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Notes and miscellanea

Hanford radiation study

A note on "Hanford radiation study III: a cohort study of the cancer risks from radiation to workers at Hanford (1944-77 deaths) by the method of regression models in life tables"

In their analysis of the cancer experience of the Hanford workers Kneale *et al*[1] made a praiseworthy attempt to examine a possible bias by comparing certificates of causes of death for the immediate locality of the Hanford works, for the State of Washington (in which Hanford is situated), and for elsewhere in the United States. There was indeed a corresponding decreasing gradient in the proportion of certificates giving cancer as the cause of death. This was interpreted as resulting from increased under-reporting of cancer with distance from the works because doctors at a distance were probably less aware of the occupational hazards (of cancer). If it is believed that specificity of death certification can be and is affected in this way by medical awareness, it seems just as plausible to suggest that cancer has been over-reported by the local doctors working near Hanford. They should have been specifically aware that type A cancers are more easily induced by radiation than type B, their over-reporting would then have been greater for type A than type B, and the discrepancy in the level of reporting of type A (but not type B) cancer according to geographical location would have been just what was found by Kneale *et al.*[1] This "probability"—derived according to their own argument—can account for their "positive finding for group A cancers" and so can absolve them from the need to invoke occupational radiation dose, even as a contributory cause, to the observed frequencies of cancer in Hanford workers.

Nevertheless, a factor other than medical awareness seems potentially a much more relevant source of bias for some cancers but not others and is specifically linked with the geographical distribution of death certificates in relation to the place of work. It is to be expected that cancers for which there is commonly a short time interval between diagnosis and death would be over-represented in those cancer death certificates provided by doctors in the locality of the works. Patients who fall ill while active members of the Hanford work force are inevitably dealt with selectively by the local Hanford doctors as compared with doctors in more distant places. Any bias of this type would be correlated with duration of employment at the works and therefore with magnitude of radiation dose for all workers monitored for external radiation exposure. Duration of employment could also be correlated with persistently positive urine assays for plutonium (level 4 of monitoring by bioassay of Kneale *et al*). Thus the bias described may underline the apparent need to stratify according to level of monitoring for internal irradiation if conclusions statistically acceptable to Kneale *et al* were to be reached.

Three categories of cancer have been claimed to show an excess in Hanford workers that is correlated with occupational radiation dose. Two are precisely of the type with a short time interval between diagnosis and death—namely, cancers of the pancreas and of the lung. The point made in this letter was brought to mind by the observation that pancreatic cancer was found in excess (of expectations from national statistics) even in workers with under two years' employment at the Hanford works.[2]

Geographical bias relating to the third category of cancer, multiple myeloma, could arise in a different way. Its national incidence has been rapidly increasing over the past decades in the United States as in the United Kingdom, especially in the elderly, and much, if not all, of this increase is attributable to the increasing use of much more advanced means of laboratory diagnosis. The possibility of diagnosis by means of superior local facilities may well have been greater for those living in the vicinity of the Hanford works, but over-representation in death certificates of local origin may be less than expected from this reason, given the chronicity of the disease and the correspondingly increased possiblity of changing the place of residence after the diagnosis had been made.

Kneale *et al*[1] are naturally interested in the "healthy worker effect" so clearly evident at Hanford, where the SMR for all causes of death was only 75. They say that this may be "the result of workers being made to pass a special fitness test before holding certain positions" and that this may explain why living Hanford workers have higher radiation doses than dead workers. They note that the SMR for cancer deaths was 89, higher than for all causes, and refer to "inefficient rejection of cancer-prone workers by the pre-employment health checks." This must imply that they believe that such health checks can select those naturally prone to cancer or (in the Hanford context) those naturally more sensitive to radiation-induced cancer, or both, and can do this 20 years or more before the cancer kills. Such a hypothesis has two important corollaries firstly, that those at Hanford who select workers for employment (in general or for certain positions, or both) have known for several decades how to select against the cancer-prone and, secondly, that those selectors have at the same time been wholly effective in concealing this knowledge from everyone else, in or outside Hanford. A priori, is this more likely than the alternative, if admittedly simplistic, hypothesis that work at Hanford has not yet been shown to involve a measureable overall cancer risk?

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Dr Kneale and Dr Stewart reply

Mole's first point is that if there is differential reporting of causes of death then it might just as well explain a positive association with radiation for some types of cancer (A cancers of radiosensitive tissues) as a negative association for other types (B cancers). This is superficially plausible, but the reasonableness of the argument is much reduced on a closer examination of what it entails.

The counter argument goes as follows. Cancer is generally a chronic illness with specific signs and symptoms and is easily diagnosed (if once suspected) by such procedures as biopsy or operation. Thus it is very unlikely that a non-cancer cause of death could mimic all the signs of cancer and be mistakenly entered on the death certificate as a cancer. Contrariwise, precisely because cancers have long latent periods, it is possible that an as yet unsuspected cancer might be undermining the integrity of the biological system and thus be (like the missing nail of the horse shoe that was the ultimate cause of a kingdom being lost) the underlying cause of a death whose certified cause was a heart condition, or some ascription, which really meant that the certifying doctor was ignorant of all the factors contributing to the death. Because "heart failure" is the immediate cause of all non-sudden deaths, certifying doctors are not allowed to use this term. Nevertheless, heart conditions are by far the commonest cause of certified deaths. To put the result of this argument in statistical terms; false-positive cancer diagnoses are bound to be much rarer than false-negatives.

The second point to notice in the counter argument is that at Hanford the dose distribution is very skew, so that doses near zero are much commoner than high doses. Consequently, a given number of deaths misdiagnosed at high dose will cause a much larger change in the test statistic, of mean dose, than the same number of mistakes at low dose.

Consider the table, which gives the distribution of cumulative dose, on an approximately logarithmic scale, for A and B cancers and non-cancers. The mean doses of the three causes of deaths are significantly different, and the fact that this difference persists after statistical control for a wide range of factors has been shown in many papers.[1 3 4] To bring the mean dose of the B cancers into line with that for non-cancers would require about 10 false-negative diagnoses at high dose or 100 false-positives at low dose. It has already been shown, however, that the possibility of false-positives can be effectively ignored and, consequently, that the dose distribution of the B cancers is consistent with about 10 misdiagnoses at high dose—which is a very reasonable error rate.

Now consider the similar argument applied to the A cancers. One would need about 20 false-positives at high dose or 200 false-negatives at low dose to bring A cancers into line with non-cancers. But 200 false-negatives is far too high an error rate to be reasonable, and it has already been shown that false-positives are very unlikely. Therefore, by the Sherlock Holmes method of eliminating all but the most unlikely alternatives, it is shown that the only reasonable explanation of what is observed is that there were about 20 genuinely *radiogenic* A cancers in the Hanford data.

Mole's second point about the joint association of high dose, long periods of employment, and diagnosis by Hanford doctors is precisely how we explain the association of dose and misdiagnosis of B cancers. In other words, we believe it is probably *Hanford doctors* who missed the 10 cases of B cancer postulated above. If Mole were right and it were these doctors who really made 20 false-positive diagnoses of A cancer, it would be the first time in the history of occupational epidemiology that factory doctors have been found to exaggerate the industrial risk with which they were most concerned.

Mole's third point about "the inefficient rejection

Total external dose of three groups of Hanford deaths

Dose levels (Rem)	*Group B cancers*	*Non-cancer deaths*	*Group A cancers*
Never monitored	96	1068	174
0·00	71	754	101
0·01 – 0·07	23	377	63
0·08 – 0·31	39	626	93
0·32 –	45	446	77
0·64 –	37	480	90
1·28 –	36	344	60
2·56 –	12	157	38
5·12 –	5	98	24
10·24 –	6	61	14
20·48	1	61	20
Total	371	4472	754
Mean dose	0·87	1·18	1·77

of cancer-prone workers by pre-employment health checks" is really a red herring. We hold no particular theory about how the healthy worker effect exerts its influence; all we were concerned to point out is that, however it is measured, it is evidently very strong at Hanford and, therefore, any method of analysis ought to take account of it. Again it is simply a pragmatic observation of ours that residual effects of selective recruitment of healthy workers can, in an internally controlled cohort analysis, be minimised by using "level of internal monitoring" as an extra controlling factor. Clearly, in any future analysis of Hanford data this extra factor should be related in some way to specific occupations in the work history of each individual. We are at present investigating this approach to the problem and hope to publish our findings in the near future.

A further point to notice about measures of the healthy worker effect is perhaps in order. The figures of 75 for the all-causes SMR and 89 for the cancer SMR were calculated not by us but by Gilbert and Marks.[5] They are, however, strongly supported by a similar SMR analysis by Darby and Reissland,[6] therefore, the facts are not in doubt. If, on the most simplistic interpretation, pre-employment health checks have reduced the all-causes death rate by 25%, then similarly the cancer death rate has been reduced by only 11%. Both these figures differ significantly from zero; and it is in this sense that the rejection of precancers by pre-employment health checks is only about half as efficient as the rejection of other illnesses. A final point to be noted is that, though we claim to show that risks of radiation cancer at Hanford are significantly higher than previous experience (such as that based on A bomb survivors) would lead one to expect, we have never claimed that the proportion of all cancers induced by radiation at Hanford is higher than 6%, and our later studies might reduce this to 5%. Thus it is clear that figures for the healthy worker effect would be only marginally altered by taking into account any cancer effects of radiation.

References

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