

CHAPTER 10

MALIGNANCY

INTRODUCTION

Cancer is a major suspect disease following exposure to chlorophenols, phenoxy herbicides, and dioxin. Both systemic cancer and skin cancer are key focal points of this study.

The issue of military service related cancer in Vietnam veterans first arose in 1978-1979. Media presentations emphasized several early cancer deaths in several Army veterans, which were allegedly caused by exposure to Agent Orange. The media reinforced the causal allegations by citing animal studies, which demonstrated a carcinogenic effect, and a few human studies, which showed excessive cancer in specific occupational groups. So effective and sustained were the media presentations that today the public equates dioxin and Agent Orange exposure to cancer.

In the larger context of environmental controversies, Young aptly described the Agent Orange issue as being at the crossroads of science and social concern. The scientific community has responded to the dioxin question by a massive research effort, which in concert with class action lawsuits, is expected to cost more than a billion dollars in the near future.² The core of the overall research effort is basic and applied cancer research.³

Traditional animal-to-man extrapolation difficulties and interspecies variability have limited the direct applicability of much of the experimental work to the controversy. Major epidemiologic challenges have included: the ability to control/characterize bias; selection of suitable controls or reference groups; quality/quantity of exposure; misclassification of exposure; confounding exposure to known injurious chemicals; sample size and statistical power; number and selection of relevant risk factors; lack of antecedent disease or syndromes (other than chloracne); time to event (latency); rarity of the endpoint; and tumor type (carcinoma, sarcoma) differences found in many studies.

For these reasons, there is no scientific consensus on the dioxin-cancer question. There is, however, a common thread, raising concern over soft tissue sarcomas (STS) and non-Hodgkin's lymphoma (NHL). Pertinent animal and human studies underscore the concern over cancer.

Numerous animal studies have been conducted to delineate the role of TCDD on tumor initiation, tumor promotion, mutagenesis, cocarcinogenesis, and DNA reactivity. The consensus of most research is that TCDD is only weakly mutagenic, does not covalently bind to DNA or cause it to initiate repair synthesis, and behaves as a strong tumor promoter in already initiated cells.⁴

The oncogenic response to TCDD in animals has been repeatedly shown to depend upon animal species and strain, dose, age, sex, and route of administration. Conventional skin bioassays in mice produced mixed results in some studies^{5,6} but caused significant dermal fibrosarcomas in other studies using different strains of animals.⁷ In the presence of a strong carcinogen, TCDD induced skin papillomas in homozygous hairless mice (but not in the heterozygous strain), clearly supporting the promoter role of TCDD, a non-genetic mechanism judged to be related to receptor binding.⁸

Ingestion studies in several rat strains at doses of 0.07-0.1 µg/kg/day produced hepatocellular carcinomas, squamous cell carcinomas of the oropharynx and lung, and follicular cell thyroid adenomas.^{9,10} In two mouse strains, gavage doses of 0.07-0.3 µg/kg/day produced hepatocellular carcinomas and thyroid tumors.¹⁰ In the presence of partial hepatectomy and diethylnitrosamine, subcutaneous TCDD administration to rats resulted in hepatocellular carcinomas, demonstrating the promoter mechanism of TCDD.¹¹

Based upon these and other studies, the International Agency for Research on Cancer (IARC) designated TCDD as carcinogenic in 1982. There are insufficient data to implicate 2,4-D and 2,4,5-T as carcinogens. The majority of animal studies have shown carcinomas rather than sarcomas, the tumor cited in some human studies. If TCDD oncogenicity in humans is to be supported, the differences in tumor types between animals and man requires explanation.

In a series of publications beginning in 1974, commonly known as the "Swedish studies," extensive inquiry was made into occupational cancer following exposure to a variety of herbicides. Four related efforts¹²⁻¹⁵ using Swedish railroad workers found an increased cancer incidence mostly associated with non-TCDD herbicides. However, a case-control analysis of these data by other investigators suggested cancer promotion following phenoxy acid exposure.¹⁶

Prompted by a slight increase in STS in the railroad workers and clinical experience with a case series of STS, Hardell and coworkers launched an extensive second round of studies.¹⁷⁻²⁵ These efforts showed statistically significant increased risks for STS, Hodgkin's Disease (HD), and NHL. For exposure to phenoxy acids alone, the risk ratio ranged from 5.3 to 6.8 for STS in northern and southern Sweden, respectively, while a range of 3.3 to 6.6 was noted for exposure to chlorophenol alone. For malignant lymphoma (HD plus NHL), risk ratios of 8.4 and 4.8 were respectively demonstrated for chlorophenol and phenoxy acid exposures. An association of nasal and nasopharyngeal cancer to chlorophenol exposure (risk ratio, 6.7) was also detected,²⁵ but other specifically focused studies of primary liver cancer and colon cancer were negative with respect to phenoxy acid or chlorophenol exposure.^{22,24} The colon cancer study was conducted specifically to demonstrate a lack of respondent bias to "validate" previous questionnaire and interview methods used in the STS studies.

From the outset,²⁶⁻²⁸ the Swedish studies have been criticized on methodologic issues, prompting the primary authors, Axelson and Hardell, to respond with clarifications, new calculations, amplifying studies on additional cohorts, and studies on other cancers.^{22,25,29-31} The chief criticisms centered upon possible respondent and observational biases,

selection of controls, confounding exposures, and degree of true exposure to phenoxy acids and chlorophenols. The authors answered these criticisms within the inherent constraints of the case-control methodology. Their efforts have been characterized as careful, clever, and properly stated, and have received favorable reviews.^{32,33}

Four small industrial mortality studies were conducted in the late 1970's and early 1980's.³⁴⁻³⁷ NIOSH investigators pooled the data from these studies and noted that three of the 105 deaths (2.9%) in these studies were due to STS as contrasted to an expected 0.07 percent in the U.S. general population.³⁸ This study has been criticized for the hasty addition of possibly noncomparable industrial cohorts, and the lack of histologic confirmation of the STS cases.³⁹ A subsequent case report added another STS case to the industrial studies,³⁹ and two other reports revealed three unrelated STS cases also arising from the industrial sector.^{40,41} However, upon closer inspection, only two of the first four cases were confirmed as STS by an independent histologic review.⁴² Other review findings of the seven total cases were noteworthy: there was poor agreement on the histologic subtype of the soft tissue tumors, and because of a quirk in the International Classification of Diseases (ICD) System, wherein organ-specific sarcomas are coded separately from soft and connective tissue tumors (ICD 171), death-certificate based studies will underascertain STS by approximately 40 percent.^{42,43} This latter problem did not affect the Swedish studies.

Other cancer studies throughout the world showed mixed support for the Swedish findings. An Italian case-control effort⁴⁴ showed a weak association between ovarian mesothelial tumors and herbicide exposure, whereas a Finnish study of a small number of pesticide sprayers understandably did not detect any cases of STS or malignant lymphomas (ML).⁴⁵ A study of more than 4,000 Danish phenoxy herbicide workers noted five STS cases (versus 1.8 expected) and seven ML cases (versus 5.4 expected).⁴⁶ The author concluded that the STS observation supported the Swedish work and that the ML rate did not. One New Zealand case-control study showed a nonsignificant relative risk of 1.3 for STS among occupations consistent with phenoxy herbicide exposure, although a risk of 7.2 was noted for STS and potential chlorophenol exposure in tanneries.

A related second cancer registry-based case-control study revealed significant excesses of agricultural and forestry occupations from ML cases and multiple myeloma cases (odds ratio 1.25).⁴⁸ In a similar but larger cancer registry study in Sweden, there was no increased risk of STS (relative risk 0.9) in agricultural or forestry workers as contrasted to other industrial workers.⁴⁹ Further, the STS risk was constant over time in spite of increased usage of phenoxy acid herbicides from 1947 to 1970. This Swedish study did not confirm or show a trend consistent with the earlier Hardell Swedish studies.

A recent U.S. case-control study from the Kansas cancer registry has provided partial support for Hardell's observations.⁵⁰ The Kansas study was very similar in methodology to the early Swedish studies and tried to avoid bias and misclassification. An overall risk of 1.6 was found for NHL in men exposed to herbicides, particularly 2,4-D. As the frequency of herbicide exposure increased to more than 20 days per year, the risk of NHL increased to sixfold vis-a-vis nonfarmers. For herbicide applicators, the risk for NHL

was 8.0. A simultaneously published review of the Kansas work noted that this should shift scientific concern from STS to NHL.⁵¹ A population-based case-control study of STS and NHL in western Washington found no overall increased risk of these diseases associated with an occupational history of exposure to chlorophenols or phenoxy herbicides.⁵² However, risks of NHL were significantly elevated in the specific occupational categories of farmers, forestry herbicide applicators, and those individuals potentially exposed to phenoxy herbicides in any occupation for 15 years or more. An increased risk of NHL was also noted among those with occupational exposure to insecticides, organic solvents, lead, and welding fumes.

A number of Vietnam veteran studies has attempted to determine whether veterans have experienced excessive mortality, particularly from cancer.⁵³⁻⁶⁰ Most of the studies used proportionate mortality ratio (PMR) methodology and equated Vietnam service with potential exposure to Agent Orange, a procedure of considerable imprecision (misclassification). These exposure allocation difficulties, coupled with the inherent methodological weaknesses of the PMR technique, have minimized the contribution of these studies to the overall cancer issue.

As might be predicted by these problems, almost all of the veteran studies were negative for generic cancer associations, as well as for STS, HD, and NHL associations. As an example of the veteran studies, the Australian retrospective cohort mortality effort revealed an overall relative mortality ratio of 0.99, an overall cancer mortality ratio of 0.95, and nonsignificant statistical differences for STS, NHL, and HD.⁵⁶ In a recent Vietnam experience study of STS using the case-control method, no significant association was found between military service in Vietnam and the subsequent occurrence of STS.⁶¹

No consistent pattern for other cancer types has emerged from the entire body of herbicide literature. None of the leukemias has been associated with exposure to Herbicide Orange nor any of its constituents. Two studies noted slight increases in gastric cancer^{15,62} and two others cited modest risks for lung cancer.^{63,64} A recent Swedish study reported slight excesses of rectal cancer in male workers and increased cervical cancer from the exposed female cohort.⁴⁶ Overall, these and other observations have not been consistent with the expectation that dioxin, as a cancer promoter, should increase the occurrence of common "background" cancers.

From another perspective, if clear-cut exposure to 2,4-D or dioxin is shown to cause an immunological deficiency (see Chapter 19), an expectation would be an excessive representation of B-cell tumors from the population of NHL cases.⁶⁵⁻⁶⁷ An excess of B-cell neoplasms has, in fact, not been described in NHL cases from industrial or veteran cohorts to date.

It is unlikely that the cancer question will be clearly resolved in the near future. Dioxin exposure in industry and agriculture has fallen precipitously since the 1970's, while exposures to 2,4-D and non-TCDD containing herbicides have continued. Veteran studies characterized by low or undocumented exposure to Agent Orange, and/or of small cohort size are unlikely to contribute substantive data for the evaluation of type-specific cancers although they may contribute to the resolution of the generic cancer issue.

In summary, Swedish studies first noted an approximate sixfold risk of soft tissue sarcoma and malignant lymphoma in forestry workers exposed to both phenoxy acid herbicides (not containing the dioxin contaminant) and chlorophenols (containing dioxin). A large number of international studies were predominantly nonsupportive of the Swedish observations. Recent U.S. research on agricultural workers, however, provided some support for a non-Hodgkin's lymphoma-phenoxy acid exposure association. The future scientific focus is expected to shift from dioxin herbicides to nondioxin herbicides and from soft tissue sarcomas to malignant lymphomas. Studies of other veteran populations will not likely contribute to the new emphasis, largely because of exposure uncertainties.

Baseline Summary Results

Cancer received major emphasis during the 1982 AFHS. The assessment of malignancy used data from both the in-home questionnaire and the review-of-systems questionnaire obtained during the physical examination as well as data from the examination itself. All subjective data were verified by medical record reviews. In addition, tabulation of mortality count data from the Baseline Mortality Report⁸⁸ was used in conjunction with cancer morbidity information. The overall results showed an equivalence of systemic cancer ($p=0.46$) in the two groups but significantly more nonmelanotic skin cancer ($p=0.03$) in the Ranch Hands.

Of 50 reported systemic cancers from the Ranch Hand and Comparison groups, 28 (14 in each group) were verified by medical records and pathology reports. A visual inspection of anatomic sites showed a slight excess of genitourinary cancer and oropharyngeal cancer but a relative deficit of digestive system neoplasms in the Ranch Hands. A combined morbidity-mortality analysis derived from the initial 1:1 match (Ranch Hand to the C-1 Comparison member) disclosed similar distributions. One case of soft tissue sarcoma and one case of Hodgkin's Disease were confirmed, both in the Comparison group. Exposure analyses for industrial chemicals and x rays were negative as were most of the herbicide exposure analyses in the Ranch Hand group. All of the exposure analyses were based upon very small numbers, and interactions were noted in several strata.

Questionnaire data verified by medical record reviews revealed significantly more skin cancer in the Ranch Hands (relative odds 2.35). Basal cell carcinoma accounted for 83.9 percent of the reported skin cancers in both groups and was concentrated anatomically on the face, head, and neck. The few melanoma and squamous cell cancers were evenly distributed between the Ranch Hand and Comparison groups. All skin cancers occurred in nonblacks. Adjustments for occupational exposures (e.g., asbestos, degreasing chemicals) did not alter the increased rate of skin cancer in the Ranch Hand group.

Skin cancer in both groups was associated with exposure to industrial chemicals ($p=0.03$). Herbicide exposure analyses in the Ranch Hand group were essentially negative, although confounding was noted in many of the analyses. Outdoor occupations subsequent to military service as a covariate did not account for the significant skin cancer association.

Parameters of the 1985 Malignancy Assessment

The emphasis on cancer was increased during the first followup study in 1985. With the Baseline finding of excessive skin cancer in the Ranch Hands, and the lack of covariate data to refine that association, considerable attention was devoted to skin cancer. The questionnaire was altered to collect information on each geographic location in which a participant lived for more than 12 months in order to calculate a cumulative "lifetime" sun exposure index based on geographic latitude, since ultraviolet light exposure has been acknowledged as the primary cause of basal cell carcinoma. Detailed data on skin tannability, eye, skin, and hair color, and parental ethnicity were also obtained. In addition, emphasis at the dermatologic examination was shifted from acne/chloracne to skin cancer, and punch biopsies were sought for all suspected malignant lesions.

The participants were asked to bring copies of their medical records to facilitate the verification of reported malignancies. Highly structured smoking data were collected for more detailed covariate adjustments, and Baseline questions on exposure to other carcinogens were repeated to gather interval data. No invasive procedures were used at the followup physical examination to detect evidence of systemic cancer.

Thus, the dependent variables of the analyses below are similar to the Baseline analyses, but covariate analyses have been expanded for both skin and systemic cancers. The lifetime occurrence of cancer, as well as the interval occurrence of skin and systemic cancers between the Baseline and followup examinations, is analyzed.

Minor numeric differences in various tables that follow reflect missing data from the covariates. The statistical methods used throughout this chapter are Fisher's exact test, chi-square tests of association, and logistic regression models (BMDP®-LR) for adjusted group contrasts of neoplasm incidence rates.

RESULTS AND DISCUSSION

General

Malignant and benign neoplasms, carcinomas in situ, and neoplasms of uncertain behavior or unspecified nature are studied in this chapter. The term "systemic" is used throughout to denote a nonskin neoplasm. The term "unspecified" is used to denote a neoplasm of uncertain behavior or unspecified nature. Neoplasm refers to any new and abnormal growth which may or may not be malignant. Malignant neoplasms (malignancies, cancer) are those neoplasms that are capable of invasion and metastasis.

Questionnaire Data

At the followup examination, participants provided information on cancer during the interval between examinations and participants who were new to the study gave their lifetime history. All reported neoplasms entered the medical records review process for verification. Only 11 Ranch Hands (1.1%) and 12 Comparisons (0.9%) reported neoplastic conditions which could not be

substantiated (all of the skin); the group difference was nonsignificant ($p=0.833$).

Physical Examination Data

Some possible neoplastic conditions were discovered by the physicians at the physical examination. Many suspicious skin lesions were biopsied and the pathology determined. However, for some suspected skin neoplasms and all suspected systemic neoplasms, verification was not complete at the time of writing this report, and thus both verified and suspected neoplasms are described and analyzed. The term suspected is used throughout to denote those possible neoplastic conditions noted by the physicians at the followup examination for which the results of verification are not yet available. Consideration of suspected neoplasms was justifiable in particular for skin neoplasms, for which the biopsy confirmation rate is high.

Statistical Analysis

The statistical analysis is described in three sections. The first section presents unadjusted and adjusted analyses of skin and systemic neoplasm incidence in the Baseline-followup interval, and is referred to as interval analysis. In the second section, unadjusted and adjusted analyses of lifetime skin and systemic neoplasm incidence are analyzed for the followup participants, incorporating Baseline information. Since there were very few neoplasm occurrences before the SEA tours, this combined interval and Baseline analysis is referred to throughout as lifetime analysis. Lastly, the neoplasm history and mortality of the fully compliant Baseline participants subsequent to Baseline are described. All analyses are of the numbers of participants with (one or more) neoplasms, and not of the total number of neoplasms.

The purpose of these three analyses is to present a comprehensive picture of the neoplasia history of the followup participants, and to provide some additional information on the neoplasia status of the Baseline participants subsequent to Baseline. There was a slight difference between the Baseline and followup cohorts. The interval and lifetime analyses pertain to neoplasm incidence among followup participants only. The third section pertains to Baseline participants only, describing their history of neoplasm incidence and mortality since Baseline. A fully combined morbidity-mortality analysis was not feasible for this report.

Assuming a (two-sided) α -level of 0.05 and power 0.8, the sample sizes were sufficient to detect a relative risk of 2.56 when the Comparison neoplasm incidence rate is 1 percent, and a relative risk of 1.63 when the Comparison neoplasm incidence rate is 5 percent. For nonblacks only, the corresponding detectable relative risks are 2.63 and 1.65, respectively.

All analyses of data from Ranch Hands and the Original Comparisons only are given in Appendix H. This appendix also contains other tabulations, such as covariate and interaction tables.

Baseline-Followup Interval

Table 10-1 shows the Baseline-followup interval neoplasm history for the followup participants. The interval began in January 1982 for participants new to the study, i.e., the 45 new Ranch Hands, the 71 new replacement Comparisons, and 83 newly compliant Original Comparisons.

The total numbers of participants with verified neoplasms were 161/1,016 (15.8%) Ranch Hands and 170/1,293 (13.1%) Comparisons; the group difference was marginally significant ($p=0.073$). The relative frequencies of participants with verified plus suspected neoplasms, 17.4 percent of Ranch Hands and 16.2 percent of Comparisons, did not differ significantly between groups ($p=0.466$).

Appendix Table H-1 gives the numbers of participants with verified or suspected neoplasms and unadjusted analyses for the Ranch Hands and Original Comparisons in the Baseline-followup interval.

Interval Skin Neoplasms

Of Ranch Hands with verified neoplasms of all types (malignant, benign, and uncertain) 70.8 percent (114/161) had skin neoplasms; the corresponding percentage for the Comparisons was 68.2 percent (116/170). The difference in these proportions was not significant ($p=0.634$). When suspected neoplasms were included, the contrast was 70.1 percent (124/177) versus 67.6 percent (142/210), again not significant ($p=0.660$).

No Blacks were found to have skin cancer, as anticipated since Blacks have a lower susceptibility to sun-induced skin cancer. Therefore, analysis of skin cancer was limited to nonblacks.

Of Ranch Hands with skin neoplasms, 32.5 percent (37/114) had malignant neoplasms, as contrasted to 34.5 percent (40/116) of the Comparisons ($p=0.781$). When suspected malignant skin neoplasms were included, the contrast was 37.9 percent (47/124) versus 42.3 percent (60/142), and was not significant ($p=0.531$).

For the remainder of this section, only malignant skin neoplasms are analyzed. The dependent variables examined were basal cell carcinomas, melanomas, squamous cell carcinomas, all skin cancers combined, and a group of skin cancers called sun exposure-related skin malignancies. The sun exposure-related skin malignancies were defined as basal cell carcinomas, melanomas, and malignant epithelial neoplasms not otherwise specified (NOS). The latter were included because they are frequently misdiagnosed basal cell carcinomas; three Ranch Hands had this diagnosis.

Interval Malignant Skin Neoplasms

Table 10-2 presents the numbers of participants with verified and suspected malignant skin neoplasms by cell type: basal cell carcinomas, squamous cell carcinomas, melanomas, all skin malignancies combined, and the sun exposure-related skin malignancies, together with the results of unadjusted group contrasts. For the sake of completeness, the total numbers of malignancies of each type are also given. The majority of the

TABLE 10-1.

**Unadjusted Analyses of Followup Participants with Verified
and Suspected Neoplasms in the Baseline-Followup Interval by Group
(Nonblacks and Blacks)**

Site	Neoplasm Behavior and Status	Group*				Total**	p-Value***
		Ranch Hand		Comparison			
		Number**	Percent	Number**	Percent		
Skin	Malignant						
	Verified	37	3.6	40	3.1	77	0.485
	Verified and Suspected	47	4.6	60	4.6	107	0.999
	Benign						
	Verified	76	7.5	77	6.0	153	0.152
	Verified and Suspected	78	7.7	83	6.4	161	0.250
	Uncertain Behavior and Unspecified Nature:						
	Verified	1	0.1	1	0.1	2	0.999
	Verified and Suspected	1	0.1	1	0.1	2	0.999
	Any Skin Neoplasm ^a						
Verified	114	11.2	116	9.0	230	0.080	
Verified and Suspected	124	12.2	142	11.0	266	0.393	
Systemic	Malignant						
	Verified	8	0.8	7	0.5	15	0.603
	Verified and Suspected	12	1.2	12	0.9	24	0.680
	Benign						
	Verified	42	4.1	50	3.9	92	0.749
	Verified and Suspected	48	4.7	61	4.7	109	0.999
	Uncertain Behavior and Unspecified Nature:						
	Verified	6	0.6	7	0.5	13	0.999
	Verified and Suspected	6	0.6	11	0.9	17	0.625
	Any Systemic Neoplasm ^b						
Verified	55	5.4	61	4.7	116	0.445	
Verified and Suspected	65	6.4	80	6.2	145	0.863	
All	Malignant, Benign, Uncertain Behavior, Unspecified Nature ^c						
	Verified	161	15.8	170	13.1	331	0.073
	Verified and Suspected	177	17.4	210	16.2	387	0.466

*Sample sizes: 1,016 Ranch Hands and 1,293 Comparisons.

**Number of participants.

***Fisher's exact test.

^aParticipant has one or more malignant, benign, or unspecified skin neoplasms.

^bParticipant has one or more malignant, benign, or unspecified systemic neoplasms.

^cParticipant has one or more malignant or benign skin or systemic neoplasms.

TABLE 10-2.

Unadjusted Analyses of Nonblack Followup Participants with Verified and Suspected Malignant Skin Neoplasms in the Baseline-Followup Interval by Cell Type and Group

Cell Type	Status	Statistic**	Group*		Est. Relative Risk (95% C.I.)	p-Value		
			Ranch Hand	Comparison				
Basal Cell Carcinoma	Verified	Number/% Total Neoplasms	29 42	3.0%	30 40	2.5%	1.23 (0.73,2.07)	0.429
	Verified & Suspected	Number/% Total Neoplasms	36 53	3.8%	48 63	4.0%	0.95 (0.61,1.47)	0.824
Squamous Cell Carcinoma	Verified	Number/% Total Neoplasms	4 6	0.4%	4 4	0.3%	1.27 (0.32,5.08)	0.738
	Verified & Suspected	Number/% Total Neoplasms	4 6	0.4%	5 5	0.4%	1.01 (0.27,3.78)	0.999
Melanoma	Verified	Number/% Total Neoplasms	1 2	0.1%	3 3	0.3%	0.42 (0.04,4.06)	0.635
	Verified & Suspected	Number/% Total Neoplasms	1 2	0.1%	6 7	0.5%	0.21 (0.03,1.75)	0.142
All Malignant Skin Neoplasms	Verified	Number/% Total Neoplasms	37 56	3.9%	40 52	3.3%	1.18 (0.75,1.86)	0.486
	Verified & Suspected	Number/% Total Neoplasms	47 70	4.9%	60 81	5.0%	0.99 (0.67,1.47)	0.999
Sun-Exposure Related Malignant Neoplasms ^a	Verified	Number/% Total Neoplasms	32 47	3.4%	33 43	2.7%	1.24 (0.75,2.02)	0.447
	Verified & Suspected	Number/% Total Neoplasms	39 58	4.1%	53 71	4.4%	0.93 (0.61,1.42)	0.749

*Number of participants--956 Ranch Hands and 1,210 Comparisons.

**Number and percent of participants; total number of malignant neoplasms of specified cell type.

^aBasal cell carcinoma, melanoma, and malignant epithelial neoplasms NOS.

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participants with verified skin malignancies had basal cell carcinomas: 78.4 percent (29/37) Ranch Hands versus 75.0 percent (30/40) Comparisons; the difference between the groups was not significant ($p=0.792$).

Unadjusted Analyses

Table 10-2 shows that no significant group differences were found in the incidence rates of either verified or verified plus suspected malignant skin neoplasms. For verified basal cell carcinomas, the estimated relative risk of Ranch Hands versus Comparisons was 1.23 (95% C.I.: [0.73,2.07]) and was not significant ($p=0.429$). The estimated relative risk for verified squamous cell carcinoma, 1.27 (95% C.I.: [0.32,5.08]), was also not significant ($p=0.738$). The estimated relative risk for verified melanoma, 0.42 (95% C.I.: [0.04,4.06]), was also not significant ($p=0.635$). There were very few occurrences of melanoma (one Ranch Hand and three Comparisons) since this is a much rarer condition than other kinds of skin cancer. There were no significant differences between the groups for all verified malignant skin cancers combined (Est. RR: 1.18, 95% C.I.: [0.75,1.86], $p=0.486$) or for the category of sun exposure-related skin malignancies (Est. RR: 1.24, 95% C.I.: [0.75,2.02], $p=0.447$). When both verified and suspected malignant skin neoplasms were analyzed, the conclusions were similar, namely, there were no significant differences between the groups, and moreover, the estimated relative risks were closer to 1. No group differences were found in the parallel contrasts of Ranch Hands versus Original Comparisons (see Table H-2 of Appendix H).

As shown in Table 10-3, additional analyses contrasted group differences in the anatomic location of basal cell carcinomas, melanomas, and sun exposure-related skin malignancies. Most occurrences of basal cell carcinoma and sun exposure-related skin malignancies were on the face, head, or neck, or the upper extremities. The relative frequency of occurrences of verified basal cell carcinomas at these combined sites was 89.7 percent for Ranch Hands and 80.0 percent for Comparisons of the total number of occurrences in each group, respectively. The group contrast (26/29 versus 24/30) was not significant ($p=0.472$). These combined sites accounted for 90.6 percent (29/32) of the sun exposure-related malignancies for Ranch Hands versus 72.7 percent (24/33) for Comparisons; this contrast was also not significant ($p=0.108$). The corresponding contrasts, when suspected malignant neoplasms were included with the verified malignant neoplasms, were also not significant. One Ranch Hand had verified melanoma of the face, and three Comparisons had verified melanoma on the trunk. Two other Comparisons had suspected melanoma, also on the trunk. The group contrast for melanomas on the trunk was not significant for verified conditions ($p=0.260$), but was marginally significant for verified plus suspected conditions ($p=0.071$), the detriment being in the Comparison group.

Table 10-4 gives the frequencies of participants with face, head, and neck skin malignancies by group and occupation. Specifically, nonmelanoma malignant skin neoplasms and the sun exposure-related malignant skin neoplasms are listed by occupational category. For officers and enlisted groundcrew, the frequencies of participants with face, head, and neck malignant skin neoplasms (both malignant nonmelanoma and the malignant sun exposure-related skin neoplasms) did not differ significantly by group. However, the Ranch Hand enlisted flyers had a significantly higher frequency

TABLE 10-3.

Unadjusted Analyses of Nonblack Followup Participants with Verified and Suspected Malignant Skin Neoplasms in the Baseline-Followup Interval by Anatomic Site and Group

Site	Status**	Basal Cell Carcinoma			Sun-Exposure Related Malignancies			Melanoma								
		Group*			Group*			Group*								
		Ranch	Hand	Comparison	p-Value	Ranch	Hand	Comparison	p-Value	Ranch	Hand	Comparison	p-Value			
Face, Head, Neck	Number/% Verified	24	2.5%	23	1.9%	0.374	27	2.8%	23	1.9%	0.194	1	0.1%	0	0.0%	0.441
	Verified & Suspected	29	3.0%	35	2.9%	0.899	32	3.4%	36	3.0%	0.622	1	0.1%	1	0.1%	0.999
Upper extrem- ities	Number/% Verified	5	0.5%	3	0.3%	0.313	5	0.5%	3	0.3%	0.313	0	0.0%	0	0.0%	— ^a
	Verified & Suspected	5	0.5%	4	0.3%	0.520	5	0.5%	5	0.4%	0.757	0	0.0%	0	0.0%	— ^a
Trunk	Number/% Verified	2	0.2%	6	0.5%	0.479	2	0.2%	9	0.7%	0.126	0	0.0%	3	0.3%	0.260
	Verified & Suspected	4	0.4%	11	0.9%	0.200	4	0.4%	14	1.2%	0.093	0	0.0%	5	0.4%	0.071
Lower Extrem- ities	Number/% Verified	0	0.0%	0	0.0%	— ^a	0	0.0%	0	0.0%	— ^a	0	0.0%	0	0.0%	— ^a
	Verified & Suspected	0	0.0%	0	0.0%	— ^a	0	0.0%	0	0.0%	— ^a	0	0.0%	0	0.0%	— ^a
Other Sites and Sites NOS	Number/% Verified	1	0.1%	2	0.2%	0.999	1	0.1%	2	0.2%	0.999	0	0.0%	0	0.0%	— ^a
	Verified & Suspected	1	0.1%	2	0.2%	0.999	1	0.1%	2	0.2%	0.999	0	0.0%	0	0.0%	— ^a
All Locations	Number/% Verified	29	3.0%	30	2.5%	0.429	32	3.4%	33	2.7%	0.447	1	0.1%	3	0.3%	0.635
	Verified & Suspected	36	3.8%	48	4.0%	0.824	39	4.1%	53	4.4%	0.749	1	0.1%	6	0.5%	0.142

*Number of participants — 956 Ranch Hands, 1,210 Comparisons.

**Number and percent of participants.

^aNo occurrences in either group.

TABLE 10-4.

Unadjusted Analyses of Nonblack Followup Participants with Nonmelanoma Malignant Skin Neoplasms and Sun-Exposure Related Skin Malignancies in the Baseline-Followup Interval Occurring on the Face, Head, or Neck by Occupation

Occupation	Status	Statistic	Nonmelanoma Malignant Skin Neoplasms				Sun-Exposure Related Skin Malignancies					
			Ranch Hand		Comparison		p-Value	Ranch Hand		Comparison		p-Value
			Number	Percent	Number	Percent		Number	Percent	Number	Percent	
	Verified	n	373		477			373		477		
Officer	Verified	Face, Head, Neck	14	3.8	17	3.6	0.999 ^a	12	3.2	13	2.7	0.688 ^a
		Other Site	5	1.3	4	0.8	0.516 ^b	3	0.8	5	1.1	0.999 ^b
		No Cancer	354	94.9	456	95.6		358	96.0	459	96.2	
	Verified & Suspected	Face, Head, Neck	20	5.4	23	4.8	0.754 ^a	17	4.6	20	4.2	0.866 ^a
		Other Site	7	1.9	8	1.7	0.999 ^b	4	1.1	9	1.9	0.408 ^b
		No Cancer	346	92.8	446	93.5		352	94.4	448	93.9	
	Verified	n	167		193			167		193		
Enlisted Flyer	Verified	Face, Head, Neck	8	4.8	3	1.6	0.121 ^a	8	4.8	2	1.0	0.049 ^a
		Other Site	1	0.6	0	0.0	0.456 ^b	1	0.6	1	0.5	0.999 ^b
		No Cancer	158	94.6	190	98.5		158	94.6	190	98.5	
	Verified & Suspected	Face, Head, Neck	8	4.8	5	2.6	0.396 ^a	8	4.8	4	2.1	0.238 ^a
		Other Site	1	0.6	1	0.6	0.999 ^b	1	0.6	2	1.0	0.999 ^b
		No Cancer	158	94.6	187	96.9		158	94.6	187	96.9	
	Verified	n	416		540			416		540		
Enlisted Groundcrew	Verified	Face, Head, Neck	7	1.7	9	1.7	0.999 ^a	7	1.7	8	1.5	0.800 ^a
		Other Site	1	0.2	4	0.7	0.395 ^b	1	0.2	4	0.7	0.395 ^b
		No Cancer	408	98.1	527	97.6		408	98.1	528	97.8	
	Verified & Suspected	Face, Head, Neck	7	1.7	13	2.4	0.500 ^a	7	1.7	12	2.2	0.644 ^a
		Other Site	3	0.7	6	1.1	0.739 ^b	2	0.5	6	1.1	0.477 ^b
		No Cancer	406	97.6	521	96.5		407	97.8	522	96.7	

*Number and percent of participants.

^aFisher's exact test for face, head, or neck versus no malignancy.

^bFisher's exact test for other site versus no malignancy.

of malignant sun exposure-related skin neoplasms than the corresponding Comparisons, 4.8 percent versus 1.0 percent ($p=0.049$). For nonmelanoma malignant skin neoplasms, the contrast was 4.8 percent versus 1.6 percent, but the difference was not significant ($p=0.121$). Inclusion of suspected malignant neoplasms with the verified malignant neoplasms reduced the significance of the difference between the groups for both the sun exposure-related skin malignancies and the nonmelanoma malignant skin neoplasms.

Adjusted group contrasts of the incidence rate of basal cell carcinomas and malignant sun exposure-related skin neoplasms were done for verified and verified plus suspected conditions. Adjusted analyses were not carried out, however, for melanomas or squamous cell carcinomas because of the small frequencies.

Covariates

The covariates considered for the adjusted analyses of malignant skin neoplasm incidence, listed in Table 10-5, were the matching variables age and occupation; history of alcohol and cigarette use; host factors, comprising skin color, eye color, hair color, and ethnic background; reaction of skin to sun exposure; average lifetime residential latitude; and exposure to recognized carcinogens. Age was used as a continuous variable in the adjusted analyses, but was categorized for ease of presentation in the report.

Eye color, hair color, and skin color were coded by the dermatologist at the physical examination. Hair color was determined by comparing the hair at the back of the neck with 17 numbered standardized hair samples⁶⁹ and selecting the most closely matching hair sample. Similarly, skin color groupings from dark brown to pale peach were determined by comparing standardized flesh-colored squares⁷⁰ against the skin of the inside upper arm. For the analysis, hair and skin colors were grouped as shown in Table 10-5. Each participant was assigned to one of four ethnic groups according to his responses to questions on race, as given in Table 10-5. (Blacks were omitted from the table because the analysis of malignant skin neoplasia was restricted to nonblacks.) These ethnic categories are approximate groupings in terms of susceptibility to sun-induced skin damage. The ethnic categories also generally correlate to skin color, a commonly known important risk factor for skin cancer.

A lifetime residential history was obtained from all participants by a questionnaire. Residential history, relative to the equator, is a surrogate measure of sun exposure (but does not account for altitude or average sun-days at each location), an important risk factor for skin cancer. Each participant was asked to list all residences chronologically, citing both the city (or military installation) and the years of residence at each location since birth. Residences of less than 1 year were not sought because of the frequent short-term military travels of these cohorts.

By standardized geographic atlases, the latitude (in degrees and minutes) of each residence was recorded. The Air Force subsequently checked all of the latitude determinations for accuracy. The average lifetime residential latitude of each participant was calculated by dividing the total degree-years (i.e., sum of latitude [degrees] times number of years lived there) from all residences by the total number of residential years listed.

TABLE 10-5.

Covariates for Analyses of Malignant Skin Neoplasms

Covariate	Category
Age	Born \geq 1942, 1923-1941, \leq 1922 ^a
Occupation	Officer, Enlisted Flyer, Enlisted Groundcrew
Lifetime Cigarette Smoking	Pack-years: 0, >0-20, >20-40, >40
Lifetime Alcohol Consumption	Drink-years: 0, >0-5, >5-30, >30-100, >100
Ethnic Background	A, B, C, D ^b
Skin Color	Dark, medium, pale, dark peach, pale peach
Hair Color	Black, dark brown, light brown, blond, red
Eye Color	Brown, hazel, green, gray, blue ^c
Reaction of Skin to Sun Exposure ^d :	
(A.1) After first 30 minutes of summer sun	Burns, usually burns, burns mildly, rarely burns
(A.2) After \geq 2 hours, after first exposure	Burns painfully, burns, becomes red, no reaction
(A.3) After repeated sun exposures	Freckles with no tan, tans mildly, tans moderately, tans deep brown
Sun-Reaction Index (Composite) ^d	(1) Burns painfully (A.2) and/or freckles with no tan (A.3) (2) Burns (A.2) and/or tans mildly (A.3) (3) All other reactions
Residential History (Average Latitude)	Average latitude $<$ 37°, \geq 37°
Exposure to Carcinogens/Groups of Carcinogens Set 1 ^d	
Asbestos	Yes, No
Nonmedical X Rays	Yes, No
Industrial Chemicals	Yes, No
Herbicides	Yes, No
Insecticides	Yes, No
Degreasing Chemicals	Yes, No

TABLE 10-5. (continued)

Covariates for Analyses of Malignant Skin Neoplasms

Covariate	Category
Set 2 ^a	
Anthracene	Yes, No
Arsenic	Yes, No
Benzene	Yes, No
Benzidene	Yes, No
Chromates	Yes, No
Coal Tar	Yes, No
Creosote	Yes, No
Aminodiphenyl	Yes, No
Chloromethyl Ether	Yes, No
Mustard Gas	Yes, No
Naphthylamine	Yes, No
Cutting Oils	Yes, No
Trichloroethylene	Yes, No
Ultraviolet Light (not sun)	Yes, No
Vinyl Chloride	Yes, No
Composite Carcinogen Exposure	Yes, if yes for exposure to any carcinogen in set 2, otherwise no.

^aUsed as a continuous variable in adjusted analysis.

^bA - English, Welsh, Scottish, Irish.

B - Scandinavian, German, Polish, Russian, other Slavic, Jewish, French.

C - Spanish, Italian, Greek.

D - Mexican, American Indian, Asian.

^cParticipant with one green eye and one brown eye is coded as green.

^dQuestionnaire data (see Appendix B).

^eAFHS Form 2 (see Appendix C).

Recognizing that both total degree-years and average lifetime latitude could be covariates for malignant sun exposure-related skin neoplasms, average latitude was selected because of the high correlation of degree-years with chronological age, a separate risk factor already used in the analyses. Further, average residential latitude was believed to be a more stable measure in the presence of some lack of precision in the source data. In all analyses, the average residential latitude was used as a dichotomous variable (less than 37° N latitude, greater than or equal to 37° N latitude). A line across the United States at 37° N approximates a line from San Francisco, California, to Richmond, Virginia.

Examination of the group distributions of the latitude variable suggest that it is a significant confounding variable. Specifically, 56.7 percent of the nonblack Ranch Hands had an average lifetime residential latitude greater than or equal to 37° N latitude versus 49.4 percent of the nonblack Comparisons ($p=0.001$). Although the average lifetime group residential latitudes appear similar (37.21° N latitude for the Ranch Hands, and 36.74° N latitude for the Comparisons), this difference is also highly significant ($p=0.003$), reflecting the substantial power of the analysis of continuous data.

Participants reported their susceptibility to the effects of sun-exposure damage by answering three questions about their skin reaction to sun: the reaction after the first 30 minutes of exposure to summer sun, the reaction after 2 or more hours of sun exposure after the first 30-minute exposure, and the reaction after repeated exposures (see questions 10-12 on page 71 of the questionnaire provided in Appendix B). Since these three responses are highly correlated, a composite sun-reaction variable for use in the adjusted analysis, called the sun-reaction index, was constructed from the last two questions (2-hour and repeated exposure reactions) after examination of the association between basal cell carcinoma incidence and the three skin reaction variables. The sun-reaction index had three categories. The first category corresponded to the most sensitive reaction on the last two questions, the second category corresponded to the next less sensitive reaction on these two questions, and the third category comprised the remaining responses.

Detailed questionnaire information on exposure to asbestos, nonmedical x rays, industrial chemicals, herbicides, insecticides, and degreasing chemicals was obtained from each participant. Self-reported information on exposure to 15 individual carcinogens was obtained at the physical examination. A composite carcinogen exposure variable was constructed from these responses on individual carcinogens: A participant had a positive score for this variable if he reported exposure to one or more of the 15 carcinogens, otherwise he had a negative score. Self-reported information on asbestos and radiation exposure was not used because this information was obtained in more detail from the questionnaire.

The nonblack Ranch Hands differed significantly from the nonblack Comparisons in their exposure (yes/no) to nonmedical x rays (19.3% versus 25.6%, $p<0.001$). They also differed significantly from the Comparisons in their exposure to herbicides (94.1% versus 29.8%, $p<0.001$) and insecticides (70.2% versus 53.1%, $p<0.001$), possibly reflecting Vietnam experience. These variables were not used in the adjusted analysis. Further, there were significant or marginally significant group differences in the self-reported exposures to several individual carcinogens, in each instance relatively more (nonblack) Ranch Hands than Comparisons reported exposure: arsenic (2.7%

versus 1.2%, $p=0.016$), naphthylamine (3.3% versus 1.7%, $p=0.024$), cutting oils (12.7% versus 8.7%, $p=0.003$), benzene (4.3% versus 2.7%, $p=0.056$), and benzidine (0.8% versus 0.3%, $p=0.070$). Results were similar when Blacks were included in the analysis.

Covariate Associations

Table 10-6 gives a summary of the chi-square tests of association between all covariates and the incidence of basal cell carcinomas and sun exposure-related malignancies. Details of these tests of association are provided in Appendix H, Table H-3.

There was a significant increase in the incidence rate of verified basal cell carcinomas with increasing age ($p=0.001$). There was a significant difference in the incidence rate of basal cell carcinomas among occupation groups, with enlisted groundcrew having a lower incidence rate (1.8%) than officers (3.7%) and enlisted flyers (3.1%) ($p=0.047$). Since officers are, on the average, 5 years older than enlisted participants, this occupation effect may be due to some confounding with age. There was a higher incidence rate for average lifetime residential latitude less than 37° N versus greater than or equal to 37° N latitude ($p=0.008$). Furthermore, there was a strong difference for different levels of the sun-reaction index ($p<0.001$), and the three skin-reaction-to-sun variables ($p\leq 0.001$ for all). Participants who tended to burn most had a lower rate (1.4%) than those with a milder reaction (6.0%), and a similar rate to those who tended to tan (1.9%) (an unexpected finding). There was a significant relationship between the incidence rate of basal cell carcinoma and total pack-years of lifetime smoking ($p=0.023$ for verified). This effect may also be due to confounding with age rather than to a primary smoking effect (see Table H-5 of Appendix H). No significant association was found between the incidence rate of verified basal cell carcinoma and lifetime drink-years.

No significant associations were found with ethnic group, skin color, eye color, and hair color. However, when the ethnic group categories were dichotomized as Celtic or English versus other ethnic groups, the association was marginally significant ($p=0.093$). Skin color was dichotomized as dark peach or light peach versus other colors, and the association was significant (Est. RR: 3.00, 95% C.I.: [1.08, 8.33], $p=0.024$). Hair color was dichotomized as blond or red versus other colors. The association of hair color with basal cell carcinoma incidence was not significant ($p=0.384$). Furthermore, no significant relationship was found between basal cell carcinoma incidence and the composite carcinogen-exposure variable ($p=0.523$) or the grouped or individual carcinogens.

The associations between the covariates and the incidence of verified plus suspected basal cell carcinomas paralleled those for the verified basal cell carcinomas only, except that the difference in rates among ethnic groups was significant ($p=0.046$), hair color was significant ($p=0.040$), and a marginally significant positive relationship was found with nonmedical x-ray exposure ($p=0.084$) and herbicide exposure ($p=0.072$). The difference among occupation groups, however, was more significant ($p=0.003$).

TABLE 10-6.

Summary of Associations Between Incidence Rates
of Basal Cell Carcinoma and Sun Exposure-Related Skin Malignancies
and the Covariates, in the Baseline-Followup Interval
for Combined Followup Ranch Hand and Comparison Nonblack Participants

Covariate	Basal Cell Carcinoma		Sun Exposure-Related Skin Malignancies	
	<u>Verified</u> p-Value	<u>Verified & Suspected</u> p-Value	<u>Verified</u> p-Value	<u>Verified & Suspected</u> p-Value
Age	0.001	<0.001	0.004	<0.001
Occupation	0.047	0.003	NS*	0.006
Lifetime Cigarette Smoking	0.023	0.005	0.012	0.007
Lifetime Alcohol Consumption	NS	NS	NS	NS
Ethnic Background	NS	0.046	NS	0.036
Skin Color	NS**	NS	NS	NS**
Hair Color	NS	0.040	NS	NS*
Eye Color	NS	NS	NS	NS
Reaction of Skin to Sun Exposure:				
(0.1) After first 30 minutes of summer sun	0.001	<0.001	<0.001	<0.001
(0.2) After ≥2 hours, after first exposure	<0.001	0.027	0.001	0.016
(0.3) After repeated sun exposures	<0.001	0.001	<0.001	<0.001
Sun-Reaction Index (Composite)	<0.001	<0.001	<0.001	<0.001
Residential History (Average Latitude)	0.008	0.004	0.011	0.003
Exposure to Carcinogens/Groups of Carcinogens				
Set 1 ^a				
Asbestos	NS	NS	NS	NS
Non-medical X Rays	NS	NS*	NS	NS
Industrial Chemicals	NS	NS	NS	NS
Herbicides	NS	NS*	NS	NS
Insecticides	NS	NS	NS	NS
Degreasing Chemicals	NS	NS	NS	NS

TABLE 10-6. (continued)

Summary of Associations Between Incidence Rates
of Basal Cell Carcinoma and Sun Exposure-Related Skin Malignancies
and the Covariates, in the Baseline-Followup Interval
for Combined Followup Ranch Hand and Comparison Nonblack Participants

Covariate	Basal Cell Carcinoma		Sun Exposure-Related Skin Malignancies	
	<u>Verified</u> p-Value	<u>Verified & Suspected</u> p-Value	<u>Verified</u> p-Value	<u>Verified & Suspected</u> p-Value
Set 2 ^b				
Anthracene	NS	NS	NS	NS
Arsenic	NS	NS	NS	NS
Benzene	NS	NS	NS	NS
Benzidene	NS	NS	NS	NS
Chromates	NS	NS	NS	NS
Coal Tar	NS	NS	NS	NS
Creosote	NS	NS	NS	NS
Aminodiphenyl	NS	NS	NS	NS
Chloromethyl Ether	NS	NS	NS	NS
Mustard Gas	NS	NS	NS	NS
Naphthylamine	NS	NS	NS	NS
Cutting Oils	NS	NS	NS	NS
Trichloroethylene	NS	NS	NS	NS
Ultraviolet Light (not sun)	NS	NS	NS	NS
Vinyl Chloride	NS	NS	NS	NS
Composite Carcinogen Exposure	NS	NS	NS	NS

NS: Not significant ($p < 0.10$).

NS*: Borderline significant ($0.05 < p \leq 0.10$).

**Not significant when five categories of skin color examined; however, when dichotomized, $p = 0.024$ for verified basal cell carcinoma and $p = 0.036$ for verified and suspected sun exposure-related skin malignancies.

^aQuestionnaire data.

^bAFHS Form 2.

As expected, the relationships between the incidence of verified sun exposure-related skin malignancies and the covariates were similar to those just described for basal cell carcinomas (Table 10-6 and Table H-4 of Appendix H). For verified conditions, there was a strong increase in incidence rate with age ($p=0.004$), total lifetime smoking ($p=0.012$), average lifetime residential latitude ($p=0.011$), the reaction-to-sun exposure variables ($p\leq 0.001$ for all), and the sun-reaction index ($p<0.001$), with similar strong associations for the verified plus suspected conditions. The difference among occupation groups was marginally significant ($p=0.077$) for verified conditions; this difference was significant ($p=0.006$) for verified plus suspected sun exposure-related skin malignancies (officers 5.9%, enlisted flyers 4.2%, enlisted groundcrew 2.8%). There was no association with the composite carcinogen-exposure variable, either for verified ($p=0.879$) or for verified plus suspected conditions ($p=0.608$).

Table 10-6 shows no significant association between the incidence rate of verified sun exposure-related skin malignancies and ethnic group, hair color, skin color, or eye color. When suspected conditions were included, the ethnic group association was significant ($p=0.036$), and the association with hair color became borderline significant ($p=0.051$). There were higher incidence rates among those of Celtic or English background as opposed to other ethnic backgrounds, and among participants with blond or red hair as opposed to other colors (see Table H-4 of Appendix H). As in the analysis of basal cell carcinomas, the ethnic group, hair color, and skin color categories were collapsed, resulting in (for verified conditions): $p=0.054$ for those of Celtic or English backgrounds versus other ethnic backgrounds (Est. RR: 2.04, 95% C.I.: [1.00, 4.17]) and $p=0.031$ for skin color peach versus not-peach (Est. RR: 2.61, 95% C.I.: [1.04, 6.58]), but no significant association with hair color grouped as blond or red versus other ($p=0.268$) was found.

Adjusted Analyses

Because of the obvious interrelatedness among the host factors of hair color, skin color, eye color, ethnic background, and reaction of skin to sun, and because a smaller set of covariates was required for the adjusted analyses, a "main-effects" statistical model of basal cell carcinoma with the following covariates was used: age, occupation, total pack-years, lifetime drinking, ethnic background (dichotomized), hair color (blond or red versus other), eye color, skin color (peach tones versus other), the three skin-reaction-to-sun variables, average lifetime residential latitude (less than 37° N versus greater than or equal to 37° N), and the composite carcinogen exposure variable. The results of this analysis are given in Appendix H, Table H-5. The results showed that ethnic background, hair color, and the 30-minute skin-reaction-to-sun variable, while individually associated with basal cell carcinoma incidence, are relatively less important than the other host factors, namely skin color, and the 2-hour and repeated-exposure skin-reaction-to-sun variables, and were thus not included in the adjusted analyses. Total drink-years and the composite carcinogen exposure variable were not significant and thus were not used in the adjusted analyses. A parallel analysis was conducted in which the composite sun-reaction index replaced all three skin-reaction-to-sun variables, and it was found that this substitution could be made without altering the relative contributions of the other covariates. For further reduction of the number of covariates, pack-years of smoking, although of interest ($p=0.096$), was

also omitted. Thus, a reduced set of covariates for further analysis of the group contrasts was identified as age, occupation, skin color, average lifetime residential latitude, and the sun-reaction index.

The results of adjusted analyses of group contrasts in the incidence rate of basal cell carcinoma and sun exposure-related skin malignancies are presented in Table 10-7. Parallel results for Ranch Hands contrasted with the Original Comparisons are given in Appendix H, Table H-6. A significant group-by-occupation interaction was found for verified interval basal cell carcinoma ($p=0.044$). Significant covariates were age ($p=0.003$), average residential latitude ($p=0.003$) and the sun-reaction index ($p<0.001$). The interaction was due to a significant difference in rates for enlisted flyers but not for officers or enlisted groundcrew: Ranch Hand enlisted flyers had a significantly ($p=0.019$) greater incidence rate of basal cell carcinomas than the corresponding Comparisons, 5.4 percent versus 1.0 percent (Adj. RR: 6.50, 95% C.I.: [1.36,31.01]) (see Appendix H, Table H-7).

There was a significant group-by-sun-reaction index interaction in the analysis of verified plus suspected basal cell carcinomas ($p=0.024$); this was in part attributable to the absence of Ranch Hands who reported burning easily. The group frequencies for the three levels of this variable (burn easily, intermediate reaction, tan easily) were: Ranch Hands 0 (0%), 17 (8.9%), and 19 (2.7%), respectively, and Comparisons 4 (5.2%), 15 (5.7%), and 28 (3.2%), respectively. The incidence rate for Ranch Hands who had a moderate reaction to sun was (nonsignificantly) greater than that of the Comparisons. The details of this interaction are given in Appendix H, Table H-7. A skin color-by-age interaction ($p=0.044$) and average latitude ($p=0.003$) made significant contributions to the model.

Results of the analyses for Original Comparisons were nonsignificant for verified conditions, although a marginally significant group-by-sun reaction interaction was found ($p=0.051$). The results for verified plus suspected conditions revealed a significant group-by-sun reaction index interaction ($p=0.007$) (see Table H-6 of Appendix H). Ranch Hands who had a moderate skin reaction to sun revealed a significantly greater incidence rate of verified basal cell neoplasms than corresponding Original Comparisons (Adj. RR: 2.81, 95% C.I.: [1.05,7.55], $p=0.040$) (Table H-8). This finding was marginally significant with the inclusion of suspected carcinomas (Adj. RR: 2.38, 95% C.I.: [0.98,5.76], $p=0.055$).

The adjusted relative risk for the incidence rate of verified sun exposure-related skin malignancies was 1.37 (95% C.I.: [0.83,2.28]) and was not significant ($p=0.221$) (Table 10-7). Age ($p<0.001$), the sun-reaction index ($p<0.001$), and average lifetime residential latitude ($p=0.008$) contributed to the adjustment. No group difference was apparent when suspected malignancies were included. The adjusted relative risk was 1.05 (95% C.I.: [0.68,1.62], $p=0.825$), and the significant covariates were a skin color-by-sun-reaction index interaction ($p=0.028$), a skin color-by-age interaction ($p=0.028$), and a skin color-by-residential latitude interaction ($p=0.041$).

TABLE 10-7.

Adjusted Analyses of Nonblack Followup Participants for Malignant Skin Neoplasm Incidence During the Baseline-Followup Interval

Variable	Status	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks*
Basal Cell Carcinoma	Verified	****	****	AGE (p=0.003) LAT (p=0.003) SUNREAC (p<0.001) GRP*OCC (p=0.044)
	Verified & Suspected	****	****	LAT (p=0.003) GRP*SUNREAC (p=0.024) SKIN*AGE (p=0.044)
Sun-Exposure Malignant Skin Neoplasms	Verified	1.37 (0.83,2.28)	0.221	AGE (p<0.001) SUNREAC (p<0.001) LAT (p=0.008)
	Verified & Suspected	1.05 (0.68,1.62)	0.825	SKIN*SUNREAC (p=0.028) SKIN*AGE (p=0.028) SKIN*LAT (p=0.041)

*Abbreviations:

LAT: average lifetime residential latitude
 SUNREAC: sun reaction index
 GRP: group
 OCC: occupation
 SKIN: skin color

****Group-by-covariate interaction--adjusted relative risk, confidence interval, and p-value not presented.

Analysis of the Ranch Hands versus Original Comparisons contrasts found a significant group-by-skin color interaction for verified sun exposure-related malignancies ($p=0.036$), and a significant group-by-sun reaction index interaction ($p=0.030$), similar to that found for basal cell carcinoma, for the verified plus suspected malignant neoplasms (see Appendix H, Tables H-6 and H-8, for details). The group-by-skin color interaction was due to a lower incidence rate for nonpeach Ranch Hands than Original Comparisons (Adj. RR: 0.20, 95% C.I.: [0.02,1.80], $p=0.150$), but a higher incidence rate for peach toned Ranch Hands than Original Comparisons (Adj. RR: 1.70, 95% C.I.: [0.95,3.04], $p=0.073$). The group-by-sun reaction index interaction (verified and suspected) was again due to Ranch Hands who react moderately to the sun having a higher incidence rate than similar Original Comparisons (Adj. RR: 2.74, 95% C.I.: [1.14,6.63], $p=0.025$).

Interval Systemic Neoplasms

As shown in Table 10-1, eight Ranch Hands (0.8%) and seven Comparisons (0.5%) had verified malignant systemic neoplasms in the interval between the Baseline and followup examinations. When suspected malignant systemic neoplasms were included, the numbers were 12 Ranch Hands (1.2%) and 12 Comparisons (0.9%). The proportions of malignancies among the systemic neoplasms of all types (malignant, benign, uncertain) were similar in the two groups: 14.5 percent (8/55) for Ranch Hands and 11.5 percent (7/61) for Comparisons ($p=0.783$). Inclusion of suspected conditions did not change the conclusion from this contrast: 18.5 percent (12/65) Ranch Hands versus 15.0 percent (12/80) Comparisons ($p=0.656$).

For the remainder of this section, only malignant (verified and suspected) systemic neoplasms occurring in the Baseline to followup interval are analyzed. These occurrences were distinct from those reported at Baseline. No new metastatic systemic neoplasms were reported in the interval.

Interval Malignant Systemic Neoplasms

Table 10-8 shows the sites of the new malignant neoplasms reported by the eight Ranch Hands and seven Comparisons. Classification of malignancies was based on ICD-9 with special coding for tumor type as well as site, thus avoiding problems of underreporting of STS. Six Ranch Hands and five Comparisons had suspected systemic neoplasms in this interval (Table 10-9), making a total of 12 in each group, since 2 Ranch Hands with verified systemic neoplasms also had suspected systemic neoplasms. The frequencies were too small for indepth analysis of individual sites. Table 10-8 shows that two Ranch Hands had malignant neoplasms of the oral cavity and pharynx versus no Comparisons, and three Comparisons but no Ranch Hands had malignant neoplasms of the colon. For all digestive system malignancies (esophagus plus colon), there were four occurrences among Comparisons but none among Ranch Hands. The analyses that follow are based on the combination of all interval malignant systemic neoplasms regardless of specific site, both verified and verified plus suspected.

Table H-9 of Appendix H lists the malignancy sites for the eight Ranch Hands and the six Original Comparisons in the Baseline-followup interval.

TABLE 10-8.

Summary of Followup Participants with Verified Malignant Systemic Neoplasms in Baseline-Followup Interval by Group

Site	Group		Total
	Ranch Hand	Comparison	
Oral Cavity and Pharynx	2 ^{a, b}	0	2
Thyroid Gland	0	1	1
Esophagus	0	1 ^c	1
Bronchus and Lung	1	0	1
Colon	0	3 ^{d, e}	3
Kidney and Bladder	2	1	3
Prostate	1	1	2
Testicles	1	0	1
Connective and Other Soft Tissue	<u>1</u>	<u>0</u>	<u>1</u>
Total	8	7	15

^aIncludes one Ranch Hand with separate malignancies of tongue and epiglottis and also malignant neoplasm of bone.

^bIncludes one Ranch Hand with separate malignant neoplasms of tongue and oropharynx and secondary malignant neoplasm of other site.

^cAlso has malignant neoplasm of bone.

^dIncludes one Comparison with secondary malignant neoplasms of liver and bone and bone marrow.

^eIncludes one Comparison with secondary malignant neoplasm of liver.

TABLE 10-9.

Summary of Followup Participants with Suspected Malignant Systemic Neoplasms at Physical Examination by Group

Site	Group		Total
	Ranch Hand	Comparison	
Bronchus and Lung	4 ^{a, b}	2	6
Rectum	0	1	1
Liver	1 ^c	0	1
Prostate	0	1	1
Lymphatic and Hematopoietic Tissue	1 ^d	0	1
Unspecified Site	<u>0</u>	<u>1</u>	<u>1</u>
Total	6	5	11

^aIncludes one Ranch Hand with a suspected malignant neoplasm of either lung, mediastinum, esophagus, or ill-defined site within digestive organs and peritoneum.

^bIncludes one Ranch Hand with a suspected secondary malignant neoplasm of lung.

^cNot specified as primary or secondary.

^dSuspected as either Hodgkins disease, leukemia, or lymphoma.

There is no parallel table for suspected malignant systemic neoplasms since the five Comparisons with suspected conditions in Table 10-9 are Original Comparisons.

Unadjusted Analyses

As shown in Table 10-10, the unadjusted group contrast for all verified malignant systemic neoplasms was not significant ($p=0.603$), with an estimated relative risk of 1.46 (95% C.I.: [0.53,4.03]). When suspected malignant neoplasms were included with the verified malignancies, the estimated relative risk was 1.28 (95% C.I.: [0.57,2.85]), and was also not significant ($p=0.680$). A parallel unadjusted analysis for Ranch Hands versus Original Comparisons gave similar nonsignificant results (Appendix Table H-10).

Covariates

The covariates considered for the adjusted analysis of all interval malignant systemic neoplasms combined were age, race, occupation, smoking and drinking history, exposure to the groups of carcinogens, exposure to the individual carcinogens, and the composite carcinogen exposure variable as listed in Table 10-5. The categories used for age, pack-years, and drink-years were the same. Age was used as a continuous variable in the adjusted analyses but was categorized for ease of presentation in the report. No Blacks had verified systemic neoplasms, but in contrast to the skin cancer analysis, Blacks were retained in the analysis.

Covariate Associations

Table 10-11 summarizes the results of chi-square tests of association between the incidence rate of all malignant systemic neoplasms combined and the covariates considered for use in the adjusted analyses. Details of the covariate relationships are given in Appendix H, Table H-11.

There was a significant increase in the incidence rate of all verified interval malignant systemic neoplasms with increasing age ($p<0.001$) and a marginally significant difference among occupations ($p=0.056$). The incidence rates for officers, enlisted flyers, and enlisted groundcrew were 1.2 percent, 0.5 percent, and 0.3 percent, respectively. There was a marginally significant association with total lifetime alcohol consumption ($p=0.082$). The test for differences in incidence rates among pack-year levels of smoking was not significant ($p=0.220$), although an increasing trend was apparent. Some of the occupation effect may be attributable to confounding with age.

There was a significant negative association with insecticide exposure for verified malignant systemic neoplasms ($p=0.014$). Table H-11 of Appendix H shows that there were a few significant or marginally significant positive associations with individual carcinogens: e.g., with naphthylamine ($p=0.050$), benzidine ($p=0.088$), and coal tar ($p=0.079$). However, in many instances the self-reported exposure frequencies were very small.

TABLE 10-10.

Unadjusted Analyses of Followup Participants with Verified and Suspected Malignant Systemic Neoplasms in the Baseline-Followup Interval by Group

Status	Statistic	Group		Est. Relative Risk (95% C.I.)	p-Value
		Ranch Hand	Comparison		
Verified	Number of Participants/%	8 0.8%	7 0.5%	1.46 (0.53,4.03)	0.603
	Total Neoplasms	12	10		
Verified & Suspected	Number of Participants/%	12 1.2%	12 0.9%	1.28 (0.57,2.85)	0.680
	Total Neoplasms	23	16		

TABLE 10-11.

Summary of Associations Between Incidence Rates of All Malignant Systemic Neoplasms Combined and the Covariates in the Baseline-Followup Interval for Combined Followup Ranch Hand and Comparison Groups

Covariate	Verified p-Value	Verified & Suspected p-Value
Age	<0.001	0.001
Race	NS	NS
Occupation	NS*	NS
Lifetime Cigarette Smoking	NS	NS
Lifetime Alcohol Consumption	NS*	NS
Exposure to Carcinogens/Groups of Carcinogens:		
Set 1 ^a		
Asbestos	NS	NS
Non-medical X Rays	NS	0.049
Industrial Chemicals	NS	NS
Herbicides	NS	NS
Insecticides	0.014	NS*
Degreasing Chemicals	NS	NS
Set 2 ^b		
Anthracene	NS	NS
Arsenic	NS	NS*
Benzene	NS	NS
Benzidene	NS*	NS
Chromates	NS	NS
Coal Tar	NS*	NS
Creosote	NS	NS
Aminodiphenyl	NS	NS*
Chloromethyl Ether	NS	0.023
Mustard Gas	NS	NS*
Naphthylamine	0.050	0.019
Cutting Oils	NS	NS
Trichloroethylene	NS	NS
Ultraviolet Light (not sun)	NS	NS
Vinyl Chloride	NS	NS
Composite Carcinogen Exposure	NS	NS

NS*: Borderline significant (0.05 < p ≤ 0.10).

NS: Not significant (p > 0.10)

^a Questionnaire data.

^b AFHS Form 2.

The covariate associations for verified plus suspected malignant systemic neoplasms were similar to those for verified only. The association with occupation was no longer significant ($p=0.193$), and there was a significant positive association with nonmedical x-ray exposure ($p=0.049$). There were some significant and marginally significant positive associations with individual carcinogens: with naphthylamine ($p=0.019$), chloromethyl ether ($p=0.023$), arsenic ($p=0.069$), mustard gas ($p=0.090$), and aminodiphenyl ($p=0.061$) (see Appendix H, Table H-11).

The covariates used for the adjusted group contrast of the incidence rate of all malignant systemic neoplasms were race, age (continuous), occupation, and pack-years.

Adjusted Analyses

The adjusted relative risks for all verified and verified plus suspected malignant systemic neoplasms are presented in Table 10-12. For verified malignant systemic neoplasms, there was no significant difference between groups (Adj. RR: 1.51, 95% C.I.: [0.54,4.22], $p=0.434$). Age made a significant contribution to the adjustment ($p<0.001$). Parallel results for Ranch Hands contrasted with Original Comparisons are given in Table H-12 of Appendix H.

A significant group-by-occupation interaction was found in the adjusted analysis of verified plus suspected malignant systemic neoplasms ($p=0.027$). This was due to significantly more cases of malignant systemic neoplasms among Ranch Hand enlisted flyers than among corresponding Comparisons (4/175 [2 verified, 2 suspected] versus 0/209, Fisher's exact test=0.042), whereas the incidence rate for officers was lower (but not significantly) for Ranch Hands than for the corresponding Comparisons, and equivalent for the enlisted groundcrew (see Table H-13 of Appendix H). Age ($p<0.001$) and a race-by-pack-year interaction ($p=0.035$) made significant contributions to the adjustment. Comparable results were found for the contrast of Ranch Hands with the Original Comparisons (see Tables H-12 and H-14 of Appendix H).

Lifetime (Baseline and Interval)

Data from the Baseline and followup examinations were merged to obtain records of the lifetime history of neoplasm incidence for those followup participants who participated at Baseline. New participants provided lifetime information at the followup examination. Neoplasms prior to service in Southeast Asia were excluded from all analyses. All data from the Baseline study have been verified, but as described in the previous section, the status of some suspected interval neoplasms remains unclear, and thus both verified and verified plus suspected neoplasms are described and analyzed in this section.

Table 10-13 shows that 21.3 percent (216/1,016) of Ranch Hands and 16.2 percent (209/1,293) of Comparisons had skin or systemic neoplasms of some type (malignant, benign, and uncertain). The group difference in incidence rates was significant ($p=0.002$), with an estimated relative risk of 1.40 (95% C.I.: [1.13,1.73]). When suspected neoplasms were included, the contrast was less marked (22.7% [231] of Ranch Hands versus 19.3% [249] of Comparisons) but still statistically significant ($p=0.044$), with an estimated relative risk of 1.23 (95% C.I.: [1.01,1.51]).

TABLE 10-12.

Adjusted Analyses of Followup Participants for the
Incidence of All Malignant Systemic Neoplasms During the
Baseline-Followup Interval

Variable	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks
Malignant Systemic Neoplasms (Verified)	1.51 (0.54,4.22)	0.434	AGE (p<0.001)
Malignant Systemic Neoplasms (Verified & Suspected)	****	****	GRP*OCC (p=0.027) AGE (p<0.001) RACE*PACKYR (p=0.035)

****Group-by-covariate interaction--adjusted relative risk, confidence interval, and p-value not presented.

TABLE 10-13.

**Unadjusted Analyses of Followup Participants with Lifetime
Occurrence of Verified and Suspected Neoplasms by Group
(Nonblacks and Blacks)**

Site	Neoplasm Behavior and Status	Group*				Total**	p-Value***
		Ranch Hand		Comparison			
		Number**	Percent	Number**	Percent		
Skin	Malignant						
	Verified	66	6.5	66	5.1	132	0.175
	Verified and Suspected	75	7.4	85	6.6	160	0.458
	Benign						
	Verified	84	8.3	79	6.1	163	0.049
	Verified and Suspected	86	8.5	85	6.6	171	0.093
	Uncertain Behavior and Unspecified Nature:						
	Verified	1	0.1	1	0.1	2	0.999
	Verified and Suspected	1	0.1	1	0.1	2	0.999
	Any Skin Neoplasm ^a						
	Verified	150	14.8	140	10.8	290	0.005
Verified and Suspected	159	15.7	165	12.8	324	0.053	
Systemic	Malignant						
	Verified	17	1.7	17	1.3	34	0.491
	Verified and Suspected	21	2.1	22	1.7	43	0.538
	Benign						
	Verified	51	5.0	64	5.0	115	0.999
	Verified and Suspected	57	5.6	75	5.8	132	0.857
	Uncertain Behavior and Unspecified Nature:						
	Verified	15	1.5	14	1.1	29	0.453
	Verified and Suspected	15	1.5	18	1.4	33	0.862
	Any Systemic Neoplasm ^b						
	Verified	81	8.0	87	6.7	168	0.259
Verified and Suspected	91	9.0	106	8.2	197	0.548	
All	Malignant, Benign, Uncertain Behavior, Unspecified Nature ^c						
	Verified	216	21.3	209	16.2	425	0.002
	Verified and Suspected	231	22.7	249	19.3	480	0.044

*Sample sizes: 1,016 Ranch Hands, 1,293 Comparisons.

**Number of participants.

***Fisher's exact test.

^aParticipant has one or more malignant, benign, or unspecified skin neoplasm.

^bParticipant has one or more malignant, benign, or unspecified systemic neoplasm.

^cParticipant has one or more malignant or benign skin or systemic neoplasm.

Table H-15 of Appendix H is parallel to Table 10-13 for Ranch Hands and Original Comparisons only.

Lifetime Skin Neoplasms

As seen in Table 10-13, 69.4 percent (150/216) of Ranch Hands with neoplasms had skin cancer; the corresponding percentage for Comparisons was 67.0 percent (140/209). The group difference in these proportions was not significant ($p=0.604$). This contrast, when suspected neoplasms were included, was 68.8 percent (159/231) versus 66.3 percent (165/249), which again was not significant ($p=0.560$).

The overall percentage of Black and nonblack Ranch Hands with verified lifetime skin neoplasms of any type was 14.8 percent (150/1,016), versus 10.8 percent (140/1,293) for Comparisons. No Black followup participants had ever had skin neoplasms, nor did any Baseline Black participants. The overall percentage of nonblack Ranch Hands with skin neoplasms of any type was 15.7 percent (150/956) and was significantly ($p=0.006$) greater than that of the Comparisons with 11.6 percent (140/1,210). The estimated relative risk was 1.42 95% C.I.: [1.11,1.82]). When both verified and suspected neoplasms were in the analysis, the contrast was marginally significant ($p=0.060$): Ranch Hands 16.6 percent (159/956) versus Comparisons with 13.6 percent (165/1,210) (Estimated RR: 1.26, 95% C.I.: [1.00,1.60]).

For the remainder of this subsection, only malignant skin neoplasms are examined. Furthermore, the analysis was restricted to nonblacks.

The dependent variables examined were the same as those of the previous section (basal cell carcinoma, melanoma, squamous cell carcinoma, all malignant skin neoplasms combined and sun exposure-related skin malignancies).

Lifetime Malignant Skin Neoplasms

Table 10-14 presents the unadjusted analyses of the frequencies of nonblack participants in each group with lifetime occurrences of basal cell carcinoma, squamous cell carcinoma, melanoma, all malignant skin neoplasms, and the sun exposure-related skin malignancies. For completeness, the total number of malignancies of each type is also given. Table H-16 of Appendix H presents parallel analyses for Ranch Hands and Original Comparisons.

Unadjusted Analyses

There was a higher relative frequency (5.5%) of Ranch Hands who had basal cell carcinomas than of Comparisons (4.1%), but the difference was not significant ($p=0.128$). The estimated relative risk was 1.36 (95% C.I.: [0.92,2.02]). With the inclusion of suspected basal cell carcinoma, the estimated relative risk was also not significant ($p=0.579$).

Of the 53 Ranch Hands with verified basal cell carcinomas, 17 (32.1%) had 2 or more occurrences. The corresponding number for the Comparisons was 14/50 (28.0%). The group contrast of the percentages with multiple basal cell carcinomas versus no basal cell carcinomas was not significant (17/920 versus 14/1,174, $p=0.274$), nor was the corresponding contrast when suspected basal cell carcinomas were included (19/916 versus 16/1,159, $p=0.234$).

TABLE 10-14.

**Unadjusted Analyses of Nonblack Followup Participants with Lifetime Occurrence
of Verified and Suspected Malignant Skin Neoplasms by Cell Type and Group**

Cell Type	Status	Statistic**	Group*		Est. Relative Risk (95% C.I.)	p-Value		
			Ranch Hand	Comparison				
Basal Cell Carcinoma	Verified	Number/% Total Neoplasms	53 77	5.5%	50 76	4.1%	1.36 (0.92,2.02)	0.128
	Verified & Suspected	Number/% Total Neoplasms	59 88	6.2%	67 99	5.5%	1.12 (0.78,1.61)	0.579
Squamous Cell Carcinoma	Verified	Number/% Total Neoplasms	4 6	0.4%	6 7	0.5%	0.84 (0.24,3.00)	0.999
	Verified & Suspected	Number/% Total Neoplasms	4 6	0.4%	7 8	0.6%	0.72 (0.21,2.47)	0.764
Melanoma	Verified	Number/% Total Neoplasms	5 6	0.5%	5 6	0.4%	1.27 (0.37,4.39)	0.757
	Verified & Suspected	Number/% Total Neoplasms	5 6	0.5%	8 10	0.7%	0.79 (0.26,2.42)	0.784
All Malignant Skin Neoplasms	Verified	Number/% Total Neoplasms	66 100	6.9%	66 100	5.5%	1.29 (0.90,1.83)	0.175
	Verified & Suspected	Number/% Total Neoplasms	75 114	7.9%	85 129	7.0%	1.13 (0.82,1.56)	0.508
Sun-Exposure Related Malignant Neoplasms ^a	Verified	Number/% Total Neoplasms	59 87	6.2%	55 83	4.6%	1.38 (0.95,2.02)	0.100
	Verified & Suspected	Number/% Total Neoplasms	65 98	6.8%	74 111	6.1%	1.12 (0.79,1.58)	0.537

*Number of participants--956 Ranch Hands and 1,210 Comparisons.

**Number and percent of participants; total number of malignant neoplasms of specified cell type.

^aBasal cell carcinoma, melanoma, and malignant epithelial neoplasms NOS.

The frequencies of participants who had squamous cell carcinoma were very small: 4 Ranch Hands (0.4%) and 6 Comparisons (0.5%). The estimated relative risk was 0.84 (95% C.I.: [0.24,3.00]), and the contrast was far from significant ($p=0.999$). Inclusion of suspected squamous cell carcinoma did not change this finding.

The frequency of Ranch Hands who had melanoma, 5 (0.5%), was slightly greater than that of the Comparisons, 5 (0.4%), but the contrast was not significant ($p=0.757$); the estimated relative risk was 1.27 (95% C.I.: [0.37,4.39]). Inclusion of suspected melanoma inverted the relative risk to 0.79, which was again not significant. This analysis had little power due to small frequencies.

For sun exposure-related skin malignancies, there was a higher percentage of Ranch Hands than Comparisons (6.2% versus 4.6%), but the contrast was only of borderline significance ($p=0.100$); the estimated relative risk was 1.38 (95% C.I.: [0.95,2.02]). When suspected sun exposure-related skin malignancies were included, the group difference was not significant ($p=0.537$), with estimated relative risk 1.12 (95% C.I.: [0.79,1.58]).

As in the previous section, adjusted analyses were only carried out for basal cell carcinoma and the sun exposure-related skin malignancies.

Covariates

The same covariates as for the interval analysis (Table 10-5) were considered for the adjusted analysis of the lifetime incidence rates of basal cell carcinoma and sun exposure-related skin malignancies: age, occupation, history of cigarette smoking and alcohol consumption, the same host factors and average latitude, and exposure to the same recognized carcinogens. The covariates used for the adjusted analyses were the same as in the interval analysis, namely age, occupation, sun reaction index, average lifetime residential latitude, and skin color.

Covariate Associations

Table 10-15 presents details of the associations between the incidence rate of basal cell carcinoma and the following covariates: age; occupation; pack-years of smoking, lifetime drink-years; ethnic background, hair color, skin color, eye color; skin-reaction-to-sun variables, sun-reaction index; average residential latitude, and exposure to individual carcinogens and groups of carcinogens.

For the incidence of verified basal cell carcinoma, the same associations were found as in the interval analysis, namely, an increasing incidence rate with increasing age ($p<0.001$), a significant difference among occupations ($p=0.017$; officers 6.4%, enlisted flyers 4.2%, enlisted ground-crew 3.6%), and significant associations with average lifetime residential latitude ($p=0.026$), all the skin-reaction-to-sun variables ($p<0.001$ for all), the sun-reaction index ($p<0.001$), and increasing total pack-years ($p=0.024$). There was evidence of a higher incidence rate of basal cell carcinomas among the heavy drinkers, although the test for the difference among drinking categories was not significant.

TABLE 10-15.

Association Between Lifetime Incidence of Basal Cell Carcinoma and the Covariates
for Combined Followup Ranch Hand and Comparison Nonblack Participants

Covariate	Covariate Category	Total Participants	Verified			Verified and Suspected		
			Number*	Percent	p-Value	Number*	Percent	p-Value
Age	Born \geq 1942	882	21	2.4	<0.001	24	2.7	<0.001
	Born 1923-41	1,197	75	6.3		91	7.6	
	Born \leq 1922	87	7	8.1		11	12.6	
Occupation	Officer	850	54	6.4	0.017	68	8.0	0.002
	Enlisted Flyer	360	15	4.2		18	5.0	
	Enlisted Groundcrew	956	34	3.6		40	4.2	
Total Lifetime Smoking (Pack-Years)	0	616	32	5.2	0.024	37	6.0	0.010
	>0-20	998	36	3.6		43	4.3	
	>20-40	391	21	5.4		31	7.9	
	>40	157	14	8.9		15	9.6	
Total Lifetime Alcohol Consumption (Drink-Years)	0	141	7	5.0	0.548	8	5.7	0.855
	>0-5	717	37	5.2		43	6.0	
	>5-30	655	29	4.4		34	5.2	
	>30-100	479	19	4.0		30	6.3	
	>100	104	8	7.7		8	7.7	
Ethnic Background ^a	A	1,582	85	5.4	0.132	107	6.8	0.016
	B	424	16	3.8		16	3.8	
	C	63	1	1.6		1	1.6	
	D	42	0	0.0		0	0.0	
Skin Color	Dark	1	0	0.0	0.339	0	0.0	0.263
	Medium	73	2	2.7		2	2.7	
	Pale	308	9	2.9		11	3.6	
	Dark Peach	1,262	69	5.5		82	6.5	
	Pale Peach	520	23	4.4		31	6.0	

TABLE 10-15. (continued)

Association Between Lifetime Incidence of Basal Cell Carcinoma and the Covariates
for Combined Followup Ranch Hand and Comparison Nonblack Participants

Covariate	Covariate Category	Total Participants	Verified			Verified and Suspected		
			Number*	Percent	p-Value	Number*	Percent	p-Value
Eye Color	Brown	645	30	4.7	0.338	35	5.4	0.853
	Hazel	455	29	6.4		30	6.6	
	Green	119	3	2.5		6	5.0	
	Grey	93	5	5.4		7	7.5	
	Blue	850	36	4.2		48	5.7	
Hair Color	Black	439	20	4.6	0.278	24	5.5	0.120
	Dark Brown	1,038	42	4.1		53	5.1	
	Light Brown	563	32	5.7		38	6.8	
	Red	16	2	12.5		3	18.8	
	Blond	108	7	6.5		8	7.4	
Residential History (Average Latitude)	≥37°	1,136	43	3.8	0.026	51	4.5	0.006
	<37°	1,022	60	5.9		75	7.3	
Skin Reaction to First 30 Min. of Sun Exposure	Burns	247	21	8.5	<0.001	25	10.1	<0.001
	Usually Burns	429	36	8.4		44	10.3	
	Burns Mildly	805	29	3.6		32	4.0	
	Rarely Burns	681	16	2.4		24	3.5	
Skin Reaction to >2 Hrs of Sun After First Exposure	Burns Painfully	120	9	7.5	<0.001	11	9.2	0.001
	Burns	338	31	9.2		33	9.8	
	Becomes Red	1,043	42	4.0		54	5.2	
	No Reaction	663	21	3.2		28	4.2	
Skin Reaction After Repeated Exposure to Sun	Freckles, No Tan	45	4	8.9	<0.001	5	11.1	<0.001
	Tans Mildly	314	31	9.9		36	11.5	
	Tans Moderately	1,019	37	3.6		47	4.6	
	Tans Deep Brown	783	30	3.8		37	4.7	

TABLE 10-15. (continued)

Association Between Lifetime Incidence of Basal Cell Carcinoma and the Covariates
for Combined Followup Ranch Hand and Comparison Nonblack Participants

Covariate	Covariate Category	Total Participants	Verified			Verified and Suspected		
			Number*	Percent	p-Value	Number*	Percent	p-Value
Sun Reaction Index	Tends to Burn	145	10	6.9	<0.001	12	8.3	<0.001
	Mild Reaction	454	41	9.0		46	10.1	
	Tends to Tan	1,562	51	3.3		67	4.3	
Exposures to Carcinogens	Asbestos	Yes	458	18	0.389	25	5.5	0.822
		No	1,708	85		5.0		
	Nonmedical X Rays	Yes	494	29	0.187	37	7.5	0.080
		No	1,672	74		4.4		
	Industrial Chemicals	Yes	1,126	49	0.365	60	5.3	0.314
		No	1,040	54		5.2		
	Herbicides	Yes	1,261	65	0.357	81	6.4	0.164
		No	905	38		4.2		
	Insecticides	Yes	1,313	69	0.181	82	6.3	0.303
		No	853	34		4.0		
	Degreasing Chemicals	Yes	1,261	60	0.999	72	5.7	0.852
		No	905	43		4.8		
Composite Carcinogen Exposure		Yes	489	21	0.716	24	4.9	0.379
		No	1,653	80		4.8		

TABLE 10-15. (continued)

Association Between Lifetime Incidence of Basal Cell Carcinoma and the Covariates
for Combined Followup Ranch Hand and Comparison Nonblack Participants

Covariate	Covariate Category	Total Participants	Verified			Verified and Suspected			
			Number*	Percent	p-Value	Number*	Percent	p-Value	
Exposure to Individual Carcinogens	Anthracene	Yes	2	0	0.0	0.999	0	0.0	0.999
		No	2,161	103	4.8		126	5.8	
	Arsenic	Yes	41	4	9.8	0.124	5	12.2	0.084
		No	2,124	98	4.6		120	5.7	
	Benzene	Yes	74	6	8.1	0.162	7	9.5	0.198
		No	2,091	97	4.6		119	5.7	
	Benzidine	Yes	11	1	9.1	0.416	1	9.1	0.484
		No	2,154	102	4.7		125	5.8	
	Chromates	Yes	84	4	4.8	0.999	5	6.0	0.812
		No	2,079	97	4.7		119	5.7	
	Coal Tar	Yes	68	2	2.9	0.770	3	4.4	0.795
		No	2,097	101	4.8		123	5.9	
	Creosote	Yes	159	9	5.7	0.560	10	6.3	0.726
		No	2,007	94	4.7		116	5.8	
	Aminodiphenyl	Yes	6	0	0.0	0.999	0	0.0	0.999
		No	2,157	102	4.7		125	5.8	
	Chloromethyl Ether	Yes	21	2	9.5	0.264	2	9.5	0.348
		No	2,142	101	4.7		124	5.8	
Mustard Gas	Yes	6	0	0.0	0.999	0	0.0	0.999	
	No	2,159	103	4.8		126	5.8		

TABLE 10-15. (continued)

Association Between Lifetime Incidence of Basal Cell Carcinoma and the Covariates
for Combined Followup Ranch Hand and Comparison Nonblack Participants

Covariate	Covariate Category	Total Participants	Verified			Verified and Suspected		
			Number*	Percent	p-Value	Number*	Percent	p-Value
Exposure to Individual Carcinogens (continued)	Naphthylamine	Yes 52	3	5.8	0.734	4	7.7	0.540
		No 2,112	99	4.7		121	5.7	
	Cutting Oils	Yes 226	12	5.3	0.622	15	6.6	0.549
		No 1,939	91	4.7		111	5.7	
	Trichloroethylene	Yes 184	5	2.7	0.207	7	3.8	0.253
		No 1,979	98	5.0		119	6.0	
	Ultraviolet Light	Yes 44	5	11.4	0.055	5	11.4	0.179
		No 2,120	98	4.6		121	5.7	
	Vinyl Chloride	Yes 31	0	0.0	0.399	1	3.2	0.999
		No 2,133	103	4.8		125	5.9	

*Number of participants with basal cell carcinomas.

*Ethnic Background:

- A - English, Welsh, Scottish, Irish
- B - Scandinavian, German, Polish, Russian, Other Slavic, Jewish, French
- C - Spanish, Italian, Greek.
- D - Mexican, American Indian, Asian.

There was a significant ($p < 0.001$) association with the sun-reaction index. Participants with the most sensitive skin had a somewhat lower rate (6.9%) of verified basal cell carcinoma lifetime than the participants in the next most sensitive category (9.0%), although the difference was not as marked as in the Baseline-followup interval. However, the rate for those who tanned easily was much lower (3.3%) than for those who did not. A marginally significant positive association was found with self-reported exposure to non-sun ultraviolet light ($p = 0.055$).

The results were similar for the verified plus suspected basal cell carcinomas. There was a significant ($p = 0.016$) difference among ethnic backgrounds, with participants with Celtic or English backgrounds having higher incidence rates than those with other backgrounds. Further, there were marginally significant positive associations in incidence rates with non-medical x-ray exposure ($p = 0.080$) and arsenic ($p = 0.084$), a recognized skin carcinogen, but the association with ultraviolet light was not significant.

The details of associations between the incidence rates of verified and suspected sun exposure-related skin malignancies and the covariates are given in Appendix H, Table H-17. The significant covariates for verified conditions were age ($p < 0.001$), occupation ($p = 0.009$), total pack-years ($p = 0.021$), average latitude ($p = 0.026$), and sun-reaction index ($p < 0.001$). The same pattern held for verified plus suspected sun exposure-related skin malignancies. There was a marginally significant positive association with ultraviolet light exposure ($p = 0.078$) for the verified conditions only, and with herbicide exposure ($p = 0.076$) for the verified plus suspected conditions.

The covariates chosen for the adjusted analysis were age, occupation, skin color, average lifetime residential latitude and the sun-reaction index.

Adjusted Analysis

The results of adjusted analyses of group contrasts for lifetime skin malignancies are given in Table 10-16. There was significant evidence of a higher incidence rate of verified basal cell carcinoma in the Ranch Hand group as contrasted with the Comparisons ($p = 0.035$). The adjusted relative risk was 1.56 (95% C.I.: [1.03, 2.37]). A sun-reaction index-by-average latitude interaction ($p = 0.026$), a skin color-by-sun-reaction index interaction ($p < 0.001$), and an occupation-by-age interaction ($p = 0.047$) made significant contributions to the model. The adjustment by average residential latitude, which is greater for Ranch Hands than Comparisons, contributed to a higher relative risk resulting from the adjusted analysis than from the unadjusted (see Table 10-14). When suspected basal cell carcinomas were included in the analysis, a significant group-by-sun-reaction index interaction ($p = 0.040$) was found. Age ($p < 0.001$), a skin color-by-average residential latitude ($p = 0.024$), and a skin color-by-sun-reaction index interaction ($p < 0.001$) made significant contributions to the adjustment. This was due to a significant increase in basal cell carcinoma incidence for Ranch Hands with an intermediate skin reaction to sun over similar Comparisons (Adj. RR: 1.97, 95% C.I.: [1.04, 3.73], $p = 0.038$) (Appendix H, Table H-18).

Similar results were found in the contrast of Ranch Hand versus Original Comparisons (Table H-19). Namely, for verified basal cell carcinoma, and for verified plus suspected basal cell carcinomas, significant group-by-sun-reaction index interactions were found ($p = 0.010$ and $p = 0.003$, respectively [see Table H-20 for additional details on the interactions]).

TABLE 10-16.

Adjusted Analyses of Nonblack Followup Participants for
Lifetime Malignant Skin Neoplasm Incidence

Variable	Status	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks
Basal Cell Carcinoma	Verified	1.56 (1.03,2.37)	0.035	SKIN*SUNREAC (p<0.001) OCC*AGE (p=0.047) SUNREAC*LAT (p=0.026)
	Verified & Suspected	****	****	AGE (p<0.001) GRP*SUNREAC (p=0.040) SKIN*LAT (p=0.024) SKIN*SUNREAC (P<0.001)
Malignant Sun-Exposure Skin Neoplasms	Verified	1.54 (1.04,2.29)	0.030	AGE (p<0.001) SKIN*LAT (p=0.016) SKIN*SUNREAC (p<0.001)
	Verified & Suspected	1.23 (0.86,1.77)	0.252	AGE (p<0.001) SKIN*LAT (p=0.013) SKIN*SUNREAC (p<0.001)

****Group-by-covariate interaction--adjusted relative risk, confidence interval, and p-value not presented.

As shown in Table 10-16, there was a significantly higher incidence rate of sun exposure-related skin malignancies among Ranch Hands as contrasted with Comparisons (Adj. RR: 1.54, 95% C.I.: [1.04,2.29], $p=0.030$). Significant contributions were noted for age ($p<0.001$), a skin color-by-sun-reaction index interaction ($p<0.001$), and an average latitude-by-skin color interaction ($p=0.016$). When suspected sun exposure-related skin malignancies were included in the analysis, the adjusted relative risk became 1.23 (95% C.I.: [0.86,1.77]) and was no longer significant ($p=0.252$). Age ($p<0.001$), a skin color-by-sun-reaction index interaction ($p<0.001$), and average latitude-by-skin color interaction ($p=0.013$) contributed significantly to the adjustment. When Ranch Hands were contrasted to Original Comparisons, significant group-by-sun reaction index interactions were found for verified, and verified plus suspected, sun-exposure related skin neoplasms ($p=0.045, p=0.016$, respectively). These interactions were due to significant relative risks for those participants with intermediate reactions of skin to sun, as was also found for basal cell carcinomas only (see Appendix Tables H-19 and H-20 for details).

Lifetime Systemic Neoplasms

Table 10-13 shows that 81 (8.0%) Ranch Hands and 87 (6.7%) Comparisons had a verified history of systemic neoplasms of any type (malignant, benign, or uncertain). The estimated relative risk was 1.20 (95% C.I.: [0.88,1.65]), and was not significant ($p=0.259$). With the inclusion of suspected systemic neoplasms, the frequencies were 9.0 percent (91/1,016) for Ranch Hands and 8.2 percent (106/1,293) for Comparisons, with an estimated relative risk of 1.10 (95% C.I.: [0.82,1.48]), and the contrast was also not significant ($p=0.548$).

For Ranch Hands with systemic neoplasms of any type, the percentage with malignant neoplasms was 21.0 percent (17/81) and the corresponding rate for Comparisons was 19.5 percent (17/87), a nonsignificant group difference ($p=0.849$). Including suspected systemic malignancies, these frequencies were 23.1 percent (21/91) for Ranch Hands and 20.8 percent (22/106) for Comparisons. Again, the group difference was not significant ($p=0.731$).

For the remainder of this section, only malignant systemic neoplasms are discussed.

Lifetime Malignant Systemic Neoplasms

Table 10-17 presents the frequencies of verified lifetime malignant systemic neoplasms by site. Three Ranch Hands versus no Comparisons had malignant neoplasms of the oral cavity and pharynx; these occurred at ages 45, 52, and 57. The group difference in incidence rate was marginally significant ($p=0.085$). No Ranch Hands but 5 Comparisons had malignant neoplasms of the colon; the group difference in incidence rate was also marginally significant ($p=0.072$). Three Ranch Hands but no Comparisons had testicular malignancies, but the group difference in incidence rates was only marginally significant ($p=0.085$). These occurred at ages 35, 38, and 54. The suspected malignant neoplasms are listed in Table 10-9. Table H-21 of Appendix H gives a list of verified lifetime malignant systemic neoplasms for Ranch Hands and Original Comparisons.

TABLE 10-17.

**Summary of Followup Participants With Lifetime
Incidence of Verified Malignant Systemic Neoplasms by Group**

Site	Group		Total
	Ranch Hand	Comparison	
Eye	1	0	1
Oral Cavity and Pharynx	3 ^{a, b}	0	3
Larynx	0	1	1
Thyroid Gland	0	2	2
Esophagus	0	1 ^c	1
Bronchus and Lung	2	0	1
Colon	0	5 ^{d, e}	5
Kidney and Bladder	4	3	7
Prostate	2	2	4
Testicles	3	0	3
Connective and Other Soft Tissue	1	1	2
Hodgkin's Disease	0	1	1
Ill-Defined Sites	1 ^f	1 ^g	2
Total	17	17	34

^aIncludes one Ranch Hand with separate malignancies of tongue and epiglottis and also malignant neoplasm of bone.

^bIncludes one Ranch Hand with separate malignant neoplasms of tongue and oropharynx and secondary malignant neoplasm of other site.

^cAlso has malignant neoplasm of bone.

^dIncludes one Comparison with secondary malignant neoplasms of liver and bone and bone marrow.

^eIncludes one Comparison with secondary malignant neoplasm of liver.

^fMalignant neoplasm of thorax.

^gMalignant neoplasm of face, head, or neck.

One Ranch Hand and one Comparison had neoplasms of connective and other soft tissue. The Comparison had a fibrosarcoma at age 28 (reported at Baseline) and the Ranch Hand participant had malignant fibrous histiocytoma at age 63 (reported at followup). Both of these conditions are classified as soft tissue sarcoma.

Since soft tissue sarcoma and malignant neoplasms of the lymphatic system are of concern in this study, the occurrences of these malignancies are shown by group in Table 10-18. The occurrences of these four malignancies are too small to support further statistical analysis.

TABLE 10-18.

Summary of Followup Participants with Lifetime Soft Tissue Sarcoma, Leukemia or Lymphoma by Group

Site	Group	
	Ranch Hand	Comparison
Verified Soft Tissue Sarcoma	1	1
Verified Hodgkin's Disease	0	1
Suspected Leukemia, Hodgkin's Disease, or non-Hodgkin's Lymphoma	1	0

Unadjusted Analysis

Table 10-19 shows the results of unadjusted analyses of the frequencies of participants in each group with verified or verified plus suspected malignant systemic neoplasms combined. The estimated relative risk for all malignant systemic neoplasms was 1.28 (95% C.I.: 0.65,2.51) and was not significant (p=0.491). With the inclusion of suspected malignant neoplasms, the estimated relative risk was 1.22 (95% C.I.: 0.67,2.23) and was also not significant (p=0.538). Similar nonsignificant results were found for Ranch Hands contrasted with Original Comparisons (see Table H-22 of Appendix H).

Covariates

The same covariates used for the interval history of malignant systemic neoplasms were used for the adjusted analysis of lifetime malignant systemic neoplasms, namely, age, race, occupation, history of cigarette smoking and alcohol consumption, and exposure to carcinogens. Total smoking and alcohol consumption were estimated up to the followup examination, and may be different if estimated only up to the year of diagnosis of a neoplasm (if any). Further, age at followup rather than age at diagnosis was used in the analysis.

TABLE 10-19.

**Unadjusted Analyses of Lifetime Incidence Rates
of All Malignant Systemic Neoplasms Combined, by Group**

Status	Statistic	Group		Est. Relative Risk (95% C.I.)	p-Value
		Ranch Hand	Comparison		
Verified	Number of Participants/% Total Neoplasms	17 1.7%	17 1.3%	1.28 (0.65, 2.51)	0.491
		25	22		
Verified & Suspected	Number of Participants/% Total Neoplasms	21 2.1%	22 1.7%	1.22 (0.67, 2.23)	0.538
		36	27		

Covariate Associations

Associations between the incidence rate of all malignant systemic neoplasms combined and the covariates are presented in Table 10-20. For verified malignant systemic neoplasms, strong associations were found with increasing age ($p < 0.001$) and occupation (officers 2.3%, enlisted flyers 1.3%, and enlisted groundcrew 0.9%, $p = 0.028$). These same associations were also found for verified plus suspected systemic malignancies. The association with smoking history was not significant, either for verified or for verified plus suspected malignancies. The incidence rate of all malignant systemic neoplasms increased marginally significantly ($p = 0.073$) with increasing levels of total lifetime alcohol consumption. For verified plus suspected malignancies, the difference among drink-year categories was also marginally significant ($p = 0.080$). No significant association was found with the composite carcinogen exposure variable. A significant association was found between the incidence of verified malignant systemic neoplasms and naphthylamine ($p = 0.048$). There was a significant positive association between the verified plus suspected conditions and naphthylamine ($p = 0.019$), and a marginally significant association with chloromethyl ether ($p = 0.067$).

The covariates used for the adjusted analysis of the incidence of malignant systemic neoplasms were race, age (continuous), occupation, pack-years, drink-years, and the composite carcinogen-exposure variable.

Adjusted Analysis

Table 10-21 shows that, in the adjusted analysis of the group contrast in incidence of all systemic malignancies combined, there was a significant group-by-occupation interaction ($p = 0.023$). This was due to a difference in rates for the enlisted flyers, 5 Ranch Hands versus 0 Comparisons (unadjusted p -value = 0.019), whereas the incidence rates for officers and enlisted groundcrew did not differ significantly between groups ($p = 0.698$ and 0.922 , respectively) (Table H-23). Age made a significant contribution to the adjustment. When suspected systemic malignancies were combined with the verified systemic malignancies, a group-by-occupation interaction ($p = 0.002$)

TABLE 10-20.

**Association Between Lifetime Incidence of All Malignant
Systemic Neoplasms Combined and the Covariates for Combined
Followup Ranch Hand and Comparison Participants**

Covariate	Category	Total Participants	Verified			Verified and Suspected		
			Number*	Percent	p-Value	Number*	Percent	p-Value
Age	Born ≥1942	961	4	0.4	<0.001	7	0.7	<0.001
	Born 1923-41	1,261	24	1.9		30	2.4	
	Born ≤1922	87	6	6.9		6	6.9	
Race	Nonblack	2,166	34	1.6	0.267	42	1.9	0.517
	Black	143	0	0.0		1	0.7	
Occupation	Officer	864	20	2.3	0.028	23	2.7	0.069
	Enlisted Flyer	387	5	1.3		7	1.8	
	Enlisted Groundcrew	1,058	9	0.9		13	1.2	
Total Lifetime Smoking (Pack-Years)	0	658	6	0.9	0.237	8	1.2	0.324
	>0-20	1,081	15	1.4		20	1.9	
	>20-40	406	9	2.2		11	2.7	
	>40	158	4	2.5		4	2.5	
Total Lifetime Alcohol Consumption (Drink-Years)	0	151	1	0.7	0.073	2	1.3	0.080
	>0-5	760	7	0.9		10	1.3	
	>5-30	703	8	1.1		10	1.4	
	>30-100	508	11	2.2		13	2.6	
	>100	108	4	3.7		5	4.6	

TABLE 10-20. (continued)

Association Between Lifetime Incidence of All Malignant Systemic Neoplasms Combined and the Covariates for Combined Followup Ranch Hand and Comparison Participants

Covariate	Category	Total Participants	Verified				Verified and Suspected		
			Number*	Percent	p-Value	Number*	Percent	p-Value	
Exposures to Carcinogens	Asbestos	499	Yes	5	1.0	0.405	7	1.4	0.459
		1,810	No	29	1.6				
	Nonmedical X Rays	541	Yes	9	1.7	0.684	14	2.6	0.150
		1,768	No	25	1.4				
	Industrial Chemicals	1,199	Yes	14	1.2	0.229	20	1.7	0.539
		1,110	No	20	1.8				
	Herbicides	1,339	Yes	18	1.3	0.601	23	1.7	0.538
		970	No	16	1.7				
	Insecticides	1,389	Yes	17	1.2	0.223	23	1.7	0.432
		920	No	17	1.9				
	Degreasing Chemicals	1,343	Yes	18	1.3	0.600	26	1.9	0.876
		966	No	16	1.7				
Composite Carcinogen Exposure	519	Yes	7	1.4	0.999	8	1.5	0.711	
	1,762	No	27	1.5					34

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TABLE 10-20. (continued)

Association Between Lifetime Incidence of All Malignant Systemic Neoplasms Combined and the Covariates for Combined Followup Ranch Hand and Comparison Participants

Covariate	Category	Total Participants	Verified			Verified and Suspected			
			Number*	Percent	p-Value	Number*	Percent	p-Value	
Exposure to Individual Carcinogens	Anthracene	2	Yes	0	0.0	0.999	0	0.0	0.999
		2,303	No	34	1.5		43	1.9	
	Arsenic	42	Yes	0	0.0	0.999	2	4.8	0.183
		2,266	No	34	1.5		41	1.8	
	Benzene	83	Yes	2	2.4	0.348	2	2.4	0.666
		2,225	No	32	1.4		41	1.8	
	Benzidine	14	Yes	1	7.1	0.188	1	7.1	0.227
		2,293	No	33	1.4		41	1.8	
	Chromates	88	Yes	2	2.3	0.375	2	2.3	0.679
		2,218	No	32	1.4		41	1.9	
	Coal Tar	73	Yes	2	2.7	0.292	2	2.7	0.397
		2,235	No	32	1.4		41	1.8	
Creosote	164	Yes	2	1.2	0.999	4	2.4	0.543	
	2,145	No	32	1.5		39	1.8		
Aminodiphenyl	6	Yes	0	0.0	0.999	1	16.7	0.107	
	2,300	No	34	1.5		42	1.8		
Chloromethyl Ether	23	Yes	1	4.4	0.291	2	8.7	0.067	
	2,282	No	33	1.5		41	1.8		
Mustard Gas	9	Yes	0	0.0	0.999	1	11.1	0.156	
	2,299	No	34	1.5		42	1.8		

TABLE 10-20. (continued)

Association Between Lifetime Incidence of All Malignant Systemic Neoplasms Combined and the Covariates for Combined Followup Ranch Hand and Comparison Participants

Covariate	Category	Total Participants	Verified			Verified and Suspected		
			Number*	Percent	p-Value	Number*	Percent	p-Value
Exposure to Individual Carcinogens (continued)	Naphthylamine	56	Yes 3	5.4	0.048	4	7.1	0.019
		2,251	No 31	1.4			39	
	Cutting Oils	243	Yes 5	2.1	0.396	7	2.9	0.209
		2,065	No 29	1.4			36	
	Trichloroethylene	200	Yes 5	2.5	0.211	6	3.0	0.264
		2,106	No 29	1.4			37	
	Ultraviolet Light	51	Yes 1	2.0	0.535	1	2.0	0.621
		2,256	No 33	1.5			42	
	Vinyl Chloride	33	Yes 0	0.0	0.999	1	3.0	0.465
		2,273	No 34	1.5			42	

*Number of participants with malignant systemic neoplasms.

TABLE 10-21.

Adjusted Analyses for Lifetime Incidence of All
Malignant Systemic Neoplasms Combined

Variable	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks
Systemic Malignancies (Verified)	****	****	GRP*OCC (p=0.023) AGE (p<0.001)
Systemic Malignancies (Verified & Suspected)	****	****	GRP*OCC (p=0.002) AGE (p<0.001) RACE*PACKYR (p=0.032)

****Group-by-covariate interaction--adjusted relative risk, confidence interval, and p-value not presented.

was also found; this was also due to the high rates for the Ranch Hand enlisted flyers.

Comparison of Baseline, Interval, and Lifetime Results

Table 10-22 compares the unadjusted and adjusted contrasts from the Baseline report with those from the Baseline-followup interval and the whole post-SEA period, for the incidence of all verified malignant skin neoplasms combined, verified basal cell carcinomas, and all verified malignant systemic neoplasms combined. There were, of course, differences in the Baseline and followup cohorts, but there was a sufficiently large overlap to make such a comparative tabulation useful.

Malignant Skin Neoplasms

The significant relative risks for all malignant skin neoplasms seen at Baseline were not evident for the Baseline-followup interval. However, for lifetime basal cell carcinoma, a significant adjusted group contrast was found (p=0.035). The difference in the incidence rates of all skin neoplasms and in basal cell carcinomas only between the Ranch Hands and the Comparisons appears to have decreased over time, as evidenced by the fact that the interval estimated and adjusted relative risks were closer to 1 than those for the lifetime, i.e., interval plus Baseline period.

Malignant Systemic Neoplasms

The unadjusted group contrasts in incidence rates of all malignant systemic neoplasms combined were not significant for Baseline, for the Baseline-followup interval, or for lifetime (Baseline plus interval), nor was the adjusted group contrast for the Baseline-followup interval. The

TABLE 10-22.

Unadjusted and Adjusted Analyses of the Incidence of All Verified Malignant Skin
and Systemic Neoplasms and Basal Cell Carcinoma:
Baseline, Baseline-Followup Interval, and Lifetime Occurrence

Site	Statistic	Baseline ^a		Baseline-Followup Interval ^b		Lifetime Occurrence ^b	
All Malignant Skin Neoplasms	Number of Participants with Neoplasms/Percent: ^c						
	Ranch Hand	35	3.3%	37	3.9%	66	6.9%
	Comparison	25	2.0%	40	3.3%	66	5.4%
	Est. RR/p-Value	1.62	(0.07) ^d	1.18	(0.486) ^e	1.29	(0.175) ^e
	Adj. RR/p-Value	—*	—*	—*	—*	—*	—*
Basal Cell Carcinoma	Number of Participants with Neoplasms/Percent: ^c						
	Ranch Hand	31	3.0%	29	3.0%	53	5.5%
	Comparison	21	1.7%	30	2.5%	50	4.1%
	Est. RR/p-Value	1.71	(0.047) ^d	1.23	(0.429) ^e	1.36	(0.128) ^e
	Adj. RR/p-Value	—*	—*	****	****	1.56	(0.035)
All Malignant Systemic Neoplasms	Number of Participants with Neoplasms/Percent: ^f						
	Ranch Hand	13	1.2%	8	0.8%	17	1.7%
	Comparison	11	0.9%	7	0.5%	17	1.3%
	Est. RR/p-Value	1.35	(0.46) ^d	1.46	(0.603) ^e	1.28	(0.491) ^e
	Adj. RR/p-Value	—*	—*	1.51	(0.434)	****	****

—*Analysis not done

^aBaseline participants: 1,045 Ranch Hands, 1,224 Comparisons.

^bFollowup participants: 1,016 Ranch Hands, 1,293 Comparisons.

^cNonblacks only for followup participants (956 Ranch Hands, 1,210 Comparisons), both nonblacks and Blacks for Baseline participants.

^dChi-square test.

^eFisher's exact test.

^fAll participants.

****Group-by-covariate interaction.

estimated lifetime relative risk appears closer to 1 than for the two intervals separately, but the small number of occurrences and intervening mortality preclude more definitive statements.

Baseline Participants

This brief section summarizes the mortality and malignant neoplasm history of the fully compliant Baseline participants in the interval up to the followup examination. Mortality information up through the end of 1985 was considered. This discussion is directed to the question of whether competing mortality affected the preceding analysis of incident cancers among living participants.

Of the 1,045 Ranch Hands and 1,224 Comparisons who were fully compliant at Baseline, 971 Ranch Hands and 1,139 Comparisons returned to the followup examination. Table 10-23 presents the numbers of Baseline participants according to whether they completed the followup examination and whether they were alive at the end of 1985.

TABLE 10-23.

Fully Compliant Baseline Participants by Status at Followup Examination and Group

Participated in Followup Examination	Status	Group		Total
		Ranch Hand	Comparison	
Yes	Dead ^a	3	2	5
	Alive	968	1,137	2,105
No	Dead	9	15	24
	Alive	65	70	135
Total		1,045	1,224	2,269

^aDied in 1985, but subsequent to participation in the examination.

For the participants who did not return for the followup examination, Table 10-24 shows that 2 of the 9 deaths among Ranch Hands were due to malignant neoplasms, compared with 5 of the 15 deaths among the Comparisons. One Ranch Hand who died had a malignant skin neoplasm, but this was not the primary cause of death. Among the 65 Ranch Hands who did not return for the followup examination, 5 had verified malignant neoplasms at Baseline, including 1 systemic neoplasm (of the kidney), as contrasted with 2 among 70 Comparisons who had verified malignant (skin) neoplasms. Thus, among the 74 Ranch Hands not returning for followup, there were 8 with incident or fatal neoplasms, as compared to 7 of 85 Comparisons; the group difference was not significant ($p=0.788$).

TABLE 10-24.

Fully Compliant Baseline Participants
Who Did Not Participate in Followup Examination
by Status and Group

Status	Group		Total
	Ranch Hand	Comparison	
Dead--Primary Cause of Death:			
Malignant Neoplasm	2 ^a	5 ^b	7
Other Causes	7 ^c	10	17
Lost to Followup:			
Verified Malignant Neoplasm at Baseline	5 ^d	2 ^e	7
No Malignant Neoplasm at Baseline	60	68	128

^aBoth with lung cancer.

^bThree with lung cancer, one with malignant neoplasm of intestine (location unspecified), one with malignant neoplasm of an ill-defined site (face, head, or neck).

^cIncludes one Ranch Hand with malignant skin neoplasm.

^dFour with malignant skin neoplasms, one with malignant systemic neoplasm (kidney).

^eTwo with malignant skin neoplasms.

For the participants who did return for the followup examination, Table 10-25 gives the frequencies and percentages of the respective group totals according to neoplasm status at Baseline and at followup. Analysis showed that there was no significant group difference ($p=0.115$) in the pattern of neoplasm incidence at Baseline and/or at followup.

The results of this section show approximate equivalence between the groups for the disease of cancer (fatal or nonfatal) since Baseline, and in the proportions of participants with malignancies at Baseline, followup, or both.

EXPOSURE INDEX ANALYSES

Unadjusted and adjusted exposure index analyses were conducted within each occupational cohort of the Ranch Hand group (see Chapter 8 for details on the exposure index). Interval and lifetime occurrences of basal cell carcinomas, sun-exposure related malignant skin neoplasms, and malignant systemic neoplasms were examined. As was done in the core analyses, verified conditions and verified plus suspected malignancies were each investigated. Blacks were excluded from all malignant skin neoplasm analyses. Group contrasts in incidence rates of malignant skin neoplasms were adjusted for the covariates of age, sun reaction index, and average residential latitude. Adjusted analyses for malignant systemic neoplasms accounted for the effects of age and race.

For each dependent variable, exposure level frequencies and percentages are presented in Appendix Tables H-26 and H-27, for interval and lifetime, respectively, along with the results of the unadjusted analyses. Pearson's chi-square test was used to reflect overall exposure index differences, and Fisher's exact test was used to investigate medium versus low and high versus low exposure level contrasts. Results of the adjusted analyses are presented in Tables 10-26 and 10-27, for interval and lifetime, respectively. These results are presented in the context of a main effects model containing exposure index and all adjusting covariates.

Several significant or marginally significant overall results were found. None was suggestive of a strictly increasing dose response effect; in fact, most showed decreasing incidence rates with increasing exposure.

Among officers, in the unadjusted interval analysis, significant or marginally significant results were found among nonblacks for verified and suspected basal cell carcinomas (overall $p=0.042$), sun-exposure related malignant skin neoplasms (verified: overall $p=0.096$, verified plus suspected: overall $p=0.021$), and among Blacks and nonblacks for verified plus suspected malignant systemic neoplasms (overall $p=0.081$). These findings were primarily due to higher percentages of malignancies in the medium exposure level than in the high or low categories for each variable (see Appendix Table H-26 for frequencies). The corresponding adjusted analyses were nonsignificant for basal cell carcinoma (overall $p=0.156$), verified sun-exposure malignancies (overall $p=0.272$), and systemic malignant neoplasms (overall $p=0.109$). The adjusted results were marginally significant for verified plus suspected sun-exposure malignancies (overall $p=0.095$).

TABLE 10-25.

Fully Compliant Baseline Participants Also
in Followup Examination by Malignant Neoplasm Status

Malignant Neoplasm at Baseline	Malignant Neoplasm at Followup	Group				Total
		Ranch Hand		Comparison		
		Number	Percent	Number	Percent	
Yes	Yes	10	1.0	15	1.3	25
	No	37	3.8	28	2.5	65
No	Yes	36	3.7	31	2.7	67
	No	888 ^a	91.5	1,065 ^a	93.5	1,953
Total		971		1,139		2,110

^aIncludes three Ranch Hands and two Comparisons who died after followup.

TABLE 10-26.

Adjusted Exposure Index Analysis for Followup Participants for occurrence of Malignant Neoplasms in the Baseline-Followup Interval

Variable	Occupation	Exposure Index			Contrast	Adj. Relative Risk (95% C.I.)	p-Value
		Low Total*	Medium Total*	High Total*			
Basal Cell ^a Carcinoma (Verified Only)	Officer	124	127	121	Overall		0.415
					M vs. L	2.02 (0.50,8.10)	0.320
					H vs. L	0.91 (0.18,4.68)	0.908
	Enlisted Flyer	54	61	51	Overall		0.080
					M vs. L	0.35 (0.05,2.20)	0.261
					H vs. L	0.11 (0.01,1.10)	0.061
	Enlisted Groundcrew	138	149	129	Overall		0.346
					M vs. L	0.51 (0.07,3.53)	0.496
					H vs. L	0.19 (0.02,2.14)	0.179
Basal Cell ^a Carcinoma (Verified and Suspected)	Officer	124	127	121	Overall		0.156
					M vs. L	2.40 (0.73,7.88)	0.149
					H vs. L	0.91 (0.22,3.76)	0.892
	Enlisted Flyer	54	61	51	Overall		0.080
					M vs. L	0.35 (0.05,2.20)	0.261
					H vs. L	0.11 (0.01,1.10)	0.061
	Enlisted Groundcrew	138	149	129	Overall		0.165
					M vs. L	0.36 (0.06,2.25)	0.274
					H vs. L	0.14 (0.01,1.44)	0.098

TABLE 10-26. (continued)

Adjusted Exposure Index Analysis for Followup Participants for Occurrence of Malignant Neoplasms in the Baseline-Followup Interval

Variable	Occupation	Exposure Index			Contrast	Adj. Relative Risk (95% C.I.)	p-Value
		Low Total*	Medium Total*	High Total*			
Sun-Exposure ^a Related Malignancies (Verified Only)	Officer	124	127	121	Overall		0.272
					M vs. L	2.38 (0.61,9.30)	0.214
					H vs. L	0.95 (0.18,4.88)	0.949
	Enlisted Flyer	54	61	51	Overall		0.080
					M vs. L	0.35 (0.05,2.20)	0.261
					H vs. L	0.11 (0.01,1.10)	0.061
	Enlisted Groundcrew	138	149	129	Overall		0.767
					M vs. L	0.83 (0.15,4.55)	0.826
					H vs. L	0.50 (0.07,3.39)	0.481
Sun-Exposure ^a Related Malignancies (Verified and Suspected)	Officer	124	127	121	Overall		0.095
					M vs. L	2.68 (0.83,8.67)	0.100
					H vs. L	0.93 (0.22,3.86)	0.921
	Enlisted Flyer	54	60	51	Overall		0.080
					M vs. L	0.35 (0.05,2.20)	0.261
					H vs. L	0.11 (0.01,1.10)	0.061
	Enlisted Groundcrew	138	149	129	Overall		0.514
					M vs. L	0.59 (0.12,2.94)	0.519
					H vs. L	0.36 (0.06,2.20)	0.268

TABLE 10-26. (continued)

Adjusted Exposure Index Analysis for Followup Participants for Occurrence of Malignant Neoplasms in the Baseline-Followup Interval

Variable	Occupation	Exposure Index			Contrast	Adj. Relative Risk (95% C.I.)	p-Value	
		Low Total*	Medium Total*	High Total*				
Systemic ^b Malignancies (Verified Only)	Officer	127	130	123	Overall	1.60 (0.15,17.22)	0.365	
					M vs. L		0.696	
					H vs. L		--	
		Enlisted Flyer	55	65	57	Overall		--
					M vs. L	--	--	
					H vs. L	--	--	
		Enlisted Groundcrew	154	163	142	Overall		--
					M vs. L	--	--	
					H vs. L	--	--	
Systemic ^b Malignancies (Verified and Suspected)	Officer	127	130	123	Overall	2.95 (0.31,27.73)	0.109	
					M vs. L		0.344	
					H vs. L		--	
		Enlisted Flyer	55	65	57	Overall		0.557
					M vs. L	0.25 (0.02,3.90)	0.326	
					H vs. L	0.38 (0.03,4.90)	0.458	
		Enlisted Groundcrew	154	163	142	Overall		--
					M vs. L	--	--	
					H vs. L	--	--	

*Total number of participants.

^aNonblacks only.

^bBlacks and nonblacks.

--Analyses not done due to sparse cells.

TABLE 10-27.

Adjusted Exposure Index Analysis for Followup Participants for
Lifetime Occurrence of Malignant Neoplasms

Variable	Occupation	Exposure Index			Contrast	Adj. Relative Risk (95% C.I.)	p-Value
		Low Total*	Medium Total*	High Total*			
Basal Cell Carcinoma (Verified Only) ^a	Officer	124	127	121	Overall		0.841
					M vs. L	1.33 (0.48,3.66)	0.580
					H vs. L	1.27 (0.45,3.60)	0.647
	Enlisted Flyer	54	61	51	Overall		0.024
					M vs. L	0.23 (0.03,1.61)	0.141
					H vs. L	0.08 (0.01,0.78)	0.030
	Enlisted Groundcrew	138	149	129	Overall		0.937
					M vs. L	1.10 (0.31,3.86)	0.881
					H vs. L	0.87 (0.24,3.20)	0.832
Basal Cell Carcinoma (Verified and Suspected) ^a	Officer	124	127	121	Overall		0.699
					M vs. L	1.49 (0.59,3.78)	0.404
					H vs. L	1.22 (0.46,3.24)	0.694
	Enlisted Flyer	54	60	51	Overall		0.024
					M vs. L	0.23 (0.03,1.61)	0.141
					H vs. L	0.08 (0.01,0.78)	0.030
	Enlisted Groundcrew	138	149	129	Overall		0.860
					M vs. L	0.89 (0.27,2.97)	0.849
					H vs. L	0.71 (0.20,2.48)	0.589

TABLE 10-27. (continued)

Adjusted Exposure Index Analysis for Followup Participants for
Lifetime Occurrence of Malignant Neoplasms

Variable	Occupation	Exposure Index			Contrast	Adj. Relative Risk (95% C.I.)	p-Value
		Low Total*	Medium Total*	High Total*			
Sun-Exposure Related Malignancies (Verified Only) ^a	Officer	124	127	121	Overall		0.906
					M vs. L	1.19 (0.47,3.00)	0.717
					H vs. L	0.99 (0.37,2.64)	0.980
	Enlisted Flyer	54	61	51	Overall		0.045
					M vs. L	0.42 (0.08,2.19)	0.300
					H vs. L	0.09 (0.01,0.89)	0.039
	Enlisted Groundcrew	138	149	129	Overall		0.785
					M vs. L	1.35 (0.40,4.58)	0.627
					H vs. L	0.88 (0.24,3.25)	0.850
Sun-Exposure Related Malignancies (Verified and Suspected) ^a	Officer	124	127	121	Overall		0.722
					M vs. L	1.33 (0.56,3.16)	0.518
					H vs. L	0.97 (0.38,2.47)	0.952
	Enlisted Flyer	54	60	51	Overall		0.045
					M vs. L	0.42 (0.08,2.19)	0.300
					H vs. L	0.09 (0.01,0.89)	0.039
	Enlisted Groundcrew	138	149	129	Overall		0.785
					M vs. L	1.10 (0.34,3.52)	0.879
					H vs. L	0.72 (0.20,2.52)	0.603

TABLE 10-27. (continued)

Adjusted Exposure Index Analysis for Followup Participants for
Lifetime Occurrence of Malignant Neoplasms

Variable	Occupation	Exposure Index			Contrast	Adj. Relative Risk (95% C.I.)	p-Value
		Low Total*	Medium Total*	High Total*			
Systemic Malignancies (Verified Only) ^b	Officer	127	130	123	Overall		0.902
					M vs. L	1.11 (0.18,7.01)	0.911
					H vs. L	1.49 (0.24,9.16)	0.669
	Enlisted Flyer	55	65	57	Overall		0.806
					M vs. L	0.86 (0.11,7.08)	0.892
					H vs. L	0.46 (0.04,5.46)	0.540
	Enlisted Groundcrew	154	163	142	Overall		0.073
					M vs. L	--	--
					H vs. L	--	--
Systemic Malignancies (Verified and Suspected) ^b	Officer	127	130	123	Overall		0.829
					M vs. L	1.69 (0.30,9.65)	0.554
					H vs. L	1.47 (0.24,8.95)	0.679
	Enlisted Flyer	55	65	57	Overall		0.741
					M vs. L	0.51 (0.08,3.47)	0.494
					H vs. L	0.54 (0.08,3.57)	0.527
	Enlisted Groundcrew	154	163	142	Overall		0.087
					M vs. L	--	--
					H vs. L	--	--

*Total number of participants.

^aNonblacks only.^bBlacks and nonblacks.

--Analyses not done due to sparse cells.

For the interval analysis, enlisted flyers exhibited a marginally significant decreasing dose-response effect for verified basal cell carcinomas in both the unadjusted ($p=0.073$) and adjusted analyses ($p=0.080$). (All Ranch Hand enlisted flyer interval malignant skin neoplasms were verified basal cell carcinomas; thus, interval results for verified and verified plus suspected basal cell carcinoma and the corresponding sun-exposure related neoplasms were identical. Similarly, for lifetime analyses, verified and verified plus suspected analyses were the same). The percentages of participants with interval basal cell neoplasms were 11.1 percent, 3.3 percent, and 1.9 percent for the low, medium, and high exposure categories, respectively. The enlisted groundcrew exhibited a nonsignificant decreasing dose-response effect for basal cell carcinomas and sun-exposure related malignant neoplasms.

In the adjusted lifetime analysis for enlisted flyers (Table 10-27), there were significant findings, similar to the interval analysis, namely a decreasing dose-response effect for basal cell carcinomas (overall $p=0.024$; Adj. RR [medium versus low]: 0.23, 95% C.I.: [0.03, 1.61], Adj. RR [high versus low]: 0.08, 95% C.I.: [0.01, 0.78]), and for sun-exposure related skin malignancies (overall $p=0.045$; Adj. RR [medium versus low]: 0.42, 95% C.I.: [0.08, 2.19], Adj. RR [high versus low]: 0.09, 95% C.I.: [0.01, 0.89]). The percentages of participants with lifetime basal cell carcinomas were 13.0 percent, 3.3 percent, and 1.9 percent for the low, medium, and high exposure categories, respectively. The corresponding percentages for lifetime sun-exposure related skin malignancies were 13.0 percent, 4.9 percent, and 1.9 percent. For the enlisted groundcrew cohort, a marginally significant result was found for all systemic malignancies combined in the adjusted analyses (verified only: overall $p=0.073$; verified plus suspected: overall $p=0.087$). Of the four verified systemic malignancies, three were in the medium exposure category and one was from the high category. There was one additional suspected malignant neoplasm in the high exposure category. No significant results were found for officers in the lifetime analysis.

DISCUSSION

The statistical analyses of cancer endpoints in this chapter have carefully followed the prescribed boundaries of the SAIC analytic plan approved by the Air Force. Specific latency analyses of certain cancers associated with environmental exposures were not performed, nor were contrasts of cancer-specific incidence rates to SEER data judged appropriate. Further, embedded case control studies on selected cancers were not performed due to concern for bias.

The statistical analyses focused on neoplasms occurring during the time interval between 1982 and 1985 (Baseline to followup). However, because these relatively young and healthy cohorts yielded small numbers of cancers in this short interval, and because of the intense scientific interest in malignant disease, the analysis went beyond the assessment of the incidence of malignant neoplasms in this interval. Lifetime (Baseline and followup data combined) analyses of malignant incident neoplasms were conducted. Cancers occurring prior to military duty in SEA were excluded. A full cancer mortality-morbidity analysis was not attempted but simple tabulations of cancer incidence and mortality of Baseline participants were made. Interval and lifetime analyses were expanded to include suspected cancers noted at followup. Further, grouped cancers that were not likely related were

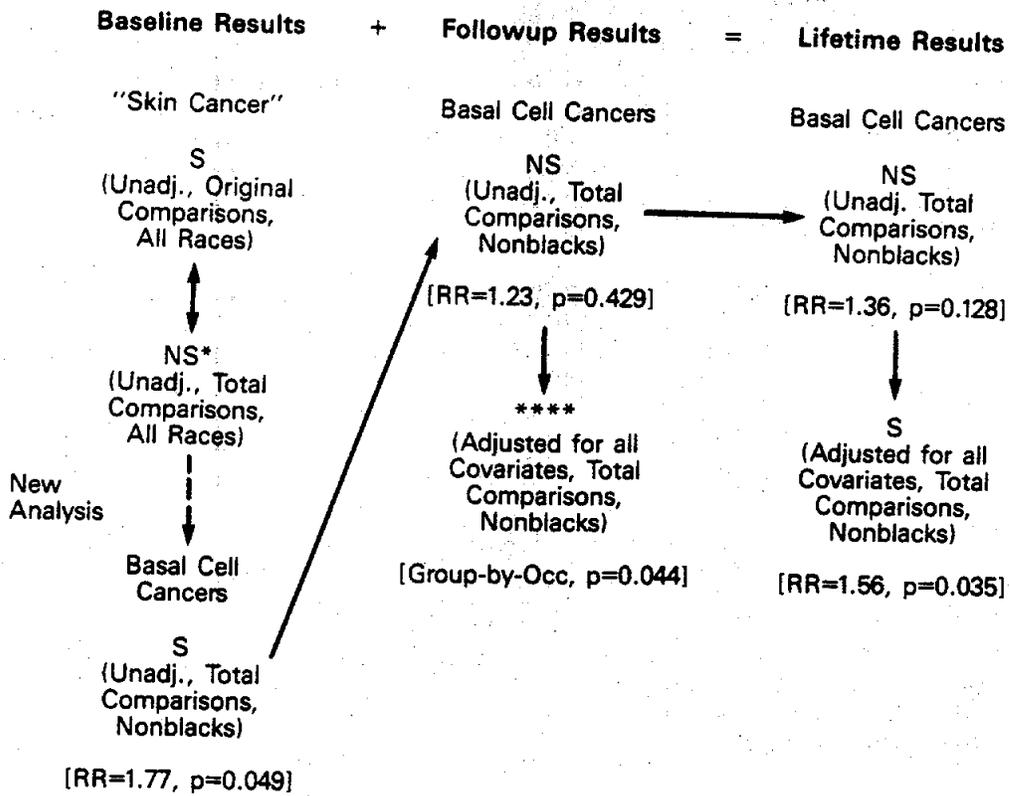
analyzed (all systemic cancers and malignant sun exposure-related skin neoplasms). These efforts, however, have introduced several subtle interpretive issues that should be noted, e.g., skin cancer rates are for nonblacks only, whereas systemic cancer rates are for all races; lifetime group rates are on only those attending the followup examination; and verified and suspected cancer categories included more cases but the data are less reliable. Further, contrasts of cancer rates, particularly skin cancer, between the Baseline results and followup results, or lifetime results, must account for the slight differences in the Baseline and followup cohorts, racial adjustment (Blacks were not omitted from skin cancer analyses at Baseline), skin cancer classification, the change in focus from the Original Comparisons to the total Comparison group, and whether the data were adjusted for covariates.

Skin Cancer

The emphasis on skin cancer at the followup examination was predicated upon the finding of a significant excess of such cancers at the Baseline examination, and the lack of risk factor data to conduct appropriate adjusted analyses. Because of shifting factors (cited above) between the examinations, a "direct look" at the skin cancer association is not straightforward. Figure 10-1 is presented as an aid to clarify the skin cancer observations over the two examinations.

This diagram compares the Baseline and followup analyses. So that the unadjusted Baseline results could be contrasted to the followup results, the estimated relative risk of basal cell carcinoma among nonblack Ranch Hands versus all nonblack Comparisons (not just Originals) was calculated, using data in the Baseline Report. This unadjusted analysis gave a significant relative risk of 1.77 ($p=0.049$). These results could then be directly contrasted to the unadjusted followup results, which showed a narrowing of group differences over the 3-year interval (Est. RR: 1.23, $p=0.429$). (It is noted that this contrast compares skin cancer rates of approximately 23 years to 3 years at different levels of age risk.) The adjusted analysis revealed a significant group-by-occupation interaction, due to a significantly higher rate of basal cell carcinomas among Ranch Hand enlisted flyers than the corresponding Comparisons (Adj. RR: 6.50, $p=0.019$), but very similar rates in the two groups for officers and enlisted groundcrew were seen.

The Baseline data were carefully merged (to avoid duplicate counts) with the followup data to assess the total lifetime incidence of basal cell carcinomas between groups. The addition of the nonsignificant followup results to the significant Baseline results produced a nonsignificant lifetime assessment (Est. RR: 1.36, $p=0.128$), as expected. However, when the lifetime data were adjusted for covariate effects, a significant result emerged (Adj. RR: 1.56, $p=0.035$), with Ranch Hands having a significant excess of lifetime basal cell carcinoma. A careful examination of the covariates showed that the variable of average residential lifetime latitude was most likely responsible for the significant adjusted results. The latitude variable was a significant confounding variable since it was associated with basal cell carcinomas and with average lifetime latitude which varied significantly by group.



S: Significant ($p \leq 0.05$).
 NS: Not significant ($p > 0.10$).
 NS*: Borderline significant ($0.05 < p \leq 0.10$).
 ****: Group-by-covariate interaction.

Figure 10-1.
Schematic Diagram of Unadjusted and Adjusted Skin Cancer Results, by Significance and Relative Risk, and by Examination Period (Time).

Because of the significant confounding effect of the latitude variable, it was examined closely for misclassification or bias. An initial review of the residential history forms showed occasional discrepancies between total residential years and chronologic age. This was generally due to sporadic underreporting, and to the data collection instructions which required the citation only of residences of one year or longer. However, analyses showed fairly good concordance between reported residential years and chronologic age. No significant group difference was found for the inaccuracy of residential reporting ($p=0.684$), validating the use of all residential histories even though some were slightly imprecise.

In the course of reviewing the covariate effects on basal cell carcinoma, the data suggested some unexpected associations. To sharpen these contrasts, adjusted risks were estimated at set levels of skin reaction to sun, skin color, average lifetime residential latitude, and age, relative to the lowest risk observed, i.e., Comparisons 40 years old (at Baseline) who have lived on average in northern latitudes and tan easily were arbitrarily assigned a risk of 1.00. These computed risks are given in Table 10-28.

These results show uniform increased risks in the Ranch Hands over both the base level of one and the Comparisons in the same covariate strata. Further, in all strata, age, latitude, and skin color behave as expected. However, the sun-reaction index does not behave as expected since those who burn easily have lower relative risks than those who have an intermediate reaction to sun, although they do have higher relative risks than those who tan easily. This may represent avoidance of sun exposure or the use of sunblock by those individuals.

Skin cancer, and particularly basal cell carcinoma, has been emphasized in this report because of the significant group differences detected at Baseline (and the theoretical link to TCDD causation), and the borderline significant adjusted results found for the lifetime rates. The results of the third-year followup analysis suggest that if group differences continue to narrow (where $p \geq 0.15$) at the fifth-year followup examination, the lifetime results would likely not be significant even with full adjustment.

Systemic Cancer

The analyses of systemic cancer for both the interval and lifetime periods have necessarily been limited by scant data. Cancer specific analyses, in particular, have not provided meaningful results because of low counts. However, some variation in tumor type was noted in the two groups: colon cancer (5 Comparisons, 0 Ranch Hands), testicular cancer (3 Ranch Hands, 0 Comparisons), and smoking related tumors of the oral cavity, pharynx, bronchus, and lung (5 Ranch Hands, 0 Comparisons). Testicular and smoking related tumors have not been associated with exposure to herbicides or TCDD. Table 10-18 cited counts of malignancies that have been associated to herbicides and dioxin exposure. Because of the relative rareness of the diseases soft tissue sarcoma (STS), Hodgkin's disease, and non-Hodgkin's lymphoma, lifetime rates were expected to be exceptionally low.

Most of the covariate associations with systemic cancer were anticipated, but the change in significance for smoking (significant at Baseline, borderline significant for lifetime cancers) was not expected, particularly as the cancer cases increased during the interval.

TABLE 10-28.

Computed Risks of Basal Cell Carcinoma
by Group at Varying Levels of Four
Risk Factors, Relative to Comparisons at Low Risk*

Skin Reaction to Sun	Covariate Categories		Skin Color: Not Peach		Skin Color: Peach	
	Average Lifetime Residential Latitude	Age at Baseline	Comparison	Ranch Hand	Comparison	Ranch Hand
Tans Easily	≥37°N	40	1.00**	1.48	1.55	2.30
		60	2.99	4.43	4.62	6.85
	<37°N	40	1.63	2.42	2.52	3.74
		60	4.87	7.23	7.53	11.18
Intermediate Reaction	≥37°N	40	3.04	4.52	4.71	6.99
		60	9.09	13.50	14.06	20.87
	<37°N	40	4.97	7.37	7.68	11.40
		60	14.83	22.02	22.93	34.04
Burns Easily	≥37°N	40	2.02	3.00	3.13	4.64
		60	6.04	8.96	9.33	13.86
	<37°N	40	3.30	4.90	5.10	7.57
		60	9.85	14.62	15.22	22.60

*Computed from main effects model with latitude, skin reaction to sun, and skin color as covariates.

**Base Category (Lowest Risk).

All Cancers

As previously noted, the interrelatedness of many of the analyzed cancer variables has created a compounding of statistical significance, and care should be taken in making inferences and final conclusions. An almost uniform dilutional effect was created by adding "suspected" cancers to the analyses, as there were more of this category in the Comparisons than in the Ranch Hands. The use of suspected neoplasms was deemed necessary in order to best describe the complete cancer findings, recognizing that confirmation of all suspected cases was difficult.

Two patterns emerged from the analyses. All relative risks exceeded the value of one, except that of lifetime verified melanoma and verified or verified plus suspected squamous cell carcinoma. Some of the elevated risks were due to the relatedness of the variables as stated, but the relative risks for the unrelated variables skin cancer and systemic cancer both exceeded one. The joint consideration of both yielded a significant relative risk. The second pattern was of the group-by-covariate interactions observed for seven of the analyses; 3 of them involved the covariate of occupation and 4 involved skin reaction to sun. The three group-by-occupation interactions all showed a significant detriment to the Ranch Hand enlisted flying cohort. Further analyses of air crewmembers versus noncrewmembers revealed a significant risk of basal cell carcinoma for the Ranch Hand air crewmembers (RR: 1.94, $p=0.049$). Since enlisted Ranch Hand flyers in the interval exhibited more basal cell carcinomas (RR: 6.5, $p=0.019$) and more verified and suspected systemic cancers (4/175 RH with systemic neoplasms versus 0/209 Comparisons, $p=0.042$), there may be more reason to assume a biologic foundation than chance, although the reason is obscure. The four group-by-sun reaction index interactions all revealed a significant or marginally significant detriment to Ranch Hands who reacted mildly to the sun.

In full context, the cancer observations cannot be viewed as disturbing at this time. The skin cancer group differences have narrowed over a 3-year period. An additional analytic observation on skin cancer is that inclusion or exclusion of only one or two cases was shown to alter the choice of the best statistical model, affecting the presence or absence of both covariates and group-by-covariate interactions, and also change the p -value of the adjusted group difference above or below the alpha level of 0.05. For systemic cancer, both groups are at the lower end of the expected ascending cancer curves, where numeric and tumor type fluctuations are expected. A recognized bench-mark for the latency of many cancers is 20 years, and this will not be achieved by most participants until the 5-year followup examination, 2 years from now. Cancer findings at that time will be the basis upon which firm conclusions can be made.

SUMMARY AND CONCLUSIONS

The cancer analysis focused on cancer occurrences in the Baseline-followup interval, and also included analyses of the Baseline plus interval cancer history. A summary of the cancer findings is given in Table 10-29.

No significant unadjusted differences were found between nonblack Ranch Hands and Comparisons in the Interval (Baseline-Followup) incidence rates of basal cell carcinoma, melanoma, squamous cell carcinoma, all malignant skin cancers, sun-exposure related malignant neoplasms (comprising basal cell

TABLE 10-29.

**Overall Summary Table: Unadjusted and Adjusted Analysis of Interval
and Lifetime Skin and Systemic Cancer Incidence**

Cancer Type	Baseline-Followup Interval		Lifetime (Baseline & Followup)	
	Unadjusted	Adjusted	Unadjusted	Adjusted
<u>Malignant Skin Cancer (Nonblacks only)</u>				
Verified Basal Cell Carcinoma	NS	****	NS	S
Verified plus Suspected Basal Cell Carcinoma	NS	****	NS	****
Verified Melanoma	NS	-- ^a	NS	-- ^a
Verified plus Suspected Melanoma	NS	-- ^a	NS	-- ^a
Verified Squamous Cell Carcinoma	NS	-- ^a	NS	-- ^a
Verified plus Suspected Squamous Cell Carcinoma	NS	-- ^a	NS	-- ^a
Verified Sun Exposure Skin Cancers	NS	NS	NS*	S
Verified plus Suspected Sun Exposure Skin Cancers	NS	NS	NS	NS
All Verified Malignant Skin Cancers	NS	-- ^a	NS	-- ^a
Verified plus Suspected Malignant Skin Cancers	NS	-- ^a	NS	-- ^a
Verified Skin Cancers of Any Type	NS*	--	S	--
Verified plus Suspected Skin Cancers of Any Type	NS	--	NS*	--

TABLE 10-29.

Overall Summary Table: Unadjusted and Adjusted Analysis of Interval and Lifetime Skin and Systemic Cancer Incidence (continued)

Cancer Type	Baseline-Followup Interval		Lifetime (Baseline & Followup)	
	Unadjusted	Adjusted	Unadjusted	Adjusted
<u>Malignant Systemic Cancer (Blacks and Nonblacks)</u>				
Verified Systemic Cancer	NS	NS	NS	****
Verified plus Suspected Systemic Cancer	NS	****	NS	****
<u>All Neoplasms (Blacks and Nonblacks)</u>				
Any Type, Any Location ^b Verified	NS*	-- ^a	S	-- ^a

NS: Not significant ($p > 0.10$).

****Group-by-covariate Interaction.

--^aAnalysis not done.

NS*: Borderline significant ($0.05 < p \leq 0.10$).

^bComprises malignant, benign, uncertain behavior.

S: Significant ($p \leq 0.05$).

carcinoma, melanoma, and epithelial neoplasms NOS) or all malignant skin cancers as a group. The unadjusted group contrast of all skin neoplasms (comprising malignant and benign neoplasms, and neoplasms of uncertain behavior or unspecified nature) was marginally significant, with a higher rate among Ranch Hands. When suspected malignant skin cancers (noted at Followup but not verified at the time of writing) were included in the analyses with the verified conditions, all the unadjusted group contrasts were nonsignificant.

The covariates used for the adjusted analyses of basal cell carcinoma and the sun exposure related skin malignancies were age, occupation, skin color, reaction of skin to sun, and average latitude, all of which were highly associated with skin cancer incidence. Other host factors were related to skin cancer incidence, but not as strongly as those included in the analysis. A borderline association with smoking history was noted, and was determined to be partly an age effect.

Analysis of the incidence of interval basal cell carcinoma revealed a significant group-by-occupation interaction, due to a significant group difference for enlisted flyers, but not for officers or enlisted groundcrew. Inclusion of suspected basal cell carcinoma resulted in a group-by-sun reaction index interaction. This was due to Ranch Hands with an intermediate reaction to sun having a higher relative risk than the corresponding Comparisons. The adjusted group contrast of the incidence rates of verified sun-exposure related skin cancers was not significant; inclusion of suspected conditions did not alter this lack of significance.

There was no significant group difference for Blacks and nonblacks in the unadjusted incidence rates of all interval verified malignant systemic neoplasms combined, nor was there a significant difference in the adjusted group rates. Analysis of the verified plus suspected interval systemic cancers showed a nonsignificant unadjusted group difference, but a group by occupation interaction was found in the adjusted analysis. This was due to a significant group difference of verified plus suspected systemic malignancies among the enlisted flyers with five occurrences among the Ranch Hands, but none among the Comparisons. Age and a race-by-packyear interaction were important adjusting factors.

The Baseline and Followup data were combined for the assessment of lifetime incidence of cancer; occurrences of cancer prior to Vietnam were excluded.

There were no significant unadjusted group differences in lifetime incidence rates among nonblacks for basal cell carcinoma, melanoma, squamous cell carcinoma, the sun exposure related skin cancers, or all malignant skin cancers combined. The unadjusted group contrast of all lifetime skin malignancies was significant, with a higher rate among Ranch Hands. Inclusion of suspected cancers with the verified cancers reduced the difference between the groups for all these malignant skin contrasts, except for the sun exposure related skin cancers, for which a marginally significant group difference was found. However, the contrast of all skin malignancies remained close to significance.

Adjusted analysis of the incidence rates of lifetime basal cell carcinoma revealed a significantly higher incidence rate among Ranch Hands

(Adj. RR: 1.56, p=0.035). Significant effects of an occupation-by-age interaction, a skin color-by-sun reaction index interaction, and a sun reaction index-by-average residential latitude interaction were seen. The adjustment resulted in a significant relative risk that, moreover, was higher than the unadjusted relative risk. Average residential latitude, associated with both group and skin cancer, and skin color, which was associated with the disease and marginally associated with group, played a major part in the change from the unadjusted analysis due to confounding. Inclusion of suspected basal cell carcinoma in the adjusted analysis resulted in a group by sun reaction index interaction, as was noted for the interval analysis.

The adjusted group contrast in incidence rates of the sun-exposure related skin cancers was also significant (Adj. RR: 1.54, p=0.030), which is not surprising since the majority are basal cell carcinoma. Inclusion of the suspected conditions resulted in a non-significant group contrast.

The unadjusted group contrasts of the incidence rates of all systemic cancers combined were not significant, both for verified and verified plus suspected conditions.

There was one new occurrence of a soft tissue sarcoma (Ranch Hand) and one suspected cancer of the lymphatic system (Ranch Hand), in addition to the one previously reported soft tissue sarcoma and one Hodgkin's disease in the Comparison group.

Adjusted analysis of all lifetime malignant systemic neoplasms as a group, however, revealed a group by occupation interaction, due to a significantly higher rate for Ranch Hand enlisted flyers as contrasted to Comparisons. The same result was found for verified plus suspected systemic cancers.

In conclusion, there were no adjusted or unadjusted differences between groups in basal cell carcinoma incidence in the Baseline-followup interval. At Baseline, a significantly higher rate of basal cell carcinoma was found for Ranch Hands when contrasted with Original Comparisons. When the Baseline data were combined with the interval data, adjusted analysis, but not the unadjusted analysis, revealed a significantly higher rate of basal cell carcinoma among the Ranch Hands than among all Comparisons. The relative risk of basal cell carcinoma appears to be declining over time.

Relative risks of basal cell carcinoma and systemic cancer were found to be consistently larger than 1. Most of the skin cancers were basal cell carcinomas, upon which most of the skin cancer analysis focused, thus relative risks for sun-exposure related skin neoplasms and all malignant skin cancers as a group were very similar to those for basal cell carcinoma. The number of occurrences of systemic cancer was small, in part because the cohort is relatively young, and although the relative risks (lifetime and interval) are greater than 1, the difference between groups is not significant. Sufficient time may not have elapsed since Vietnam to enable a group difference in systemic neoplasms, if one exists, to be apparent.

CHAPTER 10

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