OBJECTIVE:

The objective of this document is to provide a detailed review of the recent study Lazovich D, Vogel RI, Berwick M, Weinstock MA, Anderson KE, Warshaw EM. Indoor tanning and risk of melanoma: A case-control study in a highly exposed population. Cancer Epidemiol Biomarkers Prev; 19(6); 1557- 68.

SUMMARY:

The study by Lazovich and colleagues attempted to address the question of the association between tanning use and risk of melanoma. Given the rising prevalence of tanning use, this is an important question. The study by Lazovich, though, suffers from methodological limitations, including selection and recall bias, that make it difficult to interpret their study findings. A modest association between tanning use and melanoma has been reported in previous findings of this association. Individuals with known risk factors for melanoma such as having a family history, eye/hair color, skin pigmentation, mole frequency should be cautious in their exposure to UV radiation, either through tanning or sun exposure. Additional studies are warranted to attempt to address the limitations in the previous research regarding tanning use and melanoma and to tease out the effect of tanning use that may exist over and above the impact of known risk factors. In addition the impact of timing of sunburns and sun exposure (i.e. sunburns in pre-adolescence), and other modifiable risk factors such as dietary factors, smoking, alcohol and oral contraceptive use and risk of melanoma is unclear and warrants further study.

RATIONALE FOR LAZOVICH STUDY

Study hypothesis: indoor tanning use is associated with an increase risk of melanoma. Lazovich describes two primary reasons for conducting the current research study. They are discussed below.

Lazovich states: *Melanoma incidence is increasing*

Rebuttal:

Although the incidence might be increasing, it is unknown if this is due to a true increase in the number of cases or simply due to better detection methods, awareness, and screening of individuals by physicians,especially among those with known risk factors for melanoma i.e. number of moles, skin/hair color, sunburns, family history.

Melanoma mortality has increased much less rapidly and a recent plateau has been seen possibly due to improved early detection and

treatment. The same techniques that may be the reason for the increasing incidence have resulted in stable mortality estimates.

Lazovich states: *Previous research of tanning and melanoma have documented an association*

Rebuttal:

Known limitations of previous studies of tanning use and melanoma

International Agency for Research on Cancer (IARC) examined 19 studies which, when combined, showed a weak association of indoor tanning and melanoma (OR = 1.15, 95% CI 1.0, 1.31), most likely due to several limitations of the study designs employed within this body of research.

Clearly more research is needed to attempt to address some of the previous limitations of the studies investigating this association. Ideally, the evidence will be based upon well done cohort studies that assess exposure prior to the diagnosis of melanoma. Lazovich's study falls short of addressing the previously documented limitations within this field of research.

DETAILED REVIEW OF LAZOVICH ET. AL., 2010

The authors state that the overall findings form this study are that, “Our study provides strong evidence that indoor tanning is a risk factor for melanoma” p. 1567

The strong evidence within this study is that the odds of tanning use was found to be 1.74 times greater in cases than in controls (OR = 1.74, 95% CI: 1.42-2.14)

QUESTION: Was this study able to overcome the limitations of previous research examining this hypothesis?

ANSWER: This study is subject to several limitations that would lead to caution in the interpretation of the measures of association found for indoor tanning use and melanoma.

Within epidemiologic research, caution should always be used in order to not over interpret study findings. Associations found within our research do not always imply causality, especially if the research is limited in their assessment of exposure measures.

Bias and confounding may explain the association observed. Bias is “any systematic error in the design, conduct, or analysis of a study that results in a mistaken estimate of an exposure's effect on the risk of disease” (Gordis, L. Epidemiology). And a confounder is defined to be “a third factor that is both a risk factor for disease and is associated with the exposure” This confounder may be the true underlying cause for the exposure-disease relationship found.

The results of the study by Lazovich may be due to possible bias and confounding present in the study, therefore caution is warranted. Two types of bias, selection and recall are discussed in detail. In addition, limitations in exposure classification and analytic strategy are presented.

SELECTION BIAS

Selection bias is defined as a distortion of the estimate of effect resulting from the manner in which the study population is selected.

- In studying the relationship between indoor tanning and melanoma, if individuals who tan and have melanoma are more likely to participate in your study than individuals who do not tan and have melanoma, an association between tanning use and melanoma will be found, even though in reality one may not exist at all.

- Within the Lazovich study, 1380 cases were screened by staff and physicians are were eligible to participate. Of these cases, 1167 (84.5%) completed the questionnaire and the study results were based on this sample of cases. The major reason why cases did not participate was because they did not send back the self-administered questionnaire.

- The self administered questionnaire contained detailed information on exposure assessment with multiple pictures of tanning beds. Although the researchers state that they did their best to ensure that the hypothesis was not evident to the study subjects, once you see a questionnaire such as this, and given the debate regarding tanning use in the popular press, it is hard to imagine that individuals receiving this information would not know what the study was about.

- If individuals with melanoma who used tanning beds were more likely to respond to the questionnaire than those who did not use tanning beds, selection bias may be at work within this study.

- Individuals who used tanning beds may have been more interested in the study, having familiarity with the devices upon seeing the pictures, and may have been more motivated to respond to the questionnaire than individuals who have no familiarity with the subject.

- The researchers try to address selection bias within this study, but they were only able to contact a small percentage of non-respondents with melanoma (30%). They state that the association found between tanning and melanoma risk in these non-participants was similar to the overall study findings (OR = 1.62).

- But this still leaves us wondering about the 2/3 of the non-respondents and still raises a question about the role of selection bias.

- For example, if only 28 more melanoma cases who did not respond were not tanning bed users, then among the non-responders there would have

been no association between tanning use and melanoma (OR = 0.99), instead of the OR of 1.62 the study researchers found.

- Therefore, selection bias may still play a role in the study findings and the results should in interpreted with caution. If this were the only limitation within this study, the findings may be suggestive of a possible association, but this hypothesis would need to be investigated in future studies that are better designed to address the possibility of selection bias

- Yet, this was not the only limitation evident in this study. Of even greater concern is the possibility of recall bias within the chosen study design.

RECALL BIAS

Recall bias is defined as a systematic error due to differences in accuracy or completeness of recall to memory of past events or experiences.

- Recall bias is the most serious potential problem within case-control studies (Gordis L. Epidemiology) because the exposure estimate is assessed after the individual is already diagnosed with disease.

- Exposure within this study is based on self-report; therefore the quality of exposure information depends upon an individuals' ability to recall past information with regard to tanning use.

- Previous research has shown that individuals who have disease may be more likely to accurately recall events when compared to controls (individuals with no disease). When this happens, there is a possibility of recall bias.

- Recall bias will play a role in this study if individuals with melanoma are more likely to remember past use of tanning and intensity of use of tanning when compared to controls, who do not have melanoma.

- In addition, recall bias is also possible if cases overestimate their exposure when compared to controls. For example, an individual with melanoma may be more likely to try to come up with a cause for their cancer and overestimate their tanning usage when compared to someone who does not have cancer.

- Recall bias will then lead to a spurious overestimation of the association between tanning use and melanoma.

- The authors within the current study state that they try to address this issue by asking whether the study participants spoke with their physician about the study prior to the researchers making contact with them. Although they found that the odds ratio for tanning use and melanoma was similar among cases and controls who did not speak with a physician; they were only able to ask this of 12% of cases and 18% of controls.

- In addition, there were a few controls (n=3) who said they spoke with a physician about the study, which is not possible. Clearly, this brings up the question as to the validity of response to the question of physician discussion and question is raised as to whether this is a true assessment of recall bias within this study.

- The researchers did not ask the study participants about whether or not they thought tanning use increased the risk of melanoma, which may have been a better indicator of possible recall bias.

- Given the exposure measurement tool used, a detailed tanning use questionnaire with pictures and dates, and the general public awareness of the possible association between in door tanning and melanoma, it is hard to imagine that the majority of individuals within this study would not have guessed at the hypothesis under study, regardless of whether they spoke with a physician.

- In addition, the researchers do not attempt to validate the exposure data collected. Without an attempt of validation of the exposure measure among cases and controls, recall bias may play a key role within this study

- Although sometimes, the magnitude and direction of recall bias on the measure of association is difficult to predict, it has been shown to lead to dramatic overestimations of the true association.

- Lazovich et al, state that “a recent nested case-control study reported no consistent pattern of recall bias for indoor tanning or other melanoma risk factors” (Parr et al, AJE 2009).

- But, Parr specifically states that, “the limited body of literature at present indicates that retrospective measures of melanoma risk are susceptible to recall bias..”

- In an age where access to information is so widely available, recall bias may be of great concern in well informed populations given the general public awareness of melanoma risk factors.

EXPOSURE MISCLASSIFICATION

- Misclassification of exposure can lead to over or underestimates of the measure of association, especially if diseased individuals are more likely to misclassify their exposure when compared to non-diseased individuals, which may be a possibility in this study given the retrospective nature of exposure measurement.

- Novel detailed exposure measurement developed for the use of this study to obtain indoor tanning use duration, frequency and timing.

- Validation of measurement within this study is not available so the amount of possible misclassification is unknown.

ANALYTIC STRATEGY

Finally, this section will describe how limitations in the analytic strategy weaken the strength of the conclusions derived within this investigation.

- Statistical techniques are used within epidemiologic research to obtain an estimate of association between exposure and outcome. Modeling strategies are typically employed to examine the effects.

- Within an analytic model, independent effects of exposure are estimated after controlling for other confounders, that is other factors that may be associated with both the exposure and the outcome and not on the disease pathway between exposure and outcome.

- Within any model there are assumptions that need to be met in order to get valid estimates of association.

- One issue that is raised within this study is the issue of multicolinearity of the model, that is that the confounders that are included in the model are highly correlated with each other and with the exposure of interest. When highly correlated variables are thrown into a model, the assumptions needed to fit these regression models are violated and the measures of association become unstable.

- The authors fail to provide data of the association between many of the known risk factors for melanoma (# of sunburns, # of moles, hair color, skin sensitivity) and tanning use. Without these data it is difficult to assess the quality of their model building strategies and the possibility that these models have violated basic statistical assumptions needed to accurately measure the relationship of interest.

- For example the authors state in a letter to the editor that family history modified the association between tanning use and melanoma. yet, they adjust for family history within their regression models. Once the association between tanning use and melanoma risk was shown to differ by family history, then the family history variable can no longer be added within a model, but results should be shown for those with and without a family history separately. The authors fail to do this.

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