Cancer Incidence Among Employees of the Lawrence Livermore National Laboratory, 1969-1980

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The cancer incidence from 1969 through 1980 among active members of an occupational cohort (the Lawrence Livermore National Laboratory [LLNL]) was compared with that of the same-age sector of the total population of the San Francisco-Oakland Standard Metropolitan Statistical Area. Excesses were found for malignant melanoma of the skin and salivary gland tumors and a deficit for lung cancer in men. No excesses were noted for radiosensitive tissue groups. The overall incidence of cancer among LLNL employees for this time period is approximately that for the general population.

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An earlier study established that a fourfold excess incidence of malignant melanoma of the skin occurred among employees of the Lawrence Livermore National Laboratory (LLNL) between 1972 and 1977.[1] The LLNL is a high-technology, high-energy physics research facility in Alameda County, California. This study was undertaken to establish whether or not there was an unusual occurrence for any other site of cancer in this occupational cohort.

This has not been designed to be a study of radiation and cancer, but because of public and professional interest in the etiologic significance that radiation may have in this very specialized work force, we have grouped cancer sites by radiosensitivity criteria. This may serve as an indirect indicator of any unusual patterns of radiation-induced tumors.

There are three major sources of epidemiologic information on radiosensitive sites of cancer: follow-up studies of Hiroshima and Nagasaki survivors, occupational mortality studies of radiologists and patient series of persons exposed to therapeutic sources of radiation (primarily those with tinea capitis, ankylosing spondylitis, tuberculosis and thyroid disease).[2-4] There have also been a few mortality studies of radiation workers.[5-8] Interpretation of these data is complex because the probable carcinogenic effects of radiation are thought to be both a function of tissue-specific responses to the source and dosage of radiation and of host factors such as age and sex. There is a high level of agreement that human leukemia (excluding chronic lymphocytic leukemia) and cancers of the thyroid and bone marrow can be induced by a variety of radiation sources. The evidence is less clear for other sites of cancer, but tissues of the lung and female breast appear to be moderately radiosensitive.

Our study was designed to compare the incidence of all sites of cancer among active LLNL employees with that expected in the same age/sex population of the San Francisco-Oakland Standard Metropolitan Statistical Area (SMSA). We have also considered the LLNL cancer experience in three broad cancer categories (high, medium and low) of risk associated with ionizing radiation.

Subjects and Methods

The study cohort consisted of all active 1969-1980 LLNL employees between the ages of 20 and 69 years who resided in the San Francisco-Oakland SMSA. Person-years of observation were computed for the 12-year period by summing the annual distribution of eligible employee months by sex and 5-year age groups. No minimum period of employment was required to be included in the population at risk. The period of observation was limited to the period of active employment at the LLNL and ended with termination of employment or December 31, 1980, whichever came first. Total person-years of observation are listed in Table 1.

For this study, "observed" cases of cancer were tabulated only for employees whose date of diagnosis was concurrent with active employment at the LLNL and whose residence was within the Resource for Cancer Epidemiology (RCE) case ascertainment area. Cancer diagnoses (observed num-

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ABBREVIATIONS USED IN TEXT
LLNL = Lawrence Livermore National Laboratory
RCE = Resource for Cancer Epidemiology
SEER = Surveillance Epidemiology and End Results
SMSA = Standard Metropolitan Statistical Area

bers) were ascertained via automated record linkage between the annual LLNL employee files and the RCE's cancer incidence files for 1969 through 1980. The RCE has maintained a population-based registry for the San Francisco-Oakland SMSA since 1969 as part of the National Cancer Institute's Surveillance Epidemiology and End Results (SEER) Program and the Third National Cancer Survey. Ascertainment has been estimated to be 98% complete.[9] Hence, all new cases of cancer (excluding common nonmelanoma skin cancers) occurring among LLNL employees residing in the SEER surveillance area are likely to have been collected by the RCE.

The expected number of cancers for the study cohort was calculated by multiplying the 1973 to 1977 age- and sex-specific rates for the San Francisco-Oakland SMSA[10] for each site of cancer by the age- and sex-specific LLNL person-years of observation and summing across age groups. Published San Francisco-Oakland SMSA rates for 1973 through 1977 were chosen as representative of the total time interval 1969 through 1980 and as a practical alternative to costly new rate computations. A simpler procedure was used than that adopted for our earlier analysis of the incidence of malignant melanoma of the skin because there is less socioeconomic and environmental variation among other cancer sites. Also, because the rates during this time interval (except for melanoma and female lung and uterine cancer) appear to be stable, it was not as important to weight the comparison rates by temporal and residential patterns.

A total of 49 sites of invasive cancer and 11 sites of in situ cancer are reported here. For each site and sex an observed-to-expected ratio was computed. For each comparison ratio that exceeds the 95% confidence interval (for the ratio of an observed value of a Poisson variable to its expectation), as tabled by Bailar and Ederer,[11] significance indicators are reported. These values are not adjusted for multiple testing, as more than 100 comparisons were made. They are merely included as a relative scale for the observed differences.

TABLE 1.—*Lawrence Livermore National Laboratory Study: Total Person Years of Observation of San Francisco-Oakland SMSA Residents Only, 1969-1980*

Age Group Years	Person-Years		
	Men	Women	Totals
20-24	2,458.50	1,307.72	3,766.22
25-29	5,299.10	1,691.45	6,990.55
30-34	7,236.33	1,645.49	8,881.82
35-39	7,842.84	1,602.01	9,444.85
40-44	8,029.85	1,465.50	9,495.35
45-49	8,008.34	1,191.52	9,199.86
50-54	6,912.53	991.01	7,903.54
55-59	4,737.88	697.56	5,435.44
60-64	1,936.89	285.36	2,222.25
65-69	216.27	30.67	246.94
TOTALS	52,678.53	10,908.29	63,586.82

SMSA = Standard Metropolitan Statistical Area

Results

In Tables 2 and 3 are summarized the observed and expected incidences of all cancers among the LLNL work force between 1969 and 1980. Among invasive cancers there appears to be an excess incidence of malignant melanoma of the skin and rectal and salivary gland cancers among women. Men had an excess of malignant melanoma of the skin and nervous system cancers other than brain and a deficit of lung cancers. No excess incidence of in situ cancers is evident.

Because the SEER Program does not include ascertainment of common skin cancers, namely basal and squa-

TABLE 2.—*Observed and Expected Number of Cancers Among San Francisco-Oakland SMSA-Resident Female Employees of Lawrence Livermore National Laboratory, 1969-1980*

Site	Number Observed	Number Expected	O/E Ratio
Invasive Cancers			
All sites combined	43	32.62	1.32
Lip (140)*	0	0.03	0
Tongue (141)	0	0.19	0
Salivary gland (142)	2	0.10	20.00†
Gum and other mouth (143,145)	0	0.16	0
Floor of mouth (144)	1	0.12	8.33
Oropharynx (146)	0	0.13	0
Nasopharynx (147)	0	0.07	0
Hypopharynx (148)	0	0.06	0
Pharynx, NOS (149)	0	0.01	0
Esophagus (150)	1	0.19	5.26
Stomach (151)	0	0.37	0
Small intestine (152)	0	0.05	0
Colon (153)	4	1.59	2.52
Rectum, anus (154)	4	0.76	5.26‡
Liver (155.0)	0	0.09	0
Gallbladder, other biliary tract (155.1,156)	1	0.13	7.69
Pancreas (157)	0	0.44	0
Retroperitoneum, peritoneum (158)	0	0.05	0
Other digestive organs (159)	0	0	0
Nasal cavity, sinuses, ear (160)	0	0.04	0
Larynx (161)	0	0.19	0
Lung and bronchus (162.2-162.9)	3	2.67	1.12
Mediastinum and other respiratory (162.0,163,164.2-164.9,165)	0	0.05	0
Bones and joints (170)	0	0.04	0
Soft tissue (incl. heart) (164.1,171)	0	0.20	0
Malignant melanoma of the skin (172)	7	1.35	5.19†
Other skin cancers (173)§	0	0.07	0
Breast (174)	8	11.02	0.73
Uterus, NOS (179)	0	0	0
Cervix uteri (180)	2	2.05	0.98
Corpus uteri (182)	4	3.85	1.04
Ovary (183.0)	4	1.70	2.35
Other female genital organs (181,183.2-183.9,184)	0	0.29	0
Urinary bladder (188)	0	0.33	0
Kidney and other urinary organs (189)	1	0.28	3.57
Eye (190)	0	0.04	0
Brain (191)	1	0.40	2.50
Other nervous system (192)	0	0.05	0
Thyroid gland (193)	0	1.20	0
Other endocrine (incl. thymus) (164.0,194)	0	0.05	0
Hodgkin's disease (201)	0	0.31	0
Non-Hodgkin's lymphomas (200,202)	0	0.66	0
Multiple myeloma (203)	0	0.14	0
Leukemias (204-208)	0	0.44	0
Primary unknown (199)	0	0.66	0

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(TABLE 2 *continued*)

Site	Number Observed	Number Expected	O/E Ratio
In Situ Cancers			
All sites combined	13	10.86	1.20
Buccal cavity and pharynx (140-149)	0	0	0
Stomach (151)	0	0	0
Colon (153)	0	0.07	0
Rectum, anus (154)	0	0.06	0
Larynx (161)	0	0.01	0
Lung and bronchus (162.2-162.9)	0	0	0
Malignant melanoma of the skin (172)	0	0.08	0
Breast (174)	0	0.81	0
Cervix uteri (180)	12	8.92	1.35
Corpus uteri (182)	1	0.54	1.85
Vagina, vulva (184)	0	0.32	0
Urinary bladder (188)	0	0.05	0

SMSA = Standard Metropolitan Statistical Area, NOS = not otherwise specified

*Number(s) in parentheses represent *International Classification of Diseases, 9th Edition* (ICD-9) code.

†Exceeds 99% confidence interval.

‡Exceeds 95% confidence interval.

§Excludes basal and squamous cell carcinoma.

mous cell carcinomas, we cannot determine by this method whether or not an excess of those tumors has occurred. Of rare skin tumors (excluding the melanomas), however, only two cases occurred during this interval, both in men. One of these was a dermatofibrosarcoma and the other a malignant histiocytoma.

Table 4 presents observed-versus-expected ratios for cancer incidence of sites grouped on the basis of radiosensitivity. Included in the highly radiosensitive-site group are bone, thyroid and blood (the leukemias, excluding chronic lymphocytic leukemia). The moderately radiosensitive-site group consists of the lung and female breast. All other sites are included in the nonradiosensitive group, except melanoma of the skin, which is excluded from the table. No excess incidence appears among those sites associated with ionizing radiation by these criteria.

Discussion

This analysis confirms, using a broader time period and cruder reference rates, our previous finding[1] that an excess of malignant melanoma of the skin exists among LLNL employees. Cancer of a few other sites also differs significantly from expectation. Possible reasons for those differences must be considered.

Because more than 100 site and sex comparisons have been made, one would expect that a small number of observed-to-expected ratios would appear to be significant by chance alone. For a P value of .05, one might expect approximately 5 out of 100 comparisons to be significant by chance alone and, for a P value of .01, one might expect one comparison to emerge as significant by chance. Further, one might also expect the direction of differences to be about equal. We find six comparisons to exceed the 95% confidence interval and four of those to also exceed the 99% confidence interval. All but one of these comparisons is in the direction of an excess rather than deficit, though it is impossible to estimate the relative magnitude of the deficit for those sites with an observed value of zero—such as Hodgkin's disease and multiple myeloma among men and thyroid cancer among women.

TABLE 3.—*Observed and Expected Number of Cancers Among San Francisco-Oakland SMSA-Resident Male Employees of Lawrence Livermore National Laboratory, 1969-1980*

Site	Number Observed	Number Expected	O/E Ratio
Invasive Cancers			
All sites combined	134	140.63	0.95
Lip (140)*	1	1.97	0.51
Tongue (141)	2	1.69	1.18
Salivary gland (142)	2	0.67	2.99
Gum and other mouth (143,145)	1	1.33	0.75
Floor of mouth (144)	0	1.39	0
Oropharynx (146)	0	1.33	0
Nasopharynx (147)	2	1.01	1.98
Hypopharynx (148)	1	0.84	1.19
Pharynx, NOS (149)	0	0.10	0
Esophagus (150)	1	2.18	0.46
Stomach (151)	2	4.87	0.41
Small intestine (152)	0	0.30	0
Colon (153)	11	10.59	1.04
Rectum, anus (154)	4	6.49	0.62
Liver (155.0)	1	1.54	0.65
Gallbladder, other biliary tract (155.1,156)	1	0.83	1.20
Pancreas (157)	5	4.28	1.17
Retroperitoneum, peritoneum (158)	0	0.29	0
Other digestive organs (159)	0	0.07	0
Nasal cavity, sinuses, ear (160)	1	0.50	2.00
Larynx (161)	1	4.71	0.21
Lung and bronchus (162.2-162.9)	18	33.22	0.54†
Mediastinum and other respiratory (162.0,163,164.2-164.9,165)	1	0.72	1.39
Bones and joints (170)	0	0.53	0
Soft tissue (incl. heart) (164.1,171)	1	1.37	0.73
Malignant melanoma of the skin (172)	21	6.46	3.25†
Other skin cancers (173)‡	2	0.38	5.26
Breast (175)	0	0.39	0
Prostate gland (185)	14	10.06	1.39
Testis (186)	7	3.12	2.24
Penis and other male genital organs (187)	0	0.38	0
Urinary bladder (188)	10	7.49	1.34
Kidney and other urinary organs (189)	3	4.82	0.62
Eye (190)	1	0.36	2.78
Brain (191)	1	3.51	0.28
Other nervous system (192)	3	0.23	13.04†
Thyroid gland (193)	3	2.53	1.19
Other endocrine (incl. thymus) (164.0,194)	1	0.24	4.17
Hodgkin's disease (201)	0	2.24	0
Non-Hodgkin's lymphomas (200,202)	6	5.56	1.08
Multiple myeloma (203)	0	1.69	0
Leukemias (204-208)	3	3.33	0.90
Primary unknown (199)	3	5.02	0.60
In Situ Cancers			
All sites combined	3	2.79	1.08
Buccal cavity and pharynx (140-149)	0	0	0
Stomach (151)	0	0.03	0
Colon (153)	1	0.62	1.61
Rectum, anus (154)	0	0.56	0
Larynx (161)	0	0.36	0
Lung and bronchus (162.2-162.9)	0	0.03	0
Malignant melanoma of the skin (172)	1	0.34	2.94
Urinary bladder (188)	1	0.85	1.18

SMSA = Standard Metropolitan Statistical Area, NOS = not otherwise specified

*Number(s) in parentheses represent *International Classification of Diseases, 9th Edition* (ICD-9) code.

†Exceeds 99% confidence interval.

‡Excludes basal and squamous cell carcinoma.

TABLE 4.—*Lawrence Livermore National Laboratory Study: Observed (Obs) Versus Expected (Exp) Cancer Incidence by Radiosensitive Site Groups, 1969-1980*

Site Group	Men			Women			Total		
	Obs Number	Exp Number	O/E Ratio	Obs Number	Exp Number	O/E Ratio	Obs Number	Exp Number	O/E Ratio
Highly radiosensitive—bone, thyroid and blood (ICD-9 codes 170, 193, 204.0, 204.2-208)	6	5.42	1.11	0	1.55	0	6	6.97	0.86
Moderately radiosensitive—lung and female breast (ICD-9 codes 162.2-162.9 and 174)	18	33.22	0.54*	11	13.69	0.80	29	46.91	0.62*
Nonradiosensitive—all other sites except MM (ICD-9 code 172)	89	95.53	0.93	25	16.03	1.56†	114	111.56	1.02*
All sites, excluding MM	113	134.17	0.84	36	31.27	1.15	149	165.44	0.91

ICD-9 = *International Classification of Diseases, 9th Edition;* MM = malignant melanoma of the skin.

*Exceeds the 99% confidence interval.
†Exceeds the 95% confidence interval.

Even if it were possible to observe one-half case for each of these three-deficit site/sex categories, none of the observed-to-expected ratios would exceed their 95% confidence intervals.

These comparisons have been made for all races in both the LLNL and comparison populations. Because the LLNL work force has a higher proportion of whites (about 93%) than the San Francisco-Oakland SMSA (about 83%), sites that are less common among nonwhite races will be slightly underrepresented in the expected numbers. Hence, the overall observed:expected ratio for malignant melanoma of the skin may be overestimated by this method by as much as 10%. Likewise, sites more common among nonwhites will be somewhat overrepresented in the expected numbers, so that the observed:expected ratios for lung and prostate among men and uterine cervix among women may be slightly underestimated. These variations would not, however, have a major impact on the direction or magnitude of differences.

The observed-expected differences for malignant melanoma of the skin we accept as real, based not only on the consistency and strength of these data, but on our earlier analysis as well.[1] The observed deficit in the expected incidence of lung cancer among LLNL male employees may be a function of the higher socioeconomic status of LLNL men compared with their population counterparts. Although we have no reliable evidence regarding the prevalence of smoking among LLNL employees, we do know that the male LLNL work force is a highly educated group. Among men it has been well established that smoking, the primary cause of lung cancer, is inversely related to education.

Among women, higher socioeconomic status is usually associated with increased rates of cancers of the uterine corpus and breast and decreased rates of cervical cancer. The distribution of these cancers among female LLNL employees suggests that they represent average socioeconomic status. Social class is therefore not a likely explanation for the excess incidence of rectal cancer among women.

One way to assess if an environmental factor is likely to be responsible for an excess incidence in one sex is to see if the excess also exists in the other gender sharing the same environment. The rectal cancer excess is not confirmed in men. The excess incidence of malignant lesions of the nervous system (excluding brain) observed among men is not shared by women. Two other sites, however, do share consistency between genders. These are malignant melanoma and cancers of the salivary glands—although the salivary gland excess is not significant among men.

The excess incidence of salivary gland cancer in this cohort is difficult to interpret due to the small number involved. It should be noted, however, that malignant tumors of the salivary glands (particularly the parotid gland) have been reported to be significantly elevated among exposed A-bomb survivors, with a relative risk of 10 compared with unexposed persons.[12,13] A similar excess has also been clinically noted for exposure to x-rays.[14] Finally, in a recent case-control study of Los Angeles residents, salivary gland tumors were found to be associated with both radiation treatment of the head and neck and certain dosages of dental x-rays.[15]

The data by radiosensitivity-site groupings are presented to explore the possibility of an excess that may be etiologically related to exposure to ionizing radiation. As considerable debate exists in the literature on the biologic effects of low-level radiation on different tissues, these groupings may not necessarily be agreed upon by other investigators. Other site groupings are certainly plausible. The highly radiosensitive-site group, however, represents a well-founded, if conservative, selection of sites. These data do not suggest the existence of any excess. However, this analysis does not take into account individual differences in measured exposure to radiation. Also, these data are for morbidity among concurrently employed members of the LLNL work force compared with their same sex/age counterparts in the general population. This does not preclude the possibility of increased cancer morbidity later in life or of differences in cancer mortality, although this analysis provides no evidence for or against such possibilities.

In summary, the overall cancer experience of active LLNL employees does not appear to differ greatly from that of the general population of the San Francisco-Oakland Bay Area. A small number of sites would be expected to appear to be in excess or deficit in this cohort by chance alone. This is likely to be the explanation for the observed excesses for rectal cancer in women and cancers of the nervous system in men. Small deficits may also exist by chance for Hodgkin's disease and multiple myeloma among men and thyroid tumors among women, though the differences are not quantifiable. The observed deficit of lung cancer among LLNL men is likely to be due to a low smoking prevalence in this highly

educated group. The excess incidence for malignant melanoma of the skin is also not likely to be due to chance. Malignant melanoma has been considered separately elsewhere.[1] Cancers of the salivary gland are extremely rare and not well studied. The excess incidence noted for this site in this cohort is based on such a small number (four cases) that these results are difficult to interpret.

Grouping cancer sites by radiosensitivity criteria suggests that no excess incidence is evident as a function of general radiation exposure, though a stringent test of this hypothesis would require a determination of individual radiation dosages and an assessment of cancer by dose category. Overall, the evidence from this analysis for all sites of cancer suggests that aside from malignant melanoma, no other major excesses are evident among current LLNL employees.

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