraviolet radiation (UVR) from sunlight and other sources is considered an established risk factor for all major skin malignancies including melanoma (ACS, 2017; Elwood and Jopson, 1997; El Ghissassi et al., 2009). Solar UVR that reaches the surface of the earth is composed of UVB (with wavelength of 315–280 nm) and UVA (with wavelength of 400–315 nm) (Lucas et al., 2006, 2008). UVB is considered the carcinogenic component of UVR based on animal and laboratory studies (Lazovich et al., 2004; Horneck, 2000) that suggest effect on the DNA; UVA is also believed to be relevant based on its deep penetration of human skin (El Ghissassi et al., 2009; Wang et al., 2001).

Similar to other countries in the Middle East and to developing countries elsewhere, Iran does not have a comprehensive and/or centralized population-based cancer registration program. As such, regional cancer registries in existence in some provinces can provide incidence data for some cancers. During 1996–2000, the most complete and centrally-administered ascertainment and registration of melanoma in Iran was conducted for cases diagnosed in five provinces (Ardabil, Golestan, Mazandaran, Gilan and Kerman) (Fallah, 2007; Sadjadi et al., 2007). Therefore, we conducted a study to compare melanoma incidence rates from those provinces during that time period with rates in the United States (US) while standardizing ambient UVR. Ecologic studies describe patterns of disease and exposure at the population level and may be hypothesis-refining or -generating. As such, our ecologic study using perspectives from an understudied population may provide clues with respect to other influences on melanoma risk in the context of standardized UVR.

## 2. Methods

All cases of melanoma diagnosed in five provinces (Ardabil, Golestan, Mazandaran, Gilan and Kerman) during 1996–2000 were actively ascertained by Iran's Cancer Registry Unit at the Digestive Disease Research Center (DDRC) of the School of Medical Sciences at the University of Tehran as previously reported (Fallah, 2007; Sadjadi et al., 2007). As described in their publications, survey teams composed of one medical doctor and two medical students in each province, specifically trained for the task by the DDRC, actively collected data on cancer cases diagnosed in 1996–2000 from all hospitals, oncologists' offices, pathology laboratories, radiology clinics, and central death registry offices in each province. A copy of the pathology reports on each diagnosed case was sent to the Cancer Registry Unit where extensive quality control measures were employed prior to registration. These measures included careful review of all records to ensure inclusion of malignant primaries only (i.e., all benign and metastatic cases as well as cases with unknown origin were excluded) and deletion of all duplicates from the system (Fallah, 2007; Sadjadi et al., 2007). Thus, all cases of melanoma diagnosed for the first time between 1996 and 2000 among residents of the five provinces were registered. We obtained published (Fallah, 2007; Sadjadi et al., 2007) and updated incidence data from the DDRC for our study.

Population-based rates representing all incident cases of melanoma (1996–2000) across the five Iranian provinces were compared to rates of melanoma among white non-Hispanics in the US during 1996–2000 by calculating age-standardized rates (ASR) per 100,000 person-years adjusted using the 2000 world population. The overall rates for the US were calculated across the 13 areas of the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program (SEER), which include San Francisco-Oakland, Connecticut, Metropolitan Detroit, Hawaii, Iowa, New Mexico, Seattle-Puget Sound, Utah, Metropolitan Atlanta, San Jose-Monterey, Los Angeles, Alaska, and Rural Georgia. SEER rates are representative of cancer incidence in the total US population. SEER*Stat (Surveillance Research Program) and International Classification of Diseases for Oncology (ICD-O-3), Third Edition, site recode 25010 for melanoma of the skin (Fritz et al., 2000) were used for the analyses.

US rates for white non-Hispanics were used for comparison based on similarities in ancestry and pigmentation. Individuals from Iran are classified as white non-Hispanic in the census and in cancer registries in the US. There is no Spanish or Latino heritage or admixture among the Iranian population. In addition to exhibiting close genetic distance with European Caucasian populations (Cavalli-Sforza et al., 1994), Iranians are classified as “lightly pigmented” (i.e., skin types I to IV from north to south, respectively, on the Fitzpatrick pigmentation scale (Fitzpatrick, 1988)) similar to white non-Hispanics in the US and to European Caucasians (Lucas et al., 2006).

Standardized rate ratios (SRR), estimating the relative risks of melanoma in the US compared to Iran, were calculated by taking the ratios of the overall ASRs and calculating 95% confidence intervals (95% CI) using standard formulas (Cancer Registration, 1991); comparison was considered significant if the interval did not include 1.

In order to select US states to be matched to Iranian provinces on ambient UVR, the geographic coordinates of each province and their distances from the equator were obtained from the World Atlas (The World Atlas). US states were chosen based on similarity in latitude, altitude, and ambient erythemally-weighted average solar UVR to the Iranian provinces as well as availability of age-specific cancer incidence data in the North American Association of Central Cancer Registries (NAACCR) for the entire period 1996–2000. Grid points corresponding to geographic resolution of one degree were assigned to each province and state and were used for analysis of ambient UVR exposures. Erythemally-weighted average solar UVR exposure was measured using data from the National Aeronautics and Space Administration (NASA) Total Ozone Mapping Spectrometer (TOMS) (NASA; NASA, 2005). Data consisted of an ongoing time series of erythemally-weighted UVR exposure values ($mW/m^2$) for the entire globe, derived from directly-measured noon irradiance values which took into account length of day, cloud conditions, and ozone column. The erythemally-weighted average exposure was the combination of wavelengths from 280 to 400 nm and therefore included contributions from both UVA (starting at 315 nm) and UVB (starting at 280); this average best describes the susceptibility of Caucasian skin to sunburn.

Erythemally-weighted average solar UVR exposure values were based on measurements between January 1, 1997 and December 31, 2000 at a geographic resolution of one degree. Data for 1996 were recorded but excluded from analysis due to incompleteness. A degree was about 111 kilometers north to south and between 75 and 101 kilometers east to west in the continental US and between 85