Topic: Is tropical UV exposure linked with development of Malignant Melanoma? A Case-Control Study in Adult population of the Australian Subcontinent

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Literature Review

The Earth landmass is divided into regions using a set of imaginary lines that act as a geographic tool. Between the Tropic of Cancer and Tropic of Capricorn lies the tropical region which comprises approximately 36% of the Earth's landmass and is home to one-thirds of the global population (1). The tropical region of the Earth is comparatively warmer to the other regions with an average temperature of 77 to 82 degrees Fahrenheit as a result of which the UV (ultra-violet) share of the tropical regions is higher than any other region, under ideal circumstances. Upon the exposure of UV radiations on melanin-producing melanocytes, the DNA gets damaged and the cell gets mutated, contributing towards its carcinogenic nature (2). Malignant melanoma is one of the most potentially serious types of skin cancer diseases prevalent in areas with high sun UV levels. Approximately 130,000 cases of malignant melanoma are recorded worldwide each year, majorly in tropical regions or places with ozone depletion (3). The consequences of high UV radiation on our skin can produce non-deleterious changes in our body in the childhood years that can further develop into a melanoma (3). Thus, there is an ardent need of action in spreading the awareness and implementing interventions sanctioned by the Public Health authorities.

Adding to the evidence, a pooled analysis of 15 case controls studies (5700 cases and 7216 controls) published by the international journal of epidemiology investigated the risks of suffering with melanoma due to sun exposure (4). This data consisted of studies from Europe, North America, Australia and Hawaii (4). The studies varied in terms of age of subjects. This analysis indicates the risk of melanoma in various body parts relating to different patterns and frequencies of sun exposure (4). Recreational sun exposure and sunburns (before the age of 15) proved to be strong factors predicting melanoma at all latitudes (4). Sun exposure is directly

linked with UVB radiations which are known to cause DNA damage and induced immunosuppression (4). These risks are expected to increase with an increment in the exposure to UV radiations (4). The exposure to UV radiation is a more preventable factor as compared to genetics and hereditary when discussing skin cancer which calls for greater action and attention from the public health systems (4). In Australia alone, cutaneous malignant melanoma caused approximately 1700 mortalities in 2020 (5) despite the lockdown enforced by the central government which limits the exposure to the UV radiations. Australia claims the 2nd position worldwide to record the highest number of melanoma cases (5). It is highly crucial for the general population to understand that anyone can acquire skin cancer, and living in a geographical location like the tropics that receives higher frequencies of sun exposures, the risk goes up much higher. Early exposure of high doses of UV radiations poses a great threat to the health outcomes of the future. Measures taken by the health authorities in terms of primary prevention from overexposure of the sun UV radiations rather than post exposure treatment, can reduce the risk of developing melanoma in other stages of life.

Study Design

The aim of the research is to bridge a link between the high levels of UV radiations and the risk of cutaneous malignant melanoma in tropical regions of the Australian subcontinent. A case-control study design has been chosen to determine if exposure i.e. ultraviolet radiations of the sun is associated with disease i.e. prevalence of melanoma, a type of skin cancer (6). The study will be conducted in a primary healthcare setting, targeting individuals aged between 18 -39 years, residing in the province of Queensland in Australia. The study design is retrospective in nature, therefore, it begins with the outcome and is traced back in time to

investigate the underlying cause of effect i.e. exposure (6, 7). The study comprises two groups: a case that is known to contain the disease and control which is disease-free. In this scenario, patients suffering from melanoma constitute the case group while healthy individuals make up the control population (6). The duration of the study is estimated to be around 3-4 weeks long where the majority of time is spent interviewing participants and collecting evidence of exposure by recalling incidences of the past.

Advantages of a Case-Control Design

A case-control design was opted over a cohort design because it is a retrospective study instead of a longitudinal one and the outcome of interest (malignant melanoma) is predetermined in a case-control study and requires a long follow up to come across in a cohort study (6). Therefore, the data recovery through recalling and review of medical records is less time consuming in case-control whereas for a condition like melanoma, a long follow up of participants will be needed to determine a relation between UV exposure and occurrence of melanoma (6). Because of this very feature of case-control studies, not only are they time-effective but are significantly cost-effective as well as compared to the latter. Since malignant melanoma is a relatively rare disease as compared to ailments like cardiovascular diseases, pulmonary diseases and other cancers, choosing the kind of study design where the disease outcome is already determined is the apt way to go because observational study methods will be inefficient in relating the exposure to the disease (which is already a rather rare phenomenon).

A randomized control trial is not applicable to satisfy the research question as it is impossible to allot individuals into placebo and intervention groups and blind the exposure to the UV radiations of the sun.

A cross-sectional study design wasn't chosen because it is only an efficient way of calculating prevalence ratios which are based on current information without referring to a follow-up (6). Hence, the exposure of UV radiations and melanoma are being studied at the same time. This will make it an impossible task to determine the relation between the two as individuals with and without the disease are not being observed with respect to a timeline in this study design.

A case-series design was also not followed as it is descriptive in nature as it only refers to a single group with the disease and has no control/placebo group to compare the outcomes with (6). Therefore, in this case, it will only deal with individuals who have been exposed to the UV radiations of the sun but not the unexposed group which won't provide sufficient tools to establish a cause and effect relationship. A case-series is also subjected to a selection bias as the participants (generally a low number) are selected from health care settings (6), which challenges the external validity of the results.

Disadvantages of a Case-Control Design

Despite the positives associated with this design, it includes confounders and effect modifiers that can alternatively affect the outcome in indirect ways. Matching is required to eliminate any confounders in the study (6). Matching here could include healthy individuals in the hospital setting, like staff workers or friends and family of the diseased individuals to prevent confounding effects of underlying health conditions in the development of melanoma. The process of matching complicates the study as finding participants who perfectly fall under a given group are tough to find (6). Effect modifiers like complexion, use of sunscreen and a higher tendency to wear dark clothes may require modifications in the selection criteria of the participants. They might provide scope to better highlight or degrade the association between

mentioned factors and development of melanoma but this might result in over or under interpretation of results. Being a retrospective study, recall bias is another challenge that can affect the follow up of UV exposure with gaps of information or inclusion of incorrect information due to time lapse, resulting in a reporting bias (6).

In a nutshell, the strengths of a case-control study design like quickness, cost effectiveness, ability to analyze multiple exposures and factors at a single time for melanoma, outweigh the few shortcomings associated with it, making it the desired method of research in this context.

Study Features

A case-control study design will be used to assess the relationship between exposure to solar UV radiations and the incidence of melanoma in the tropical population (6, 8). The study is conducted in the northeast region of the Australian continent, within the subtropical state of Queensland. The community present in the region experiences high rates of skin cancers and therefore, allows better opportunity to evaluate the risk factors associated with the prevalence of the mentioned skin disease (9). The inclusion criteria for the case-control study would include males and females aged between 18 years and 39 years. The specific age group is chosen because melanoma is most prevalent in young age-groups as opposed to Carcinoma (BCC or SCC) which appears in later stages of life (age $\geq$ 60) (2). Participants should be willing to provide written consent prior to admission and comply with the study protocol (10). The case group comprises patients diagnosed with skin pigmentation cancer, also called melanoma. Patients with both history and a new diagnosis of disease will be included. It will ensure that participants have melanoma confirmed by the evaluation of tissue of cutaneous melanoma origin using the procedures: S-100, HMB-45 or Melan-A (10, 11). The control group comprises a general community population who have made visits to any primary care settings or counselling interventions. Targeting local health settings and institutes helps integrate

populations of different socioeconomic status, exposure, ethnicity and health level. The exclusion criteria revolves around the presence of symptoms such as: uncontrolled hypertension, serious cardiac arrhythmia and active infection (10). Patients suffering from Squamous cell carcinoma (SCC) and basal cell carcinoma (BCC) will not be listed since the focus remains on skin pigmentation cancer caused due to melanocytes. Cases involving pre-pubertal melanoma (also known as childhood melanoma) are dropped (11). People undergoing major surgical procedures and pregnant females will also be excluded from the study. It will be ensured that controls and cases are individually matched i.e., the number of males equal to the number of females.

The exposure of our study design is related to the susceptibility to sun UV radiations. Our focus is to measure exposure throughout specific stages of life i.e., childhood and early adulthood. Data related to the measurement of UV intensity can be collected using questionnaires seeking information related to outdoor activities, time and frequency of sunburns (12, 13). There are chances that self-reported data by participants on 'outdoor times' may not be detailed and lead to confusion. Therefore, we will make use of additional factors such as latitudes of residence and sun exposure levels monitored via satellites to assess the stratum of sun exposure (13). Additional information related to season-of-birth and geographical movement will be taken into consideration while formulating the level of individual-sun exposure. Microtopography of the skin using silicone casts would be done to ensure the validity of data from questionnaires (13). The process helps in measuring the damage done to the skin from UV by gauging loss of collagen fibrils and abnormal accumulation of elastin in the dermis (photoaging). Conjunctival UV auto-fluorescence (CUVAF) is another technique used to measure the eye damage caused by sun UV radiations, however, due to its limited scope of diagnosing damage pertaining to the last 6 months, the method will be ignored (13). Data collected from satellite measurements of UV radiations in conjunction with the

findings from questionnaires and microtopographic assessment will be compiled to generate individual scores for the received dosage of UV radiations. Averages of daily ambient UV radiation will be taken into consideration while categorizing participants into exposed and non-exposed categories based on these score levels.

The measure of association would be calculated using the Odds ratio (OR) (6). OR will further help in examining how the intensity of UV radiations is related to the incidence of melanoma. It would represent the odds of occurrence of disease (melanoma) in the presence as well as the absence of the given exposure (UV radiations). Since matching is done on the basis of sex, the calculation of OR would involve the use of discordant pairs only (6). All the concordant pairs are excluded since they would not show how cases and controls may differ on exposure (6). For instance, 10 people suffered from melanoma out of which 6 scored high on the UV radiation exposure scale. One-on-one matching will be done to get 10 controls matched to cases on basis of sex. Out of them, 2 people were exposed to high levels of UA radiations (meaning scored high on the scale). Table 1 represents the matched pairs and related calculations (6). The 95% confidence interval (CI) is used to estimate the precision of the OR. A large CI represents a low level of precision of OR while a small CI indicates a higher precision of the OR (5).

Potential Pitfalls

The case-control design brings up its own set of challenges and biases that can significantly challenge the acceptability of results. The use of such a study design involves many factors that one should keep into account while analyzing the outcomes. This could include potential associations with various effect modifiers and confounding variables that can alter the interpretation of outcomes.

While comparing the individuals for melanoma, the prevalence of the control group would be significantly higher than the case group as patients with melanoma will have a higher

likelihood of death and hence will contribute to a lower participation. This gives rise to a survivor bias (6) which would affect the fair share of data between the two groups for comparison. This bias can be ruled out by maintaining a balance of data between each of the groups and understanding that a lower share of data by case group is largely because of mortality factors not prevalence of healthy individuals (6), hence the consideration of only currently valid sources is necessary.

A major task to be accomplished is the inclusion of participants who can in turn be divided into case exposed, case unexposed, control exposed, and control unexposed groups. Another challenge is the search process for such individuals who would fit in a certain study group that they pertain to and are willing to share their medical history and personal data for the research. To tackle this, researchers should be given more time to eliminate any information biases as a result of wrong grouping when allocating the participants into their respective groups. Friends and relatives of the patients suffering from melanoma should be consulted for effective participation by making them aware of the positive prospects of the research in future understanding of these ailments.

A recall bias might also come into play when researchers tend to gain information from the participants relevant to the study based on their memory and ability to recall (6). Over time, this memory might get too tarnished to be accurately remembered or some integral part of the information might not be conveyed due to reduced retention of past events and experiences causing a report bias (6). This is another drawback of a retrospective study method. In order to improve the quality of the retrospective experiences, family involvement can also help to provide a stronger basis to any memory that may be relevant to the analysis. Linking each year of life to significant events like old residences, workplaces etcetera also might help reconnect some dots (13).

One could also talk about the selection bias (6) that can occur as a result of the poor inclusion criteria. As previously mentioned, the participants in the case and control groups belong to a primary healthcare setting or counselling homes. This indicates that all the participants potentially have or have had an underlying ailment that they are or were healing from. Thus, assuming that all individuals in the study will have the same magnitude of biological response towards the levels of exposure of UV radiations would be incorrect. Also, the current health status of each such individual could in turn act as a confounding variable towards the outcome of interest, i.e. malignant melanoma. These underlying ailments could also be classified under confounders as their association with the outcome is not direct but in the presence of an exposure (6) (strong UV radiation) the health outcomes might change due to higher susceptibility and poor immune response of such individuals. Selection bias can be handled through an increased randomization (6) into the study, adding participants from outside primary care homes that do not have underlying ailments. Individuals sharing the same neighbourhood with the participants of interest can provide scope for a fair analysis of risk, both sharing a similar environment minimizing the confounding effects.

The confounders in the study are vast therefore considering and addressing each of such variables is an integral part of our research. The genetic makeup of each individual is different therefore some individuals may have a higher susceptibility of adjusting towards UV radiations while some may have a family history of melanoma that can further act as a positive confounder. Individuals who have a sensitive skin with amplified histamine response might tend to cover their skin to prevent sun burns and rashes. This could act as a negative confounder in case any such individual for their skin exposure to UV rays will be significantly lower, even if they have a poor immune response and a high tendency of mutation in their melanocytes. To prevent the genetic factors from impeding the validity of the results, a questionnaire asking about any such family history of melanoma or possessing sun sensitive skin can be provided

and the participants who reply affirmative to any of the questions can be easily ruled out from the data sets. This can be achieved through efficient matching in the case-control design to eliminate any confounding effects (6).

Considering the fact that field athletes and outdoor work atmospheres like construction and farming can contribute to a higher chance of UV exposure that can indirectly result in a higher risk of melanoma, this can act as a potential effect modifier. Individuals with excess field work should be included under the exposed groups. Since the magnitude of exposure in these individuals remains higher, the researcher gets a better opportunity to trace any possible links to logically answer the research question.

Individuals who tend to wear a darker shade coloured clothes outdoors can potentially be at a reduced risk of melanoma. This is because darker shades of colour like black absorb UV radiations more efficiently than other colours (14). This can result in a weaker exposure of these rays to the melanocytes of the skin that can trigger an enhanced DNA damage response to the cells. Using the same logic, one can deduce that ethnicities with darker skin tones have a slightly higher chance of absorbing more of these radiations through skin (3) for the same reasoning and be less affected but given that the occurrence of the outcome of interest is not dependent on just one variable. Calculation of results amongst people of similar skin colour would bring an additional strength to the analysis and participants should be encouraged to wear similar tones of cloth colours (light or dark) for increasing the accuracy of the findings.

Another effect modifier would be the use of sunscreen and high SPF body lotions that can decrease the effect (absorption of sunlight) and reduce the chances of developing melanoma (15). Therefore, exclusion of participants using high SPF sunscreen lotions is another objective that can be reached by providing participants with an added criterion in the previous questionnaire and their results too should be excluded from the analysis. Even though this reduces the sample size but still benefits the study purpose by giving it an unhampered,

unbiased and unaltered view, independent of any effect modifiers. The focus here is to establish the quality of the findings, not quantity.

An evident drawback of this study will be the assumption of the unexposed group in the study. It is an obvious fact that sunlight is available universally over the earth's surface, and hence, it will be a highly unlikely practice to deprive any participant of UV radiation, hence, to call it "unexposed" would be terminologically incorrect. To address the challenge of having an unexposed group with individuals deprived of sunlight exposure, we can modify the definition by rather considering it as individuals who have had less exposure to tropical UV radiations (early emigrants, recent immigrants etc.) over the course of their life. This gives more relevance to the findings and emits out any terminological conflicts thereafter.

Overall, the case-control design will be instrumental in determining a valid association between the exposure to UV radiations of the sun and development of malignant melanoma in the Australian subcontinent, given that all the confounders and effect modifiers are adjusted in accordance with the given recommendations. Not only will this act as a basis for future research opportunities but will provide awareness to the readers about the epidemiology of malignant melanoma and the need to take precautions wherever applicable.

Table 1: Matched Pairs OR (Derived from Lectures) (7)

Matched Pairs		
Pair #	**Case**	**Control**
1 – Female	Not Exposed	Exposed
2 – Female	Exposed	Not Exposed
3 – Female	Not Exposed	Not Exposed
4 - Male	Not Exposed	Not Exposed
5 – Female	Exposed	Not Exposed
6 – Female	Exposed	Exposed
7 – Male	Exposed	Not Exposed
8 – Female	Not Exposed	Not Exposed
9 – Male	Exposed	Not Exposed
10 – Female	Exposed	Not Exposed

Calculations:

$$OR_{MP} = \frac{\text{case exposed:control not exposed}}{\text{case not exposed:control exposed}}$$

$$= 5/1 = 5$$

Table 2: 2X2 cross between concordant and discordant pairs (6)

	Controls Exposed	**Controls Not Exposed**
Cases Exposed	1	6
Cases Not Exposed	2	1

Interpretation:

The odds of suffering from melanoma are 5 times greater in individuals who were exposed to high levels of UA radiations in the past, versus individuals who were exposed to lower levels of UA radiations, after matching on sex.

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