An investigation of brain tumours and other malignancies in an agricultural research institute

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Abstract

A historical cohort study was carried out in an agricultural research institute in the Republic of Ireland to investigate a perceived excess of cancer deaths among employees. The objectives of the study were (a) to confirm whether or not total or cause specific death rates among selected employees were higher than expected based on national figures, and to quantify any excess, and (b) to identify centres and employee grades associated with any excess risk. The cohort comprised all administrative, research, and technical staff employed for at least two years between 1960 and 1980, giving a final total for analysis of 1323 employees.

Employment history was categorised by place of work and employment grade. Deaths among the cohort were identified and causes of deaths verified. Overall the cohort had a lower than expected mortality compared with national rates (O/E = 0.67). Female deaths were too few for analysis but, among the male employees, there was an excess of all cancers (O/E = 1.24; 95% confidence interval (95% CI) 0.8-1.9), in particular brain cancer (O/E = 4.69; 95% CI 1.2-11.4) and bladder cancer (O/E = 9.31, 95% CI 1.9-27.2). The pattern of brain tumour deaths was consistent with an occupational aetiology but it was not possible to identify specific exposures associated with the excess. All four cases occurred among research workers in the plant and soil science area. The pattern of bladder cancers was difficult to interpret. The authors are at present participating in a multicentre study to further investigate cancer risk in laboratory workers.

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There have been reports of an increase in cancer risk among laboratory research workers. A review by Sasco¹ describes reports of higher than expected risks of cancers of the haemopoietic system, bone, brain and pancreas in chemists and laboratory workers. Cordier² reported an excess of bone cancer in men and of pancreatic and brain tumours in women in the first results of a mortality study in the Institut Pasteur in Paris. Belli³ and his colleagues in the Institute Superior di Sanita in Rome found low mortality from total cancers but an excess of pancreatic, brain, and

haemopoietic cancers in technical staff and of breast cancer in female workers overall. Most reports are, however, based on small numbers of malignancies with few statistically significant results.

This study was undertaken to investigate a perceived excess of cancer deaths among employees of a large agricultural research institute in the Republic of Ireland. Concern was expressed by staff at the institute in the mid-1980s that deaths from malignant disease, particularly brain tumours, among research and technical staff were higher than expected. It was impossible, however, to evaluate this claim without investigating the mortality experience of the total workforce and it was therefore decided to carry out a historical cohort study, to which the management and workforce gave full cooperation.

The objectives were as follows: (a) To identify whether or not total or cause specific death rates among the study population were higher than expected based on national rates, and to quantify any excess seen. (b) To identify locations and employee grades associated with any increased risk.

Materials and methods

COHORT DEFINITION

The defined cohort for the study comprised all administrative, research, and technical staff employed in the institute for at least two consecutive years in the period 1960 to 1980. Employment up to the end of 1986 was included as contributing to exposure, and vital status was determined for all cohort members up to 1 July 1989. The basic requirements for cohort membership were satisfied by 1333 persons but 10 persons were excluded from analysis (nine had date of birth missing and for one employee who left the institute in 1966 and subsequently died neither date nor cause of death could be ascertained). The final cohort was 1323 employees.

FOLLOW UP AND VITAL STATUS

Vital status was determined from employment or pension records and interview of existing staff. There were 58 deaths during the period and all but 82 (6.2%) of the remaining employees were known to be alive on the review date of 1 July 1989. These 82 persons were included up to the date that they were last seen.

Person-years of follow up were counted from the date at which the employee achieved

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Table 1 Mortality by sex

Sex	Observed deaths	Rate (per 1000)	Expected deaths	O/E
Men	54	3.1	77.2	0.70
Women	4	0.5	9.1	0.44
Total	58	2.3	86.4	0.67

two years of cumulative employment in the institute within the study period. The institute did not exist before 1960, thus this criterion was used for all cohort members. Follow up was truncated when a subject reached the age of 85. Altogether there were 25 199.39 person-years of follow up, an average of just over 19 years for each employee.

Cause of death was determined from death certificates or the registrar general's computerised register for all but two of the 58 deaths. Medical records were obtained for 17 of the 23 cancer deaths and the coded cause of death was checked against the clinical and pathological data. One case had a death certificate coding of non-malignant brain tumour (International Classification of Diseases (ICD) code—239.6—9th revision) that was confirmed histologically to have been malignant and the coding was adjusted for the analysis. This reclassification introduced an element of bias into the brain tumour analysis, but exclusion of the death could have biased the study even more (see discussion). Although other causes of death are considered, this report concentrates on the four deaths from brain tumours that comprise ICD codes 193 (7th revision) or 191–192 (8th and 9th revisions).

EXPOSURE ASSESSMENT

It was impossible to determine an employee's exposure to biological or chemical agents with any degree of accuracy. Instead employees were grouped according to their place of work and employment grade. The 27 research centres and field stations that make up the institute were categorised into one of four activity areas: administration and office, plant and soil sciences, animal sciences, and animal farms. Three levels of employment grade were used in the analysis: administration/clerical, research, and technical. Thus a subject's entire employment history in the institute was broken up into periods defined by the combination of four activity areas and three employment grades. Subjects changed category if they changed either their activity area or employment grade.

Table 2 Causes of death (men)

Cause of death	Observed deaths	Expected deaths	O/E	p Value
All deaths	54	77.2	0.70	0.998
All cancer deaths	22	17.7	1.24	0.182
Cancer of digestive tract	6	6.0	1.00	0.554
Respiratory cancer	3	5.4	0.55	0.906
Bladder cancer	3	0.3	9.31	0.004
Brain cancer	4	0.9	4.69	0.011
Leukaemia/Hodgkin's disease	4	1.7	2.37	0.092
Diseases of circulatory system	19	33.9	0.56	0.998
Accidents/poisonings	7	10.2	0.69	0.881

Employment history was determined from personnel records and leave of absence and other breaks in employment were also recorded.

STATISTICAL ANALYSIS

Standard person-years techniques were employed for statistical analysis with concentration on the calculation of the observed over expected (O/E) ratios for mortality.⁴ Expected figures were based on the national vital statistics reports over the study period and the O/E ratios are adjusted for age, sex, and calendar time. The computer program PYRS developed by the International Agency for Research on Cancer was used for these calculations and significance of the individual O/E ratios was based on a one sided Poisson test.⁵ One sided tests were employed because the thrust of the analysis was the detection of a greater than expected mortality. For estimation purposes, however, two sided confidence intervals (CIs) were considered more appropriate as only a Bayesian approach would allow a one sided interval constrained to lie in the direction of an excess mortality. These CIs are based on the Poisson distribution.⁶

Results

Eight hundred and seventy two (66%) of the cohort of 1323 employees were men, with 52.7% of the men and 88.7% of the women first employed in the institute under the age of 25 years ($p < 0.001$). Table 1 shows the observed and expected deaths, the O/E ratios, and the death rates for men and women separately. The healthy worker effect is pronounced, especially in women, who were much younger at first employment. The four deaths in women did not allow for further analysis and the remainder of this report deals with the 54 deaths among the 872 male employees.

In men the O/E ratios tended to decrease with age at death suggesting that within the institute mortality may have been highest in younger persons. This trend was not statistically significant. A similar non-significant effect was seen when mortality was examined by years since first employment.

Table 2 shows the distribution of causes of death among the men. Twenty two of the 54 deaths were from cancer giving an O/E ratio for all cancers of 1.2 (95% CI 0.8–1.9). Only bladder cancer (O/E = 9.3; 95% CI 1.9–27.2) and brain cancer (O/E = 4.7; 95% CI 1.2–11.4) showed a significant excess above expected and leukaemia/Hodgkin's disease showed a non-significant increase (O/E = 2.4;

Table 3 Brain cancer by age at death (men)

Age at death	Observed deaths	Expected deaths	O/E	p Value
<44	1	0.27	3.70	0.237
45–54	2	0.36	5.52	0.052
55–64	1	0.17	5.78	0.159
65–84	0	0.05	0.00	—
Total	4	0.85	4.69	0.011

Table 4 Brain cancer by years since first employment (men)

Years since first employment	Observed deaths	Expected deaths	O/E	p Value
-9	0	0.17	0.00	—
10-19	1	0.29	3.48	(0.250)
≥20	3	0.40	7.58	(0.008)
Total	4	0.85	4.69	0.011

Table 5 Brain cancer by duration of employment (men)

Duration of employment (y)	Observed deaths	Expected deaths	O/E	p Value
-9	1	0.30	3.32	0.260
10-19	1	0.26	3.91	0.226
≥20	2	0.30	6.73	0.036
Total	4	0.85	4.69	0.011

Table 6 O/E ratios for brain cancer by years worked in plant and soil sciences and years worked in research (men)

	Years worked			
	Never	0-9	10-19	≥20
Plant/soil science	0.00	6.02	7.79	12.75*
Research	0.00	7.34	8.77	15.70**

* $p < 0.05$; ** $p < 0.01$.

95% CI 0.6-6.1). Table 3 shows that the risk of brain cancer, unlike total mortality, increased with age. There was no trend with age at first employment, but all four deaths occurred in those first employed in 1960 when the institute started. Results in tables 4 and 5 show that the risk of brain tumours increased with years since first employment and with the duration of employment.

For activity area, all four cases of brain cancer occurred among those employed in plant and soil sciences. For this group of employees the O/E ratio was 8.9 (95% CI 2.4-22.8). In terms of employment grade the four cases were among researchers only with an O/E ratio of 10.6 (95% CI 2.9-27.0) for this group. The O/E ratio for researchers in plant and soil sciences was 22.6 (95% CI 6.1-56.9).

Table 6 shows the effect of duration of employment on brain tumours separately among researchers and workers in plant and soil sciences. A strong trend within both categories is apparent.

Detailed analysis of mortality from bladder cancer showed no consistent patterns. Three different employment locations and different exposure categories were associated with this cancer and there was no trend with duration of exposure.

Discussion

In this agricultural research institute there was a clear demonstration of the healthy worker effect; total death rates were lower than the national rate as were deaths from diseases of the circulatory system and accidents. Deaths from all cancers were raised, however, with a statistically significant increase in deaths from brain and bladder cancer. There was a non-significant increase in deaths from leukaemia/Hodgkin's disease whereas deaths

from the common cancers, lung and gastrointestinal tract, were respectively lower than or equal to expected. The study cannot, however, be considered an independent test of the effect of an occupational exposure as it was undertaken because there was already a perceived problem.

There are other factors that must be considered in interpreting these results. Firstly the numbers of deaths in this, as in many previous studies, are small, 22 cancer deaths overall including three from bladder cancer and four from malignant brain tumours. Because variable and subgroup analyses were decided on before the data were collected, however, the analysis was not biased towards detecting spurious effects.

The histologically based reclassification of the non-malignant brain tumour from ICD code 239.6 to code 191 biased the analysis towards finding an excess in this cancer as no corresponding upward adjustment could be made to the expected numbers. Three brain tumour deaths are however, still above expected (O/E = 3.5; 95% CI 0.7-10.3), and the national brain tumour death rate would have to be increased by at least 28% to transform the excess based on four deaths to non-significance. Aggregating the Irish vital statistics figures from 1980 to 1989, 77% of all "neoplasms of unspecified nature" (ICD 239) would have to have been reclassified as brain tumours to achieve this result. Death certificate miscoding of this order of magnitude is unlikely and although the quoted O/E ratio based on four deaths from brain tumours may be inflated to some degree, including only three deaths could have biased the results to a far greater extent in the other direction.

Apart from these caveats, does the evidence of this study point to an occupational risk among research workers in this institute for bladder or brain cancer? All deaths from brain cancer occurred in research workers in the plant and soil science area, and a trend of increasing risk with duration of employment was seen. These data do suggest a possible occupational aetiology with a cumulative effect over time. It is interesting that these cancers occurred in research scientists only; technicians working in the same areas were not affected although the expected number of deaths was similar to that of researchers and one would have expected at least equal levels of exposure. Unfortunately, the fact that no reliable data were available on exposures to specific biological or chemical agents makes it impossible to identify a particular carcinogen.

Overall, however, the results are indicative of an increased risk of brain cancer, of occupational aetiology, among researchers in plant and soil sciences in this agricultural institute. Primary brain tumours are uncommon, accounting for about 0.5% of total deaths from cancer, and their aetiology is poorly understood. Environmental risk factors have been described and include head injury,⁷ exposure to ionising radiation,⁸ toxoplasmosis,⁹ and exposure to the vinyl chloride monomer.¹⁰ Excess mortality has also been

associated with employment in industries with exposure to lubricating oils and solvents,¹¹ in electricity related occupations,¹² the rubber¹³ and petrochemical industries,¹⁴ and in laboratories.¹⁻³ Apart from exposure to vinyl chloride monomer no specific carcinogen has been identified. A study of brain tumours in children identified living on a farm or contact with farm animals as risk factors,¹⁰ and a significant excess in a small town in the United States was associated with living in proximity to a chicken hatchery and with eating fish caught in local ponds that were previously used as coal mining strip pits.¹⁵

For bladder cancer the results are more difficult to interpret. The excess was greater than for brain tumours but there were no consistent patterns. The results do not rule out an occupational exposure to a carcinogen but neither are they strongly suggestive of one.

It is clear then that further research is needed. This cohort is being followed up for at least a further 10 years to endeavour to elucidate further the association between deaths from brain and bladder cancer and employment in this institute. There is also a European multicentre study underway, co-ordinated from the International Agency for Research on Cancer, which is investigating cancer risk among staffs of biological research institutes. This study, in which we are participating, will accrue large numbers of subjects and, it is hoped, will contribute to the identification and quantification of cancer risk in laboratory workers and to the recognition of potential carcinogens in the occupational setting.

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