TABLE 9-6. (continued)

Adjusted Exposure Index for General Health Variables by Occupation

Variable	Occupation	Statistic	Exposure Index			Exposure Index Contrast	Adj. Relative Risk (95% C.I.)	p-Value
			Low	Medium	High			
Percent Body Fat	Officer	n	130	124	125	Overall		0.955
		Adj. Mean	20.94	20.80	20.78	M vs. L	—	0.806
		95% C.I.	(19.11,22.78)	(19.00,22.60)	(18.96,22.61)	H vs. L	—	0.781
		n	130	124	125	Overall[c]		0.534
						M vs. L[c]	0.80 (0.41,1.54)	0.497
						H vs. L[c]	0.68 (0.35,1.34)	0.271
	Enlisted Flyer	n	55	63	53	Overall		0.182
		Adj. Mean	20.51	21.91	22.54	M vs. L	—	0.198
		95% C.I.	(17.99,23.03)	(19.60,24.22)	(20.12,24.95)	H vs. L	—	0.073
		n	55	63	53	Overall[c]	****	****
						M vs. L[c]	****	****
						H vs. L[c]	****	****
	Enlisted Groundcrew	n	147	158	140	Overall		0.822
		Adj. Mean	21.35	21.33	20.99	M vs. L	—	0.972
		95% C.I.	(20.24,22.46)	(20.22,22.44)	(19.84,22.14)	H vs. L	—	0.575
		n	147	158	140	Overall[c]		0.899
						M vs. L[c]	0.89 (0.51,1.55)	0.674
						H vs. L[c]	0.99 (0.57,1.73)	0.976

TABLE 9-6. (continued)

Adjusted Exposure Index for General Health Variables by Occupation

Variable	Occupation	Statistic	Exposure Index: Low	Exposure Index: Medium	Exposure Index: High	Exposure Index Contrast	Adj. Relative Risk (95% C.I.)	p-Value
Sedimentation Rate	Officer	n	122	121	117	Overall		0.644
		Adj. Mean[d]	5.77	5.48	5.20	M vs. L	—	0.635
		95% C.I.[d]	(4.10,8.12)	(3.92,7.65)	(3.70,7.31)	H vs. L	—	0.348
		n	122	121	117	Overall		0.400
						M vs. L	0.83 (0.28,2.49)	0.741
						H vs. L	0.41 (0.10,1.65)	0.208
	Enlisted Flyer	n	53	63	51	Overall		0.752**
		Adj. Mean**[d]	4.85	5.26	4.67	M vs. L	—	0.612**
		95% C.I.**[d]	(3.35,7.02)	(3.76,7.37)	(3.28,6.66)	H vs. L	—	0.825**
		n	53	63	51	Overall		0.703**
						M vs. L	0.94 (0.25,3.56)	0.928**
						H vs. L	1.52 (0.94,5.20)	0.509**
	Enlisted Groundcrew	n	144	151	133	Overall		0.692
		Adj. Mean[d]	4.93	5.36	5.22	M vs. L	—	0.402
		95% C.I.[d]	(4.13,5.88)	(4.48,6.41)	(4.33,6.30)	H vs. L	—	0.571
		n	144	151	133	Overall		0.634
						M vs. L	1.13 (0.46,2.78)	0.795
						H vs. L	0.72 (0.28,1.83)	0.490

[a]Outcome categories: Fair/Poor vs. Excellent/Good.
[b]Outcome categories: Older vs. Younger/Same.
[c]Outcome categories: Obese vs. Lean/Normal.
[d]Transformed from natural logarithm scale.
****Exposure index-by-covariate interaction ($p<0.01$) — adjusted mean, confidence interval, and p-value not presented.
**Exposure index-by-covariate interaction ($0.01 \leq p < 0.05$) — adjusted mean, confidence interval, and p-value derived from model fitted after deletion of interaction(s).
—Adjusted relative risks not applicable for continuous analysis of a variable.

interaction is explored further in Table F-2, Appendix F, where the results are presented stratified by age. There were only two individuals from the oldest age cohort, both in the medium exposure level category. For individuals born between 1923 and 1941, adjusted relative risks (adjusted for race) exceeded 1 for the medium versus low and high versus low contrasts, but were not statistically significant. In the youngest age group, 4 of 11 individuals in the high exposure level category were obese, compared to 2 of 18 in the medium exposure category and none of 11 in the low exposure category. This difference was significant (p=0.048), but the p-value should be viewed with caution due to the sparse cell sizes. The apparent increase in percent body fat with increased risk of exposure is inconsistent with a decrease in body weight expected from extrapolation of animal data.[7,8,9]

Laboratory Examination Variable

Sedimentation Rate

Unadjusted exposure index analyses for sedimentation rate did not reveal any significant dose-response relationships, when analyzed either in continuous or discrete forms. The same was true in the adjusted analyses for the officers and enlisted groundcrew. In the enlisted flyer cohort, however, there were significant exposure index-by-age and exposure index-by-race interactions (p=0.043 and p=0.050, respectively) in the continuous analysis, as well as a significant exposure index-by-age interaction (p=0.023) in the discrete analysis. These interactions are explored more fully in Appendix F, Table F-2. Since all interactions were between 0.01 and 0.05 significance levels, Table 9-6 also presents adjusted least squares means or adjusted relative risks after deleting the interaction terms from the respective model. None of these main effects analyses revealed significant exposure level effects.

Table F-2 in Appendix F gives the results of continuous analysis on (log) sedimentation rate within each race-by-age stratum (adjusting for personality type). In several cases, the numbers were quite small, but in the two strata containing modest numbers of individuals (nonblacks born between 1923 and 1941 and nonblacks born in or after 1942), there were no apparent dose-response relationships. Likewise, in discrete analyses stratified by age, no exposure index effects were suggested.

A summary of the exposure index-by-covariate interactions is presented in Table 9-7. All occurred in the enlisted flyers and three involved age (two of the three were for the same variable, analyzed in continuous and discrete forms). However, Table F-2 of Appendix F shows that tests carried out within the various strata were not statistically significant and no clear picture emerges.

Longitudinal Analysis

Two variables, self-perception of health and sedimentation rate, were investigated by longitudinal analyses between the 1982 Baseline and 1987 followup examinations. Self-perception of health was dichotomized into fair/poor and excellent/good categories. The respective laboratory norms of

TABLE 9-7.

Summary of Exposure Index-by-Covariate Interactions From Adjusted Analyses for General Health Variables*

Variable	Occupation	Covariate	p-Value
Percent Body Fat (D)	Enlisted Flyer	Age	0.005
Sedimentation Rate (C)	Enlisted Flyer	Age	0.043
Sedimentation Rate (C)	Enlisted Flyer	Race	0.050
Sedimentation Rate (D)	Enlisted Flyer	Age	0.023

D: Discrete analysis.

C: Continuous analysis.

*Refer to Table F-2 for a further investigation of these interactions.

12 or less mm/hr and more than 12 mm/hr for the Baseline sedimentation rates conducted at the Kelsey-Seybold Clinic, and 20 or less mm/hr and more than 20 mm/hr for the followup examination conducted at SCRF, were used to categorize the sedimentation rate data into normal and abnormal groups.

Table 9-8 gives the summary statistics for the two examinations, as well as the summary statistics of the 1985 followup examination, for reference purposes. As noted earlier, the decline in both groups in the percentage of individuals reporting their health as fair or poor over the three examinations is clearly seen. Table 9-9 presents tables for each group, giving the number of individuals reporting their health as fair/poor at both the Baseline and 1987 followup examinations, the number reporting their health as fair/poor at the Baseline examination and excellent/good at the 1987 followup examination, etc. The change in self-perception of health between the two examinations was not significantly different between the Ranch Hand and Comparison groups ($p=0.395$).

The data for sedimentation rate abnormalities appear in Tables 9-10 and 9-11. Fewer Ranch Hands than Comparisons were abnormal at Baseline, but a higher percentage of Ranch Hands than Comparisons were abnormal at the 1985 and 1987 followup examinations. Correspondingly, the odds ratio between the Baseline and 1987 followup was 4.0 in the Ranch Hands and less than 1.0 in the Comparisons; the difference between these odds ratios was highly significant ($p<0.001$).

TABLE 9-8.

Summary Statistics for the Longitudinal Analysis of Self-Perception of Health: 1982 Baseline, 1985 Followup, and 1987 Followup Examinations

Variable	Examination	Statistic	Group: Ranch Hand	Group: Comparison
Self-Perception of Health	1982 Baseline	Number/% Fair/Poor	179 19.0%	172 15.5%
		Excellent/Good	762 81.0%	940 84.5%
	1985 Followup	Number/% Fair/Poor	81 8.8%	73 6.7%
		Excellent/Good	843 91.2%	1,023 93.3%
	1987 Followup	Number/% Fair/Poor	65 6.9%	72 6.5%
		Excellent/Good	876 93.1%	1,040 93.5%

Note: Summary statistics for the 1982 Baseline and the 1987 followup are based on 941 Ranch Hands and 1,112 Comparisons who participated in the 1982 Baseline and the 1987 followup examinations. Summary statistics on 924 of these Ranch Hands and 1,096 of these Comparisons who also participated in the 1985 followup are included for reference purposes only.

TABLE 9-9.

Longitudinal Analysis of Self-Perception of Health: A Contrast of 1982 Baseline and 1987 Followup Examination Abnormalities

Variable	Group	1982 Baseline Exam	1987 Followup Exam: Fair/Poor	1987 Followup Exam: Exc./Good	Odds Ratio (OR)*	p-Value (OR_{RH} vs. OR_C)
Self-Perception of Health	Ranch Hand	Fair/Poor	45	134	0.149	0.395
		Exc./Good	20	742		
	Comparison	Fair/Poor	46	126	0.206	
		Exc./Good	26	914		

*Odds Ratio: $\frac{\text{Number Excellent/Good Baseline, Fair/Poor 1987 Followup}}{\text{Number Fair/Poor Baseline, Excellent/Good 1987 Followup}}$

TABLE 9-10.

Summary Statistics for the Longitudinal Analysis of Sedimentation Rate: 1982 Baseline, 1985 Followup, and 1987 Followup Examinations

Variable	Examination	Statistic	Group: Ranch Hand	Group: Comparison
Sedimentation Rate	1982 Baseline	Number/%		
		Abnormal	33 3.5%	50 4.5%
		Normal	910 96.5%	1,060 95.5%
	1985 Followup	Number/%		
		Abnormal	53 5.7%	38 3.5%
		Normal	871 94.3%	1,058 96.5%
	1987 Followup	Number/%		
		Abnormal	66 7.0%	47 4.2%
		Normal	877 93.0%	1,063 95.8%

Note: Summary statistics for the 1982 Baseline and the 1987 followup are based on 943 Ranch Hands and 1,110 Comparisons who participated in the 1982 Baseline and the 1987 followup examinations. Summary statistics on 924 of these Ranch Hands and 1,096 of these Comparisons who also participated in the 1985 followup are included for reference purposes only.

TABLE 9-11.

Longitudinal Analysis of Sedimentation Rate: A Contrast of 1982 Baseline and 1987 Followup Examination Abnormalities

Variable	Group	1982 Baseline Exam	1987 Followup Exam: Abnormal	1987 Followup Exam: Normal	Odds Ratio (OR)*	p-Value (OR_{RH} vs. OR_C)
Sedimentation Rate	Ranch Hand	Abnormal	22	11	4.00	<0.001
		Normal	44	866		
	Comparison	Abnormal	15	35	0.91	
		Normal	32	1,028		

*Odds Ratio: $\frac{\text{Number Normal Baseline, Abnormal 1987 Followup}}{\text{Number Abnormal Baseline, Normal 1987 Followup}}$

DISCUSSION

In clinical practice, the assessment of general health must be based on subjective and objective indices. In ambulatory medicine, particularly, the presence of occult disease cannot be excluded by negative laboratory tests directed at specific organ systems. Further, in the present study, it is reasonable to assume that the self-perception of health might be influenced by a participant's perception or concern of prior herbicide exposure.

The five variables considered in this section are frequently employed by clinicians in outpatient practice. On physical examination, the facial appearance of distress or of premature aging can often alert the physician to the presence of occult disease despite the absence of abnormalities in laboratory testing.

The erythrocyte sedimentation rate can be a sensitive, if nonspecific, index of general health. Pertinent to the longitudinal design of the current study is the effect of age: a rate as high as 40 mm per hour is considered within the range of normal for age 65. Extreme elevations in the erythrocyte sedimentation rate are consistently associated with serious underlying disease, usually malignancy.

Like the erythrocyte sedimentation rate, the percent body fat is an easily measurable, objective parameter of good health. Whereas obesity is a risk factor for cardiovascular disease and can contribute to hypertension and diabetes mellitus, it is often the patient with unexplained weight loss who is clinically of concern. Among the disorders considered in the current study that can induce unintentional weight loss were metabolic diseases (such as diabetes mellitus and hyperthyroidism); occult malignancy (most often lung or colon); drug abuse (for example, alcoholism and cocaine addiction); and emotional illness (such as anxiety or depression). To the extent that it can reflect significant weight gain or loss, the percent body fat can serve as a clinical clue to the presence of occult disease.

With regard to the self-perception of health, both Ranch Hand and Comparison group distributions were similar, with 6.7 percent of the members in each group reporting fair or poor health. Also, a trend of fewer individuals reporting fair or poor health in 1987 than at the Baseline or 1985 followup studies was observed. As expected, analysis of the age covariate reveals slightly poorer self-perception of health with advancing age.

In the present study, only 16 participants were reported as appearing ill; 9 from the Ranch Hand group and 7 from the Comparisons. The total number is small and the difference was not statistically significant. In addition, the chronically ill suffered from a diverse group of illnesses, including severe anemia, diabetes, renal failure, and malignancy. No single diagnosis or group of similar diagnoses contributed to the appearance of illness or distress. As would be anticipated, there was an increased incidence of chronic illness over time.

With regard to relative age, there was no difference found between the two groups. In 1985, the mean percent body fat was lower in the Ranch Hand group than in the Comparisons, but by 1987, the difference was not statistically significant.

Though (geometric) mean sedimentation rates were very similar in the two groups, there was a statistically significant difference in the percentage of individuals with a sedimentation rate above 20 mm/hr (7.0% of the Ranch Hands vs. 4.2% of the Comparisons). However, only three participants (two Ranch Hands and one Comparison) were found to have rates in excess of 100 mm/hr. One participant, a Comparison, proved to have lung cancer and died in early 1989. In neither of the other participants was a diagnosis established during the course of the 1987 followup.

In summary, based on the current examination variables, no clinically significant group differences were found in the general health of the Ranch Hands versus the Comparisons. Some concern is raised in the overall and longitudinal analyses of the erythrocyte sedimentation rate data. In contrast to the 1982 Baseline, a higher percentage of Ranch Hands was found to have abnormally elevated (>20 mm/hr) levels in both the 1985 and 1987 followup examinations ($p=0.013$ and $p=0.003$, respectively). Though of uncertain cause, this finding raises the possibility that some clinically occult disease process may be present in the Ranch Hand cohort and highlights the need to follow the sedimentation rate in subsequent examination cycles.

SUMMARY

General health was assessed by five measures (self-perception of health, appearance of illness or distress, relative age, percent body fat, and erythrocyte sedimentation rate). Table 9-12 presents a summary of all of the unadjusted and adjusted analyses performed for these five variables.

There were no significant differences, unadjusted or adjusted for covariates, nor any significant group-by-covariate interactions, for self-perception of health, appearance of illness or distress, relative age, or percent body fat. The percentage of participants reporting their health as fair or poor was equal in the Ranch Hand and Comparison groups, namely, 6.7 percent. This percentage was slightly less than that observed at the 1985 followup examination and less than half of that noted at the Baseline examination.

Sixteen individuals were reported by their examining physicians as appearing acutely ill or distressed at the 1987 Followup, nine (0.9%) from the Ranch Hand group and seven (0.5%) from the Comparisons. Relative age was likewise distributed similarly in the two groups, with 5.5 percent of the Ranch Hands and 5.8 percent of the Comparisons appearing older than their stated ages, and approximately 1 percent in each group appearing younger than their stated ages.

Only nine individuals (four Ranch Hands and five Comparisons) were lean (<10% body fat); 19.3 percent of the Ranch Hands and 22.0 percent of the Comparisons were obese (>25% body fat). The mean percent body fat was 21.6 in the Ranch Hands and 21.8 in the Comparisons. These means were not significantly different.

Continuous analyses of sedimentation rate did not reveal a significant group difference. Geometric mean values were 5.3 mm/hr in the Ranch Hands and 5.1 mm/hr in the Comparisons. However, there was a highly significant group

TABLE 9-12.

Overall Summary Results of Unadjusted and Adjusted Group Contrast Analyses of General Health Variables

Variable	Unadjusted		Adjusted		Direction of Results
	Discrete	Continuous	Discrete	Continuous	
Questionnaire					
Self-Perception of Health	NS	--	NS	--	
Physical Examination					
Appearance of Illness/Distress	NS	--	NS	--	
Relative Age	NS	--	NS	--	
Percent Body Fat	NS	NS	NS	NS	
Laboratory					
Sedimentation Rate	0.003	NS	0.005	NS	RH>C

--Analysis not performed.
NS: Not significant ($p>0.05$).
RH>C: Ranch Hand percent abnormal greater than Comparison percent abnormal.

difference in the percentage of individuals with an abnormal sedimentation rate (>20 mm/hr): 7.0 percent of the Ranch Hands compared to 4.2 percent of the Comparisons (Est. RR: 1.74, 95% C.I.: [1.21, 2.51], $p=0.003$). The relative risk was essentially unchanged after adjustment for age, race, occupation, and personality type (Adj. RR: 1.70). A significant group difference in the percentage of individuals with an abnormal sedimentation rate was also found at the 1985 followup examination, but not at the Baseline examination.

Unadjusted exposure index analyses did not detect any significant dose-response relationships in any of the occupational cohorts (officers, enlisted flyers, enlisted groundcrew). Adjusted exposure index analyses did reveal a significant exposure index-by-age interaction for percent body fat within the enlisted flyers and significant exposure index-by-age and exposure index-by-race interactions for sedimentation rate, also within the enlisted flyers. Further examination of these interactions, however, did not reveal significant dose-response relationships except for percent body fat among individuals born in or after 1942 ($p=0.048$, based upon small numbers). None of the 11

individuals in the low exposure category was obese, compared to 2 of 18 in the medium exposure category and 4 of 11 in the high exposure category.

Longitudinal analyses of self-perception of health and sedimentation rate found no significant difference for health perception, with a similar decline in both groups over time in the percentage of individuals reporting their health as fair or poor. For sedimentation rate, there was a significant group difference in the change from the Baseline to the 1987 followup examination: four times as many Ranch Hands went from normal at Baseline to abnormal at the 1987 followup than vice versa, whereas roughly equal numbers shifted in each direction among the Comparisons. The clinical implication of the statistical difference in this nonspecific medical parameter is unclear, and its relevance to the health of the Ranch Hand group must be evaluated in the light of the results in the other clinical areas.

CHAPTER 9

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CHAPTER 10

MALIGNANCY

INTRODUCTION

Background

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 early cancer deaths in several Army veterans, which were allegedly caused by exposure to Agent Orange. The media reinforced this perception of increased cancer risk by citing animal studies, which demonstrated a carcinogenic effect, and a few human studies, which showed excessive cancer in specific occupational groups.

Traditional difficulties in extrapolating animal data to humans and interspecies variability have limited the direct applicability of much of the experimental work. Other major challenges have included difficulties in the ability to control or characterize bias; selection of suitable controls or reference groups; quality and quantity of exposure; misclassification of exposure; confounding exposure to known injurious chemicals; sample size and statistical power; number and selection of relevant risk factors; and the lack of clearly defined clinical endpoints for study.

For these reasons, there is no scientific consensus on the dioxin-cancer question. There is, however, concern over soft tissue sarcomas (STS) and non-Hodgkin's lymphoma (NHL).

Numerous animal studies have been conducted to delineate the role of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) on tumor initiation, tumor promotion, mutagenesis, cocarcinogenesis, and deoxyribonucleic acid (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.[1] Recent animal studies have supported the theory that TCDD-induced response is mediated by a nongenotoxic mechanism. TCDD, binding to the Ah receptor, appears to alter cellular regulatory mechanisms that are reflected by enhanced cellular proliferation.[2-6]

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.[7,8] Conventional skin bioassays in mice produced mixed results in some studies[7,8] but caused significant dermal fibrosarcomas in other studies using different strains of animals.[9] 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.[10]

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.[11,12] In two mouse strains, gavage doses of 0.07-0.3 μg/kg/day produced hepatocellular carcinomas and thyroid tumors.[12] In the presence of partial hepatectomy and diethylnitrosamine, subcutaneous TCDD administration to rats resulted in hepatocellular carcinomas, demonstrating the promoter mechanism of TCDD.[13] TCDD has been shown to affect the action of estrogen in a number of tissues, possibly leading to carcinogenesis. In rats, TCDD has been shown to promote liver cancer but to inhibit uterine and mammary tumors due to interference with estrogen activity.[14,15] Evidence has also been shown in human cancer cells that TCDD exhibits antiestrogenic activity.[16-18]

Based upon these and other studies, the International Agency for Research on Cancer 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 increased risk for carcinomas rather than sarcomas, the tumor type of concern in some human studies.

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 efforts[19-22] 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.[23]

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.[24-32] These efforts showed statistically significant increased risks for STS, Hodgkin's Disease, 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 (Hodgkin's Disease 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,[30] but other specifically focused studies of primary liver cancer and colon cancer were negative with respect to phenoxy acid or chlorophenol exposure.[29,31] 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, the Swedish studies have been criticized on methodologic issues,[33-35] prompting the primary authors, Axelson and Hardell, to respond with clarifications, new calculations, amplifying studies on additional cohorts, and studies on other cancers.[29,32,36-38] 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.[39,40]

Four small industrial mortality studies were conducted in the late 1970's and early 1980's.[41-44] National Institute for Occupational Safety and Health investigators pooled the data from these studies and noted that 3 of the 105 deaths in these studies were due to STS,[45] as contrasted to an expected 0.07 percent in the U.S. general population.[45] This study has been criticized for the addition of possibly noncomparable industrial cohorts, and the lack of histologic confirmation of the STS cases. A subsequent case report added another STS case to the industrial studies,[46] and two other reports revealed three unrelated STS cases also arising from the industrial sector.[47,48] However, upon closer inspection, only two of the first four cases were confirmed as STS by an independent histologic review.[49] Other reviews of the seven total cases were noteworthy: there was poor agreement on the histologic subtype of the soft tissue tumors, and because of a feature of 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 underascertain STS by approximately 40 percent.[49,50] This latter problem did not affect the Swedish studies. Two studies of workers from Dow's Midland facility have indicated slightly increased levels of some (primarily soft-tissue) cancers, but none of statistical significance.[51,52] A study of workers exposed during a 1953 accident at a BASF plant in Germany also showed no statistically significant increases in cancers, but this effort may have suffered from an insufficient cohort size.[53]

Other cancer studies throughout the world showed mixed support for the Swedish findings. An Italian case-control effort[54] 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).[55] A study of more than 4,000 Danish phenoxy herbicide workers noted five STS cases (vs. 1.8 expected) and seven ML cases (vs. 5.4 expected).[56] The author concluded that the STS observation supported the Swedish work and that the ML data 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,[57] although a risk of 7.2 was noted for STS and potential chlorophenol exposure in tanneries.

A related 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).[58] A recent (1987) expanded version of this study found no increases of risk of NHL and no trend toward increasing risk with increasing duration and intensity of exposure.[59] 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.[60] Further, the STS risk was constant over time in spite of increased usage of phenoxy acid herbicides from 1947 to 1970.

A recent U.S. case-control study from the Kansas cancer registry has provided partial support for Hardell's observations.[61] The Kansas study was very similar in methodology to the early Swedish studies. An overall relative 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 relative risk of NHL increased to 6.0 as compared to nonfarmers.

For herbicide applicators, the relative 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.[62] 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.[63] 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 have attempted to determine whether veterans have experienced excessive mortality, particularly from cancer.[64-71] 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 clarification of the cancer issue. As might be predicted, almost all of the studies of veterans were negative for aggregate cancer associations, as well as for STS, Hodgkin's Disease, 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 Hodgkin's Disease.[67] 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.[72]

No consistent pattern for other cancer types has emerged. None of the leukemias has been associated with exposure to Herbicide Orange nor any of its constituents. Two studies noted increases in gastric cancer[22,73] and two others cited modest risks for lung cancer.[74,75] A recent Swedish study reported slight excesses of rectal cancer in male workers and increased cervical cancer from an exposed female cohort.[56]

From another perspective, if exposure to 2,4-D or dioxin causes an immunologic deficiency (see Chapter 19), one would expect an excess of B-cell tumors among NHL cases.[76-78] An excess of B-cell neoplasms has, in fact, not been described in NHL cases from industrial or veteran cohorts to date.

Baseline Summary Results

Cancer received major emphasis during the Baseline Air Force Health Study (AFHS) in 1982. The malignancy assessment 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 Report[79] was used in conjunction with cancer morbidity information. The overall results did not show a significant difference in systemic cancer between the two groups but did show significantly more 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 assessment derived from the initial 1:1 match (Ranch Hand to the Original Comparison member) disclosed similar distributions. One case of STS 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 (odds ratio 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.

1985 Followup Study Summary Results

The Baseline and 1985 followup data were combined for the assessment of lifetime incidence of cancer; occurrences of cancer prior to Vietnam were excluded.

For the unadjusted analyses (Blacks and nonblacks included), Ranch Hands had a significantly greater frequency of verified skin neoplasms (malignant, benign, uncertain behavior, and unspecified nature) than the Comparisons. Inclusion of the suspected skin neoplasms with these verified skin neoplasms resulted in the Ranch Hands having a marginally significantly higher frequency than the Comparisons. There were no significant unadjusted group differences among nonblack participants for basal cell carcinoma, squamous cell carcinoma, melanoma, or all malignant skin neoplasms. For verified sun exposure-related malignant skin neoplams, Ranch Hands had a marginally significantly greater frequency than the Comparisons. The groups did not differ for verified and suspected sun exposure-related malignant skin neoplasms.

The adjusted group contrast in incidence rates of the sun exposure-related skin cancers was also significant ($p=0.030$), the majority of which were basal cell carcinoma. Inclusion of the suspected conditions resulted in a nonsignificant group contrast. The unadjusted group contrasts of the incidence rates of all systemic cancers combined were not significant, both for verified and verified and supected conditions. There was one new occurrence of an STS (Ranch Hand) and one suspected cancer of the lymphatic

system (Ranch Hand), in addition to the one previously reported STS and one Hodgkin's Disease in the Comparison group. There were no cases of NHL in either group at the time of the 1985 report.

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 and suspected systemic cancers. These findings were in error due to miscoded records. Reanalysis of corrected data revealed no significant group difference (odds ratio = 1.1).

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 1985 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 appeared 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 malignant 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 was relatively young, and although the relative risks were sometimes greater than 1, the difference between groups was not significant.

Parameters of the 1987 Malignancy Assessment

Dependent Variables

The 1987 malignancy assessment was based on lifetime incidence of neoplasms exclusive of the few neoplasm occurrences before duty in Southeast Asia (SEA). Information on the occurrence of neoplasms was captured in the health questionnaires and the physical examinations at Baseline and both followups. The questionnaire and physical examination information on neoplasms collected in the Baseline, 1985 followup, and 1987 followup studies was combined to form a lifetime incidence of neoplasms for each participant. In this chapter, lifetime is used to refer to lifetime exclusive of time before duty in SEA.

Neoplasm refers to any new growth that may or may not be malignant. Malignant neoplasms are those neoplasms that are capable of invasion and metastasis. Malignant and benign neoplasms, carcinomas in situ, and neoplasms of uncertain behavior or unspecified nature were studied. Both skin and systemic neoplasms were studied. Systemic neoplasm is used to denote a nonskin neoplasm.

There were slight differences among the Baseline, 1985 followup, and 1987 followup cohorts. Unless otherwise noted, the 1987 assessment was based on the participants of the 1987 followup. All of the analyses were based on the

number of participants with one or more neoplasms, and not on the total number of neoplasms.

Questionnaire and Physical Examination Data

During the 1987 health interview, each study participant was asked a series of questions on the occurrence of cancer since the date of his last health interview. Participants who were new to the AFHS also completed the Baseline health questionnaire. The self-reported occurrences were verified by medical record review. The verification status of each self-reported neoplasm was classified as one of the following: (1) verified (supported by medical record), (2) nonverifiable (not supported by medical record), or (3) pending (medical record not yet provided). The reported neoplasms for which the verification status is pending are referred to as suspected neoplasms. Other than the analysis of nonverifiable neoplastic conditions, only data on verified and suspected neoplasms were used in the malignancy assessment.

Some possible neoplastic conditions were discovered by the physicians at the physical examination. No invasive procedures were used to detect systemic neoplasms. Punch biopsies were sought for all suspected malignant skin lesions. Contingent upon participant authorization, suspicious skin lesions were biopsied, and the pathology was determined. However, for some suspicious skin lesions and all suspected systemic neoplasms, the verification process has not been completed. Both the verified and suspected (verification not completed) neoplasms from the physical examination were used in the analysis. This is deemed necessary in order to best describe the complete neoplasm findings, recognizing that confirmation of all suspected cases was difficult.

The verified questionnaire data and the verified physical examination data were combined and are denoted as verified. The verified neoplasms plus the suspected neoplasms identified during the physical examination or those reported pending final verification by medical record, are referred to as verified and suspected neoplasms.

Skin Neoplasms

The analysis of skin neoplasms for the 1987 malignancy assessment was divided into the five sets described below. Each set was analyzed twice. The first analysis was limited to verified skin neoplasms only. For the second analysis, the skin neoplasms were expanded to include the verified neoplasms as well as the suspected neoplasms.

Set 1 consisted of analyses of skin neoplasms by behavior. Four behavior types were examined: (1) malignant, (2) benign, (3) uncertain behavior or unspecified nature, and (4) all (all skin neoplasms combined).

Set 2 consisted of analyses of malignant skin neoplasms by cell type. Four types were analyzed: (1) basal cell carcinoma, (2) squamous cell carcinoma, (3) melanoma, and (4) sun exposure-related malignant skin neoplasms. Sun exposure-related malignant skin neoplasms included basal cell carcinoma, squamous cell carcinoma, melanoma, and malignant epithelial neoplasms not otherwise specified (NOS).

Set 3 consisted of analyses of basal cell carcinoma, melanoma, and sun exposure-related malignant skin neoplasms by location. Five locations were used: (1) ear, face, head, and neck; (2) trunk; (3) upper extremities; (4) lower extremities; and (5) other sites including sites NOS.

Set 4 consisted of analyses on basal cell carcinoma and sun exposure-related malignant skin neoplasms. For both groups of neoplasms, Ranch Hands and Comparisons were contrasted on the number of participants with neoplasms on the ear, face, head, and neck, versus the number of participants with no neoplasms. These analyses were repeated using all other sites combined except ear, face, head, and neck. These analyses were stratified by occupation.

Set 5 consisted of five conditional analyses: (1) skin neoplasm conditioned on the occurrence of any neoplasm; (2) malignant skin neoplasm conditioned on the occurrence of any skin neoplasm; (3) basal cell carcinoma conditioned on malignant skin neoplasm; (4) basal cell carcinoma on the ear, face, head, neck, or upper extremities conditioned on the occurrence of basal cell carcinoma; and (5) sun exposure-related malignant skin neoplasm on the ear, face, head, neck, or upper extremities conditioned on the occurrence of sun exposure-related malignant skin neoplasm.

In addition, analyses of participants with multiple basal cell carcinomas versus no basal cell carcinomas were conducted; once limited to verified data only and repeated for verified and suspected malignancies.

Since Blacks have a lower susceptibility to sun-induced skin cancer, the analysis of skin neoplasms was limited to nonblacks. No participants were excluded for medical reasons from the analyses of these variables.

Systemic Neoplasms

The systemic neoplasms were analyzed by behavior and body site. As with skin neoplasms, each analysis was conducted twice, once limited to verified data and expanded to encompass the suspected neoplasms. The analysis of the systemic neoplasms was divided into the two sets described below.

Set 1 consisted of analyses of systemic neoplasms by behavior. Four behavior types were examined: (1) malignant, (2) benign, (3) uncertain behavior and unspecified nature, and (4) all (all systemic neoplasms combined).

Set 2 consisted of analyses of malignant systemic neoplasms by site or certain types of malignant systemic neoplasms. The site or type of neoplasm classifications were as follows: (1) oral cavity, pharynx, and larynx; (2) thyroid gland; (3) bronchus and lung; (4) colon; (5) kidney and bladder; (6) prostate; (7) testicles; (8) Hodgkin's Disease; (9) ill-defined sites; (10) thymus and mediastinum; (11) head, face, and neck; (12) brain; (13) other malignant neoplasms of lymphoid and histiocytic tissue; (14) leukemia; (15) carcinoma in situ of the penis; and (16) carcinoma in situ of other specified sites.

In addition, analyses were conducted on malignant systemic neoplasms conditioned on the occurrence of any systemic neoplasm.

No participants were excluded for medical reasons from the analysis of these variables.

Skin and Systemic Neoplasms

All neoplasms (skin and systemic combined) were analyzed, once limited to verified neoplasms and also based on verified and suspected neoplasms. In addition, nonverifiable neoplasms were analyzed to examine overreporting.

There were no medical exclusions in the analysis of these variables.

Morbidity and Mortality Data

This portion of the analysis addressed the mortality and malignant neoplasms of fully compliant Baseline participants. For this portion, mortality and morbidity information was combined. Mortality data through the end of 1987 were used. This analysis addressed the question of whether mortality from and incidence of malignant neoplasms, among individuals not participating in the 1987 followup, affected the preceding analyses of incidence of malignant neoplasms among 1987 followup participants.

Frequencies of fully compliant Baseline participants by status (living or deceased) at the 1987 followup examination by group were tabulated. An analysis of the participants who did not return to the 1987 followup with incident or fatal neoplasms was conducted. In addition, the pattern of neoplasm incidence at the Baseline, 1985 followup, and 1987 followup was summarized, based on the fully compliant Baseline participants who also attended the 1985 and 1987 followup examinations.

No participants were excluded for medical reasons from these analyses.

Covariates

The emphasis on cancer was increased during the 1985 followup. In particular, the interval health questionnaire was modified to collect information on each geographic location in which a participant lived for more than 12 months. Because ultraviolet light exposure has been acknowledged as the primary cause of basal cell carcinoma, this information was used to compute a cumulative sun-exposure measure based on residential history. In addition, detailed information on skin tannability; eye, skin, and hair color; parental ethnicity; and lifetime smoking history was obtained. This information was obtained for participants in the 1987 followup who did not attend the 1985 followup.

In the 1987 followup, the questionnaire was expanded to capture a detailed history of alcohol consumption. Baseline questions on exposure to selected carcinogens were repeated to collect interval data. Interval smoking patterns were also captured.

The effects of 34 covariates were examined in the skin malignancy assessment in pairwise associations with basal cell carcinoma and sun exposure-related malignant skin neoplasms. Two of the matching variables, age and occupation, were used as candidate covariates in the adjusted analyses of these dependent variables. Race was not used as a covariate because analyses of skin neoplasms were limited to nonblacks. Other covariates considered for the adjusted analyses were lifetime cigarette smoking history, lifetime alcohol history, ethnic background, skin color, hair color, eye color, reactions of skin to sun exposure, a composite sun-reaction index, average lifetime residential latitude, exposure to carcinogens and groups of carcinogens, and composite carcinogen exposure. Based on an evaluation of the pairwise associations between the individual candidate covariates and the dependent variables, and a statistical modeling strategy (both of which are discussed later in this chapter), the set of 34 candidate covariates was reduced. The reduced subset of covariates that were used for the adjusted analyses of skin neoplasms consisted of occupation, age, reaction of skin after at least 2 hours sun exposure and after repeated sun exposure, ethnic background, and average lifetime residential latitude.

Definitions and categories of selected covariates are provided below:

- Ethnic Background: (A) English, Welsh, Scottish, or Irish; (B) Scandinavian, German, Polish, Russian, other Slavic, Jewish, or French; (C) Spanish, Italian, or Greek; and (D) Mexican, American Indian, or Asian; (E) African. From information collected at the 1985 followup, participants were assigned to one of these five categories based on their responses to questions on racial or ethnic group. These categories are approximate groupings in terms of susceptibility to sun-induced skin damage. Information from the 1987 followup was used for participants who did not attend the 1985 followup.

- Skin Color: dark, medium, pale, dark peach, and pale peach. Skin color was coded by the dermatologist at the 1985 physical examination. Skin color groupings from dark brown through pale peach were determined by comparing standardized flesh-colored squares[80] against the skin of the inside upper arm. Information from the 1987 followup was used for participants who did not attend the 1985 followup.

- Hair Color: black, dark brown, light brown, blonde, and red. Hair color was determined at the 1985 physical examination by comparing the hair at the back of the neck with 17 numbered standardized hair samples[81] and selecting the most closely matching hair sample. Information from the 1987 followup was used for participants who did not attend the 1985 followup.

- Eye Color: brown, hazel, green, gray, and blue. Eye color was determined during the dermatologic assessment of the 1985 physical examination. Information from the 1987 followup was used for participants who did not attend the 1985 followup.

- Reaction of Skin to Sun Exposure consisted of two reactions: (1) Assuming several preceding episodes of sun exposure, 2 or more hours of sun exposure will result in the following skin reaction: burns painfully, burns, becomes red, and no reaction. (2) Assuming repeated episodes of sun exposure, skin reaction is: freckles with no tan, tans mildly, tans moderately, and tans deep brown.

- Composite Sun-Reaction Index: A composite variable was based on the two reactions of skin to sun exposure variables and was defined as follows: (1) High: burns painfully from 2 or more hours of sun exposure (assuming several preceding episodes of sun exposure) and/or freckles with no tan (assuming repeated episodes of sun exposure); (2) Medium: burns (assuming several preceding episodes of sun exposure) and/or tans mildly (assuming repeated episodes of sun exposure); (3) Low: all other reactions.

- Average Lifetime Residential Latitude: average latitude less than 37 degrees and average greater than or equal to 37 degrees. A lifetime residential history was gathered from participants through the 1985 health interval questionnaires. The residential history, relative to the equator, was used as a surrogate measure of sun exposure. Participants were 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. Using standard geographic atlases, the latitude (in degrees and minutes) of each residence was recorded. The average lifetime residential latitude of each participant was calculated by dividing the total degree-years (i.e., the sum of latitude [degrees] times number of years lived there) from all residences by the total number of residential years listed. This information was compiled for residential histories up to the time of the 1985 followup examination.

- Exposure to Carcinogens or Groups of Carcinogens:

  Set 1: asbestos, ionizing radiation, industrial chemicals, herbicides, insecticides, and degreasing chemicals (yes/no for each). Exposure information for these items was obtained from questionnaire responses from the Baseline, 1985 followup, and 1987 followup studies and combined to create cumulative history variables.

  Set 2: anthracene, arsenic, benzene, benzidene, chromates, coal tar, creosote, aminodiphenyl, chloromethyl ether, mustard gas, naphthylamine, cutting oils, trichloroethylene, ultraviolet light (not sun), and vinyl chloride (yes/no for each). Self-reported exposure information on these 15 individual carcinogens was obtained at the 1987 followup for each participant.

  Composite Carcinogen Exposure: yes, if exposure to any carcinogen in set 2; otherwise, no.

Because of the significant confounding effect of the average lifetime residential latitude variable, an analysis of the inaccuracy of residential reporting was conducted for this covariate to evaluate reporting bias by group.

The candidate covariates for the systemic malignancy assessment were the same as those for the skin malignancy assessment with the following exceptions:

- Race was added as a candidate covariate.
- Covariates specific to skin were deleted: ethnic background, skin color, hair color, eye color, reaction of skin to sun exposure, sun-reaction index, and average lifetime residential latitude.

Relation to Baseline and 1985 Followup Studies

Most variables analyzed for the 1987 followup were analyzed in the 1985 followup. Basal cell carcinoma has replaced a similar analysis involving nonmelanoma malignant neoplasms by location and occupation (see Set 4 under Skin Neoplasm section). In general, the same variables were analyzed in the Baseline study, although less covariate information had been captured at that time.

Statistical Methods

The basic statistical analysis methods to be used in the malignancy assessment are described in Chapter 7.

Table 10-1 summarizes the statistical analyses performed for the 1987 malignancy assessment. The first part of the table identifies the dependent variables and the statistical methods. This information is presented in four sections: skin neoplasms, systemic neoplasms, skin and systemic neoplasms, and morbidity and mortality data. Data source, data form, cutpoints, and candidate covariates for dependent variables are summarized at the end of the table. The second part of the table lists the candidate covariates. Abbreviations used in the body of the table are defined in footnotes. For the skin and systemic neoplasm analyses, some covariate information was missing. The number of participants with missing data is presented in Table 10-2 by group.

RESULTS

Ranch Hand and Comparison Group Contrast

Ranch Hand and Comparison group analyses are presented for the following three sets of neoplasms: skin neoplasms, systemic neoplasms, and the combined set of skin and systemic neoplasms. For the skin and systemic neoplasm sets, the results of unadjusted analyses are presented first, followed by a discussion of covariate associations with the dependent variables, and then the results from adjusted analyses are presented. For the combined set of skin and systemic neoplasms, only unadjusted analyses were performed.

TABLE 10-1.

Statistical Analysis for the Malignancy Assessment

Dependent Variables

Category	Location/ Site	Statistical Analyses
	Skin Neoplasms	
Behavior		
Malignant	All	UC:FT
Benign	All	UC:FT
Uncertain Behavior or Unspecified Nature	All	UC:FT
All	All	UC:FT
Cell Type		
Basal Cell Carcinoma	All	UC:FT AC:LR CA:CS,FT UE:CS,FT AE:LR
Squamous Cell Carcinoma	All	UC:FT
Melanoma	All	UC:FT
Sun Exposure-Related Malignant	All	UC:FT AC:LR CA:CS,FT UE:CS,FT AE:LR
Cell Type and Location/Site		
Basal Cell Carcinoma	Ear, Face, Head, and Neck Trunk Upper Extremities Lower Extremities Other Sites and NOS	UC:FT

TABLE 10-1. (continued)

Statistical Analysis for the Malignancy Assessment

Dependent Variables

Category	Location/ Site	Statistical Analyses
	Skin Neoplasms	
Melanoma	Ear, Face, Head, and Neck Trunk Upper Extremities Lower Extremities Other Sites and NOS	UC:FT
Sun Exposure-Related Malignant	Ear, Face, Head, and Neck Trunk Upper Extremities Lower Extremities Other Sites and NOS	UC:FT
Cell Type and Location/Site by Occupation		
Basal Cell Carcinoma	Ear, Face, Head, and Neck All Other Sites and NOS None	UC:CS,FT
Sun Exposure-Related Malignant	Ear, Face, Head, and Neck All Other Sites and NOS None	UC:CS,FT
Conditional Analyses		
Skin Neoplasm Conditioned on Neoplasm	All	UC:FT
Malignant Skin Neoplasm Conditioned on Skin Neoplasm	All	UC:FT
Basal Cell Carcinoma Conditioned on Malignant Skin Neoplasm	All	UC:FT
Basal Cell Carcinoma Conditioned on Basal Cell Carcinoma	Ear, Face, Head, Neck, or Upper Extremities	UC:FT

TABLE 10-1. (continued)

Statistical Analysis for the Malignancy Assessment

Dependent Variables

Category	Location/ Site	Statistical Analyses
Skin Neoplasms		
Sun Exposure-Related Malignant Conditioned on Sun Exposure-Related Malignant	Ear, Face, Head, Neck, or Upper Extremities	UC:FT
Multiple Basal Cell Carcinoma	All	UC:CS,FT
Systemic Neoplasms		
Behavior		
Malignant	All	UC:FT AC:LR CA:CS,FT UE:CS,FT AE:LR
Benign	All	UC:FT
Uncertain Behavior or Unspecified Nature	All	UC:FT
All	All	UC:FT
Location/Site or Type		
Malignant	Oral Cavity, Pharynx and Larynx	UC:FT
Malignant	Thyroid Gland	UC:FT
Malignant	Bronchus and Lung	UC:FT
Malignant	Colon and Rectum	UC:FT
Malignant	Kidney and Bladder	UC:FT
Malignant	Prostate	UC:FT
Malignant	Testicles	UC:FT

TABLE 10-1. (continued)

Statistical Analysis for the Malignancy Assessment

Dependent Variables

Category	Location/ Site	Statistical Analyses
	Systemic Neoplasms	
Hodgkin's Disease	--	UC:FT
Malignant	Ill-Defined Sites	UC:FT
Malignant	Thymus and Mediastinum	UC:FT
Malignant	Head, Face, and Neck	UC:FT
Malignant	Brain	UC:FT
Malignant	Other Malignant Neoplasms of Lymphoid and Histiocytic Tissue	UC:FT
Leukemia	--	UC:FT
Malignant	Carcinoma In Situ of Penis	UC:FT
Malignant	Carcinoma In Situ of Other Specified Sites	UC:FT
Conditional Analysis		
Malignant Conditioned on Systemic	All	UC:FT
	Skin and Systemic Neoplasms	
All	All	UC:FT
Nonverifiable	All	UC:FT
	Morbidity and Mortality Data	
Malignant (Did Not Participate in 1987 Followup)	All	UC:FT
Neoplasm Incidence Pattern	All	UC:FS

TABLE 10-1. (continued)

Statistical Analysis for the Malignancy Assessment

Covariates

Variable (Abbreviation)	Data Source	Data Form	Cutpoints
Age (AGE)	MIL	D/C	Born >1942 Born 1923-1941 Born ≤1922
Race (RACE)	MIL	D	Nonblack Black
Occupation (OCC)	MIL	D	Officer Enlisted Flyer Enlisted Groundcrew
Lifetime Cigarette Smoking History (PACKYR) (pack-years)	Q-SR	D/C	0 >0-10 >10
Lifetime Alcohol History (DRKYR) (drink-years)	Q-SR	D/C	0 >0-40 >40
Average Lifetime Residential Latitude (LAT)	Q-SR (1985)	D	Latitude <37° Latitude ≥37°
Asbestos Exposure (ASB)	Q-SR	D	Yes No
Ionizing Radiation Exposure (RAD)	Q-SR	D	Yes No
Industrial Chemical Exposure (IC)	Q-SR	D	Yes No
Herbicide Exposure (HERB)	Q-SR	D	Yes No
Insecticide Exposure (INS)	Q-SR	D	Yes No
Degreasing Chemical Exposure (DC)	Q-SR	D	Yes No
Anthracene Exposure (ANTH)	Q-SR	D	Yes No

TABLE 10-1. (continued)

Statistical Analysis for the Malignancy Assessment

Covariates

Variable (Abbreviation)	Data Source	Data Form	Cutpoints
Arsenic Exposure (ARS)	Q-SR	D	Yes No
Benzene Exposure (BENZ)	Q-SR	D	Yes No
Benzidene Exposure (BENZID)	Q-SR	D	Yes No
Chromate Exposure (CHROM)	Q-SR	D	Yes No
Coal Tar Exposure (COALTAR)	Q-SR	D	Yes No
Creosote Exposure (CREOS)	Q-SR	D	Yes No
Aminodiphenyl Exposure (AMDIPHEN)	Q-SR	D	Yes No
Chloromethyl Ether Exposure (CHLMETETH)	Q-SR	D	Yes No
Mustard Gas Exposure (MUSTGAS)	Q-SR	D	Yes No
Naphthylamine Exposure (NAPTHYL)	Q-SR	D	Yes No
Cutting Oil Exposure (CUTOIL)	Q-SR	D	Yes No
Trichloroethylene Exposure (TRICHLETH)	Q-SR	D	Yes No
Ultraviolet Light (Not Sun) Exposure (ULTLIGHT)	Q-SR	D	Yes No
Vinyl Chloride Exposure (VINCHL)	Q-SR	D	Yes No

TABLE 10-1. (continued)

Statistical Analysis for the Malignancy Assessment

Covariates

Variable (Abbreviation)	Data Source	Data Form	Cutpoints
Composite Carcinogen Exposure (CARCIN)	Q-SR	D	Yes No
Ethnic Background (ETHBACK)	Q-SR (1985)	D	A: English, Welsh, Scottish, or Irish B: Scandinavian, German, Polish, Russian, other Slavic, Jewish, or French C: Spanish, Italian, or Greek D: Mexican, American Indian, or Asian E: African
Skin Color (SKIN)	PE (1985)	D	Dark Medium Pale Dark Peach Pale Peach
Hair Color (HAIR)	PE (1985)	D	Black Dark Brown Light Brown Blonde Red
Eye Color (EYE)	PE (1985)	D	Brown Hazel Green Gray Blue
Reaction of Skin to Sun After at Least 2 Hours of Sun Exposure (assuming several preceding episodes) (SUN2HR)	Q-SR	D	Burns Painfully Burns Becomes Red No Reaction
Reaction of Skin to Sun After Repeated Exposure (SUNREPEAT)	Q-SR	D	Freckles with No Tan Tans Mildly Tans Moderately Tans Deep Brown

TABLE 10-1. (continued)

Statistical Analysis for the Malignancy Assessment

Covariates

Variable (Abbreviation)	Data Source	Data Form	Cutpoints
Composite Sun-Reaction Index (SUNREAC)	Q-SR	D	High: Burns Painfully (for SUN2HR) or Freckles With No Tan (for SUNREPEAT) Medium: Burns (for SUN2HR) or Tans Mildly (for SUNREPEAT) Low: All Other Reactions

Dependent Variables:

Data Source: All AFHS questionnaires and physical examinations

Data Form: Discrete

Cutpoints: Yes/No

Candidate Covariates for Skin Neoplasms: all covariates listed above except race

Candidate Covariates for Systemic Neoplasms: all covariates listed above except ethnic background, skin color, hair color, eye color, reaction of skin to sun exposure, composite sun-reaction index, and average lifetime residential latitude

Analyses: All analyses were conducted twice--verified only, and verified and suspected

Abbreviations:

Data Source:
- MIL--Air Force military records
- PE (1985)--1985 SCRF physical examination: updated with 1987 SCRF information for new/rejoining participants
- Q-SR--1987 NORC questionnaire (self-reported)
- Q-SR (1985)--1985 NORC questionnaire (self-reported)

Data Form:
- D--Discrete analysis only
- D/C--Appropriate form for analysis (either discrete or continuous)

TABLE 10-1. (continued)

Statistical Analysis for the Malignancy Assessment

Abbreviations (continued):

Statistical Analyses:	UC--Unadjusted core analyses AC--Adjusted core analyses CA--Dependent variable-covariate associations UE--Unadjusted exposure index analyses AE--Adjusted exposure index analyses
Statistical Methods:	CS--Chi-square contingency table test FT--Fisher's exact test LR--Logistic regression analysis FS--Frequency summary
Other:	NOS--Not otherwise specified

TABLE 10-2.

Number of Participants With Missing Data for the Malignancy Assessment by Group

Variable	Analysis Use	Group: Ranch Hand	Group: Comparison	Total
Lifetime Alcohol History	COV	10	3	13
Average Lifetime Residential Latitude*	COV	2	6	8
Anthracene Exposure	COV	1	2	3
Arsenic Exposure	COV	1	2	3
Benzene Exposure	COV	0	1	1
Benzidene Exposure	COV	0	3	3
Chromate Exposure	COV	3	2	5
Coal Tar Exposure	COV	0	1	1
Creosote Exposure	COV	0	1	1
Aminodiphenyl Exposure	COV	0	3	3
Chloromethyl Ether Exposure	COV	2	1	3
Mustard Gas Exposure	COV	0	1	1
Naphthylamine Exposure	COV	1	2	3
Cutting Oil Exposure	COV	0	1	1
Trichloroethylene Exposure	COV	5	2	7
Ultraviolet Light (Not Sun) Exposure	COV	0	2	2
Vinyl Chloride Exposure	COV	1	2	3
Composite Carcinogen Exposure	COV	13	11	24
Ethnic Background*	COV	24	28	52

TABLE 10-2. (continued)

Number of Participants With Missing Data for the Malignancy Assessment by Group

Variable	Analysis Use	Group: Ranch Hand	Group: Comparison	Total
Skin Color*	COV	1	0	1
Hair Color*	COV	0	1	1
Eye Color*	COV	1	2	3
Reaction of Skin to Sun After at Least 2 Hours of Sun Exposure (assuming several preceding episodes)	COV	0	1	1
Reaction of Skin to Sun After Repeated Exposure*	COV	0	1	1
Composite Sun Reaction Index*	COV	0	2	2

Abbreviations: COV--Covariate

*Nonblacks only.

Skin Neoplasms

Ranch Hands and Comparisons were compared on their relative frequencies of skin neoplasms for the following six groups of analyses: behavior, cell type, cell type and location/site, selected cell type and location/site by occupation, selected neoplasms conditioned on the presence of a specified neoplasm, and the occurrence of multiple basal cell carcinomas. For the assessment of cell type, covariate associations and the adjusted group analyses were performed for basal cell carcinoma and sun exposure-related malignant skin neoplasms.

Behavior

The unadjusted skin neoplasm analyses were based on 938 nonblack Ranch Hands and 1,219 nonblack Comparisons. Table 10-3 summarizes the Ranch Hand and Comparison frequency distributions for each of the following: malignant skin neoplasms, benign skin neoplasms, skin neoplasms of uncertain behavior or unspecified nature, and all skin neoplasms. For each of these neoplasms, unadjusted analyses were performed for verified neoplasms and for the verified and suspected neoplasms combined.

The Ranch Hands and Comparisons differed significantly ($p=0.047$) on the relative frequency of verified malignant skin neoplasms. The estimated relative risk for Ranch Hands versus Comparisons was 1.38 (95% C.I.: [1.02,1.88]). Among the Ranch Hands, 9.7 percent had a verified malignant skin neoplasm, contrasted with 7.2 percent for the Comparisons. For verified and suspected malignant skin neoplasms combined, the group difference was not significant ($p=0.101$).

For verified benign neoplasms, the Ranch Hand and Comparison groups did not differ significantly ($p=0.292$). There were no suspected benign skin neoplasms for either group.

For the verified skin neoplasms of uncertain behavior or unspecified nature, the Ranch Hand and Comparison groups did not differ significantly ($p=0.442$). For the verified and suspected skin neoplasms of uncertain behavior or unspecified nature, the Ranch Hand and Comparison contrast also was not significant ($p=0.758$).

For all verified skin neoplasms (malignant, benign, or uncertain), there was a significant difference between the Ranch Hand and Comparison groups ($p=0.012$). For this aggregation of skin neoplasms, the estimated relative risk for Ranch Hands versus Comparisons was 1.37 (95% C.I.: [1.08,1.74]). The percentage of Ranch Hands with a verified skin neoplasm was 16.7 percent versus 12.8 percent for the Comparisons. For all verified and suspected skin neoplasms, the Ranch Hands and Comparisons also differed significantly ($p=0.029$) with an associated estimated relative risk of 1.31 (95% C.I.: [1.04,1.66]). The Ranch Hand and Comparison relative frequencies for the verified and suspected set of skin neoplasms were 16.8 percent and 13.4 percent, respectively.

TABLE 10-3.

Unadjusted Analysis for Skin Neoplasms by Behavior, Status, and Group (Nonblacks Only)

Behavior (Status)	Statistic	Group				Est. Relative Risk (95% C.I.)	p-Value
		Ranch Hand		Comparison			
Malignant (Verified)	n	938		1,219			
	Number/%						
	Yes	91	9.7%	88	7.2%	1.38 (1.02,1.88)	0.047
	No	847	90.3%	1,131	92.8%		
Malignant (Verified and Suspected)	n	938		1,219			
	Number/%						
	Yes	92	9.8%	94	7.7%	1.30 (0.96,1.76)	0.101
	No	846	90.2%	1,125	92.3%		
Benign (Verified*)	n	938		1,219			
	Number/%						
	Yes	66	7.0%	71	5.8%	1.22 (0.87,1.73)	0.292
	No	872	93.0%	1,148	94.2%		
Uncertain Behavior or Unspecified Nature (Verified)	n	938		1,219			
	Number/%						
	Yes	3	0.3%	1	0.1%	3.91 (0.41,37.63)	0.442
	No	935	99.7%	1,218	99.9%		

TABLE 10-3. (continued)

Unadjusted Analysis for Skin Neoplasms by Behavior, Status, and Group
(Nonblacks Only)

Behavior (Status)	Statistic	Group: Ranch Hand		Group: Comparison		Est. Relative Risk (95% C.I.)	p-Value
Uncertain Behavior or Unspecified Nature (Verified and Suspected)	n	938		1,219			
	Number/%						
	Yes	3	0.3%	2	0.2%	1.95 (0.33,11.71)	0.758
	No	935	99.7%	1,217	99.8%		
All (Verified)	n	938		1,219			
	Number/%						
	Yes	157	16.7%	156	12.8%	1.37 (1.08,1.74)	0.012
	No	781	83.3%	1,063	87.2%		
All (Verified and Suspected)	n	938		1,219			
	Number/%						
	Yes	158	16.8%	163	13.4%	1.31 (1.04,1.66)	0.029
	No	780	83.2%	1,056	86.6%		

*No suspected neoplasms; therefore, verified and suspected same as verified.

Cell Type

The occurrence of malignant skin neoplasms in the Ranch Hand and Comparison groups was also analyzed with respect to the individual neoplasm being classified as basal cell, squamous cell, melanoma, or sun exposure-related (i.e., neoplasms classified as basal cell carcinoma, squamous cell carcinoma, melanoma, and malignant epithelial neoplasm NOS). Table 10-4 presents unadjusted results of comparing the Ranch Hand and Comparison groups for each cell type, for both the verified and the verified and suspected malignant skin neoplasms.

For verified basal cell carcinoma, the Ranch Hand and Comparison contrast was borderline significant ($p=0.076$) with an estimated relative risk of 1.36 (95% C.I.: [0.98,1.89]). The Ranch Hands had a higher relative frequency of verified basal cell carcinoma than the Comparisons (8.3% vs. 6.2%). When suspected basal cell carcinomas were included with the verified basal cell carcinoma, the Ranch Hand and Comparison groups were not significantly different ($p=0.140$).

The unadjusted analysis of verified squamous cell carcinoma for the Ranch Hand and Comparison groups was not significant ($p=0.656$). There were no suspected squamous cell carcinomas.

For verified melanoma, the Ranch Hand and Comparison groups did not differ ($p=0.976$). There were no suspected melanomas.

The contrast of Ranch Hand and Comparison relative frequencies of verified sun exposure-related malignant skin neoplasms was significant ($p=0.042$) with an estimated relative risk of 1.40 (95% C.I.: [1.02,1.91]). For Ranch Hands, the frequency of verified sun exposure-related malignant skin neoplasms was 9.4 percent versus 6.9 percent for the Comparisons. For the verified and suspected sun exposure-related malignant skin neoplasms, the relative frequency of 9.5 percent for the Ranch Hand group was marginally significant ($p=0.081$) when compared to the relative frequency of 7.3 percent for the Comparison group. This Ranch Hand and Comparison contrast for verified and suspected sun exposure-related malignant skin neoplasms had an estimated relative risk of 1.33 (95% C.I.: [0.98,1.81]).

Cell Type and Location/Site

Table 10-5 summarizes the unadjusted analyses of the Ranch Hand and Comparison relative frequencies of verified basal cell carcinoma and verified and suspected basal cell carcinoma at the following locations/sites: ear, face, head, and neck; trunk; upper extremities; lower extremities; and other sites including sites NOS. For each location/site, the frequency of verified basal cell carcinoma among Ranch Hands was not significantly different from that of the Comparisons (ear, face, head, and neck: $p=0.456$; trunk: $p=0.310$; upper extremities: $p=0.193$; other sites: $p=0.462$). No verified basal cell carcinomas of the lower extremities were found for either the Ranch Hands or the Comparisons, and there were no suspected basal cell carcinomas of the upper or lower extremities for either group. No significant results were found when suspected basal cell carcinomas were included with the verified basal cell carcinomas (ear, face, head, and neck: $p=0.554$; trunk: $p=0.384$; other sites: $p=0.720$).

TABLE 10-4.

Unadjusted Analysis for Malignant Skin Neoplasms by Cell Type, Status, and Group (Nonblacks Only)

Cell Type (Status)	Statistic	Group: Ranch Hand		Group: Comparison		Est. Relative Risk (95% C.I.)	p-Value
Basal Cell Carcinoma (Verified)	n	938		1,219			
	Number/%						
	Yes	78	8.3%	76	6.2%	1.36 (0.98,1.89)	0.076
	No	860	91.7%	1,143	93.8%		
Basal Cell Carcinoma (Verified and Suspected)	n	938		1,219			
	Number/%						
	Yes	79	8.4%	81	6.6%	1.29 (0.94,1.78)	0.140
	No	859	91.6%	1,138	93.4%		
Squamous Cell Carcinoma (Verified*)	n	938		1,219			
	Number/%						
	Yes	6	0.6%	5	0.4%	1.56 (0.48,5.14)	0.656
	No	932	99.4%	1,214	99.6%		
Melanoma (Verified*)	n	938		1,219			
	Number/%						
	Yes	4	0.4%	4	0.3%	1.30 (0.32,5.22)	0.976
	No	934	99.6%	1,215	99.7%		
Sun Exposure-Related (Verified)	n	938		1,219			
	Number/%						
	Yes	88	9.4%	84	6.9%	1.40 (1.02,1.91)	0.042
	No	850	90.6%	1,135	93.1%		

TABLE 10-4. (continued)

Unadjusted Analysis for Malignant Skin Neoplasms by Cell Type, Status, and Group
(Nonblacks Only)

Cell Type (Status)	Statistic	Group				Est. Relative Risk (95% C.I.)	p-Value
		Ranch Hand		Comparison			
Sun Exposure-Related (Verified and Suspected)	n	938		1,219			
	Number/%						
	Yes	89	9.5%	89	7.3%	1.33 (0.98,1.81)	0.081
	No	849	90.5%	1,130	92.7%		

*No suspected malignant neoplasms; therefore, verified and suspected same as verified.

TABLE 10-5.

Unadjusted Analysis for Basal Cell Carcinoma by Location/Site, Status, and Group (Nonblacks Only)

Location/Site (Status)	Statistic	Group: Ranch Hand		Group: Comparison		Est. Relative Risk (95% C.I.)	p-Value
Ear, Face, Head, and Neck (Verified)	n	938		1,219			
	Number/%						
	Yes	53	5.7%	59	4.8%	1.18 (0.80,1.72)	0.456
	No	885	94.3%	1,160	95.2%		
Ear, Face, Head, and Neck (Verified and Suspected)	n	938		1,219			
	Number/%						
	Yes	54	5.8%	62	5.1%	1.14 (0.78,1.66)	0.554
	No	884	94.2%	1,157	94.9%		
Trunk (Verified)	n	938		1,219			
	Number/%						
	Yes	22	2.3%	20	1.6%	1.44 (0.78,2.65)	0.310
	No	916	97.7%	1,199	98.4%		
Trunk (Verified and Suspected)	n	938		1,219			
	Number/%						
	Yes	22	2.3%	21	1.7%	1.37 (0.75,2.51)	0.384
	No	916	97.7%	1,198	98.3%		
Upper Extremities (Verified*)	n	938		1,219			
	Number/%						
	Yes	9	1.0%	5	0.4%	2.35 (0.79,7.04)	0.193
	No	929	99.0%	1,214	99.6%		

TABLE 10-5. (continued)

Unadjusted Analysis for Basal Cell Carcinoma by Location/Site, Status, and Group
(Nonblacks Only)

Location/Site (Status)	Statistic	Group: Ranch Hand		Group: Comparison		Est. Relative Risk (95% C.I.)	p-Value
Lover Extremities (Verified*)	n	938		1,219			
	Number/%						
	Yes	0	0.0%	0	0.0%	--[a]	--[a]
	No	938	100.0%	1,219	100.0%		
Other Sites (Verified)	n	938		1,219			
	Number/%						
	Yes	4	0.4%	2	0.2%	2.61 (0.48,14.26)	0.462
	No	934	99.6%	1,217	99.8%		
Other Sites (Verified and Suspected)	n	938		1,219			
	Number/%						
	Yes	4	0.4%	3	0.2%	1.74 (0.39,7.78)	0.720
	No	934	99.6%	1,216	99.8%		

*No suspected malignant neoplasms; therefore, verified and suspected same as verified.

--[a]Estimated relative risk/confidence interval/p-value not given due to cells with zero frequency.

Table 10-6 presents the unadjusted analyses of the Ranch Hand and Comparison relative frequencies of verified melanoma by location/site. There were no suspected cases of melanoma; therefore, only unadjusted analyses for verified melanoma were performed. The Ranch Hand and Comparison groups did not differ with respect to the frequency of verified melanoma on the ear, face, head, and neck ($p=0.870$). No group difference was found for verified melanoma on the trunk ($p=0.999$). No verified melanomas on the upper extremities, lower extremities, or other sites were observed in either the Ranch Hand group or the Comparison group.

Table 10-7 summarizes the unadjusted group contrast analyses for each of the specified locations/sites of interest for verified, and verified and suspected, sun exposure-related malignant skin neoplasms. There was no significant group difference ($p=0.260$) for verified sun exposure-related malignant skin neoplasms on the ear, face, head, and neck, nor was there a significant group difference ($p=0.330$) at these sites when verified and suspected sun exposure-related malignant skin neoplasms were combined. For sun exposure-related malignant skin neoplasms on the trunk, the Ranch Hands and Comparisons also did not differ significantly for the verified set ($p=0.342$) or the verified and suspected set ($p=0.412$). For upper extremity sites, the Ranch Hand group had a significantly higher frequency of verified sun exposure-related malignant skin neoplasms relative to the Comparisons ($p=0.044$). The estimated relative risk associated with this difference was 3.15 (95% C.I.: [1.11,8.96]), based on the Ranch Hand frequency of 1.3 percent versus the Comparison frequency of 0.4 percent. For the upper extremities, there were no suspected sun exposure-related malignant skin neoplasms. Neither group had a verified or suspected sun exposure-related malignant skin neoplasm on the lower extremities. For other sites, Ranch Hands and Comparisons did not differ on the frequency of sun exposure-related malignant skin neoplasms for either the verified set ($p=0.462$) or the verified and suspected set ($p=0.720$).

Basal Cell Carcinoma and Sun Exposure-Related Malignant Skin Neoplasms Occurring on the Ear, Face, Head, and Neck by Occupation

For each occupational stratum, Ranch Hands and Comparisons were compared on their relative frequencies of both basal cell carcinoma and sun exposure-related malignant skin neoplasms for the following three categories: malignant skin neoplasms of the ear, face, head, and neck; malignant skin neoplasms of all other sites; and no malignant skin neoplasms. Malignant skin neoplasms on the ear, face, head, or neck took precedence over other locations/sites (i.e., if a participant had a malignant skin neoplasm on the ear, face, head, or neck and also another site, he was assigned to the former classification). The analyses were performed using only verified malignant skin neoplasms and were also repeated aggregating the verified and suspected malignant skin neoplasms. Table 10-8 summarizes the results of these analyses.

For each occupation, no significant group differences were found for verified basal cell carcinoma (officers: $p=0.107$; enlisted flyers: $p=0.130$; enlisted groundcrew: $p=0.857$). Analyses of verified and suspected basal cell carcinoma also produced no significant overall group differences by occupation (officers: $p=0.176$; enlisted flyers: $p=0.133$; enlisted groundcrew: $p=0.917$).

TABLE 10-6.

Unadjusted Analysis for Melanoma by Location/Site, Status, and Group (Nonblacks Only)

Location/Site (Status)	Statistic	Group: Ranch Hand	Group: Comparison	Est. Relative Risk (95% C.I.)	p-Value
Ear, Face, Head, and Neck (Verified*)	n	938	1,219		
	Number/%				
	Yes	1 0.1%	0 0.0%	--[a]	0.870
	No	937 99.9%	1,219 100.0%		
Trunk (Verified*)	n	938	1,219		
	Number/%				
	Yes	3 0.3%	4 0.3%	0.98 (0.22,4.37)	0.999
	No	935 99.7%	1,215 99.7%		
Upper Extremities (Verified*)	n	938	1,219		
	Number/%				
	Yes	0 0.0%	0 0.0%	--[a]	--[a]
	No	938 100.0%	1,219 100.0%		
Lower Extremities (Verified*)	n	938	1,219		
	Number/%				
	Yes	0 0.0%	0 0.0%	--[a]	--[a]
	No	938 100.0%	1,219 100.0%		

TABLE 10-6. (continued)

Unadjusted Analysis for Melanoma by Location/Site, Status, and Group
(Nonblacks Only)

Location/Site (Status)	Statistic	Group: Ranch Hand	Group: Comparison	Est. Relative Risk (95% C.I.)	p-Value
Other Sites (Verified*)	n	938	1,219		
	Number/%				
	Yes	0 0.0%	0 0.0%	--[a]	--[a]
	No	938 100.0%	1,219 100.0%		

*No suspected malignant neoplasms; therefore, verified and suspected same as verified.

--[a]Estimated relative risk/confidence interval/p-value not given due to cells with zero frequency.

TABLE 10-7.

Unadjusted Analysis for Sun Exposure-Related Malignant Skin Neoplasms by Location/Site, Status, and Group (Nonblacks Only)

Location/Site (Status)	Statistic	Group				Est. Relative Risk (95% C.I.)	p-Value
		Ranch Hand		Comparison			
Ear, Face, Head, and Neck (Verified)	n	938		1,219			
	Number/%						
	Yes	60	6.4%	63	5.2%	1.25 (0.87,1.81)	0.260
	No	878	93.6%	1,156	94.8%		
Ear, Face, Head, and Neck (Verified and Suspected)	n	938		1,219			
	Number/%						
	Yes	61	6.5%	66	5.4%	1.22 (0.85,1.74)	0.330
	No	877	93.5%	1,153	94.6%		
Trunk (Verified)	n	938		1,219			
	Number/%						
	Yes	26	2.8%	25	2.1%	6 (0.78,2.37)	0.342
	No	912	97.2%	1,194	97.9%		
Trunk (Verified and Suspected)	n	938		1,219			
	Number/%						
	Yes	26	2.8%	26	2.1%	.31 (0.75,2.27)	0.412
	No	912	97.2%	1,193	97.9%		
Upper Extremities (Verified*)	n	938		1,219			
	Number/%						
	Yes	12	1.3%	5	0.4	3.15 (1.11,8.96)	0.044
	No	926	98.7%	1,214	99.6		

TABLE 10-7. (continued)

Unadjusted Analysis for Sun Exposure-Related Malignant Skin Neoplasms
by Location/Site, Status, and Group (Nonblacks Only)

Location/Site (Status)	Statistic	Group: Ranch Hand		Group: Comparison		Est. Relative Risk (95% C.I.)	p-Value
Lower Extremities (Verified*)	n	938		1,219			
	Number/%						
	Yes	0	0.0%	0	0.0%	--[a]	--[a]
	No	938	100.0%	1,219	100.0%		
Other Sites (Verified)	n	938		1,219			
	Number/%						
	Yes	4	0.4%	2	0.2%	2.61 (0.48,14.26)	0.462
	No	934	99.6%	1,217	99.8%		
Other Sites (Verified and Suspected)	n	938		1,219			
	Number/%						
	Yes	4	0.4%	3	0.2%	1.74 (0.39,7.78)	0.720
	No	934	99.6%	1,216	99.8%		

*No suspected malignant neoplasms; therefore, verified and suspected same as verified.

--[a]Estimated relative risk/confidence interval/p-value not given due to cells with zero frequency.

TABLE 10-8.

Unadjusted Analysis of Basal Cell Carcinoma and Sun Exposure-Related Malignant Neoplasms on the Ear, Face, Head, and Neck or Other Sites by Occupation (Nonblacks Only)

Cell Type (Status)	Occupation	Statistic	Group: Ranch Hand		Group: Comparison		Contrast	Est. Relative Risk (95% C.I.)	p-Value
Basal Cell Carcinoma (Verified)	Officer	n	372		488				
		Number/%							
		Ear, Face, Head, and Neck	30	8.1%	26	5.3%	Overall		0.107
		Other Sites	11	3.0%	8	1.6%	EFHN vs. None	1.58 (0.92,2.73)	0.128
		No Cancer	331	89.0%	454	93.0%	Other vs. None	1.89 (0.75,4.74)	0.256
	Enlisted Flyer	n	163		196				
		Number/%							
		Ear, Face, Head, and Neck	8	4.9%	12	6.1%	Overall		0.130
		Other Sites	7	4.3%	2	1.0%	EFHN vs. None	0.82 (0.33,2.06)	0.854
		No Cancer	148	90.8%	182	92.9%	Other vs. None	4.30 (0.88,21.03)	0.104
	Enlisted Groundcrew	n	403		535				
		Number/%							
		Ear, Face, Head, and Neck	15	3.7%	21	3.9%	Overall		0.857
		Other Sites	7	1.7%	7	1.3%	EFHN vs. None	0.95 (0.48,1.87)	0.999
		No Cancer	381	94.5%	507	94.8%	Other vs. None	1.33 (0.46,3.83)	0.786

TABLE 10-8. (continued)

Unadjusted Analysis of Basal Cell Carcinoma and Sun Exposure-Related Malignant Neoplasms on the Ear, Face, Head, and Neck or Other Sites by Occupation (Nonblacks Only)

Cell Type (Status)	Occupation	Statistic	Group: Ranch Hand		Group: Comparison		Contrast	Est. Relative Risk (95% C.I.)	p-Value
Basal Cell Carcinoma (Verified and Suspected)	Officer	n	372		488				
		Number/%							
		Ear, Face, Head, and Neck	30	8.1%	27	5.5%	Overall		0.176
		Other Sites	11	3.0%	9	1.8%	EFHN vs. None	1.52 (0.89,2.60)	0.167
		No Cancer	331	89.0%	452	92.6%	Other vs. None	1.67 (0.68,4.07)	0.364
	Enlisted Flyer	n	163		196				
		Number/%							
		Ear, Face, Head, and Neck	9	5.5%	13	6.6%	Overall		0.133
		Other Sites	7	4.3%	2	1.0%	EFHN vs. None	0.85 (0.36,2.05)	0.898
		No Cancer	147	90.2%	181	92.4%	Other vs. None	4.31 (0.88,21.06)	0.104
	Enlisted Groundcrew	n	403		535				
		Number/%							
		Ear, Face, Head, and Neck	15	3.7%	22	4.1%	Overall		0.917
		Other Sites	7	1.7%	8	1.5%	EFHN vs. None	0.90 (0.46,1.77)	0.906
		No Cancer	381	94.5%	505	94.4%	Other vs. None	1.16 (0.42,3.23)	0.974

TABLE 10-8. (continued)

Unadjusted Analysis of Basal Cell Carcinoma and Sun Exposure-Related Malignant Neoplasms on the Ear, Face, Head, and Neck or Other Sites by Occupation (Nonblacks Only)

Cell Type (Status)	Occupation	Statistic	Group: Ranch Hand		Group: Comparison		Contrast	Est. Relative Risk (95% C.I.)	p-Value
Sun Exposure-Related Malignant Skin Neoplasms (Verified)	Officer	n	372		488				
		Number/%							
		Ear, Face, Head, and Neck	34	9.1%	29	5.9%	Overall		0.078
		Other Sites	13	3.5%	10	2.1%	EFHN vs. None	1.62 (0.97,2.71)	0.088
		No Cancer	325	87.4%	449	92.0%	Other vs. None	1.80 (0.78,4.15)	0.240
	Enlisted Flyer	n	163		196				
		Number/%							
		Ear, Face, Head, and Neck	10	6.1%	12	6.1%	Overall		0.284
		Other Sites	7	4.3%	3	1.5%	EFHN vs. None	1.03 (0.43,2.46)	0.999
		No Cancer	146	89.6%	181	92.4%	Other vs. None	2.89 (0.74,11.38)	0.206
	Enlisted Groundcrew	n	403		535				
		Number/%							
		Ear, Face, Head, and Neck	16	4.0%	22	4.1%	Overall		0.845
		Other Sites	8	2.0%	8	1.5%	EFHN vs. None	0.97 (0.50,1.87)	0.999
		No Cancer	379	94.0%	505	94.4%	Other vs. None	1.33 (0.50,3.58)	0.746