Research Article

Dismantling Fixations on Failed Fictions: A-Bomb Survivor Study Denies The Low-Dose Radiogenic Cancer Narrative

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ABSTRACT

The linear no-threshold (LNT) model of low dose ionizing radiation's (LDIR) role in radiogenic cancer incidence has long served as a pseudo-scientific belief arising from evidence that has never been proven, but has been contested. One source of current evidence that favors the LNT model is the Radiation Effects Research Foundation's (RERF) Life Span Study (LSS) cohort of Japanese atomic bomb survivors. The RERF has managed the input data, model development, and data analyses for the LSS cohort for 45 years, publishing research papers and reports updating the RERF's progress. In recent years, the RERF has attempted to identify other cancer risk factors that may have played a role in the cancer incidence of cohort survivors, and this effort has drawn attention to the fact that many earlier years of papers and reports from the RERF have never considered these risk factors, making such publications of questionable merit. This investigation examines two recent papers from the RERF that denominate how the RERF now analyzes specific cancer incidence for cohort members, how it treats lifestyle and other risk factors for various cancers that have arisen in the cohort, and how it continues to find and assert that bomb-blast LDIR remains a distinguishable source of radiogenic cancer in the cohort. The investigation observes that the cohort input data and modeling have extensive deficiencies and defects, many having been identified by RERF authors themselves, that substantially compromise the findings of these two papers, and offers concluding evidence that the LDIR radiogenic cancer model is highly implausible if not impossible. From such evidence, a final conclusion must arise that supports a threshold model for the dose–response relationship between LDIR exposure and radiogenic cancer.

Introduction

For more than 70 years, the linear no-threshold (LNT) model of low-dose ionizing radiation's (LDIR) role in radiogenic cancer incidence has been touted as either scientific truth arising from verified and validated evidence or the safest approach to an undetectable hazard at low doses. Since Dr. Herman Muller's research involving radiation effects on fruit flies and his Nobel Lecture in 1946 discussing his LNT model "discoveries," the scientific world has accepted the LNT cancer incidence (LNTCI) model as a safe fiction, if not the truth. However, Mueller's work has been shown to be flawed, if not falsified [1]. And the

public safety of applying the LNT model has been disproven time and again. Nonetheless, the LNTCI model remains a fixture in radiation protection and regulatory requirements, but with its validity long being contested, even repudiated, as a variety of studies clearly demonstrate [2-6]. This paper focuses on showing that the belief in the LNTCI model by governments, agencies, advisory organizations, and many scientists is badly supported, and that some of the strongest data and analysis supporting the LNTCI model is simply not accurate.

At the end of World War II (WWII), many thousands of Japanese survivors of the atomic bomb (A-bomb) blasts at Hiroshima and

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Nagasaki were determined to have received various doses of bomb-blast radiation, along with many injuries from blast effects themselves. In 1948, the Atomic Bomb Casualty Commission (ABCC, founded by the U.S. National Academy of Sciences) began extensive interviews through the 1950s to compile records for each A-bomb survivor. Based on these records, radiation doses were calculated for most A-bomb survivors. The Radiation Effects Research Foundation (RERF) was established in 1975 and began managing the Life Span Study (LSS) of the Japanese A-bomb survivors' cohort who have been followed for cancer incidence since 1958. A previous publication has discussed the RERF's purposes from its formation [7]. The RERF has developed numerous models and performed extensive studies calculating what it terms excess cancers arising from the A-bomb LDIR, but these study results are now questionable: the cancers claimed to arise from LDIR exposure are based on use of the LNTCI hypothesis with flawed methodologies, among them omitting various other known and significant risk factors as causalities, far more likely to be responsible for carcinogenesis than LDIR exposure.

RERF studies appear to make extensive use of deficient and defective input data and models for analyses, with few bases of support for the LNTCI model. Their models' outputs can be inconsistent with current cancer science, with analyses magnifying errors so that analysis output error can be substantial. The further objective herein, then, is to continue to advance the repurposing of the failed LSS cohort data supporting the LNTCI model. What will be shown is that, in the absence of fully reliable LSS cohort input data, a best estimate of radiation-only cancers within the LSS cohort's large population using current cancer risk factors for the Japanese population offers a strong indication that A-bomb blast LDIR could not produce such cancers, let alone confirm the LNTCI model.

Background and Overview

This issue becomes most significant because the U.S. National Council on Radiation Protection and Measurements (NCRP) has selected the LSS as a leading study that supports the LNTCI model. In its Commentary No. 27, the NCRP shows the LSS at the top of its list of studies that strongly support the LNTCI model, raising questions about what evidence supports Commentary No.27 [8]. Herein is shown how LSS cohort input data does not support scientific conclusions regarding radiogenic cancer incidence within that cohort. Two papers from the RERF staff are evaluated to show the shortcomings of RERF's claims for cancer incidence arising from A-bomb blast LDIR [9, 10]. This evaluation supports an earlier paper regarding a 2019 RERF report, arriving at similar conclusions [7].

Over 62 years, the ABCC and the RERF have periodically gathered data on the LSS cohort, a period during which one might conclude that a sound database on the LSS cohort has arisen. However, the RERF now takes into account the carcinogenic behaviour of a few lifestyle cancer risk factors among the LSS cohort to more finely determine the LDIR radiogenic impact on the cohort. But it has become clear that the cohort's data base including very few lifestyle risk factors is woefully lacking. The authors of RERF papers and reports have admitted to this in their writings, but once these admissions are disclosed, they seem fixated on proceeding with modeling and analyses as if the input data could still

support science-based output having credibility for demonstrable reasons.

The LSS cohort input data have at least three major areas of significant shortcomings. There are deficiencies in the survivor data gathered regarding: i) missing data that should have been requested in the surveys; the diseases respondents experienced; detailed specifics on smoking and alcohol consumption that respondents ignored; achieving more complete survey participation; insufficient selection of risk factors early on and determining those members having which risk factors and the extent; ii) data defects regarding presence of infectious disease and post-mortem pathology/histology, both due to human error and the lack of scientific understanding regarding what data should be collected; and iii) defects in collected data involving imputed and assumed data; and questionable data for drawing conclusions on cause(s) of cohort deaths, but using that data with defective modeling for determining radiogenic effects of acute LDIR exposure, yielding results of low confidence in their predictive value.

The two papers evaluated herein include just three lifestyle factors, and the input data used to support the modeling and analyses in these papers for two lifestyle factors, tobacco smoking and alcohol consumption, are presented below, just as described by RERF staff in reports on the LSS cohort. The third lifestyle factor, body mass index (BMI), is not detailed enough for critique, but the prevalence of obesity (BMI >30) in Japan is small, and experts say its cancer risk for the Japanese is also small [11, 12]. The LSS data deficiencies will now be presented, as also reported by authors of RERF publications.

Input Data Deficiencies and Defects

I Input Data and Model Deficiencies

i Tobacco Smoking

By 1965, 84% of Japanese men smoked, but, over time, the number of smokers slowly decreased, according to the National Cancer Center's (NCC) Research Center for Cancer Prevention and Screening, Tokyo, Japan [11]. The prevalence of current smokers among Japanese men has constantly decreased, from 84% in 1965 to 39% in 2005 to 30% in 2014. The 73% of men who were ever-smokers in 1990 means that there remains a high prevalence of cancer from tobacco smoking in Japanese men. For women, in contrast, the smoking prevalence has been slowly increasing since 1990 (10%–15%), likely increasing current cancer due to the 20-to-30-year latency period from tobacco exposure to cancer diagnosis [12]. With respect to smoking-only-caused cancer cases, significant LSS cohort data collection issues arise, recognized and reported by the authors of various RERF reports and papers, including the following [13-16]:

- smoking data are questionable and incomplete – the data were collected through seven data responses to surveys and questionnaires from the LSS or Adult Health Study (AHS), having only a 57.6% response rate for men and a 62.6% for women; further, the 1965 survey only addressed men of ages 40 - 69, and some cohort members only responded to one of the 7 surveys/questionnaires between 1963 and 1991;

- smoking status was unknown for about 60% of the total follow-up time of the LSS, and smoking status at the time of cancer diagnosis was unknown for about 40% of the cases (Table 4 of Grant *et al.* [13]);

- in 2010, the LSS cohort had smoking data from 1963 through 1991, some incomplete, on only 28,869 smokers out of the LSS cohort population of 105,404, when, for that period of 28 years, Japan had an average smoking percentage of about 70% - 80% of men and 15% of women, or about 40% of the LSS population; the LSS has incomplete data on about 27% of the cohort population, and the percent of Japanese smokers is about 50% higher than the percent of suspected LSS cohort smokers;

- almost half of the cancer cases having smoking data and 40% of those without smoking data were *imputed* to be associated with smoking;

- among cohort smokers' survey responses, 86% of the men and 18% of the women identified as ever-smokers, but Table 4 of Grant *et al.* shows only 50% of men and 11% of women are ever-smokers; and smoking PAFs in Grant *et al.*'s Table 8 decline in the LSS data with increased smoking prevalence from (Table 4), the opposite of national reports [11-14];

- subjects' smoking habits were assumed to be the same after the subjects' final response on smoking, which was no later than 1992;

- in 2009, the LSS cohort's average age was 78 years and it was assumed unlikely that many had begun smoking and likely that many had quit smoking by that age, but the impact on radiation effects was unclear;

- despite the large cohort and case numbers, the data permitting inference regarding radiation-smoking interaction were still limited by a highly skewed dose distribution and the unavailability of confirmed histology information in many cases.

Neither reviewed paper offers detail on the statistical LSS data on smoking. One must review smoking data in earlier RERF reports and papers, such as in Grant *et al.*, where one finds the LSS smoking data is the only risk factor considered, other than bomb-blast radiation [13]. Further, the prevalence attributable fractions (PAFs) shown in Table 8 of Grant *et al.* are well below those of all Japanese smokers in the 1950s - 1980s shown in the smoking data of the NCC, when they should be at least equal due to far greater prevalence of smoking in Japan during the 1950s - 1980s [11-13]. Such inconsistencies in Grant *et al.*, as discussed elsewhere, offer a misperception that acute LDIR above 0.5 Gy is a greater cause of solid-tumor incidence than heavy smoking, which is in disagreement with what is known by medical science [7, 11-13].

Finally, Table 8 of Grant *et al.* demonstrates how fully the RERF's tobacco smoking data and modeling appear deficient and defective for the two papers reviewed [13]. For bomb-blast doses of 0.5 Gy through 2+ Gy, average radiation-only PAFs for all solid-tumor cancer incidence in the LSS cohort from RERF models is 3.1 times higher than the average all solid-tumor, smoking-only PAFs for the same radiation dose range. And these doses are much lower than fractionated doses successfully applied for radiation therapy (RT) for cancer treatment. The LSS cohort modeling of radiation-only cancer incidence also does not account for all tobacco smoking or its doses to the body, nor does the modeling account for adaptive response by the body's immune systems to LDIR,

both the innate and the adaptive immune systems, to reduce and remove the DNA and other damage in 24 hours or so after exposure.

ii Alcohol Consumption

Data collection for alcohol consumption was accomplished with six of the seven same surveys and questionnaires as were used for tobacco smoking [9]. The first questionnaire was in 1963, and, at that time and since 1960, pure alcohol annual consumption in Japan had been a modest 4 liters per capita. Since then, the average pure alcohol annual consumption in Japan has risen to more than 8 liters per capita in 1993, and remains at a fairly steady level around 7.5 liters per capita in 2005 [18].

Pure alcohol consumption in Japan by heavy drinkers also increased for decades until 1990 and has now peaked at an annual level of about 19 liters per capita for men [19]. Further, Japanese have a high prevalence (about 50%) of an aldehyde dehydrogenase 2 (ALDH2)-deficient phenotype that results in greater exposure to acetaldehyde, a known carcinogen. No RERF reports discuss these points. Such effects must be assumed absent from their data, modeling, and analyses. As reported, alcohol consumption data was virtually identical in LSS cohort responsiveness to the smoking data shortcomings discussed above [9, 13]. A simple summary of additional shortcomings follows:

- there was apparent confusion in the data review whether one drink had 14 or 15 grams of alcohol, and respondents were not asked to specify the types/amounts of alcohol consumed;

- Table 1 of Sakata *et al.* shows about 4% more unknowns for alcohol consumption than for smoking [10];

- Sakata *et al.*, Table 1, shows 71% of all person-years of alcohol consumption data collection has produced what is termed as "unknown" for alcohol consumption for the upper digestive tract cancer analysis of the affected population; the data must be more deficient than just a 40% lack of response rate; this data deficiency is likely very similar for all other cancer cases having alcohol consumption as a risk factor [10];

- the data regarding radiation-alcohol interaction were limited by a highly skewed dose distribution and a lack of histology in many cases (for instance, liver cancer had confirmed histology on only 37% of its cases).

Authors reported many of these deficiencies in the weakly-denominated, life-style risk factors data, but pursuit of modeling and analyses using such corrupted data greatly elevates skepticism concerning their results.

iii Modeling Defects

Other sources of uncertainty regarding the results in these RERF reports and papers include modeling defects. The RERF organization seems to display preconceived beliefs on LDIR effects. Based upon RERF reports, it is clear that it prefers modeling with simple linearity of dose-response and that it tends to obscure non-linear dose responses from the data by having a linear response plotted at high doses dictate curve shape at low doses [7]. The RERF also assumes all dose-response data follow the same rules. This is simply not a true approximation of reality and has been fully rebutted recently in other studies [6, 7]. Authors of the RERF

papers also make clear they consider LDIR as capable of long-term impairment of the immune system, which has been thoroughly rebutted [6, 9]. The RERF even seems to reject proven biologic adaptive response in its models' LDIR damage considerations.

Further, the smoking model has been earlier described by RERF reports and papers as applicable to lung cancer, not all cancers, and how the model has been changed to accommodate cancer's impacts on smoking's other target organs is not addressed [13-16]. Additionally, the model ignores a major confounder regarding high levels of radionuclides in tobacco resulting from deposition of radon from the soil and its high linear-energy-transfer (LET), alpha-emitting decay products on tobacco leaves, which are released and transferred to smokers' bodies and retained for years [17]. RERF reports and papers explicitly note that there is no alpha radiation dose incorporated in its models, which distorts the modeling of low-LET, LDIR that is essentially dwarfed by smoking's high-LET doses over many years and may inflate the bomb-blast's radiation-only, solid-tumor causality, thereby over-stating LDIR's case-rate.

II Input Data Defects: Infectious Diseases as Cancer Risk Factors

At least one of the papers reviewed herein notes some LSS solid-tumor, cancer incidence data arising from an infectious disease (ID) risk factor is included in background cases [9, 10]. Indeed, it has been known for many years that IDs are the highest causative risk factors for various cancers. However, these RERF papers do not readily address IDs as major causative risk factors. Japan experienced extreme and widespread IDs before, during, and for many years following WWII, as well. The NCC's ID data for Japan are replete with an abundance of many viruses in Japan. There are at least two prime data sources for ID's PAF data to determine the expected cases in Japanese populations from such diseases, and it is also clear the LSS cohort should have experienced even higher PAFs than the general public due to the enormity of the spread of such diseases during and following WWII [11, 12]. No person in that cohort avoided experiencing outbreaks of various infections among family and friends, or personally. The following summarizes the widespread infectious diseases and solid-tumor cancers that have been major risk factors for the LSS cohort.

i Helicobacter pylori (H. pylori) Bacterium [11, 12]

H. pylori is a risk factor for non-cardia gastric cancer in Japan. The majority of gastric cancer in Japan is derived from the non-cardia stomach (91% in men and 94% in women in 2000). In 1950, approximately 80 % of adults were infected with H. pylori, but in 2010, less than 20 % of individuals younger than 40 were infected. A total of 81.5 % of men and 69.9 % of women with H. pylori infection died from non-cardia stomach cancer, along with 75.7 % of stomach MALT (mucosa-associated lymphoid tissue) lymphoma deaths in men and women. The H. pylori infection's relative risk in gastric cancer development is 6.8 for men and 4.6 for women. H. pylori prevalence is >80% in the birth cohort born before 1950 and 40%–50% in those born after 1950, with the pre-1950 birth cohort having foundational participants in the LSS cohort.

Of course, as noted in Sadakane, 76% of the person-years for collecting LSS cohort data occurred before 1990, and the understanding of cancer incidence arising from H. pylori was not as well developed [9]. The defect of the authors' unfortunate lack of data gathered from the LSS cohort on this matter should have signaled a scientific necessity to examine today's science on the sources of stomach cancer during that period.

ii Hepatitis B Virus (HBV) and Hepatitis C Virus (HCV) [11, 12]

Hepatocellular carcinoma accounts for 90% of all liver cancer cases in Japan and is primarily caused by chronic HCV infection. The peak incidence between the 1970s and the 1990s in Japanese men was affected by the birth cohort effect among those born during 1925–1934, which was attributed to HCV outbreaks in Japan [9]. This is a prime birth range for the LSS cohort, showing it would experience far more liver cancer than what was expected in 2005 through 2014 [11, 12]. The peak incidence was ended by the early 1990s, after the last surveys/questionnaires submitted by the LSS cohort. In 2014, a total of 12.5 % of liver cancer deaths was due to HBV, 72 % HCV, and 1.8 % to HBV plus HCV (the same as incidence rates [11, 12]). Again, 76% of the person-years for collecting LSS cohort data occurred before 1990, and so the understanding of hepatitis' role in cancer incidence was not as well advanced . However, the authors, while stating they understand that hepatitis was a source for liver cancer, also say they have no data on hepatitis virus infection, but there is no indication of confounding by that infection [9]. This seems unlikely since the hepatitis risk factor is still recognized as the greatest risk factor for liver cancer incidence in Japan by cancer experts [11, 12]. A number of errors of omission in data gathering and collection regarding ID contribute to the misattributions arising from the application and modeling using the LSS cohort data.

iii Human Papillomavirus (HPV)

HPV is a known risk factor for several forms of cancer in Japan, and there is evidence for a very high prevalence of HPV during and following WWII among Japanese survivors. This was especially true for the "hibakusha," the LSS cohort itself, who experienced the blast effects and who lived through social deprivation and discrimination from their injuries, as discussed below. By about 2000, the HPV trend re-emerged in Japan [20]. Today, HPV is being cited as a known risk factor in upper digestive tract cancers, such as oral cavity, oropharynx, salivary gland and esophageal, which is relevant to the RERF assessment of these cancers that follows [12].

III Other Known Cancer Risk Factors Applicable to the LSS Cohort

There are now more cancer risk factors that have only been recognized in the last 30 years or so clearly applying to the LSS cohort. But who is that cohort, and what experiences have increased its cancer risk?

i Atomic Bomb Survivor History and Stress Effects

The hibakusha had resulting injuries and exposures to radiation from an A-bomb blast. As a result, they were treated as outcasts, exposed to extreme physical and psychological distress for decades by their

countrymen and the occupation forces, who feared that these sick and injured people might be contagious [21, 22]. The hibakusha suffered on-going abuse arising from social fears and government discrimination over a period of more than a decade, including: physical abuse; intake restriction; exposure to diseases; emotional abuse; and deep psychological responses to such stressors. A 1997 mental health assessment of atomic bomb survivors indicated that they suffered from serious psychological distress (SPD) [23]. U.S. research has shown that SPD is a major factor in reduced life-expectancy and is likely a contributor to reduced life-expectancy within the hibakusha [24]. Adults with SPD experience significantly higher age-adjusted death rates compared to those without SPD. LDIR cannot account for, on any biological basis, such reduced life-expectancy. RERF acknowledges the issue, but LSS reports have neglected the study of SPD and its effects [25].

A recent observational, epidemiological study of Israeli immigrants who were Holocaust survivors determined that population had experienced an increased risk for developing cancer due to a variety of stressors [26]. The study included 152,622 people and the conditions identified are strikingly similar to, but of shorter duration than, those experienced by the hibakusha. Another recent review of stressors and cancer among the hibakusha concludes 2,000 cancers might arise among the LSS cohort from protracted SPD [7]. The possible cancer-incidence arising from SPD stressors within the hibakusha raises further questions that current LSS data and models cannot address.

ii Diabetes

A strong case is currently being made by some investigators that diabetes is a risk factor for all cancers, but more strongly with certain cancer types, such as liver, pancreatic, esophageal, gastric, renal, and endometrial cancers [27, 28]. These RERF studies do not cite diabetes as a risk factor for liver, pancreatic, esophageal, or gastric cancer.

iii Older Age

The medical literature shows older age is a major risk factor for certain cancer types, e.g., salivary gland cancer, according to the American Cancer Society, https://www.cancer.org/cancer/salivary-gland-cancer/causes-risks-prevention.html. The LSS cohort is a poster-child for older age, but it is not pursued by RERF authors.

Evaluation of Sadakane *et al.* and Sakata *et al.* for Radiogenic Cancers from A-bomb Blasts [9, 10]

These two papers are examined herein for those cancer cases they estimate arise from bomb-blast LDIR, using input-data-based modeling and analysis methods.

I Sadakane *et al.*: Liver, Biliary Tract, and Pancreatic Cancers [9]

Sadakane *et al.* investigates the cited cancers but does not find Excess Relative Risk (ERR) for biliary tract cancer, and pancreatic cancer data suffers from accuracy of diagnosis flaws. In summary, biliary and pancreatic cancer show no demonstrable evidence of LDIR as a risk factor for cancer and will not be pursued further herein. The liver cancer analysis finds a weak contribution to liver cancer from A-bomb blast LDIR. The LSS cohort has experienced a total of 2016 liver cancers since 1958. Using cohort input data for modeling and statistical applications, groupings are established for which liver cancers arose from which risk factors. The only liver cancer risk factors the authors identify are smoking, alcohol consumption, and BMI. The authors assume BMI is a risk factor for liver cancer, but the NCC does not [11, 12]. They do not acknowledge HCV is the greatest risk factor for liver cancer in Japan, although they admit that they have no hepatitis data from the LSS cohort and acknowledge that "large proportions of liver cancer are attributable to HCV . . . ." Yet, they also say that "there has been no indication of confounding by hepatitis virus infection."

The authors do not include hepatitis infection contributions in the risk factors displayed in their Table 6: lifestyle factors (smoking, alcohol consumption, and BMI); radiation-lifestyle interaction factor; and the radiation-only factor [9]. Therefore, the only place where the hepatitis liver cancer incidence can appear is in the Background cases. RERF authors rarely inform or explain what are included in Background cases. Since the LSS cohort data contains major deficiencies and defects, it is not credible to claim to arrive at scientifically based output and conclusions. An alternative path must be used for LSS input data in order to arrive at credible attributable fractions for cancers arising from all risk factors.

One can turn to the NCC to see what science says have been true liver cancer risk factors (HCV, smoking, alcohol consumption, and HBV) [11, 12]. The data by Inoue *et al.* are reported for 2005, and this data is very conservative when applied to the LSS cohort, which lived through decades in Japan of extreme levels of ID, heavy smoking, and widespread alcohol consumption [12]. Therefore, PAFs for all liver cancer's major risk factors in Japan in 2005 offer a good path for an accurate assessment of liver-cancer-case attributions for the LSS cohort. Table 1 highlights entries from Table 6 of Sadakane *et al.*, showing how liver cancer cases were apportioned to the limited risk factors the authors chose [9].

Table 1: Table 6 Highlights for Low-Dose Liver Cancer Cases from LSS Cohort Data for Risk Factors of Liver Cancer Discussed Therein [9].

DS02R1 Weighted Absorbed Liver Dose in Gy	Table 6 Expected Liver Cases- LSS Cohort	Table 6 Radiation- Only Liver Cancer Cases	Table 6 Radiation- Lifestyle Interaction Cases	Table 6 Lifestyle Factors[a] Only Cases	Table 6 Back-ground Cases
<0.005 + NIEC*	1157.3	0.3	0.1	375.8	781.1
0.005-<0.1	482.9	7.5	3.6	154.5	317.3
0.1 -<0.2	102.8	6.6	3.0	29.2	64.1

0.2 -<0.5	119.4	15.4	6.9	30.4	66.7
0.5 -<1.0	80.7	19.5	7.7	15.7	37.8
1.0 -<2.0	53.5	18.4	7.8	8.4	18.9
≥2.0	19.3	7.3	3.1	2.9	6.1
Totals	2016.0	75.0	32.2	616.8	1292.0

* Not in Either City

[a]Liver cancers are causally related with alcohol use. The Japanese have a 50% prevalence of an aldehyde dehydrogenase 2-deficient phenotype, a deficiency that results in greater exposure to acetaldehyde, which is a known carcinogen in alcohol [12]. This is accounted for herein, but whether RERF data analyses account for it is not reported. If not, alcohol-related RERF data on liver cancer causally are understated and there would certainly be less liver cancer assigned to LDIR.

Since the authors ignore both NCC risk factors for liver cancer and the deficiencies and defects of their own input data, a better approach is use of the total PAF for the four well-defined liver cancer risk factors from

Inoue *et al.* to ascertain if A-bomb LDIR played any role in the LSS' liver cancer incidence [12]. Table 2 shows the results of better data from conservative attribution fractions for LSS liver cancer. Note that a negative entry in the Totals line of the Corrected Radiation-only Cases column means that the LSS input data cannot support the likely causation of the reported cancer cases when modern cancer risk factors are attributed to the recorded cancer cases. The negative number means that no cancer cases remain within the recorded data for attribution to radiation-only or radiation-interaction risk factors.

Table 2: Table 6 Highlights and Corrections for Low-Dose Solid Tumor Liver Cancer Cases from LSS Data Including All Risk Factors for Liver Cancer Discussed Herein [9]:

Comparative LSS Low-Dose Liver Cancer Incidence

DS02R1 Weighted Absorbed Liver Dose in Gy	Table 6 Expected Liver Cases-LSS	Table 6 Radiation-Only Liver Cancer Cases	Table 6 Radiation-Lifestyle Interaction Cases	Table 6 Lifestyle Factors Only Cases	**Corrected** Table 6 Lifestyle and Infectious Disease Factors Only Cases [12]	**Corrected** Table 6 Background Cases, Excluding HCV Cases Included in Previous Column	**Corrected** Table 6 Radiation-Only Cases plus Radiation-Lifestyle Interaction Cases
<0.005 + NIEC*	1157.3	0.3	0.1	375.8	1065.9	218.7	
0.005-<0.1	482.9	7.5	3.6	154.5	444.8	88.8	
0.1 -<0.2	102.8	6.6	3.0	29.2	94.7	17.9	
0.2 -<0.5	119.4	15.4	6.9	30.4	110.0	18.7	
0.5 -<1.0	80.7	19.5	7.7	15.7	74.3	10.6	
1.0 -<2.0	53.5	18.4	7.8	8.4	49.3	5.3	
≥2.0	19.3	7.3	3.1	2.9	17.8	1.7	
Totals	2016.0	75.0	32.2	616.8	1856.8	361.8	**-202.6**

* Not in Either City.

Using Inoue *et al.*'s smoking, alcohol, and infectious disease data for a PAF of 92.1%, the attributable totals of the four liver cancer risk factors increase to 1856.8 cases [12]. However, the Background cases from Table 6 also include HCV liver cancer cases, which overlap with Table 2's Corrected Lifestyle and Infectious Disease Factors Only Cases [9]. Since the total makeup of Background cases is undisclosed by the authors, a safe, conservative assumption is that Background cases arise from hepatitis viruses, then deduct the percentage of liver cancer incidence attributable to HCV (72%) from the Background cases, leaving a very small residual of liver cancer cases attributable to other sources, as determined by the authors.

Background cases decline to 361.8, due to removing HCV overlap cases. Then, the total of liver cancer cases must rise to 1856.8 + 361.8 = 2218.6, which is more than the 200 cases above the excess cases available in the LSS cohort liver cancer data records, so there can be no radiation-only

or radiation-lifestyle factor interaction liver cancer excess cases. The deficiencies and defects of the current LSS input data, and the inability of the authors to appropriately treat all the major risk factors for liver cancer, make their claim of A-bomb blast LDIR as a source of LSS liver cancer without credible basis.

II Sakata *et al.*: Upper Digestive Tract Cancers [10]

Sakata *et al.* examines an increased LSS cohort risk of cancers of the upper digestive tract (i.e., oral cavity and pharynx, esophagus and stomach) arising from A-bomb LDIR, using a very similar approach as for the LSS liver cancer [10]. The authors examined the risk by major sub-sites of the upper digestive tract and observed what they found to be significant radiation effects for the salivary gland, esophagus, and stomach. These three cancer types and results will be reviewed separately.

i Salivary Gland Cancer

Salivary gland cancers are rare, and, therefore, need very strong input data to make any compelling determination of which risk factors have produced such a tiny number of cancers (for the LSS cohort, Sakata *et al.*'s data show that during 52 years of tracking, salivary gland cancers have occurred in 0.047% of that population). Using the reported LSS population of salivary gland cancers (SGC) and examining current PAFs for the truly applicable risk factors, we can more closely approximate whether radiation played any role in these cancers. An important aspect of the Sakata *et al.* salivary gland analyses is that there is "no indication of statistically significant effects of . . . smoking history or alcohol consumption [10]." With no significant effect from RERF's lifestyle factors shown in their data analyses (only smoking and alcohol consumption were considered, contrary to what modern cancer science says about lifestyle factors and oral cavity and pharynx cancers), this is a strong indication of how deficient and defective the LSS cohort input data is. This also results in the Background cases for SGC being comprised only of "estimates of the expected number of cases among cohort members with no radiation exposure.", since no lifestyle factors were significant.

Using data from the NCC sources, PAFs are provided for all the oral/pharyngeal locations of head and neck cancers where salivary glands (major and minor) are located (note that minor glands produce higher percentages of malignant neoplasms than do the major glands) [11, 12]. The LSS data provide the fraction of SGC cases to determine how many of these cases arise from lifestyle factors having the NCC's PAFs. Selected common lifestyle factors from both Nagao and Tsugane and from Inoue *et al.* are used to better approximate the 2009 end-point date of the LSS cohort data [11, 12]. Further, the NCC includes the HPV lifestyle factor's role in SGC, and the PAFs from Inoue *et al.* include this effect modifier [12]. These adjustments place the PAFs for lifestyle factors and SCG at 64%, contrary to what Sakata *et al.* found [10]. Using these lifestyle factors, the SCG cancer cases are determined for the LSS

cohort. This is displayed in Table 3, which shows no cases can be attributable to an A-bomb blast radiation-only factor. However, other factors that have been omitted could also be addressed for SGCs, reducing further the likelihood of radiation-only cases:

- Older age: the age of the LSS cohort is advanced to the point that diminished immune systems likely play a real role in SGC cases;
- HPV significance: HPV involvement as a risk factor for oral and oropharyngeal cancers is now recognized as a very strong one, as shown by Huang *et al.* for Japan; HPV is now recognized to be responsible for 25% to 35% of oral cavity and oropharyngeal cancer in Asia, and up to about 52% of all new cancers in Japan, much higher than included herein [29];
- Use of Areca nut and betel quid: approximately 600 million people worldwide chew areca nut combined with the *Piper betle* leaf. This habit goes back at least 1,000 years in national groupings in South China, Southeast China, Southeast Asia, and most Pacific Island groups. It is also one of the largest known risk factors for SGC. From 1868 through 1947, the Japanese colonial empire colonized, occupied, and conducted economic and military activities throughout Southeast Asia where the practice was popular [30]. Many thousands of these populations were taken to Japan as workers, or immigrated to Japan [31]. Tens of thousands of Japanese workers from the occupied colonies and territories also returned to Japan. With Hiroshima and Nagasaki as established ports, Japanese military, Japanese workers/managers, and conscripts and immigrants from occupied regions must have arrived there and established communities, with these returning populations having Areca nut/betel quid chewing habits, with their very high SGC risk. The RERF does not address this.
- Hibakusha PSD: the very difficult and protracted PSD suffered by the hibakusha must have accounted for some cancers, based upon the research previously cited.

Table 3: Sakata *et al.* Table 3 Derived Solid Tumor Salivary Cancer Cases from LSS Data Including Risk Factors Identified from NCC for Salivary Cancer Discussed Herein [10]: Corrected Comparative LSS Low-Dose Salivary Gland Cancer Incidence.

DS02R1 Weighted Absorbed Eye Dose, Gy	Table 3 Back-ground Cases: Expected Salivary Gland Cancer in Cohort Having No Radiation Exposure	Table 3 Total Salivary Gland Cancer Cases	Table 3 Excess Salivary Gland Cancer Cases: Radiation-Only	Table 3 **Corrected:** Cases Arising Only from NCC Data on Smoking and HPV[a] Causation	Table 3 **Corrected:** Cases Arising Only from NCC Data on Alcohol[b] Causation	Table 3 **Corrected:** Total Cases Arising from Smoking, HPV, and Alcohol Causation	Table 3 **Corrected:** Total Excess Cases Assigned to Radiation- Only
<0.005 + NIEC*	21.8	22	0	0	0	0	0
0.005-<0.1	9.7	12	1.1	4.0	3.7	8.0	
0.1 -<0.2	2.1	3	1.0	1.0	0.9	2.0	
0.2 -<0.5	2.2	6	2.4	2.0	1.8	4.0	
0.5 -<1.0	1.2	1	2.6	0.3	0.3	0.7	
1.0 -<2.0	0.7	4	2.9	1.3	1.2	2.6	
≥2.0	0.3	2	1.9	0.7	0.6	1.3	
Totals	38.0	50	12.0	9.3	8.5	17.8	**-5.8**

* Not in Either City.

ii Esophageal Cancer

This cancer site yields another unusual set of data and a very small number of cancers. The number of esophageal cancers found in the LSS cohort totaled 486, but only 11.3 were determined to be from A-bomb LDIR, which is 0.011% of the entire LSS cohort over 52 years. But there are so many quirks in what the accompanying data show, it appears there is something wrong with the input data. The following are just some of the disclosures within Sakata *et al.* [10]:

- Fewer than two-thirds (66%) of the esophageal cancers had a known location and, of those, 77% were in the upper/middle of the esophagus; that means that about 50% were in the upper/middle and about 50% in the lower esophagus; what was done with the 34% of cancers whose location was unknown is unclear, but most important;

- More than 55% of esophageal or stomach cancers diagnosed before 1975 lacked detailed information for morphology and topography; this would suggest a wide band of error in identifying which cancers were esophageal adenocarcinomas (EAC) and which were esophageal squamous cell carcinomas (ESCC);

- Tumor location analyses showed the risks of lifestyle factors (smoking and alcohol consumption, only) were significant for the upper/middle cancers, and insignificant for the lower cancers; this seems inconsistent with gastric cancer locations;

- For radiation effects, the upper/middle cancers displayed no radiation effect; analyses showed the radiation risks for upper/middle and lower differed significantly;

- Including smoking and alcohol consumption made little difference to the radiation effects in the esophagus;

- The percentage of cancer in the lower esophagus in the early years more than doubled in later years (suggesting a new type/form/risk factor from earlier years?);

- The authors do question if Barrett's Esophagus (BE) could be a cause of the lower esophagus cancer increase, due to shifts to a more Western diet and eating habits, and the hugely male population having esophageal cancer in the LSS cohort; but the authors claim BE is not a likely risk factor since ESCC remains dominant in Japan;

- And yet, there is evidence that BE can lead to EAC occurring in the presence of ESCC; there are several such cases discussed in the literature since 1984 that may be related to this LSS observation; the lack of morphology and topography on 55% of the LSS cases before 1975 (18 years of data), the 34% of the cancers that have no documented location, and the doubling of lower esophagus cancers in later years may point convincingly to BE's involvement, together with a substantial alcohol consumption and tobacco-smoking history [32].

Beyond the LSS data uncertainties for esophageal cancer, there are NCC data that are at variance with the LSS data, and, using the approach and methods of previous evaluations, clarify the likely impact of A-bomb blast LDIR. The NCC sources provide PAFs for all the esophagus lifestyle factors' contribution to cancer in the Japanese population, including fruit/vegetable deficiencies [11, 12]. The LSS cohort data provide the esophageal cancer cases to permit calculating the cases arising from lifestyle and other risk factors, according to the NCC's PAFs. The esophageal Background cancer cases are those expected if there were no smoking, alcohol consumption or radiation exposure. The Inoue *et al.* PAF for esophageal cancer (79.7%) provides 387.3 cases as the non-radiation excess cases leaving 98.7 cases for Background and Radiation excess [12]. Background Cases from Table 5, column 6, of Sakata *et al.* show 144.6. Deducting the RERF's determined Background cases, 98.7 - 144.6 = - 45.9 cases for radiation excess. No radiation cancer cases likely resulted from A-bomb blast LDIR. Table 4, below, shows that Japanese cancer data is far more informative of risk factors that control how and why cancer occurs over time in a large population like the LSS cohort.

Table 4: Sakata *et al.* Table 5 Derived Solid Tumor Esophageal Cancer (EC) Cases from LSS Data (Total Cases = 486) Including Risk Factors Identified from NCC for EC Discussed Herein: Corrected Comparative LSS Low-Dose Esophageal Cancer Incidence [10].

DS02R1 Weighted Absorbed Eye Dose, Gy	Table 5 Total EC Cases	Table 5 Back-ground Cases: Expected EC Cases in Cohort, No Radiation	Table 5 Non-radiation Excess Cases In Cohort	Table 5 Radiation-only Excess Cases In Cohort	Table 5 **Corrected:** EC Cases in Cohort from NCC Data for Smoking, Alcohol, Fruits/Veg. Deficiency -No Radiation	Table 5 **Corrected:** Radiation -Only Excess Cases In Cohort
<0.005 + NIEC*	276	81.8	186.7	0.0	219.0	
0.005-<0.1	130	39.1	91.0	0.1	106.7	
0.1 - <0.2	21	8.2	17.6	0.2	20.6	
0.2 - <0.5	29	8.4	17.9	0.9	21.0	
0.5 - <1.0	13	4.4	9.9	2.4	11.6	
1.0 - <2.0	9	2.1	5.4	4.8	6.3	
≥2.0	8	0.6	1.7	2.9	2.0	
Totals	486	144.6	330.2	11.3	387.3	**- 45.9**

* Not in Either City.

iii Stomach (Gastric) Cancer

Stomach cancer is the most common cancer among Japanese men and the third most common cancer among Japanese women. More than 80% of that population born before 1950 is positive for H. pylori, and an active recommendation for eradication of H. pylori in patients with gastric ulcers was started in 2000 [33]. The majority of gastric cancer in Japan is in the non-cardia stomach, 91% in men and 94% in women in 2000, likely due to the prevalence of H. pylori of >80% in the birth cohort born before 1950 [12]. Sakata *et al.* conducts the evaluation of excess LSS stomach cancer cases arising from A-bomb LDIR in similar fashion to preceding forms of cancer, except for ignoring H. pylori [10]. At no point in the paper is H. pylori ever mentioned for its widespread presence or huge contribution to gastric cancer.

Using data and analyses from the NCC sources, PAFs for all lifestyle and other risk factors' contribution to stomach cancer in the Japanese population, including H. pylori, tobacco, fruit/vegetable deficiencies and excessive salt intake, are available [11, 12]. The LSS data and analyses show all the stomach cancer Background cases are those expected in the cohort if there were no smoking or radiation exposure, but the authors ignore other risk factors like H. pylori, fruit/vegetable deficiencies, and excessive salt intake. Since the LSS data are of such questionable validity, and the size and relevance of this cancer form makes it highly important, use of all lifestyle and risk factor effects is important.

Because the H. pylori contribution to gastric cancer is so high, relative risks from Nagao *et al.* were paired with population data from Shiota *et al.* for people in the age range of 70 - 79 between 2007 and 2011, to calculate an appropriate PAF for H. Pylori [11, 34]. The same was done for smoking and excess salt intake data from Nagao *et al.* [11]. For simplicity, the PAF for fruit/vegetable deficiencies was ignored (a small number). These PAFs were applied to the Total cases to calculate the smoking, H. pylori, and excess salt intake risk factor cases. As shown, no radiation cancer cases could have resulted from A-bomb blast LDIR. Table 5, below, shows that the deficient and defective input data for the LSS cohort do not support what modern Japanese cancer data tell us about risk factors that control how and why cancer occurs over time in large populations like the LSS cohort.

Table 5: Sakata *et al.* Table 7 Solid Tumor Stomach Cancer (SC) Cases from LSS Data Including Risk Factors Identified from NCC for SC Discussed Herein [10]: Corrected Comparative LSS Low-Dose SC Incidence.

DS02R1 Weighted Absorbed Stomach Dose, Gy	Table 7 Total Cases of Stomach Cancer (SC) in Cohort	Table 7 Total Background SC Cases: No Smoking, No Radiation	Table 7 SC Cases Arising Only from Smoking	Table 7 Excess SC Cases: Assigned to Radiation-Only	Table 7 **Corrected:** SC Cases Arising from NCC Data on Smoking	Table 7 **Corrected:** SC Cases Arising from NCC Data on H. Pylori and Other Risks[a]	Table 7 **Corrected:** Total Excess Cases Assigned to Radiation-Only[b]
<0.005 + NIEC*	3,156	2923.3	253	0.6	801.6	2528.0	
0.005-<0.1	1,490	1291.2	133.9	16.6	378.5	1193.5	
0.1 -<0.2	301	272.1	28.1	15.8	76.5	241.1	
0.2 -<0.5	340	281.3	30.3	37.1	86.4	272.3	
0.5 -<1.0	205	147.8	16.5	42.5	52.1	164.2	
1.0 -<2.0	118	72.2	9.5	39.8	30.0	94.5	
≥2.0	51	21.2	2.7	25.8	13.0	40.9	
Totals	5,661	5009.1	473.8	178.1	1438.1	4534.5	**- 311.6**

* Not in Either City

[a] Conservatively assume these include all Table 7 Background Cases. Also note that the Risk Factor for SC of Fruit/Vegetable Deficiency in Inoue *et al.* has been ignored herein.

[b] Using the Inoue *et al.* data for verification, the Corrected Total Excess Cases for Radiation Only value becomes -285.1 [12].

Conclusion

Shown herein are best estimate corrections to what seems a fixation by the RERF on justifying the LNTCI model of radiogenic cancer arising from A-bomb LDIR in the LSS cohort, presented in two papers from RERF authors. There appears to be substantial evidence that the cohort input data and models have extensive deficiencies and defects. Much of this evidence is extracted from many of the RERF's own reports and acknowledged by their authors. It has been pursued in this research in the context of the current level of published cancer science from Japan, and it seems clear that there are far more cancers that should have arisen in the cohort from IDs, alcohol consumption, tobacco smoking, and other lifestyle choices that are ignored in the two papers. This investigation would say that neither the science nor its conclusions can be assured when data and modeling are so questionable.

But there are some who will certainly say what the RERF has done is satisfactory to the extent that its analyses and outputs are acceptable. Substantial advisory, regulatory, medical, and similar organizations have long ago accepted the RERF as an authority on the LNTCI modeling, and use its outputs as pure science. But this position encounters a very large obstacle that such groups do not relish, given that current cancer science in Japan shows the LSS cohort experienced some of Japan's worst years of IDs, tobacco smoking, alcohol consumption, and other

lifestyle risk factors, and far more cancers from these factors should be present in the cohort. If the RERF's data, analyses and outputs are acceptable, the only clear explanation for such a broad spectrum of missing cancers is that the bomb-blast LDIR produced hormetic effects in the cohort, reducing cancer incidence overall.

The RERF's more appropriate course should have been to offer a best estimate of how other known risk factors likely play a larger role than their present analyses conclude for cancer incidence. This investigation shows such a demonstration would absolve LDIR of a role in LSS cancer incidence. And, indeed, what is the purpose of science if not to evaluate data and test *various* hypotheses to arrive at which may be supported and which may not? Based upon this investigation, it appears that the LDIR LNTCI model is invalid, and that a linear threshold cancer incidence model (LTCI) is more correct. It is also encouraging that other current research and government agencies are beginning to show acceptance of the LNTCI model's being invalid at some threshold of low-dose, ionizing radiation [35, 36]. Since high dose/dose rate ionizing radiation has been shown to be a weak radiogenic cancer-incidence source, it now behooves those of governments, agencies, advisory groups, scientific organizations, and industries involved in medical and nuclear applications to promptly proceed with development of a safe and effective LDIR LTCI model for global application. To do otherwise is another abrogation of vested responsibility, so much like what we have suffered for more than 60 years.

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