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RADIATION-INDUCTION OF HUMAN BREAST CANCER

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Introduction

Mackenzie made some extremely important observations concerning an apparent association between the occurrence of breast cancer and prior pneumothorax therapy of pulmonary tuberculosis (1). His analysis led him to the conclusion that fluoroscopic X-ray exposure associated with the pneumothorax therapy might have been etiologic in the induction of breast cancer in women so exposed. Wanebo and co-workers were so impressed by the Mackenzie findings that they decided to make a specific study of breast cancer incidence in the survivors of Hiroshima-Nagasaki (2). Wanebo revealed an extremely important point concerning the studies of atom-bomb survivors, a point of deep importance that is not at all realized broadly. Let us quote Wanebo and co-workers directly,

"Unlike leukemia and thyroid cancer, breast cancer has hitherto received no special emphasis in the ABCC program".

The work of Mackenzie actually was a primary stimulus for Wanebo and co-workers to search out the breast cancer situation in Hiroshima-Nagasaki.

This is indeed a revelation. All cancers are not automatically searched out in the Hiroshima-Nagasaki study. Rather, when some relevant suggestion comes up concerning radiation carcinogenesis of a particular organ, a diligent search is then made among Hiroshima-Nagasaki survivors for evidence of a radiation-induction of that disease in the bomb survivors. Thus, eventually, it can be expected that all forms of cancer will be investigated adequately in Hiroshima-Nagasaki. These studies are crucial and invaluable! But what this sequence of events teaches us in that at any point in time the failure of apparent existence of radiation-induction of a particular cancer in Hiroshima-Nagasaki survivors can be more related to a failure to look at that time than to absence of radiation-induction. This is in no way a criticism of ABCC. Its work is truly of monumental importance. But this should, for once and all, silence those

who say, "But radiation-induction of cancer X hasn't been observed in Hiroshima-Nagasaki survivors". The answer appears that either (a) the ABCC staff hasn't yet completed studying that cancer, or (b) the latent period for radiation-induction may be longer than for those cancers which have already been clearly proved to be radiation-induced. In time the ABCC will undoubtedly provide data concerning every major form of human cancer induction by ionizing radiation.

The Mackenzie Breast Cancer Data

The first observation of Mackenzie was the occurrence of a breast cancer on the upper part of the inner half of the breast in a woman whose skin showed residual evidence of radiation-type dermatitis. The unusual location of the breast cancer plus the suspicion of radiation changes in the adjacent skin led finally to the information that the woman had some 15 years before been hospitalized for pulmonary tuberculosis, for which she had received numerous pneumothorax refills over a period of 4 years. With each refill a fluoroscopy (or two) was generally performed, estimated to be some 200+ times in this particular woman. The total radiation dosage was guessed to be in excess of 4000 Rads to the breast area.

Thereafter a followup study was carried through on 877 female patients who had been hospitalized for the first time in 1940-49 for re-infection (adult) type tuberculosis. Of this group of patients 510 never received pneumothorax (or the accompanying fluoroscopies). 96 cases were started on pneumothorax, but because it was not operable this form of therapy was discontinued after a very brief trial, leaving 271 cases who received pneumothorax for extended periods, >6 months in most cases. With each refill, in general, a fluoroscopy (or two) was performed. The precise number of fluoroscopies in each case could not be ascertained from the records. We shall return to this issue later.

These 877 patients were the "cohort" admitted during the decade 1940-1949, so that some 15-20 years elapsed between hospitalization and when Mackenzie's study was made. A diligent search of all the cases was made for the occurrence of carcinoma of the breast. Mackenzie found no evidence of bias, nor is it likely that the search was of any different degree of diligence for those who had pneumothorax as compared with those who had not received that therapy. The results, reproduced below, were startling and disturbing:

In 510 patients without penumothorax therapy one breast cancer was discovered to have occurred subsequent to hospitalization.

In 271 patients with extensive periods of pneumothorax (and its concomitant fluoroscopies) there were 13 breast cancers in the followup period.

This is a ~24 fold greater incidence of breast cancer in the pneumothorax series than in the other series, and as Mackenzie pointed out this result is of very high statistical significance. ($p = 0.001$). That the difference in breast cancer incidence rate is enormous is very clear. It remained for Mackenzie to inquire as to explanation for the large observed differences, and in this he was most thorough. He considered the possibility that a less diligent search had been made for breast cancer in the group without pneumothorax, but concluded there was no reason to suspect the data on this basis. Furthermore, the breast cancer incidence rate in the pneumothorax group was far higher than that expected for comparable age groups in the population-at-large.

Mackenzie considered the possibility that tuberculosis per se might increase the breast cancer rate. He could find no evidence thereof. Even if there were some association of prior tuberculosis with breast cancer 15 years later in life; one would have to stretch this to believe tuberculosis treated with penumothorax is either peculiar or more severe and increases breast cancer some 20 times more than other tuberculosis. This is indeed remote. To add to this remoteness,

one would have to postulate that tuberculosis requiring pneumothorax predisposes not to the ordinary form of breast cancer but to an uncommon form (inner half of breast) precisely in the region of maximum irradiation associated with the fluoroscopies.

After giving due and proper consideration to these remote, unlikely explanations for the excess breast cancer in the pneumothorax-treated series, Mackenzie cautiously suggested that the radiation delivered during multiple fluoroscopies (100-300 times) might very well be the etiologic agent in the induction of the tremendous excess of breast cancers in these women. While Mackenzie's caution in proposing this explanation is in the highest tradition of the science of epidemiology, it would seem extremely remote indeed that any other etiology than radiation is even worthy of serious consideration. As we shall see below the peculiar location of the breast cancers in the irradiated women points very strongly to the fluoroscopic examinations as the basis for the excess breast cancer incidence.

Dose-Response Relations in Radiation-Induced Breast Cancer (Mackenzie data)

Direct estimation of the dose in rads to the breast was not possible for any of these cases, since the only item of information available was the approximate number of fluoroscopies. For our purposes, a reasonable range of dosage can be estimated, certainly an estimate good enough to determine within a few-fold what the doubling dose for radiation-induced breast cancer might be.

Mackenzie ascertained the type of fluoroscopic equipment in use in the tuberculosis treatment centers of the relevant period (1940's) and the usual type of use. His estimate indicated that generally the examinations must have been carried through with a dose rate to the breast of between 22 and 55 rads/minute, depending on whether or not aluminum filtration had been used. His evidence suggested it might or might not have been used, so we shall retain the range,

22 to 55 Rads per minute. The physicians had been advised to avoid exceeding 10 second exposures, but he found it was likely that longer periods of exposure were not uncommon. Let us, since it is conservative and minimizes the radiation effect, assume each examination was 50% longer than recommended, i.e. 15 seconds. This would mean 1/4 x 22 to 1/4 x 55 as the dose in rads per exam $=\sim$6 to 14 Rads.

From the separate careful study of records of 40 breast cancer patients who had received pneumothorax, he estimated the following minimum distribution of fluoroscopic examinations.

Fluoroscopies	No. of Cases
Under 100	15 cases
100 - 200	16 cases
201 - 300	6 cases
>300	3 cases
Total	40 cases

Let us assign 50 fluoroscopies for the <100 group, and 400 fluoroscopies for the >300 group, and use the midpoint of the other intervals and mean number of fluoroscopies for the group. Then we calculate:

$$\text{Average No. of Fluoroscopies} = \frac{(15)(50)+(16)(150)+(6)(250)+(3)(450)}{40}$$

$$= \frac{750+2400+1500+1350}{40} = \frac{6000}{40}$$

$$= 150 \text{ times per patient}$$

Therefore at 6 to 14 Rads per fluoroscopy, this means the average patient probably received 900 to 2100 Rads. If the true number of rads were lower than this the case against radiation is even worse than it will be calculated. The only hope for any mitigation of effect per rad in breast cancer induction would be for the above dose estimates to be low. It seems extremely unlikely that the dosage could have been more than a factor of 2 higher, or radiation dermatitis would have been common in these cases of breast cancer following repeated

fluoroscopies. Such dermatitis was of low frequency. We shall remember this factor of 2 on the high side below.

Now since 13 cases of breast cancer occurred in 271 women, this corresponds to 24.5 cases per 510 women with pneumothorax therapy compared with 1 case per 510 women without pneumothorax therapy.

Excess 23.5 cases

Therefore $\frac{23.5}{1.0}$ = 23.5 Doubling Doses of Radiation

Our estimated range for mean dosage is 900 to 2100 rads for the overall group.

At 900 Rads, we have $\frac{900}{23.5}$ = 38.3 Rads as Doubling Dose.

At 2100 Rads we have $\frac{2100}{23.5}$ = 89.4 Rads as Doubling Dose

Let us allow for 2 more possibilities to "help" radiation. Suppose the average number of rads were twice the high estimate, namely 4200 Rads (an unlikely figure)

Then

$\frac{4200}{23.5}$ = 178.7 Rads as Doubling Dose

Let us further suppose our incidence figures, based upon 13 and 1 give rise to too high a number of doubling doses. Let us cut this in half; say 11.7 doubling doses instead of 23.5. Then for the extreme dose and minimum number of doublings,

We have $\frac{4200}{11.7}$ = 359 Rads as Doubling Dose for Breast Cancer Induction.

So the range is 38.3 Rads - 359 Rads as the doubling dose for radiation induced breast cancer - using extreme limits for estimates. Even the highest figure, 359 Rads, is a damning one for radiation inducing breast cancer. The other extreme figure, 38.3 Rads, well within the possibilities, is very frightening in its implications.

But, thus far, we have approached the problem in what may be regarded as a crude "overall" approach. There is a very important refinement, which makes the true doubling dose for radiation-induction of breast cancer much lower than any of the estimates above.

Let us recall that the first case that came to Mackenzie's attention showed her breast carcinoma in the inner half of the breast. In a series of 44 cases of breast cancer with prior history of pneumothorax, Mackenzie found 72.8% were either centrally located or were in the inner half of the breast. As Mackenzie points out, quoting Haagenson(3) the usual distribution of malignant breast tumors shows the outer half of the breast predominantly involved. The implication is, of course, obvious, - the fluoroscopic beam was far more likely to irradiate the inner half or central region of the breast, and hence the cancers developed there.

But let us now be quantitative on this point. From Ackerman and Regalo, we have the following data for spontaneous mammary cancer in women (4).

Upper Outer Quadrant:	47% of cases.
Lower Outer Quadrant:	7% of cases.
Upper Inner Quadrant:	14% of cases.
Lower Inner Quadrant:	2% of cases.
Central (Nipple area):	22% of cases.

Therefore, spontaneous breast cancer is (22+2+14) = 38% either in inner half of breast or centrally located, in contrast to the 72.8% for the pneumothorax cases. Now we are in a position to estimate doubling doses for radiation-induced cancer more meaningfully. If one is studying induction of a particular cancer in a particular location, the appropriate comparison of the induced disease is with the spontaneous occurrence in that same location - not elsewhere in the organ or in another organ. This is elementary, but essential.

Let us return to our input data:

24.5 cases per 510 women with pneumothorax therapy
1 case per 510 women without pneumothorax therapy.

Now let us calculate the data for (inner half + central) cancers

For the irradiated group $(0.728)(24.5) = 17.8$ cases per 510 women.
For the unirradiated group $(0.38)(1.00) = 0.38$ cases per 510 women.
Excess = 17.42 cases per 510 women.

$$\text{Doubling doses} = \frac{17.42}{0.38} = 45.8 \text{ doubling doses.}$$

$$\text{At 900 Rads, we have } \frac{900}{45.8} = 19.7 \text{ Rads, doubling dose}$$

$$\text{At 2100 Rads, we have } \frac{2100}{45.8} = 45.9 \text{ Rads, doubling dose.}$$

$$\text{At 4200 Rads, we have } \frac{4200}{45.8} = 91.8 \text{ Rads, doubling dose.}$$

So at our extremes of likely dosages, the estimated doubling dose for radiation-induction of breast cancer lies between 19.7 and 45.9 Rads. (91.8 Rads, for very extreme upper limit of dose).

If we wish to allow for errors of small numbers, let us make the rash assumption that we have only 1/3 as many doubling doses. This still corresponds to 59.1 Rads to 137.7 Rads as the range of extreme doubling doses.

Thus, at the outside, it is hard to conceive that the true doubling dose for breast cancer is higher than 140 Rads, with most of the evidence indicating it is far more likely to lie in the neighborhood of less than 50 Rads!

The Wanebo (A.B.C.C.) Breast Cancer Data - Radiation Induction

The studies of Mackenzie just discussed are for women in Nova Scotia, Canada. We can now turn our attention to the same problem, radiation-induction of breast cancer 7500 miles away in Hiroshima and Nagasaki, Japan. Let us examine the data concerning doubling doses for radiation induction of breast cancer in this epidemiologically very different group of humans.

The best epidemiological material in the Wanebo study is for cases of breast cancer arising in 10,142 women who were examined at least once as part of

the Adult Health Study Sample. Secondly, the analysis can be restricted to 20 cases where dosage is known and where only the definite cases are considered. Thirdly this group is ideal since all the breast cancers arose between 1958-1966, so that the series is not diluted unduly by cases likely still to be in the latent period of radiation-induction of breast cancer. Nevertheless, the true final incidence will undoubtedly be higher as more time elapses. Taken from Table 2 of Wanebo's paper are the data reproduced here as Table 1.(Reference 2)

Table I

Total Dose (rad)	Median Dose (rad)	Number of Examined Women	Definite Cases of Breast Cancer (1958-1966)
Not in City ATB*	0	2458	2
0-9 Rads	4.5 Rads	3082	3
10-39 Rads	25 Rads	1282	4
40-89 Rads	65 Rads	857	2
90-199 Rads	145 Rads	802	4
200+	~300 Rads	841	5
			20 Cases
Dose Unknown		840	2 Cases (Left out of analysis because dose unknown)

*ATB= at time of bombing

Out of the total of 22 cases, 20 are from groups where the dosage is estimated; 2 are from groups where dosage could not be estimated. Obviously, analysis must be restricted to the 20 cases for whom dosage is known.

First, is there a significant increase in breast cancer in the irradiated persons?

The categories involving moderate or high radiation doses are as follows:

	Exposed	Exposure (Mean, Dose, Rads)	Cases of Breast Cancer
	841	~300 Rads	5
	802	145 Rads	4
	857	65 Rads	2
	1262	25 Rads	4
Total	3762		15

For the very low exposure or non-exposure categories, we have

	Exposed	Exposure (Mean Dose, Rads)	Cases of Breast Cancer
	2458	0 Rads (Not in City)	2
	3082	4.5 Rads	3
Total	5540		5

The ratios of breast cancer incidence in the "irradiated" to "non-irradiated" groups is

$$\frac{15/3762}{5/5540} = \frac{(5540)(15)}{(3762)(5)} = \frac{83100}{18810}$$

$$= \underline{4.4} \text{ fold}$$

There would seem no reason to doubt Wanebo and co-workers' conclusion that a highly significant association is noted in these data between radiation and subsequent appearance of breast cancer.

Doubling Dose for Breast Cancer Induction by Radiation

To avoid dealing with small numbers and their statistical fluctuations, we shall make estimates of doubling doses only for combined groups with a reasonable number of cases.

(a) All Cases where dose is over 90 Rads

$$\text{Mean Dose} = \frac{(802)(145)+(841)(300)}{802 + 841}$$

$$= \frac{116290 + 252300}{1643} = \frac{368,590}{1643}$$

$$= 224.3 \text{ Rads}$$

In this over 90 Rad group, 9 cancers in 1643 women, or a rate of 54.8 cancers per 10000 women.

Now we need "spontaneous"rate of occurrence of cancer. We shall use the combined data of the Not-in-City group plus the 0-9 Rad group (assuming 4.5 Rads will hardly affect incidence compared with 224.3 rads)*

*A second-order correction could be made for this small effect here. One should not conclude 4.5 Rads is a negligible dose, however).

Not-in City =	2458 women	2 breast cancers
0 - 9 Rads =	3082 women	3 breast cancers
Total	5540 women	5 breast cancers

So, "spontaneous" rate = 9.0 cancers per 10000 women.

Excess Cancers = 54.8-9.0 = 45.8 per 10000 radiation-induced.

$$\frac{45.8}{9.0} = 5.1 \text{ Doubling Doses are represented.}$$

5.1 Doubling Doses $\stackrel{\vee}{=}$ 224.3 Rads

1 Doubling Dose = 44 Rads

(b) All Cases where Dose is over 40 Rads

For the over 40 Rad group.

$$\text{Mean Dose} = \frac{(857)(65)+(802)(145)+(841)(300)}{857 + 802 + 841}$$

$$= \frac{55705 + 116290 + 252300}{2500}$$

$$= \frac{424295}{2500} = 169.7 \text{ Rads}$$

In the over 40 Rad Group, 11 cancers in 2500 women, corresponding to a rate of 44 cancers per 10000 women.

"Spontaneous" rate (see above) = 9.0 cancers per 10000 women

Excess cancers = 35.0 cancers per 10000 women, radiation-induced

$$\frac{35.0}{9.0} = 3.9 \text{ Doubling Doses are represented}$$

3.9 Doubling Doses = 169.7 Rads

1 Doubling Dose = 43.5 Rads

(c) All Cases where Dose is over 10 Rads

For the over 10 Rad group.

$$\text{Mean Dose} = \frac{(1262)(25)+(857)(65)+(802)(145)+(841)(300)}{1262 + 857 + 802 + 841}$$

$$= \frac{31550 + 55705 + 116290 + 252300}{3762} = \frac{455845}{3762}$$

Mean Dose = 121.2 Rads.

In the over 10 Rad group, 15 cancers in 3762 women, corresponding to a rate of 39.9 cancers per 10000 women.

"Spontaneous" rate (see above) = 9.0 cancers per 10000 women

Excess cancers = 30.9 cancers per 10000 women, radiation induced

$\frac{30.9}{9}$ = 3.4 Doubling Doses are represented.

3.4 Doubling Doses = 121.2 Rads

1 Doubling Dose = 35.6 Rads

Now we can compare these results to see whether doubling dose is varying significantly as we include progressively lower dose categories. Linear theory would demand that the doubling dose remain constant in this test.

Group at Risk	Doubling Dose
All Cases above 90 Rads	44.0 Rads
All Cases above 40 Rads	43.5 Rads
All Cases above 10 Rads	35.6 Rads

Within the experimental error, linear theory is followed perfectly. If there is any deviation, the lowering of doubling dose as the lowest dose category is included suggests the risk of breast cancer per rad is more serious (at low dose) than is predicted by linear theory. This effect cannot be proved significant here, however. Above all, there is no suggestion of comfort in these data for the "threshold hopers". Recall, a threshold means that in the neighborhood of such a threshold, the doubling dose is trending to infinity. In the data above, doubling dose is trending down, if anything - not toward infinity.

Overall, the Wanebo data indicate that the doubling dose for radiation induction of breast cancer is in the neighborhood of 40 Rads.

But, the true doubling dose is probably somewhat lower than this. This must now be considered. Wanebo and co-workers indicate that the mean age of the patients with breast cancer A.T.B. who received 50 Rads or more is 28.1 years versus 39.8 years for those who received less than 50 Rads, or were not in the city A.T.B.

Or, expressed as age at time of onset of breast cancer 43.3 years versus 55.3 years. So those who were more heavily irradiated developed breast cancer 11 or 12 years earlier than those who were not heavily irradiated. We don't have the cases split by radiation dose at 50 Rads, but we do above at 40 Rads. Since breast cancer more than doubles in 11 or 12 years spontaneously the appropriate comparison bases in the "spontaneous" groups would be the rate for women 11 or 12 years younger than the group we have. Let us be conservative and divide the incidence rate for the spontaneous group in half. We have then (from above)

In over 40 Rad Group, rate = 44 cancers per 10000 women
Spontaneous rate = 9/2 = 4.5 cancers per 10000 women

Excess cancer = 39.5 cancers per 10000 women, radiation induced

39.5/4.5 = 8.8 Doubling Doses

8.8 Doubling Doses = 169.7 Rads

Therefore 1 Doubling Dose = $\frac{169.7}{8.8}$ = 19.2 Rads

This value is much more likely to be near the correct value than the 40 Rad region as the doubling dose for radiation-induction of breast cancer in the Japanese women.

From our analysis of the Mackenzie data, the best estimate of doubling dose lay between 19.7 Rads and 45.9 Rads.

The similarity of these doubling doses for such vastly different epidemiological population samples, receiving their irradiation in a different manner is indeed remarkable. Probably the data prove that humans are more alike than some humans think they are, at least with respect to susceptibility to radiation carcinogenesis.

Conclusions

1) Analyses of Mackenzie's data on women developing breast cancer subsequent to irradiation by multiple fluoroscopies associated with pneumothorax therapy indicate a best estimate for the doubling dose as ~20 to 46 Rads for radiation-induction of breast cancer.

2) Analysis of the very convincing data of Wanebo on Hiroshima-Nagasaki survivors indicates a best estimate of ~ 19.2 Rads as the doubling dose for radiation-induction of breast cancer.

3) The agreement between the Canadian and the Japanese data is truly startling.

4) The data indicate that linear theory holds up very well, in the entire dose region. (40-300 Rad region in Japanese and 900-2100 Rads in the Nova Scotia women). No suggestion of any sort that thresholds exist. If anything, the opposite is indicated.

5) In our "laws" of carcinogenesis, we suggested previously a central value of ~ 100 Rads as doubling dose and a 1% increase in cancer risk per rad (5) As we indicated there, we were trying to be as conservative as possible, so as <u>not</u> to overestimate the hazard, but we stated there,

"Furthermore, we would estimate that the absolute numbers, if anything, probably underestimate the risk. For purposes of setting radiation tolerance guidelines, one might even be advised to use lower doubling doses than estimated above" (5)

The more we refine the calculations, the more it appears that this quotation is correct, and that the true doubling doses will be <u>lower</u> than we estimated. Certainly these presented here for breast cancer are definitely lower than 100 Rads. Of course, this would mean that our estimate of 16000 additional cancers per year from FRC Guideline dosages might be nearer 32,000, or even higher (5). We would like to check further doubling doses for other cancers in a refined manner, before taking this necessarily pessimistic position.

6) It is puzzling to us to try to understand Storer's (6) and Miller's(7) difficulties in accepting the radiation-induction of human breast cancer, especially in view of the excellent agreement between the two vastly different epidemiological samples.

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