Distribution of Cancer
Among Former and Current
Brookhaven National Laboratory Workers

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Executive Summary

The New York State Cancer Registry identified 804 cancers diagnosed among former and current Brookhaven National Laboratory (BNL) workers between 1979 and 1996. Only cancers occurring through 1996 among New York residents were considered, since at the time of the linkage, 1996 was the most recent year for which Registry coverage was considered complete. Due to the unavailability of complete information on employment and residential history, it was not possible to estimate the actual risk of specific cancers among BNL employees. However, it was possible to compare the pattern of cancer types among BNL employees with those among residents of New York State exclusive of New York City and Nassau and Suffolk counties. This type of comparison was used to indicate cancer types that may be more common among the workers at Brookhaven.

The most striking result of this study, and one that impacts all other results, is the proportionate deficit of respiratory cancers among BNL employees. Malignant melanomas of the skin were proportionately elevated among males. This finding is difficult to interpret since melanomas are not well reported to the Registry. This would result in an underestimate of expected cases. Among females, a proportionate excess of leukemia cases was observed. The excess was restricted almost entirely to lymphocytic leukemias. This finding may merit further investigation including: a review of the medical records to determine the accuracy of the diagnosis; an assessment of whether the excess is due to acute or chronic lymphocytic leukemia (the latter not being associated with radiation exposure); and a review of the medical, work, and exposure histories of women with leukemia.

Except as noted above, the overall distribution of cancers in this cohort did not deviate significantly from expected. Of particular note, radiosensitive solid cancers were not proportionately elevated.

Introduction

In April 1997, the Department of Energy (DOE) requested that the New York State Cancer Registry conduct an analysis of the Brookhaven cohort to determine whether persons employed at Brookhaven National Laboratory are at higher risk of cancer than the general population. The assessment was to include all cancer sites combined and specific cancer sites. The analytic approach that was initially outlined would have been based on standardized incidence ratios (SIRs). However, this approach requires the calculation of person-time at risk of cancer and requires knowledge of such information as when persons left employment, moved out of state, or died. Since the Department of Energy was unable to gain access to this information for the entire cohort, the analytic approach was changed.

This study received approval from the New York State Department of Health's Institutional Review Board in September 1997. A file containing the cohort information was sent to the New York State Cancer Registry in November 1998. Linkage of this data file to the Registry database was conducted in April of 1999. All analyses were completed by June 2000.

The cohort file contained information on 21,271 individuals. Of the 15,444 male employees, 9,424 (61%) were classified as salaried and 6,020 (39%) as hourly wage earners. Of the 5,827 female employees, 2,202 (38%) were considered salaried and 3,625 (62%) hourly.

Methods

The cohort was matched to the New York State Cancer Registry using a probabilistic matching algorithm (Auto Match). Only cancers diagnosed in the time period 1979-1996 were retained for analysis. The reason for this is that at the time of the match, deceased cancer cases diagnosed before 1979 were no longer on the active Cancer Registry database, and reporting of cancer cases diagnosed after 1996 was incomplete. The study was limited to cancers diagnosed among Brookhaven workers while resident in New York State because the cancer status of former residents could not be ascertained.

The linked data were analyzed using a proportional incidence analysis to determine whether the distribution of cancers among the Brookhaven cohort differed from that of a comparison population (Breslow and Day, 1987). At the request of DOE headquarters, three separate comparison populations were used in the analysis: New York State exclusive of New York City (Upstate), Nassau County, and Suffolk County. The use of different comparison populations controls for possible regional variations in the distribution of cancer. To adjust for temporal and age effects, data were grouped into four time periods: 1979-1983; 1984-1988; 1989-1993; and 1994-1996, and into nine age groups: less than or equal to 14; 15-24; 25-34; 35-44; 45-54; 55-64; 65-74; 75-84; and 85 or older. Males and females were analyzed separately. Separate analyses were also conducted for salaried and hourly workers to determine whether the distribution of cancer varies by pay type. Differences by pay type could be indicative of lifestyle and/or

occupational exposure differences. The analyses by pay type were conducted using the population of New York State exclusive of New York City as the comparison group.

Proportional incidence ratios (PIRs) for specific cancer sites were calculated as follows:

$$PIR = \Sigma_i \Sigma_j d_{i,j} / \Sigma_i \Sigma_j t_{i,j} (d^*_{i,j}/t^*_{i,j})$$

where

$d_{i,j}$ = the number of incident cancer cases of a *specific site* observed in the *i-th* age group and *j-th* time interval in the study population

$t_{i,j}$ = the number of incident cancer cases of *all sites* observed in the *i-th* age group and *j-th* time interval in the study population

$d^*_{i,j}$ = the number of incident cancer cases of a *specific site* observed in the *i-th* age group and *j-th* time interval in the comparison population

$t^*_{i,j}$ = the number of incident cancer cases of *all sites* observed in the *i-th* age group and *j-th* time interval in the comparison population

As can be seen from the above formulas, the PIR is a ratio of observed to expected cases. The number of expected cases is calculated by applying the age and calendar specific proportionate distribution of cancer cases in the comparison population to the age and calendar specific totals in the study population.

The following formula was used to calculate the standard error (SE) of the log PIR:

$$SE(\log PIR) = \sqrt{[\Sigma_i \Sigma_j d_{i,j} (t_{i,j} - d_{i,j}) / t_{i,j}]} \; / \; \Sigma_i \Sigma_j d_{i,j}$$

Under the null hypothesis that the worker cohort does not differ from the comparison population, the expected value of the PIR is 1. Therefore, the expected value of the log PIR under the null hypothesis is 0. Dividing the log PIR by its standard error results in the standardized log proportional incidence ratio (SLPIR), which is a "standard measure" having mean 0 and standard deviation 1, i.e.

$$SLPIR = \log PIR / SE(\log PIR)$$

An indication of "statistical significance" can be obtained by comparing the SLPIR with the standard normal distribution. A standard normal statistic will be between +/- 2.0 95% of the time. However, this comparison does not correspond to a formal test of statistical significance (see discussion).

In addition to examining specific cancer sites as classified under the ninth revision of the International Classification of Diseases (ICD9), solid cancers were grouped into two categories: radiosensitive and non-radiosensitive. The radiosensitive category included cancers of the following sites (ICD9 codes): esophagus (150), stomach (151), colon

(153), lung (162), bone (170), breast (174), ovary (183), urinary tract (188-189, 233.7), brain (191-192), and thyroid (193). The non-radiosensitive category included all ICD9 codes between 140 and 199 inclusive with the exception of those identified as radiosensitive above.

Results

The match of the Brookhaven cohort against the Cancer Registry resulted in the identification of 1,018 neoplasms. Of these, 214 neoplasms were excluded from analysis for the following reasons: 164 were diagnosed outside the study period of 1979-1996; 34 were non-malignant neoplasms; and, 16 were diagnosed before the date of first hire at Brookhaven. In-situ bladder cancers were retained since these are usually grouped with invasive bladder cancers. This resulted in 804 cancers, 599 among men and 205 among women.

At the time that the Institutional Review Board approved this study, it was the policy of the New York State Cancer Registry to suppress cell frequencies less than six in tables that describe data for geographic areas or population subgroups below the county level. This policy was intended to safeguard against 1) the possibility of identifying an individual with cancer; and 2) the possible disclosure of specific information regarding individuals already known to have cancer (e.g., the specific type of cancer). Since this study was approved with the understanding that no cell size less than six would be displayed, results are not presented for cancer sites that occurred in fewer than six individuals. Because 73% of the BNL cohort was composed of men, the vast majority of observed cancers occurred among men. Therefore, more detailed information is presented for men than for women. When analyses were stratified by pay type, the observed number of cancers for each cancer site became even smaller, requiring the suppression of more site-specific results. Therefore, only a few broad cancer groupings are displayed for women in the tables by pay type.

Results for men are shown in Tables 1, 3 and 5. Results for women are shown in Tables 2, 4 and 6. Although frequencies for cancer sites with fewer than 6 cases are suppressed for reasons of confidentiality, these sites are included in the more general site groupings (e.g., for females, esophagus is not shown separately but is included in the digestive system) and/or in the overall groupings of radiosensitive and non-radiosensitive cancers. The one exception to this is multiple myeloma, of which there were fewer than six cases in each gender. No overall category of all lymphatic and haematopoietic cancers is given because subtraction of leukemias and lymphomas from the overall category would result in the release of frequencies below six for multiple myeloma. The PIR for multiple myeloma was less than one for both men and women.

Tables 1 and 2 are based on using the population of New York State exclusive of New York City as the comparison group. The population of Nassau County was used to generate the results shown in Tables 3 and 4, and the population of Suffolk County was used for Tables 5 and 6. As can readily be seen by comparing results across tables, use of

different comparison groups resulted in negligible differences for most cancer sites. For ease of discussion, results will be presented based on the Upstate comparison population.

Among males (Table 1), the PIR for cancers of the oral cavity and pharynx was close to unity (PIR=1.06). No overall deviation from expected was observed for cancers of the digestive system (PIR=0.98). However, stomach cancer exhibited a proportionate excess (PIR=1.45) whereas, digestive cancers other than colon exhibited slight deficits. The PIR for lung cancer was well below unity (PIR=0.78, SLPIR<-2.0) indicating proportionately fewer lung cancer cases in this cohort than in the Upstate population. This deficit was attenuated when using the Nassau County population as the comparison (Table 3). The PIR for cancers of the "Bone, Connective Tissue, Skin and Breast" was elevated (PIR=1.45, SLPIR>2.0). This proportionate elevation is entirely due to melanoma of the skin (PIR=1.77, SLPIR>2.0). No elevation in PIR was observed for any other site within this category. The number of observed prostate cancer cases was close to expected (PIR=1.08), but a proportionate excess was observed for cancers of the testis and other male genital organs (PIR=1.57). No proportionate excess was observed for urinary bladder (PIR=1.05), but a proportionate excess was observed for cancers of "Kidney and Other Urinary" (PIR=1.45, SLPIR>2.0). A proportionate deficit was observed for cancers of other and unspecified sites (PIR=0.92), which was more pronounced for brain and nervous system cancers (PIR=0.71). Of the lymphatic and haematopoietic cancers, the number of observed lymphomas was close to expected (PIR=1.08), whereas fewer leukemias were observed than expected (PIR=0.85).

Because of the smaller number of overall cancers observed among women, the site-specific results for women are much more variable than for men. The PIRs for most cancer sites did not deviate appreciably from one. As in men, a proportionate deficit was observed for respiratory cancers (PIR=0.67, SLPIR=-1.92). Unlike in men, among women lymphomas exhibited a slight deficit (PIR=0.89), whereas leukemias exhibited a proportionate excess (PIR=2.14, SLPIR>2.0). Of the female-specific cancers, neither breast (PIR=1.08) nor ovary (PIR=1.19) exhibited a substantial excess, and cancers of the cervix and uterus exhibited a proportionate deficit (PIR=0.69). In women, unlike in men, neither melanomas nor cancers of the "Kidney and Other Urinary" showed an excess; in fact, these cancers showed deficits (data suppressed due to small numbers).

When all radiosensitive cancers were combined, no proportionate excess was observed in either men (PIR=0.96) or women (PIR=1.01).

For men, a comparison of findings by pay type indicated some site-specific differences (Tables 7 and 8). The proportionate deficit in respiratory cancers, especially in lung cancer, mentioned above, was observed exclusively among salaried employees. The proportionate excesses observed for melanomas, stomach cancer, and cancers of the "Kidney and Other Urinary" were more pronounced among salaried employees than among wage earners. Radiosensitive cancers were not proportionately elevated in either pay group.

Among women the overall smaller number of observed cancers makes a comparison by pay type more difficult. Results for most cancer sites are suppressed because of cell frequencies below six (Tables 9 and 10). Unlike in men, the proportionate deficit in respiratory cancers was more pronounced among hourly employees than among salaried employees. No other substantial differences by pay type were observed. Particularly, the proportionate excess in leukemia did not differ by pay type. As in men, radiosensitive cancers were not proportionately elevated in either pay group.

Discussion

The overall results seem to indicate that the proportional distribution of cancers observed among the Brookhaven cohort does not vary substantially from what one would expect. Although PIRs were elevated for some specific cancer sites, they were decreased for others. It is a limitation of proportional incidence analysis that proportionate excesses for some sites must result in proportionate deficits for other sites. Since respiratory cancers are extremely common, accounting for a substantial proportion of overall cancers among both genders, a proportionate deficit in these cancers must give rise to proportionate excesses for cancers of other sites. PIRs do not allow one to assess whether a relative excess or deficit exists. Therefore, it is theoretically possible to observe a proportionate excess when no relative excess is present. However, it is more likely that a proportionate excess also corresponds to a relative excess, although the magnitude of the relative excess might be quite different.

In lay terms, the PIR compares the distribution of cancer in the study population to that in the comparison population. For example (see Table 11), if 28.7% of all cancers in the comparison population were breast cancers and if there were a total of 513 cancers in the study population, then without adjustment for age and temporal factors, one would expect that there would be 147.2 breast cancer cases in the study population (0.287 x 513). If the actual number of breast cancer cases in the study population were in fact 183, then the PIR would equal 1.24 (i.e., 183/147.2). A PIR of 1.24 does not imply that there is a 24% excess of breast cancer in the study population relative to the comparison population. Rather, it indicates that the *proportion* of all cancers diagnosed among the study population that are breast cancers is larger. In order to determine whether the study population is at higher risk of breast cancer, one would need to compare breast cancer rates in the two groups. To calculate rates one must know the person-time at risk in each group. Particularly, for the Brookhaven cohort, one would need to know how long each person remained living in New York after beginning employment at Brookhaven. Since that information is not available, rates could not be calculated.

Tables 11 through 13 provide hypothetical examples of the relationship of the PIR to the rate ratio, which is a comparison measure based on rates and an estimate of relative risk. For ease of computation, these examples do not adjust for age or calendar time. As shown in Table 11, if the overall cancer rates in the study population and the comparison population are the same, then the PIR equals the rate ratio. If however, the overall rate in the study population differs from the rate in the comparison population, for example, by

20%, then the PIR will differ from the rate ratio by 20%. A comparison of the last two columns of Tables 11 through 13 demonstrates this relationship. Without knowing what the overall cancer rate is in the study population, one cannot estimate relative risk.

A number of assumptions are required for formal statistical analysis of a proportional incidence study for a single cancer site. These assumptions are not verifiable given numerator data alone. Breslow and Day do not recommend that statistical inference procedures be conducted on the PIR and mention that use of the PIR remains controversial (1987). Since the present analysis was not limited to one cancer site chosen *a priori* but rather, involved all cancer sites, the statistical limitations are further compounded by "non-independence" of the PIRs and "multiple testing." We recommend that the SLPIR be interpreted cautiously, as an indicator of magnitude of deviation from expected and not as an indicator of statistical significance.

The most striking result of this study is the proportionate deficit of respiratory cancers among BNL employees. This finding suggests that smoking prevalence is lower among this cohort than in the comparison populations. The observation that among males this proportionate deficit is limited to salaried employees is consistent with smoking prevalence rates by education level (CDC, 1994).

Malignant melanomas of the skin were proportionately elevated among males in this cohort. This finding is difficult to interpret since melanomas are not well reported to the Registry. Because of under-reporting, the number of expected cases would be underestimated. Since the excess was somewhat attenuated when using the Nassau or Suffolk County comparison group, the proportionate excess may simply reflect better detection and/or reporting of these cancers for this cohort. Known risk factors for melanoma include: excessive exposure to ultraviolet (UV) radiation and sunburn; fair skin, freckling and light hair; dysplastic nevi or atypical moles; family history; and immune suppression. The proportionate melanoma excess was greater for salaried employees than for wage earners (PIR=2.00 vs. PIR= 1.51). This difference cannot be attributed to differences in racial composition. The proportion white is approximately equal in the two groups. However, the proportion Asian is higher in the salaried group whereas the proportion black is higher in the non-salaried group. Previous studies have found that professionals and scientists tend to have a higher risk of melanoma relative to unskilled workers. This difference in risk has been attributed, in large part, to differences in occupational and recreational sun exposure (Armstrong and English, 1996).

The proportionate excess observed for stomach cancer was limited to men, specifically to salaried employees. This observation is consistent with the fact that stomach cancer rates are higher among Asians.

The proportionate excess of leukemias observed among females is based on only eight cases. It is unlikely that this proportionate excess represents an etiologically significant finding because it was not observed among males, in whom there were more leukemia cases. Although the numbers were too small to permit display in the tables, the majority of the leukemia excess was attributable to lymphocytic leukemia (ICD9=204). This

ICD9 grouping includes both acute (204.0) and chronic lymphocytic leukemia (204.1). Radiation exposure has been linked to acute lymphocytic leukemia in a number of studies but has not been consistently linked to chronic lymphocytic leukemia (Linet and Cartwright, 1996). In this study, no further analyses were conducted to ascertain whether the excess in the lymphocytic category is limited to one or the other lymphocytic subgroup. Since the proportionate excess of leukemias among females was considerable (PIR=2.14), this finding may merit further investigation. In particular, it would be appropriate to consider reviewing the medical, work, and exposure histories of females with leukemia. Additionally, since coding practices with regard to haematopoietic cancers have changed over time, verification of the diagnosis may be warranted. This is especially true given that 25% of the leukemia cases were based on death certificate only diagnosis (i.e., the Registry has no other record of the diagnosis). The validity of death certificate diagnoses is subject to question. Further study should also focus on determining whether the proportionate excess corresponds to a relative excess and, if so, on the magnitude of the relative excess.

Except as noted above, the overall distribution of cancers in this cohort did not deviate significantly from expected. Of particular note, radiosensitive solid cancers were not proportionately elevated.

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