

**Reynolds, P. and D.F. Austin (1984). A case-control study of malignant melanoma among Lawrence Livermore National Laboratory employees, California Department of Health Services.**

EXECUTIVE SUMMARY

In April, 1980, the California Department of Health Services released the results of a study which established that, for the period 1972-1977, the employees of the Lawrence Livermore National laboratory (LLNL) had experienced a rate of malignant melanoma (NM) that was three to four times higher than that which would be expected under normal circumstances. This report details a follow-up investigation designed to search for the reason or reasons for that previously established excess.

The investigation was carried out as an independent study by the Resource for Cancer Epidemiology Section of the Department of Health Services with support from several sources. The primary source of support was the Department of Energy, through the LLNL. Additional sources of support were sought in January, 1982, when DOE funds for the study were reduced. They included the Department of Health Services, the Northern California Cancer Program and the California Public Health Foundation. The investigation received cooperation from the administration of the LLNL which also authorized and supported several other studies of MM and its relationship to LLNL employment, conducted by others.

We identified thirty-two cases of MM among employees of the LLNL from 1969 to mid-1980. All cases were included in a case-control study although one case was unavailable for personal contact. Data from employment and medical records were available for all cases and controls. For each case a set of four controls was selected from among LLNL employees of the same age group, sex, and race who were actively employed at the time of the diagnosis of the case. Employment records were available for all of the 32 cases and 128 controls and 97% of the cases and 88% of the controls were personally interviewed in detail about employment and lifestyle. Interview data for three deceased cases were provided by the next of kin. The results of this report are based primarily on the 31 cases for whom interview were completed and 110 out of the 113 controls with completed interviews who were matched to those cases, a total of 141 respondents.

The data were analyzed by several methods but, for the most part, pooled odds ratios (the cross-product ratios) of dichotomized variables among cases and controls were used as a device for identifying items for further study. Univariate, bivariate and multivariate logistic regression analyses were mostly limited to those items selected through the first process. Thus, multiple comparisons were made between cases and controls. Significance values are presented without adjustment for multiple comparisons since the purpose of the investigation is an exhaustive analysis rather than an hypothesis test.

A factor is considered to be a cause of a disease, in any epidemiologic investigation, when that factor influences the probability of the disease. There is not requirement that the biologic mechanisms be specified so long as the risk of disease can be manipulated by manipulating the factor. In this way alcohol has been identified as a cause of automobile accidents, even though it

does not apply in every case and other causes also exist, because it is possible to manipulate the risk of automobile accidents by controlling alcohol consumption among automobile drivers. Thus causality is a conclusion based on sufficient evidence. The results of this investigation provide sufficient evidence for causal factors of several types.

In interpreting the results, all pertinent data from this investigation, from our prior study of MM at LLNL and from other studies of MM were considered. Also, all the appropriate methodological applications of the scientific method available to epidemiologic studies of case-control design were used to augment those considerations. A lengthy discussion of these considerations is presented in the report.

Results are presented in six sections. These provide a description of the characteristics of the disease in these cases, an analysis of the relationship of MM risk to demographic factors traditionally believed to be associated with MM risk, an analysis of host susceptibility factors, an analysis of the contributions to MM risk of non-occupational exposures, and an analysis of the effect on MM risk by occupational factors related to LLNL employment.

The results of the analyses for the five sections of non-occupational factors can be briefly summarized.

Characteristics of the disease in those cases of MM occurring among the LLNL employees are unremarkable. The anatomical site distribution is not unusual nor is the distribution of histologic types. The distribution of stage (the progression of the disease at the time of diagnosis) is not unique among the LLNL cases and is consistent with a trend towards earlier diagnosis of MM noted generally. The disease is neither more nor less virulent than cases of comparable histology and stage diagnosed elsewhere. No clue to the reason for the MM excess was identified from the physical characteristics of the disease in the individual cases. The cases were unusual only in their number, since 1972 approximately 400% of what would be expected.

In the course of this investigation the factors contributing to personal susceptibility to MM were studied. The characteristics of fair hair, blue eyes and Celtic ancestry, all traditionally cited indicators of MM risk, did not impart a significant risk, although individuals with fair skin and hair did have a slightly higher but statistically insignificant risk. The characteristics of sunburning easily and not tanning upon exposure to sunlight was significantly related to MM, a finding widely reported in other studies of MM susceptibility. Of great interest was the finding of several other markers of individual susceptibility to MM; namely, the presence of multiple large moles, a history of any type of skin cancer in immediate blood relatives and a prior history of non-melanoma skin cancer in the individual. Previously these had not been reported as MM risk factors for the general population and their discovery in the LLNL group caused us to consider the possibility that LLNL employees had, for some unknown reason, an unusual inherent susceptibility to MM.

However, the findings of multiple moles and similar familial susceptibility to MM have now been found in other studies. As of this writing some are in print and some are pending publication. Thus, the findings of host factors of susceptibility in this study are not unique to the LLNL population but, rather, are hitherto unrecognized MM risk factors that are generally

present in the White population. Most importantly, the easily measurable nature of these factors allowed a determination as to whether the prevalence of susceptibility factors in the LLNL population was unusual. The distribution of key constitutional markers of MM susceptibility were also measured in Contra Costa County Whites and were found to correspond to that among LLNL employees. Thus the LLNL group was found not to have an excess of individuals who, by their nature, are more susceptible to MM.

Since exposure to sunlight is a generally accepted factor in MM risk, this was explored in the LLNL cases and controls.

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\_\_\_\_\_r outdoor days. These findings suggest that individuals who sunburn easily tend to limit their sun exposure as adults. Within the LLNL group, sunlight exposure as an adult was not positively related to MM case status.

A number of medications, illnesses and exposures to substances as a result of hobbies and non-occupational tasks were examined for their possible relationship to MM risk. None of these factors were significantly related to MM risk although exposure to paint or stain remover was more common among cases.

A common finding in other studies of MM is that the incidence of the disease is higher among individuals with higher socio-economic status (SES), whether the SES is inferred from income, occupation, education, or a combination of these. We explored each of these factors. In general, an elevated MM risk was identified by any of these three SES measures. With one exception, a significant relationship to MM was not found for specific occupations. Also, income was not significantly related to MM. The presence of an advanced degree, however, was significantly related to MM risk. A significant risk elevation remained even after controlling for all other factors found to be related to MM risk. Thus it appears that some factor related to education, and not accounted for by occupation, income, or personal risk characteristics, may contribute to MM risk. However, the prevalence of this risk factor was no more common among the LLNL population than among Contra Costa County White males which excludes it as a potential contributor to the excess of MM at the LLNL.

Although non-occupational factors that definitely contribute to an individual's chances of developing MM are present among the LLNL White employees, they are present in about the same proportions as in the White population generally. Thus, with respect to non-occupational factors that increase MM risk, the LLNL population is not unusual. Nevertheless, the LLNL population has experienced, from 1972 until the present, an occurrence of MM that is approximately four times that in the general population.

No evidence was developed to suggest that an unusual MM occurrence exists among persons not employed by the LLNL, such as dependents of employees or nearby residents.

A concerted effort was made to examine other possible explanation for the observed MM excess. Considered and excluded as a possibility was a statistically rare chance occurrence. Also ruled out was the possibility that the excess could be due to some factor that is indirectly reflected by LLNL employment (confounding). Possible sources of bias (i.e. erroneous determinations of an excess) were carefully examined and excluded as possible explanations.

In sum, all categories of possible explanations of the MM excess other than a causal factor or factors encountered through LLNL employment were critically examined and rejected.

The effect of occupation on MM risk was explored for each study respondent through a detailed history of occupation, records of personnel job classification, physical working environment, work location assignments, specific categories of tasks which determined job designation and lists of specific types of exposures that could have been experienced by several routes (inhalation, contact, etc.). From this body of data, seven factors emerged which were significantly associated with MM among LLNL employees. These factors were further analyzed with particular attention to whether they contributed MM risk independently of non-occupational factors and separately from each other. Five of the seven factors appear to be independent contributors of risk and are individually applicable to various proportions of the LLNL population.

1. Exposure to radioactive materials. This factor applies to about a third of the LLNL population and about two-thirds of the cases of MM. It carries a relative risk of 3.7 and, by itself, would be expected to produce an excess of MM of about 88%. The details collected by the study do not permit a more detailed description of the mechanism of exposure or the circumstances under which exposure occurred. It is possible that the circumstances may have varied, with the only commonality being the fact of exposure. In the epidemiologic meaning of the term, this factor is causally related to the MM excess.
2. Work at Site 300. This factor refers to more than one visit to a non-nuclear weapons testing site near the LLNL. The factor applies to about a third of the LLNL population and about half of the MM cases. It carries a relative risk of 2.4 and, by itself, would be expected to produce an excess of MM of about 45%. The MM risk associated with this factor is independent and separate from that associated with exposure to radioactive materials. No further description of the nature of the agent responsible for the risk associated with this factor was possible from the study data collected.
3. Exposure to volatile photographic chemicals. This factor applies to about 15% of the LLNL population, about 35% of the MM cases, and carries a relative risk of 3.2. It is partially confounded with exposure to radioactive materials but does appear to impart some independent risk. It is noteworthy that no risk was found to be associated with skin exposure to photographic chemicals nor to exposure to photographic chemicals encountered in non-work situations. By itself this factor would predict a MM excess of 34%.
4. Pacific Test Site. This factor refers to the presence of the employee at the nuclear testing

site in the Pacific at the time of a nuclear event. This factor applies only to about 4% of the LLNL employees and about 13% of the MM cases. It imparts a relative risk of 4.5, independent from the factor of exposure to radioactive materials. By itself it would produce a MM excess of 13%.

5. Chemist duties. This factor refers to the actual duties of an employee and not the personnel classification. It applies to less than 2% of the LLNL population but 13% of the MM cases and carries a relative risk of 12.9. It is the largest of all occupational risk factors and by itself would be expected to elevate the MM rate at the LLNL about 21%.

Of the remaining two occupational risk factors, one, exposure to fumes from high explosives, appears to be largely an indirect measure to two other risk factors, exposure to radioactive materials and work at Site 300. It is not established that any significant independent risk is contributed by this factor and it is not considered a candidate for explaining any of the MM excess.

The remaining factor, work location in a building constructed in 1969, has unusual attributes. Most of the floorspace resulting from a large construction efforts in 1969 is contained in Building 111, an office building in the LLNL complex. MM risk associated with this factor is substantial (3.4) when considering all cases. It applies to about 15% of the LLNL population and about 36% of the MM cases. While the relative risk is largely independent of other occupational and non-occupational risk factors it appears to exert its effect primarily through those who, due to constitutional factors, are more susceptible to MM and less so among those without constitutional risk factors. It also appears to have a short latency period reaching a maximum 5-6 years following exposure (OR=5.9,  $p < 0.0005$ ) and then tapering off. Finally, the risk appears to be much more strongly associated with the building(s) when new, dissipating with time. These findings are compatible with the effect of a tumor promoter. Because of the somewhat unusual characteristics of this risk factor, is it not proposed as a causal factor in the LLNL MM excess although it may be so. Rather it is regarded as a risk factor hypothesis to be confirmed in subsequent work.

On the basis of the prevalence within the LLNL population of the five independent contributors to occupational risk, and the relative risk of each factor adjusted for the effects of the others, we computed the predicted occurrence of MM among LLNL employees that would result if all five occupational factors were causal. These factors together would cause a rate of MM 4.00 times that in the general population. Thus the excess of MM among LLNL employees can be explained by the five occupational variables.

From the data obtained through this study and from all information available to date, we draw four major conclusions:

1. The previously reported excess of MM among LLNL employees is real.
2. Constitutional risk factors for MM predict risk of LLNL employees to the same degree as in the general population.

3. MM disease characteristics among LLNL cases are similar to those of MM cases in the general population.
4. A variety of occupational risk factors are usually associated with mm among LLNL employees. Five of these factors can substantially account for the observed excess.

Several recommendations are offered:

1. The LLNL should conduct a specific screening program for MM among LLNL employees.
2. The LLNL should conduct a worker notification program for present and former employees to inform them of possible increased MM risk.
3. A follow-up case-control study should be done, including the MM cases that have occurred since the close of data gathering phase of this study.
4. An industrial hygiene consultant should be retained to evaluate the occupational exposure sources identified in this study.
5. A follow-up incidence study should be conducted that includes present and former LLNL employees.
6. Recommendations 3, 4 and 5 should be carried out by a person or group independent of the LLNL.