Cancer Morbidity Study

Critique

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A - Background

This current cancer morbidity study utilizes environmental epidemiology. Environmental epidemiology investigates whether environmental exposures are associated with subsequent excess rates of disease. Ecological studies in particular, such as this one, are blunt tools. There are many limitations and biases which make it difficult to obtain an accurate picture of the relationship between exposure and disease, some of which are described below.

I - Biases

a). misclassification by disease

i). misdiagnosis

There is considerable misdiagnosis of cancer. The diagnosed cancer may not represent the primary site (where the cancer originated). The degree of misdiagnoses depends on the tumour type as well as other factors.

ii). coding errors

There will inevitably be some errors in coding of the tumour type by The Cancer Registry.

b). misclassification by exposure

i. migration

Any ecological study such as this one, makes an implicit assumption that those who lived in Port Hope when their cancer was diagnosed had lived there long enough to have been exposed there. This is often not the case. Lee's study found that nearly 1/3 did not live long enough in the community to receive a meaningful radon dose. On the other hand, some people move away to live in a different community at the time of diagnosis. Their tumour which may have been acquired due to exposures in Port Hope, will not be attributed to Port Hope. These biases may be important. This bias will generally be nondifferential which means it results in an underestimating of risk (towards the null).

ii. residency coding

The residency for this study was established by the use of either postal codes or MOH codes. Both are subject to error. A percentage of postal codes are incorrect. In the long run, as many

cases who did not live in Port Hope would be coded as living there as the other way around. MOH code errors alone tend to be differential; people in neighbouring rural areas being grouped with the nearest town. Taken alone, they would tend to inflate the measure of the SIR (standardized incidence ratio), the prime measure of risk in this study. The problem is that since both have potential bias it is difficult to tell whether using the MOH or the postal codes results is more valid without further study. We can say that use of the postal code will generally result in underestimating the SIR while the direction of bias is not clear when using the MOH data. That is because although the MOH coding bias should be away from the null it is balanced by the counterweight of other strong biases which all would usually bias towards underestimating risk.

iii. exposure determination

Obtaining accurate estimates far in the past are particularly problematic. Sometimes crude correlates of exposure have to be used such as "residence for a period of time in a high risk area", "attending certain schools", etc.. In this case, exposures are based primarily on estimation of residential radon levels. Often one short term measurement attempts to reflect actual exposures which occurred over a period of time. Additionally, the total exposure to radiation may not be closely reflected by domestic radon exposures, because of ingestion, or attendance in St. Mary's school as well as other potential exposures (occupational). Clearly people living in Port Hope will vary widely in radiological exposures in terms of magnitude, type and time of greatest exposure.

iv. standard rates

The standard rates used to determine the expected number of cancers are based on provincial rates. These rates include other areas close to nuclear facilities as well as urban areas which may have multiple exposure problems and elevated rates. Therefore we could be comparing "dirty" areas to "dirty" areas and may be falsely underestimating risk in Port Hope. This problem is not totally alleviated by comparisons to similar communities because of the limitations of these comparisons discussed elsewhere.

II - Limitations

1. This being a descriptive SIR study, there is no information on individual exposures. The principle exposure is living in Port Hope. There is no way to control for confounding for individuals: that is we don't know what other factors besides radiological exposures in Port Hope may have caused cancers. Certainly many other common causes are acting besides the one(s) of interest in this study. For these reasons, firm conclusions regarding cause and effect for such studies are generally not possible. The main purpose of this type of preliminary study is to provide leads for further research.

2. Statistical results can only be used as a guidepost. Since so many SIRs were calculated, many (5 or 10% depending on the significance level) would appear to be statistically significant even if there were no unusual exposures in Port Hope. On the other hand, small numbers result in very low statistical power (ability to detect SIRs that are truly elevated). Therefore elevated but non statistically significant results cannot provide reason for comfort. The pattern of elevated SIRs must be judged as to its suggestibility of problems. On interpretation of this pattern, reasonable people may disagree.

3. We are dealing with cancers, most of which have very long latency periods. It is difficult to assign causation for a cancer to an exposure which may have occurred 25 years ago. These problems are less important for some of the cancers such as leukemia which have a shorter induction period.

4. The accuracy of the census data for Port Hope is another limitation. Census data inherently will have some under or overcounts.

III - Burden of Proof

The statistical burden of proof is very high. Traditionally we have to be 95% or at least 90% certain (confidence level) that differences are not due to chance before we state they are likely "real" or statistically significant. That leaves the area of high but less than 90% confidence as a gray zone where results are likely real, but not statistically significant.

The arguments for using a 95% confidence level (5% significance level) centre on it being the historical standard for the burden of proof. There is, however, no logical basis for choosing the 95% level of confidence. In fact, in was originally arrived at based on the cost-benefit associated with agricultural decision making. It is arbitrary. Most people use it simply because others have, not because of its appropriateness. It was not designed with the limitations of environmental epidemiology in mind.

The 95% level would appear unrealistically stringent here for a number of reasons including the following:

1. The confidence level assumes that the data is of high quality which we know is not true for crude measures of past exposures. High levels of misclassification by exposure (people are placed in the incorrect exposure categories) and some misclassification by disease (people are incorrectly classified as either being free from or having a given cancer) will usually decrease the chance of finding significant differences between groups thereby effectively setting the burden of proof much higher than the stated level. We are dealing with highly inexact data here. Most of the biases are non directional errors which would increase the burden of proof by adding noise to the data. The misclassification may be quite large in this study due to the serious sources of bias discussed above.

2. The ramifications of incorrectly finding a significant relationship between an exposure and a cancer is not great since conclusions in a study of this type will be based mainly on patterns rather than individual associations.

For these reasons, I have advocated a less stringent burden of proof of 90% if one is to be chosen at all.

In any case, the choosing of a significance level is largely a red herring. Significance levels are chosen when we are investigating whether an exposure (or a few) is related to a disease (or a few diseases). They are used to make decisions.

This study is not to be used for decision making. It is a preliminary study searching for likely leads. We are looking at hundreds of SIRs (Standardized Incidence Ratio). This study would be expected to show many associations between risk factors and symptoms which may be interpreted in different ways. It is not useful to rely on a stringent, strict statistical cutoff as a standard of proof. In so doing, we would be imagining that the quality of evidence is far superior than the reality and not taking into account serious issues affecting the true statistical significance of each finding.

The 95% confidence level, or any other, is not magical. For example, a study comparing leukemia rates in children living around the Pickering plant to lower risk children found approximately a doubling of the risk for children living near the plant. The probability of this finding being due to chance was about 5.5%. Therefore the study was interpreted as being "negative", that is not statistically significant. If the p-value was 4.9% the study would have been seen as "positive". Clearly these divisions are arbitrary and somewhat foolish.

The only statistical measure that really matters is the p-value, which is based on the results obtained. Interpretation of the results should be based on the p-value, an estimate of the biases affecting the p-value and clinical information, other information (such as the patterns over time and demographic groups) and common sense. Interpreting study results as negative based on arbitrary significance points is nonsensical in my view, for all of the above reasons.

The choosing of important findings is an art as well as a science. The p-value along with the consistency of the finding and its plausible relationship to exposures in Port Hope should be taken into account.

For example brain cancer is elevated in all time periods for women in Port Hope. It is statistically significant at the 5% level for the period 1986-1996 using MOH data only (p-value < .05). It is also highly significant for the total study period ($p<.01$). This cancer is elevated in men for the 1986-1996 period, but the p-values are not low. Taken alone the male data would not be strongly suggestive of excess brain cancer. Brain cancer was found to be highly elevated in Port Hope children during the period 1971-1985 ($p < .05$). These findings taken together show a pattern which is quite suggestive of there being a problem with brain cancer in Port Hope, even though only some of the findings were statistically significant at the 5% level. This is because excesses were found in all three groups and in all time periods. The sum of this data is not likely to be due to chance.

The above example shows that statistical significance (at any level) should be used only as a guidepost or screen for cancers which require further scrutiny. There will be significant results that are due to chance because of the large number of SIR calculations. On the other hand, because of low statistical power, many of the nonsignificant elevations may be important particularly if they are part of a pattern of excess rates.

IV - Other Issues

a). Time Window

As previously stated there are long latency periods for cancer. This period between initial exposure and diagnosis will vary by cancer. It becomes obvious that one will not uncover excesses if one is looking in the wrong time window. For example, most leukemias have short latency periods of less than 10 years. If it is true that exposure was greatest before the mid 1970s then we would expect the greatest leukemia rates to occur in the 1971-1985 time period.

The expected pattern of excess is one of the tools we can employ to separate perhaps spuriously elevated rates from ones which require further scrutiny.

Background Summary

Environmental measures of exposures, such as in Port Hope, are usually crude and far after the fact. Most of the other biases discussed above (exception of MOH coding) serve as white noise masking any real effect between exposure and disease. The result is that most environmental epidemiological studies are biased towards producing "negative" results due to the inherently low quality of the evidence (data) being evaluated. This should be taken into account when interpreting the findings.

B - Text Review

Introduction:

Our knowledge of dose and risk for various diseases is at best very limited and historical analyses show them to be subject to frequent and often large revisions. This reflects our limited knowledge of mechanisms and the natural history of disease and our need to extrapolate from often dubious data.

Trying to predict the effects of exposure is further greatly limited if it is difficult to determine the exposure with any degree of accuracy. In Port Hope, principal exposures occurred from the 1930's to the mid 1970's (at least some exposures are thought to be lower since then). I totally concur with the author's statement that "In the case of this study, for which exposure levels are primarily based on estimation of residential radon levels, the exposure categorization is further uncertain as the study primarily relies on one short term measurement (technically called a grab sample) to reflect cumulative radon levels over a period of 10 to 30 years. That it can do so only crudely is evident, as in addition to the previous factors, exposure estimation for residential radon estimation is also problematic as seasonal factors and modifications to homes influence levels, and occupancy factors vary by age, gender and occupational status". Remember, also, that there may be many and quite variable sources of exposure to other radiation and chemical sources beyond the home. Given all this, it is a reach to say that "Based on the cumulative estimated exposures observed and existing knowledge of dose-response relationships of radiation risk an observable excess of cancer would not be expected because the cumulative doses were low". That is, given the limitations of our predictive models as well as the great uncertainty of our exposure determinations it seems presumptuous to think we can be can be this precise in our anticipation of any effects on Port Hope residents cancer rates. The possible synergy between radiation and heavy metal concurrent exposures further cloud our predictive abilities. The attempt in this introduction to predict the results of this study is ill advised. More importantly it at least gives an appearance of minimizing results and expectations which repeats itself in this report.

Methods:

Regarding comparison to other communities, it is noteworthy and rather curious that although data from Port Hope was gathered for the period 1971-1996, only data for the period 1986-1996 is tabulated and presented. It would be of great interest to see the comparison over the longer period where the numbers are greater and any existing patterns may take shape.

It is incorrect to compare SIRs to each other. They can each be compared to the standard in turn, but not to each other. This , at the least, limits the usefulness of this analysis.

The tables are incomplete. Tables which included the expected numbers of cases for each cancer would be invaluable for verification and other analyses. One would normally expect the expected values to be presented in an SIR table. P-values would be an informative addition.

SIRs and directly adjusted cancer rates were presented only for selected sites and "significant" sites. Since "significance" is arbitrary and as I argue an inappropriate tool to dichotomize the data; we are missing important data. The reader should be able to identify overall patterns and tendencies which requires a much more extensive tabulation of sites.

Clearly crucial sites are missing from these tables. For example, in Table 3b. breast cancer is not listed. This despite the fact that it may be caused by radiation exposure, is a very important female cancer and most importantly breast cancer showed excesses (except for MOH data 1986-1996) and the p-value was just above .1 for the 1971-1985 period (nearly statistically significant). As well, SIRs were not presented for the two adult age ranges.

Why were the more stringent Canadian Cancer Registry confidentiality requirements of 5 cases used here? We are using provincial data. This seemingly unnecessary constraint results in another serious limitation for the rare cancer data making it even more difficult to determine what is going on in Port Hope.

The categorization of exposure areas of Port Hope for intra-town comparison were based on radiation data alone. In fact, the entire study focuses on radiation exposures and postulated effects. But a major point that has met with some agreement during meetings between the government and the PHCHCC was heavy metal exposure and possible synergism of multiple exposures. These issues are de-emphasized in this report.

The categorization provides a crude "proxy means to assigning a gradient to exposures across the town" in relation to radiation exposures only. Even at that there was no attempt to explain the cutoff points of exposure which appear to be arbitrary. Using different points would provide different results.

The childhood cancer results were not available in the appendix. The only presented data consists of a table of a few sites. Chronic lymphocytic leukemia should have been separated from the leukemia data (if it wasn't done).

Results

Section 3a.

The results of Table 1 which describes Port Hope cancer experience in the 1986-1996 period using postal codes are described here. It is curious why this period is emphasized here as throughout the report. While it is true that it is the only time period with postal code data, it also may not truly represent the cancer risks in Port Hope.

While the exposure experience in Port Hope is extremely complex it is generally agreed that the worst exposures occurred before the mid 1970's. Therefore we would expect some of the effects on short term radiation induced cancers like leukemia to present themselves before 1986. Most of these results are already presented in Table 3, so presenting them here gives them prominence and emphasis. It is questionable that results using postal code during this period should merit a separate table. The rationale given in the report is that "postal code is considered

best for distinguishing between cases residing inside and outside of Town boundaries. Whether this statement is true or not, postal code results may well be more biased than MOH code data for the reasons described in the Background section above. There is an implication that postal code results are more valid; that would be a debatable assertion.

The SIRs for all cancers showed the Port Hope rates to be close to provincial ones. But this data is selective. For the total study period (1971-1996) the female SIRs were elevated ($p<.1$).

3b. Comparison of Port Hope to Other Communities

As pointed out earlier, comparison of SIRs to each other is not valid. Previously it was also discussed that this comparison is severely limited since only the time period 1986-1996 is considered.

An example of how this may be misleading is demonstrated by the last sentence on page 7 which states that "no excess childhood leukemia was evident in Port Hope". But this statement is only true for the 1986-1996 time period when, in fact, there was a deficit of leukemia in Port Hope. This is in line with expectations because of the lower exposures after the mid 70s and the shorter induction period of this cancer. But overall, for the entire study period there was a 41% excess of leukemia in Port Hope children which was not statistically significant. This occurred even though there was less leukemia found than expected during the 1986-1996 period. This means that the excess found in Port Hope children between 1971-1985 was larger than 41%. We don't know what it was and what the p-values were because of the privacy rules and the small number of cases. This would be important information to have.

3c Port Hope all periods -MOH code used for residence

It is confusing to discuss MOH coding results in a separate section from postal coding results when both are presented together in Table 3. It is not particularly useful when comparisons are not forthcoming.

For example, the report states that "colorectal cancer among women was not significant at the 5% level based on the MOH code. What the report doesn't tell us here is that this rate was statistically significant at the 5% level using postal code and was close to the border of statistical significance using the MOH code. Taken together there is evidence that women experienced an excess rate of colon and rectum cancer in Port Hope during the 1986-1996 period. This method of separating the commentary for postal code and MOH code results in a fragmented text that tends to diminish results. The statement " no additional cancer sites were significant based on the combined 1971-1996 period or when results for men and women were combined" displays the limitation of dichotomizing data into chance and those not likely due to chance results based on stringent statistical criteria.

For example, for the period 1971-1985 women experience a marked excess of brain cancer (73%) but due to small numbers there is more than a 5% probability that this is a chance finding (not statistically significant). Taken together with marked non statistically significant excesses that men experienced in the 1986-1996 time period and the statistically significant excesses for brain cancer found in women for 1986-1996 there is strong evidence for an excess of brain

cancer in Port Hope, particularly for the period 1986-1996. Furthermore, brain cancer was highly and statistically significantly elevated for Port Hope children for the 1971-1985 period.

3d. Childhood Cancer

Overall the data presented in Table 4 suggests that there were childhood cancer excesses in Port Hope for the period 1971-1985. This is minimized and not dealt with sufficiently in the report. For example, a suggestive finding that leukemia showed a 41% excess during the entire study period is dismissed as "not statistically significant". The numbers are too small to have a reasonable chance to achieve "significance" (low power) though the finding may be important. As discussed earlier, the SIR for the 1971-1985 period must have been higher. This is particularly interesting in light of the fact that all cancers were highly elevated over the 1971-1985 study period. There were 76% more cancers that occurred in Port Hope children over the period than would be expected based on the provincial cancer experience. This finding was nearly statistically significant at the 10% level. It is highly noteworthy that this finding was not even mentioned in the report text. It is a suggestive and important finding. Since there were no excesses found for childhood cancer for the 1986-1996 period, the excess in childhood cancer for the entire study period was somewhat lower showing a 41% excess.

An important finding is that brain cancer was highly (more than 4 times the expected amount) and statistically significantly elevated for the period 1971-1986. Taken together with excesses found in men and statistically significant excesses found in women there is strong evidence that an excess of brain cancer has occurred in Port Hope. Non-Hodgkin's lymphoma was statistically significantly elevated in all time periods. Such consistency argues against the role of chance. This cancer has been linked to radiation exposure as well, although not strongly (1).

3e Enumeration Areas of Port Hope, 1986-1996

The trend of the SIRs with EA group rather than the actual numbers should be of interest here. The statistical power is generally very low. Nevertheless of the 8 sites presented in the 2 tables, 6 showed the highest exposure group to have the highest SIR (with one tie). Only colorectal cancer amongst males showed results that went against what we would expect if increased exposures are truly causing increased cancers. Total cancers for both men and women showed increasing cancer with increasing exposure, consistent with an exposure effect. The trend was statistically significant at the 10% level for women while the p-value was .12 for men.

It is more noteworthy that in the southern enumeration area (Table 6) kidney cancer was markedly elevated. This rare cancer may be an important markers of exposures at Port Hope as it is thought to be a radiosensitive cancer (1).

The last sentence of this section appears to concede, in an indirect fashion, that radiological exposures had effects in Port Hope.

Discussion

Municipal Patterns

The first sentence in this section states that cancer rates in Port Hope "were within the expected values". This is not clear; the author(s) apparently meant that none of the rates were statistically significantly different from provincial rates. Again, I think this strict statistical burden of proof is not appropriate. It is noteworthy that for children during the 1971-1985 period and for women during the total study period these total cancer rates were elevated and statistically significant at the 10% level.

The next sentence on the bottom of page 10 says that "Further, no excess rates in 'sentinel' cancers for radiation-based exposures, such as leukemia, were seen". This statement is false. Leukemia rates in children were elevated for the entire study period, although the results were not statistically significant (small numbers). The author's understanding of 'sentinel' is very conservative. Non-Hodgkin's lymphoma is statistically significantly elevated in children in all time periods. NHL has shown an association with radiation in some studies but not others being listed as an inconsistent radiological health indicator in a 1996 Durham Region Study (1). Brain cancers were elevated in all demographic groups, some of these elevations being statistically significant. Kidney cancer rates in the southern region were significantly elevated for those living in the southern enumeration area. Uranium is known to be a kidney irritant and causes kidney damage. The kidney is classified as a possible radiological indicator where studies consistently link it with radiation exposure but the association is not strong (1). Given all of this we can ask whether the definition of 'sentinel' is based on the results or based on reasonably interpretation of the scientific evidence including the gaps in current knowledge.

Referring to the comparisons between Port Hope and other Ontario communities the report states that "This general pattern showing a few significant cancer rates out of the 45 cancer types examined in each community appeared comparable across communities". This synopsis is vague enough to be meaningless. We need to remember that it is based on the 1986-1996 postal code data. Use of MOH code may have shown the Port Hope situation to be much more troubling.

I concur with the sentiment expressed that "Examination of data for consistent patterns gives some guidance as to whether results are likely due to chance or other factors". Unfortunately the next sentence is misleading, "In terms of such consistency, it is notable that none of the cancers in any of the communities are in excess among both genders". In fact, as previously noted, brain cancer was in marked excess for both genders and statistically significant in females. To note patterns, one cannot be a slave to a decision rule based on an arbitrary burden of proof level. The next two sentences contradict: the first stating that "none of the significant difference in specific cancer rates seen during the 1986-1996 period were consistently noted across gender and or time periods, thus certainly suggesting a role for chance". The next sentence says contradictorily that "Possible exceptions are brain cancer and lung cancer among women". There is no consistency here...the burden of proof is shifting from absolute statistical significance in the first case to a more thoughtful analysis of patterns in the latter case. This confusion is underscored by the last sentence on page 11 where the author admits that strict statistical significance is not needed to see a "suggestion of consistency of raised rates over time and gender". More importantly, the extremely high burden of proof is acknowledged "Given the rarity of the cancer (brain), significant excesses would be difficult to obtain. thus a lack of significance

is not surprising". It would be reasonable to add that this is why using the strict 95% significance level as a cutoff for meaningful results is not appropriate.

Sub-municipal analyses

In the second paragraph we are told that "It was notable however that the lowest dose grouping showed statistically significant deficits in lung cancer among females, and all cancer rates and lung cancer rates among males and females combined". This is false for female lung cancers, the lung cancer rates (SIRs) among females was not statistically significantly low.

Although we are told that a "relationship with colorectal cancer (and radon) is much less plausible" (than with lung cancer) the report's justification of this statement is weak. A relationship between radiation exposure and colorectal cancer is supported by the literature. It is listed as a significant radiological health indicator (1).

In the discussion of a marked excess of kidney cancer noted in the southern EA, we are told that this is unlikely due to radiation exposure even though it is thought to be a radiologically related cancer. At the same time it is stated that associations have been found with specialized medical treatments. We know that heavy metals such as uranium can damage the kidneys so that synergism between heavy metal and radiation exposures could also account for the excesses shown. Generally speaking, in an exploratory study, we can not hide behind the limitations of current knowledge. One of the purposes of studies like this one is to expand the base of current knowledge.

At the top of page 14, it is stated that lifestyle factors such as smoking and obesity are linked to kidney cancer. There is no evidence that smoking levels and obesity are so elevated in this area as to account for such a marked excess of kidney cancer.

Confounding risk factors

"A small number of cases of non-Hodgkin's lymphoma were observed in Port Hope at younger ages; risk factors for NHL are largely unknown". We are not told here that this "small number" was a marked and statistically significant excess over the expected number of cases.

On page 15 there is a rather unusual statement. Referring to Ontario Health Survey estimates of the smoking rates in The Haliburton-Kawartha-Pine Ridge Health Unit (includes Port Hope) we are told that "it was not possible to rule out differences of this magnitude for the Health Unit from the province...". Yet the results referred to showed the percentage of smokers in the Health Unit area to be not even close to being statistically significantly elevated from Ontario smoking rates. It seems that in this case, the burden of proof has changed and statistical significance doesn't matter. It is not at all clear what is meant by "this magnitude".

Impact of the source of residence code on cancer rates

The report makes the case that classifying residence by municipal location codes inflates the estimates of risk because nearby rural cases are sometimes placed in the nearest town. It looks at this bias in isolation from all other biases, however. Migration (both within Port Hope and between Port Hope and other communities), exposures which may be somewhat independent of residence (occupational, school) and misclassification by disease (misdiagnoses) are all potentially potent biases which would tend to underestimate cancer rates due to exposures in Port Hope. As well, there would be some random error in the codes which would bias in the same direction.

On page 16 the report states that since there were 5.3% fewer cases assigned to Port Hope by using postal code than residence code for the 1986-1996 period; thereby confirming that this amount of cases resided outside of the town boundaries. But this assumes that the postal code data was accurate when as we know, it may not be. The postal code data should not have been considered to be a gold standard.

The author states that the almost 30% difference in brain cancer cases between MOH and postal code cases should lead to a "different statistical interpretation of results". This exemplifies the overemphasis on a strict statistical significance criteria that overlooks the other biases and factors that affect these estimates. Indeed the report says that the postal code data is prone to errors and these errors bias towards the null. These other biases lead to underestimates. Taken together in light of all the evidence and bias, the brain cancer evidence strongly suggests that there is a true excess in Port Hope.

Concluding Comments

The discussion of the biases in this study is not very clear and the author's viewpoint is not disclosed. The report talks about the upward effect of MOH overestimates and the tendency to bias towards the null of other important biases such as migration. The report points out that the migration bias may be quite large. Many people living in Port Hope may not have had long-term exposure to contamination and Port Hope residents may have moved away and had their cancer attributed to a different community. These biases may be very important. It is almost certain that the effects of all of these biases results in even the MOH results sometimes being underestimates. The author doesn't make his/her viewpoint clear on the magnitude of biases going in different directions. This is an important issue.

Again we are told "that the numbers of total cancer cases in Port Hope are within the expected values". This term "expected values" is not at all clear. I assume that the author means that they are not statistically significantly different than numbers expected based on provincial rates.

The second paragraph in this section is quite contentious. Here we are told that "there is an absence of an increase in leukemia rates, and other radiosensitive sites, which does not support the hypothesis that radiation exposures in the community impact on resident health". The facts are that brain cancer rates were markedly high in all demographic groups (mostly statistically significant) and that Non-Hodgkin's lymphoma rates were significantly high for children for the entire study period. Brain cancer rates were highly elevated occurring at over 4 times the provincial rate for children during the 1971-1985 period. Brain cancer is at the very least suspected by some scientists to be linked to radiation exposures. The causes of non-Hodgkin's lymphoma are not certain but it is listed as a possible radiologically sensitive cancer (1). Lung cancer and colorectal cancer rates were significantly elevated as well and although they are radiation linked, I agree with the authors that confounding may be much more important for these two common cancers. However Lees Port Hope study found that, after the confounding effect of smoking was controlled for, there was still "a suggestion from the data that the odds ratio of acquiring lung cancer after domestic exposure to above normal background radiation is greater than unity " (3) (although not statistically significant at the 5% level). The Health Canada report states that "Particularly the absence of childhood leukemia is reassuring, as the minimum latency for childhood leukemia is short and the radiation risk coefficients relatively high". But in fact, there is a 41% increase in childhood leukemia in Port Hope over the entire study period. The fact that this increase does not reach statistical significance, mainly due to small numbers, nevertheless should not be completely discounted. The best estimate of the leukemia risk is greater than one. Perhaps even more importantly, the increase in leukemia rates noted in the 1971-1985 period may be quite close to statistical significance. I say this because the rate for the overall period is weighted downward because Port Hope children actually had less leukemia than expected during the 1986-1996 period. We don't know the SIR or how close it was to being significant because of small numbers and privacy concerns. We do know that it must be greater than 1.41, the value for the entire period. The overriding point here is that there is a confusion between absence of proof and proof of absence.

The report goes on to say that the lack of a trend between regions in Port Hope is of further comfort. The numbers for these rare cancers within Port Hope are so low that it almost precludes finding a trend. Nevertheless the trends for most of the present cancers go in the direction expected if there were truly radiological effects on cancer rates in Port Hope.

The author clearly and crucially misinterprets the study results relating to rare cancers and childhood cancers here.

The author talks about the "absence of an effect among men on lung cancer", even though there was an elevation of lung cancer amongst men that was not statistically significant. This is another example of there not being overwhelming proof in favour of high lung cancer rates in men but certainly the evidence does not support an absence of high rates.

In the last paragraph the author makes an important recommendation that conducting case-control studies for specific sites would not seem to be a useful exercise. Yet no reasoning behind this decision is given. One is left to wonder how many suspect sites would need to be produced by this study in order to change this recommendation. In my opinion there are enough suspect sites to warrant further investigation.

C - Text Review - Summary

The SIR and direct rate analyses are quite comprehensive. Problems lie with certain omissions. Childhood cancers are not separated from adult cancers in the appendix so that when it comes to childhood cancers we are limited to examination of the few cancers picked to be presented in the table.

What is the burden of statistical proof in this study? There appears to be a shifting standard. Judging from the discussion and the tables, it usually is a confidence level of 95%. Yet at times the report notes that the small numbers and resultant low statistical power make it very difficult to meet that criteria. At these times it is suggested that a lower level may be appropriate for rare cancers in particular. I have made the point that the burden of proof should be lower and not rigid. We should look at the pattern of p-values along with other information to make the best judgments we can. Admittedly, interpreting data like this is difficult and reasonable people will disagree.

The tables suffered from several deficiencies. Again, in my view the statistical burden was too stringent. There should have been 90% as well as 95% confidence intervals. The expected number of cases should have been included. Besides being informative, this information would be needed for verification of the results.

The study lacks a cohesive discussion of expectation based on radiosensitivity of various cancers. It would have been useful to discuss the possible radiosensitivity of each cancer beforehand and then anticipate where and when any problems would be expected to occur. Any discussion of this type is scattered and often lacks any defense of the stated viewpoint. For example we are told that a "relationship with colorectal cancer (and radon) is much less plausible (than with lung cancer) without any substantiation. Other authors list colorectal cancer as being consistently linked with radiation exposure in the literature (1). Similar judgments without backing are made regarding the radiosensitivity of other cancers.

In fact, many important statements are made without substantiation and therefore appear arbitrary. For example, we are told that further case-control studies would not be useful without any further comment.

My main problem with this report is one of emphasis. In my view, there is a general problem with selectivity and emphasis in this report. For example, Table 1 highlights postal code data for the 1986-1996 period only. The separation of this data from the MOH data does not facilitate comparison and analyses. The fact that postal code rates and the corresponding MOH rates are discussed in separate sections is confusing. It is difficult for the reader to piece the entire story together. The report layout and organization is confusing and doesn't make the reader's job an easy one. There is not a clearly labeled logical flow and this inhibits review.

Actually, 1986-1996 data is emphasized throughout the report. Why were comparisons to other communities done using this data only? I would expect any excesses in short latency period cancers such as leukemia to occur mainly in the earlier study period. In any event, it is not correct to compare the SIRs to each other. Given that the numbers are small, the age-adjusted rates would not be very useful as the rates would be volatile. This limits the usefulness of the comparison of incidence across communities. There are some important omissions from the tables. For example, breast cancer was omitted despite its important and intriguing results.

There is a tendency to minimize the results. For example, we are told that "particularly the absence of excess leukemia rates among children is reassuring". This despite a 41% increase over the study period shown by the SIR. While this result was not statistically significant, it should not be dismissed. While it does not offer strong evidence for excess leukemia in Port Hope children, it certainly does not offer reassurance. The difference between proof of absence and absence of proof is being blurred here and elsewhere. The SIR for the 1971-1985 would be even greater, however we don't know what the SIR is due to privacy concerns.

Children in Port Hope experienced a 76% excess cancer rate during the 1971-1985 period which was statistically significant at the 10% level. This important suggestive finding was not mentioned in the report. The general point here is that in my view the discussion did not accurately reflect the study findings.

Granted, the production of a comprehensive report of this magnitude and particularly its interpretation is a difficult task. This being said the deficiencies noted as well as unanswered questions limit its utility.

D - Summary - Discussion

Table M1 has been constructed to display SIR results for the sites most likely to be radiosensitive to exposures in Port Hope. Other sites (brain) with highly suggestive results have been included. Approximate 90% confidence intervals have been calculated and included. They are shown in bold text.

Total cancers are a radiosensitive indicator. Females experienced higher than expected rates in all periods. For the entire study period the SIR of 1.06 was statistical significant at the 10% level. This is most influenced by the high rates in two common radiosensitive cancers; lung cancer and colorectal cancer. The female lung cancer rates were statistically significant for the 1986-1996 ($p < .05$) and for the entire study period ($p<.1$). For both of these cancers, females had higher SIRs for every period and coding method (often substantially) than did men.

For these two common cancers confounding could certainly be influencing these results. Smoking is of course the dominant risk factor for lung cancer while diet and lifestyle risk factors influence colon cancer rates. But in order to explain the pattern of findings, the confounding factors would have to be stronger for women than for men. That scenario is not very likely.

Female breast cancer rates were elevated during the 1971-1985 time period. This result was nearly statistically significant at the 10% significance level. This is perhaps more notable given that Port Hope is thought to be generally of lower social economic status (SES) and the disease generally increases with SES. It is a radiosensitive cancer.

Ovarian cancer is thought to be radiosensitive. It is the outlier of this data set. Rates for Port Hope women were low, particularly in the 1986-1996 period (less than half the expected rate ($p < .05$). The fact that ovarian cancer is higher in high SES groups probably explains this finding, at least in part.

Males on the other hand don't show indications of overall problems. The male lung cancer rate is slightly elevated for the overall period ($p>.1$). They do show excesses for the radiosensitive bone cancer. For the entire study period the SIR was 2.58% ($p<.1$).

Male lip cancer is statistically elevated using both coding methods for the 1986-1996 period (at the 5% and 10% levels, respectively). For men, nasal cancer was elevated for the entire study period ($p<.05$) due mainly to a high rate for the 1971-1985 period (over 5 times the expected rate). Occupational exposures may be suspect here.

Brain cancer is a site of particular concern. It is discussed in detail previously. The pattern of findings is consistent enough to support the findings being unlikely to be chance ones.

Kidney cancer rates were elevated in the southern EA group for men and women combined ($p<.05$). This cancer may be radiosensitive so it may be an important marker of high exposures in this area.

Childhood cancer is of particular concern in Port Hope. Their exposure is probably the greatest, particularly for the route of ingestion. The data suggests that there may be problems here. All cancers were elevated for the 1971-1985 time period ($p < .1$). The marked brain cancer excess in this time period ($p<.05$) is consistent with other raised rates. NHL has shown some indication of radiosensitivity (weak findings) (1). It is elevated in the 1986-1996 period and for the total study period ($p<.05$). The excess found in all time periods shows it very unlikely to be a chance finding.

Although there was actually less leukemia than expected which occurred in Port Hope children during the 1986-1996 period, for the overall study period the SIR indicated a 41% increase. The p-value was not small. Chance could easily explain this finding. The excess in the first study period must have been greater than 1.41 in order to produce the overall rate (given the 1986-1996 deficit). We don't have the SIR or the p-value for this. This could be an important finding and more specific information is needed here. This is particularly true since, chronic lymphocytic leukemia was apparently not excluded from the calculations and may have diluted the SIR.

There is some consistency with expectations based on time windows. Leukemia rates were higher during the early study period. It has a short induction time. Colon cancer and lung cancer rates in women were only high in the later time period. These cancers have longer latency periods.

These results show several areas of concern that warrant further investigation. That is because for several of the cancers, the presence as well as the pattern of excess rates result in chance not being a likely explanation. The first study stage would be a more in-depth case by case verification. If case-control studies are indicated, power studies would have to be done to determine for which sites they are feasible.

E - Conclusions

1. This report suffered from several important deficiencies, noted in this review, which limited the validity and utility of this report.

2. Parts of the discussion do not accurately reflect the findings.

3. The emphasis of the analysis was on the 1986-1996 period. This was not sufficiently justified. For cancers of short induction periods we would not expect high rates in Port Hope for this period.

4. For several common cancers the evidence from this study suggests that females have high rates (lung cancer, colorectal cancer, all cancers). The SIRs were generally higher than the corresponding ones for males. These findings suggest differential exposures by gender.

5. If confounding explains the pattern of lung cancer and colorectal rates it would have to be greater for females. Such a scenario is not a likely one.

6. The findings suggest that children have experienced high cancer rates particularly before 1986. The pattern of cancer rates in children is consistent with effects from the higher exposures before remediation.

7. The findings taken together show a pattern which is quite suggestive of there being an excess of brain cancer in Port Hope.

8. The Canadian Cancer Registry confidentiality restrictions when there were less than five cancers further constrained a study which relied on limited data.

9. Further research should look into the feasibility of a case-control study for suggestive sites.

References

1 Durham Region Health Department. Radiation and Health In Durham Region. November 1996.

2. Ulm K. A Simple Method to Calculate The Confidence Interval Of a Standardized Mortality Ration (SMR). American Journal of Epidemiology. 1990; 131(2):373-375.

3. Lees, RE, Steele R., Roberts JH. A case-control study of lung cancer relative to domestic radon exposure. Int J Epidemiology 1987;16(1):7-12.

Table M1 - Important Results

Period	Males	Females	Children	Overall
All Cancer				
71-85	0.99 [0.88. 1.11]	1.01 [0.90. 1.13]	1.76 [0.94. 3.00]	1.00 [0.92. 1.08]
			1.76 [1.09, 2.83]*	
86-96 PC	0.93 [0.82. 1.05]	1.07 [0.95. 1.17]	0.82 [0.26. 1.87]	1.00 [0.92. 1.08]
86-96 MOH	1.01 [0.89. 1.13]	1.11 [0.99. 1.23]	0.98 [0.36. 2.10]	1.06 [0.97. 1.14]
71-96	1.00 [0.92. 1.08]	1.06 [0.98. 1.14]	1.41 [0.85. 2.19]	
		1.06 [1.01, 1.22]*	**1.41 [0.95, 2.09]**	
Brain/Nervous				
71-85	<1	1.73 [.79. 3.26]	4.17 [1.35. 9.57]	NC NS > 1
		1.73 [.97, 3.06]		
86-96 PC	1.31 NS	1.61 [.70. 3.15]	< 1	1.45 [.81. 2.39]
				1.45 [.93, 2.26]
86-96MOH	1.49 NS	2.21 [1.11.3.94] 5**	< 1	
71-96	< 1	1.96 [1.2. 3.03] 5***	> 1 NC NS	
bone				
71-85	> 1 NC NS	< 1 NC	-	> 1 NC NS
86-96	< 1 NC	< 1 NC	-	< 1 NC
86-96MOH	> 1 NC NS	< 1	-	>1 NC NS
71-96	2.58 [.84.5.93]	< 1	-	1.38 [.45. 3.18]
	2.58 [1.20,5.50]10*			
Lung Ca				
1976-86	1.13 [.88. 1.44]	.93 [.57. 1.44]		1.08 [0.87. 1.33]
86-96 PC	1.05 [.80. 1.36]	1.35 [.98. 1.81]		1.16 [0.95. 1.41]
		1.35 [1.05. 175] *		
86-96 MOH	1.13 [.86. 1.45]	1.44 [1.06. 1.91] **		1.24 [1.02. 1.50]**
71-96	1.13 [.94. 1.34]	1.24 [.96. 1.57]		1.17 [1.01. 1.34]**
	1.13 [.97, 1.31]	**1.24 [1.01, 1.53] ***		

Period	Males	Females	Children	Overall
Leukemia				
71-85			> 1 NC NS	
86-96 pc			< 1	
96-96 MOH			< 1	
71-96			1.41 [0.45, 3.29]	
Breast				
71-85		1.17 [0.94, 1.44]		
		1.17 [0.99, 1.41]		
86-96 pc		1.01 [0.80, 1.25]		
86-96 MOH		0.93 [0.55, 1.48]		
71-96		1.09 [0.93, 1.26]		

* statistically signicant at the 10% significance level

** statistically signicant at the 5% significance level

*** statistically signicant at the 1% significance level

10% confidence limits are bolded (2)

NC - calculation not shown - confidentiality

NS - NS at 5% or 10% levels

Period	Males	Females	Children	Overall
Ovary				
71-85		.92 [.47. 1.60]		
86-96 PC		.43 [.14. .99] **		
86-96 MOH		.43 [.14. .99] **		
71-96		.69 [.40. 1.10]		
Colorectal				
71-85	0.93 [0.66 . 1.28]	1.03 [0.77. 1.35]		0.99 [0.79. 1.21]
86-96 PC	1.03 [0.75 1.40]	1.42 [1.09. 1.82] **		1.23 [1.01. 1.49]**
86-96 MOH	1.08 [0.79. 1.46]	1.26 [0.94. 1.64]		1.17 [0.95. 1.43]
		1.26 [0.99, 1.58]		1.07 {0.93. 1.24]
71-96	1.01 [0.80. 1.25]	1.13 [0.93. 1.37]		
		1.13 [0.96. 1.33]		
Nose/Sinuses				
71-96	5.61 [1.81. 12.88]**	< 1 NC		2.86 [0.92. 6.56]
				2.86 [1.33, 6.10]*
86-96 PC	< 1 NC	> 1 NC NS		< 1 NC NS
86-96 MOH	> 1 NC NS	> 1 NC NS		> 1 NC NS
71-96	>1 NC **	< 1 NC NS		> 1 NS SS **
Lip				
71-96	1.12 [0.36. 2.56]	< 1 NC		0.95 [0.31. 2.18]
86-96 PC	2.35 [0.86. 5.06]	< 1 NC		1.78 [0.65. 3.82]
	2.35 [1.16. 4.72]*			
86-96 MOH	2.75 [1.10. 5.60]**	< 1 NC		2.07 [.083. 4.23]
				2.07 [1.08. 3.95]*
71-96	1.71 [0.88. 2.97]	< 1 NC		1.39 [0.72. 2.42]
NHL children				
71-85			> 1 NC NS	
86-96 PC			> 1 **	
96-96 MOH			> 1 **	
71-96			> 1 **	