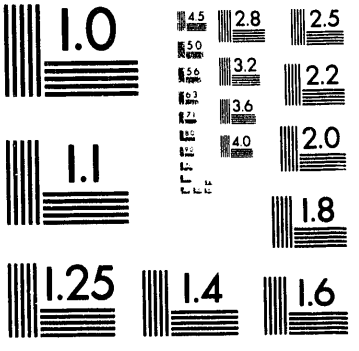
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Malignant Melanoma Slide Review Project: Patients from Non-Kaiser Hospitals in the San Francisco Bay Area

Prinicpal Investigator:
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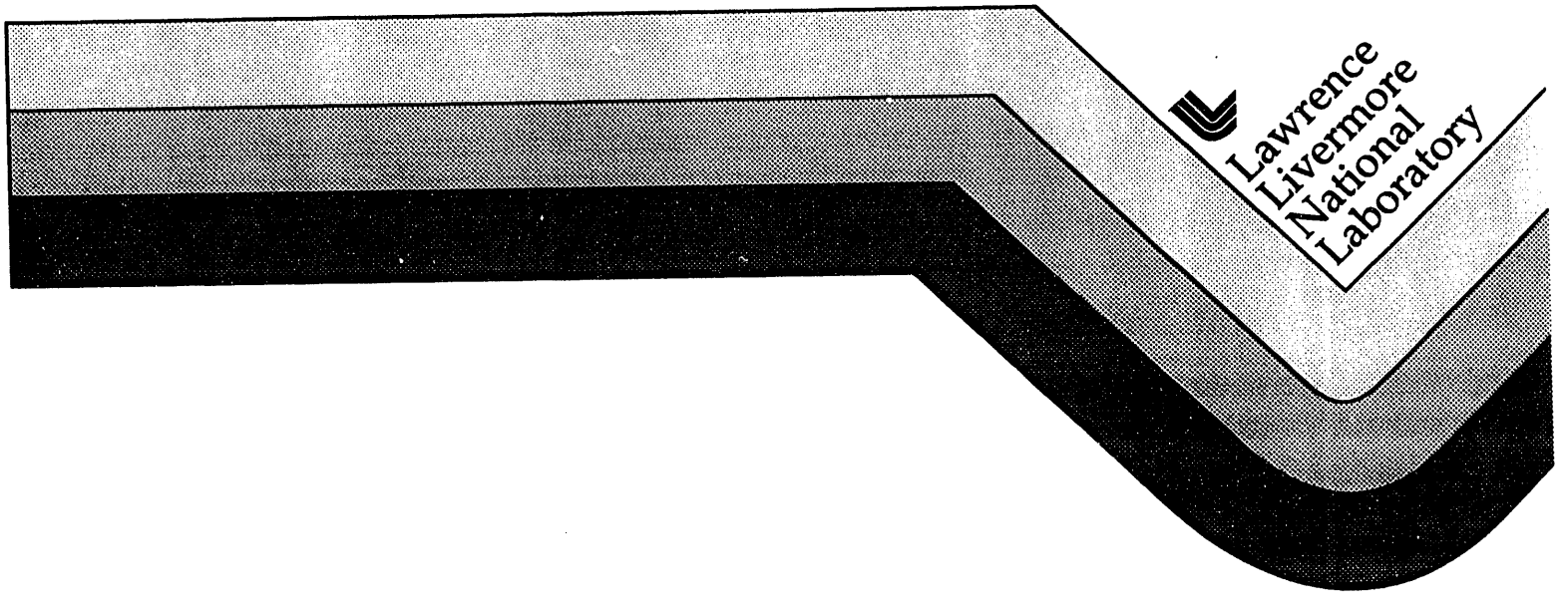
January 5, 1993



DISCLAIMER

FINAL REPORT

S/C B077753 (formerly 1415703)

MALIGNANT MELANOMA SLIDE REVIEW PROJECT: PATIENTS FROM NON-KAISER HOSPITALS IN THE SAN FRANCISCO BAY AREA

(LLNL-1A1503)

Principal Investigator: Peggy Reynolds, Ph.D.
California Department of Health Services

January 5, 1993

Background/Objectives

This project was initiated in 1987 as a companion project to one undertaken by Kaiser Permanente, in response to concerns that the observed excess of malignant melanoma among employees of Lawrence Livermore National Laboratory (LLNL) might reflect the incidence of disease diagnostically different than that observed in the general population [1]. These companion projects were designed as part of a collaborative effort with the LLNL to address this question.

LLNL sponsored a slide review project, inviting leading dermatopathology experts to independently evaluate pathology slides from LLNL employees diagnosed with melanoma and those from a matched sample of Bay Area melanoma patients who did not work at the LLNL. Kaiser Permanente was resposible for obtaining case pathology slides for LLNL employees first diagnosed at a Kaiser facility, as well as a sample of Kaiser "comparison" melanoma patient slides. The Department of Health Services (DHS) was responsible (via contract with the Northern California Cancer Program, and subcontract with the California Public Health Foundation) for obtaining case pathology slides for LLNL employees first diagnosed at other Bay Area hospitals, as well as a sample of non-Kaiser "comparison" melanoma patient slides.

The orignal DHS study objectives were to:

1. Identify all 1969-1984 newly diagnosed cases of malignant melanoma among LLNL employees resident in the San Francisco-Oakland Metropolitan Statistical Area, and diagnosed at facilities other than Kaiser Permanente.

2. Identify a comparison series of melanoma cases also diagnosed between 1969-1984 in non-Kaiser facilities, and matched as closely as possible to the LLNL case series by gender, race, age at diagnosis, year of diagnosis, and hospital of diagnosis.

3. Obtain pathology slides for the identified (LLNL) case and (non-LLNL) comparison patients for review by the LLNL-invited panel of dermatopathology experts.

A fourth study objective was added by the LLNL project officer in 1991:

4. To compare the pathologic characteristics of the case and comparison melanoma patients, as recorded by the dermatopathology panel.

The activities for this project were scheduled in collaborative meetings between the LLNL, Kaiser and DHS investigators to follow those undertaken by Kaiser, and to coordinate with the review panel schedule set by the LLNL.

Materials and Methods

Melanoma cases among LLNL employees were identified via automated record linkage between annual LLNL employee rosters, and the population-based cancer registry data maintained by the California Department of Health Services. A total of 34 eligible cases of malignant melanoma were identified, diagnosed among LLNL employees resident in the SF-O MSA between 1969 and July of 1984 (the date when LLNL initiated a melanoma screening program, "Spot Check"). Of these, 22 were first diagnosed at Kaiser facilities, and the remaining 12 at other medical facilities.

A pool of candidate comparison melanoma cases from non-Kaiser facilities was drawn from the DHS population-based registry files for each of the 12 LLNL non-Kaiser melanoma cases. In a meeting with the Kaiser, DHS and LLNL investigators it was agreed that for optimal comparability between the Kaiser and DHS selection protocols the individual matching criteria to the LLNL cases would be (in order of priority):

1. Same gender,
2. Year of diagnosis within 2 years,
3. Same hospital or geographic area, if possible,
4. Age at diagnosis within five years, and
5. Same race (all non-Kaiser cases were white).

Using these criteria, two matched comparison cases were selected for each of the 12 eligible non-Kaiser LLNL cases.

Several years delay ensued until the dermatopathology panel was assembled in the Fall of 1990. At this time, many of the identified comparison case slides were no longer available because of damages to some East Bay hospitals as a consequence of the Loma Prieta earthquake. Because of this, several substitute comparison melanoma cases were selected from the original roster of eligible comparisons, using the best match from available non-Kaiser hospitals. This series, in some cases, precluded same-hospital matches as the LLNL case (for which slides had already been obtained). All slides were, however, from East Bay hospitals.

Slides were reviewed by Drs. Richard W. Sagebiel, Wallace H. Clark, and and Martin C. Mihm in San Francisco during October 24 and 25 of 1990. The review team first did consensus readings for the Kaiser slides which had been individually read by them earlier. Following the Kaiser readings, they individually evaluated the non-Kaiser pathology slides. There were no general consensus readings for the non-Kaiser slide series, although a few of these slides were jointly evaluated by two of the three reviewers. It was the intention that reviewers be blinded to the LLNL vs. non-LLNL slide status, but since the majority of LLNL case slides had been previously reviewed by Dr. Sagebiel, and were obtained from his lab, it is unlikely that reviewers were blinded to case status. Reviewers recorded information on histogenic classification, level of invasion (Clark's microstaging), thickness in mm (Breslow's microstaging), tumor profile, ulceration, solar elastosis, and the presence of an associated nevus.

Data recorded by the review team were key-entered and linked to available tumor registry data for each of the patients enrolled in the non-Kaiser review. This file was used to generate descriptive summaries, and to conduct analyses paralleling those conducted by the Kaiser investigative team [2,3].

Results

Pathologic slides were obtained for all but one of the non-Kaiser LLNL cases, and for all but two of the non-LLNL comparison pairs. Of the eleven LLNL cases reviewed, one case (previously classified by the diagnosing hospital as melanoma) was re-classified by the review dermatopathologists as a dysplastic nevus. Of the 20 comparison cases reviewed, two case slide series were uninterpretable to the reviewers. The total number of cases with recorded data from the review panel included 10 LLNL cases and 18 non-LLNL cases.

As was the case for the Kaiser reviews, there was a lack of consensus between reviewers for a number of case characteristics [3]. In addition, data were consistently recorded by the reviewers for only three data items: histology type, level of invasion, and thickness. Because we did not have consensus readings for these variables, the analyses which follow incorporate the reviewer values for the one reviewer identified by the Kaiser investigators [3] whose readings were closest to the consensus readings for their series.

General descriptive characteristics of the LLNL vs. non-LLNL cases are summarized in Table 1. LLNL cases and non-LLNL cases were similar with respect to the matching variables of age at diagnosis and gender. Non-LLNL cases were about two years older on average, but this difference was not statistically significant. Ninety per cent (9 out of the 10) of the LLNL cases were classified with superficial spreading melanoma, compared with only 56% of the non-LLNL cases. The non-LLNL cases had more nodular, lentigo maligna, and unclassifiable melanomas. The

LLNL cases also tended to be staged earlier, using Clark's criteria for microinvasion.

For analyses of tumor thickness, we eliminated three of the non-LLNL cases. Two of these were classified as *in situ* tumors, therefore no thickness data were recorded, and a third case was classified with the very unusual outlier value of 31 mm thickness.

In the simple unmatched and unadjusted analysis (Table 2), the tumors of the LLNL employees were, on average, approximately 0.8 mm thinner than those for the non-LLNL comparison cases over the entire study period, 1969-1984. This relationship was similar for the periods 1969-1976 and 1977-1984, when the tumors of the LLNL cases were approximately 1.3 and 0.6 mm thinner than those of the non-LLNL cases, respectively. None of these differences was significant. Regression lines, drawn for the tumor thickness observations for the LLNL vs. non-LLNL case group (Figure 1), suggest that the temporal trend towards thinner tumors among the LLNL cases parallels that for the non-LLNL comparison cases. In the matched analysis (Table 3) the same differences were observed, although they were less pronounced than in the unmatched analysis.

Summary

Similar to the findings from the Kaiser series [2], we noted no significant difference in thickness between LLNL cases and non-LLNL cases during the study period. Like the Kaiser series, non-Kaiser melanomas among LLNL employees tended to be thinner than those among non-LLNL comparison cases during the time period 1969-1976. These differences were similar in magnitude (crude mean difference 1.3 mm in our series, compared to 1.5 mm in the Kaiser series), but were not statistically significant. Also, like the Kaiser series, our series indicated even less difference for the later time period, 1977-1984. Unlike the Kaiser series which indicated a slight negative difference (-0.3 mm) for those years, ours indicated a slight positive difference (0.6 mm). Also, unlike the results from the Kaiser analyses, which showed no temporal change in the thickness of LLNL case tumors, ours suggests parallel, but modest, trends towards thinner lesions in both groups.

Our series indicated a greater proportion of LLNL tumors classified as superficial spreading than among the non-LLNL cases. This is unlikely to be independent of the finding for differences in thickness and could, additionally, be in part a function of our selection of reviewer data for analysis. The Kaiser investigators reported [3] that the reviewer who most closely approximated the consensus readings for their series, also was more likely than other reviewers to classify LLNL cases as superficial spreading, as well as to equate "thin" lesions with superficial spreading.

These data are not inconsistent with the general hypothesis that LLNL melanomas have been diagnosed at earlier stages than those in the general population. They are, however, somehat at variance with the proposed hypothesis of surveillance bias which would suggest greater disparity with time due to increased awareness of melanoma risk among LLNL employees. Unlike the analyses of Schneider et al [1], which compared LLNL cases to those from a community pathology laboratory and noted greater diparities in tumor thickness for recent years, ours for a matched population-based series suggests *less* disparity in tumor thickness for recent years. Our data also suggest that fewer cases in both the LLNL and comparison groups were staged at Clark's level I or II, than were the LLNL and comparison groups, respectively, in their series.

It is important to note that the data reported here are based on a very small case series. They are generally consistent with results reported by the Kaiser group for the same time period and using a comparable study design. For more elaborate analyses, pooling the two data sets might be warranted.

References

1. Schneider JS, Moore DH, Sagebiel RW. Early diagnosis of cutaneous malignant melanoma at Lawrence Livermore National Laboratory. Arch Dermatol 126:767-769, 1990.

2. Hiatt RA, Kreiger N, Sagebiel RW, Clark WH, Mihm MC. Surveillance bias and the excess risk of malignant melanoma among employees of the Lawrence Livermore National Laboratory. (submitted for publication)

3. Kreiger N, Hiatt RA, Sagebiel RW, Clark WH, Mihm MC. Inter-observor variability among pathologists' evaluation of malignant melanoma: effects upon an analytic study. (submitted for publication)

Table 1

Summary Characersitics of the Malignant Melanoma Slide Review Series Non-Kaiser Hospital Patients

Characteristic	LLNL Cases	Non-LLNL Cases
Number	10	18
Mean age at diagnosis	43.8	45.9
Proportion of Women	10 %	11 %
Histologic Type		
Superficial Spreading	90 %	56 %
Nodular	10 %	22 %
Lentigo Maligna Melanoma	--	6 %
Acral Lentigenous Melanoma	--	--
Unclassified	--	17 %
Clark's Level:		
I	--	11 %
II	40 %	11 %
III	40 %	39 %
IV	20 %	33 %
V	--	6 %

Table 2

Unadjusted Mean Thickness of Melanoma Lesions
Non-Kaiser Hospital Patients

Time Period	LLNL Cases		Non-LLNL Cases [1]	
	n	mean mm (95% CI)	*n*	mean mm (95% CI)
1969-76	6	1.3 (0.01,2.53)	6	2.6 (0.00,5.55)
1977-84	4	0.7 (0.13,1.19)	9	1.3 (0.73,1.93)
1969-84	10	1.0 (0.34,1.72)	15	1.8 (0.76,2.88)

[1] Excludes three evaluated cases -- two *in situ* classifications (no tumor thickness data) and one case classified with a 31 mm tumor.

Table 3

Mean [1] Differences in Tumor Thickness
(Matched Analyses)
Non-Kaiser Hospital Patients [2]

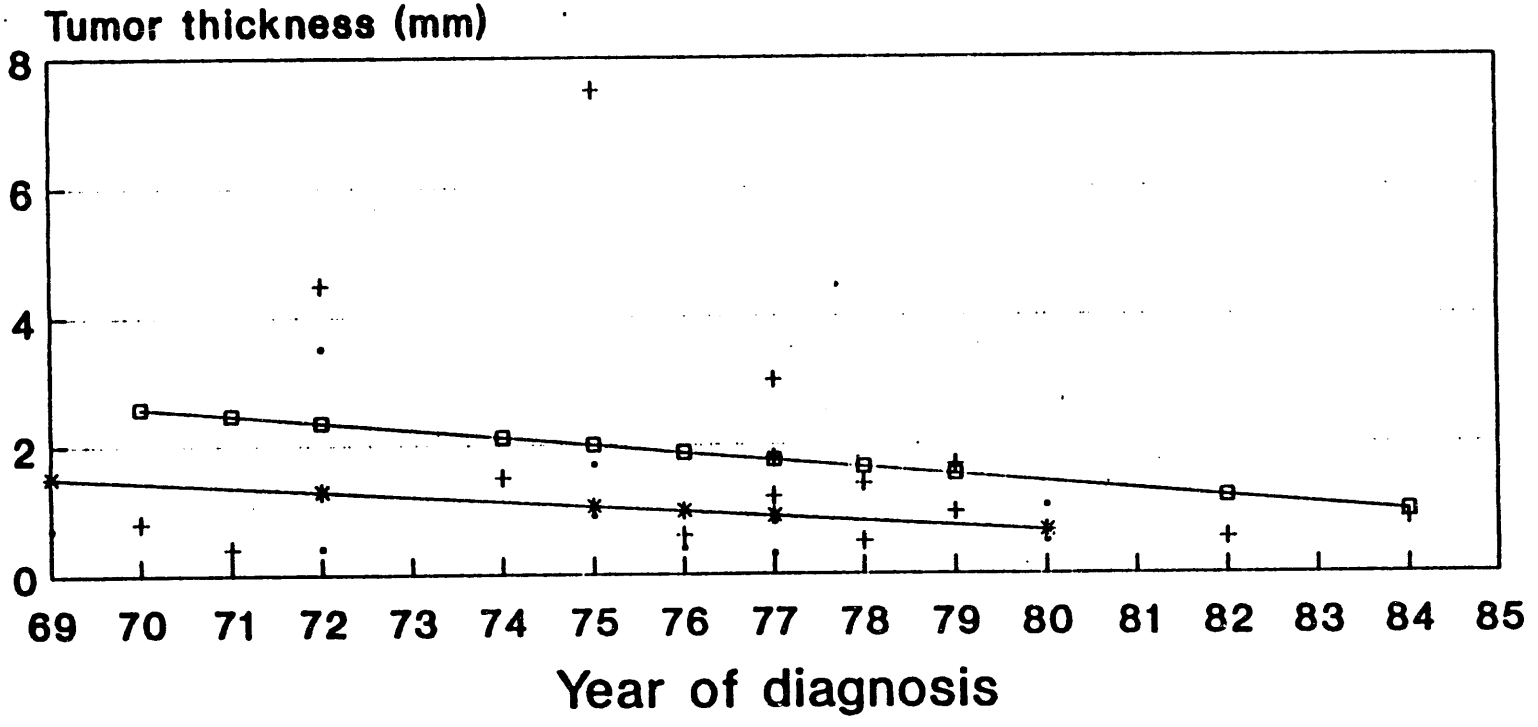
Time Period [3]	mean difference mm (95% CI)
1969-76	0.87 (-2.49,4.23)
1977-84	0.53 (-0.13,1.20)
1969-84	0.66 (-0.46,1.78)

[1] Mean thickness of non-LLNL case minus thickness of LLNL case.

[2] Excludes three evaluated cases -- two *in situ* classifications (no tumor thickness data) and one case classified with a 31 mm tumor.

[3] Diagnosis year of LLNL case for the matched set.

LLNL vs. Non-LLNL
Non-Kaiser Facilities



Excludes two in situ and one 31 mm tumor in non-LLNL cases.

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