

# An Open Letter to Advisory Bodies<sup>1</sup> Regarding Low-Dose Total Body Irradiation for Systemic Treatment of Cancer

May 30, 2014

Dear Colleagues,

Though adjuvant chemotherapy has been a standard of practice in the systemic treatment of many cancers, its adverse side effects are of considerable concern. The possible side effects include anemia, fatigue, gastro-intestinal dysfunction, hair loss, infection, memory changes, etc. (1). These side effects diminish drastically the quality of life including long-term reduced physical functioning and overall general health (2). In addition, chemotherapy is associated with a life-long reduced rate of employment (3). Hence it is very important to seek alternative approaches for systemic therapy which have less harmful side effects.

One adjuvant treatment that has similar or better outcomes with no symptomatic adverse side effects is low-dose fractionated total body irradiation (LDTBI). In the 1970s, LDTBI at the rate of 15 cGy per fraction, and 10 fractions applied over 5 weeks, had been studied in clinical trials of lymphosarcoma (4) and non-Hodgkin's lymphoma patients (5). The 4-year survival rates with adjuvant LDTBI were equivalent (4) or better (6) when compared to adjuvant chemotherapy, as seen in Figures 1 and 2 below. The main short-term side effects from LDTBI were hematological, with no observed long-term adverse side effects (5).

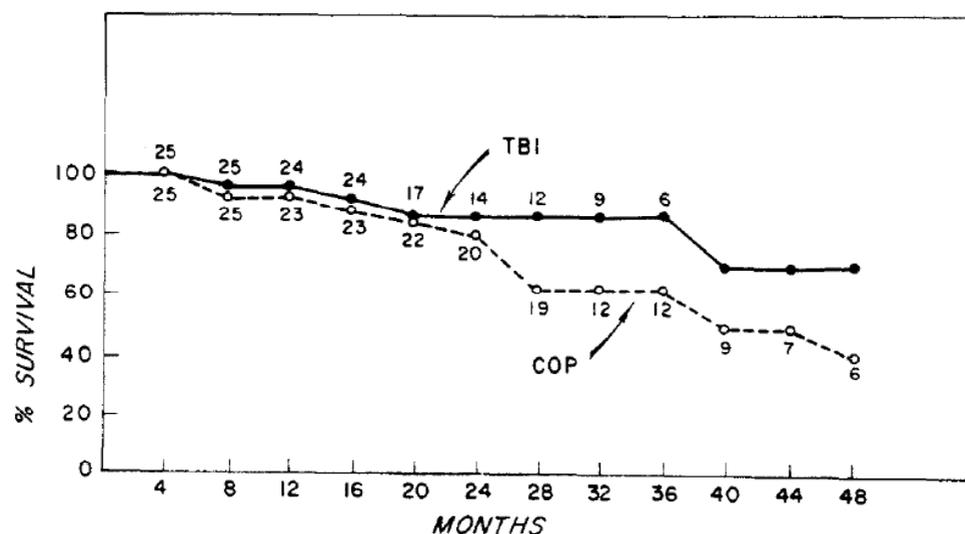


Figure 1. Comparison between TBI and matched COP-treated group. Numbers of patients at risk for each time interval are shown. Differences between groups are not statistically significant.

Figure from: Chaffey JT, Rosenthal DS, Moloney WC, Hellman S. Total body irradiation as treatment for lymphosarcoma. *Int J Radiat Oncol Biol Phys.* 1976; 1:399-405.

<sup>1</sup> ICRP, NCRP, UNSCEAR, IAEA, WHO, NAS, ...

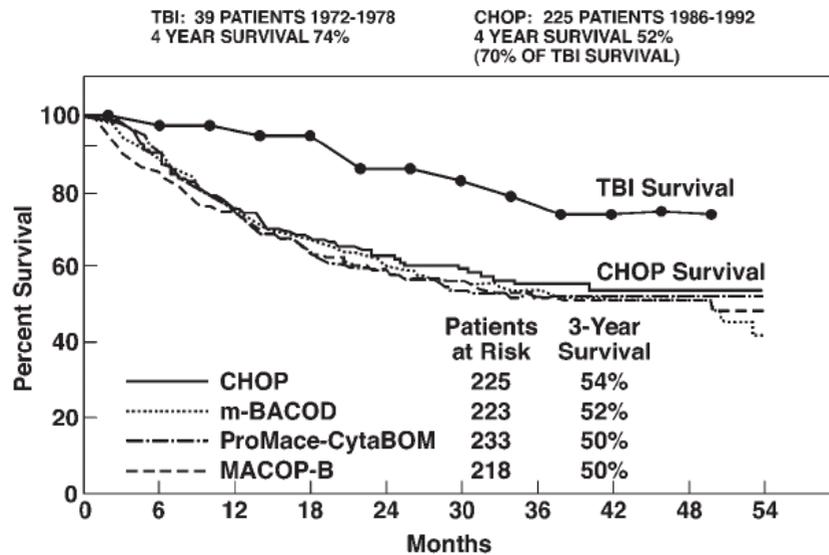


Figure 2. Comparison of TBI with CHOP chemotherapy. CHOP remains the best available chemotherapy treatment for patients with advanced-stage intermediate-grade or high-grade non-Hodgkin's lymphoma.

Figure from: Pollycove M. Radiobiological Basis of Low-Dose Irradiation in Prevention and Therapy of Cancer. Dose-Response. 2007; 5:26-38.

One of the reported concerns regarding total-body irradiation (TBI) is the increased risk of leukemias when high-dose TBI was followed with chemotherapy (7). However, all the observed increased leukemias in this study were in patients who had high cumulative TBI doses of 2 Gy or more and/or high radiation doses to the bone marrow. LDTBI using a cumulative dose of 1.5 Gy has been studied clinically (8). The hematological side effects were temporary, minimal, and well-tolerated and the efficacy of the systemic treatment was significantly advantageous. Successful results in further clinical trials should lead to its widespread acceptance as a standard effective systemic treatment of cancers without the severe side effects of the current standard-of-care chemotherapies.

A major obstacle in initiating any clinical trial of LDTBI is the current use of the linear no-threshold (LNT) model for radiation risk assessment by regulatory agencies, based on recommendations of international and national advisory bodies. Because of the LNT model-based concerns, researchers may be reluctant to propose clinical trials of LDTBI. Thus, it is not surprising that LDTBI has been under-investigated and under-utilized in spite of its potential (9, 10). However, a considerable amount of evidence has accumulated clearly demonstrating that the LNT model is inconsistent with data (please see the compilation of evidence below).

In consideration of the above evidence, and in order to facilitate the study of this less deleterious systemic treatment of cancer, we ask you to make a declaration that you encourage the study of LDTBI for systemic cancer treatment, and that the LNT model, which is a conservative approach for calculating potential radiation risks, not be used to discourage the study of LDTBI.

We would be happy to discuss this matter with you or provide additional information for your consideration. Thank you for your kind attention to this important issue.

Sincerely,

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Note: All signers of this letter are members or associate members of SARI (Scientists for Accurate Radiation Information, <http://radiationeffects.org/>). The above letter represents the professional opinions of the signers, and does not necessarily represent the views of their affiliated institutions.

### **References:**

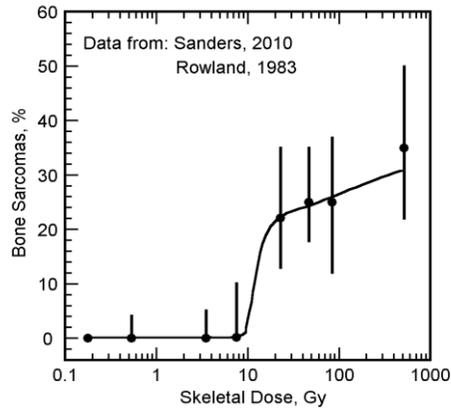
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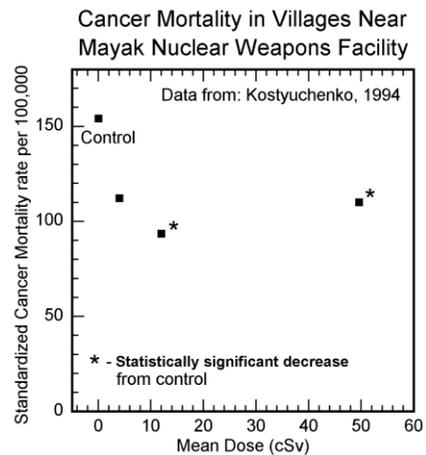
# Evidence for Threshold Dose-Response or for Radiation Hormesis in Human Studies

1. Threshold dose of ~10 Gy accumulated over many years in radium dial painters. Analysis of data from [Rowland, 1983](#) in [Sanders, 2010](#) on page 44.

Bone Cancer Incidence in Radium Dial Painters

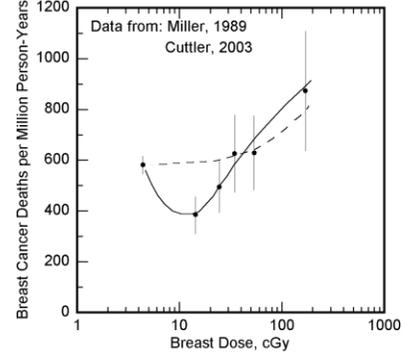


2. Reduced cancer mortality from 12 cGy and 50 cGy radiation dose in villages near Mayak nuclear weapons facility. [Kostyuchenko, 1994](#), Table 4.



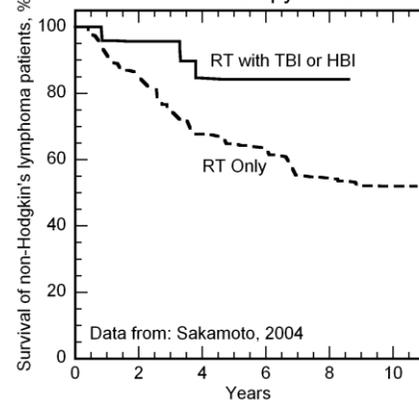
3. Reduced breast cancer mortality in Canadian TB patients having ~15 cGy breast dose from fluoroscopy. Threshold dose of >50 cGy. [Miller, 1989](#), [Cutler, 2003](#).

Breast Cancer Mortality in Canadian TB Patients Following Fluoroscopy



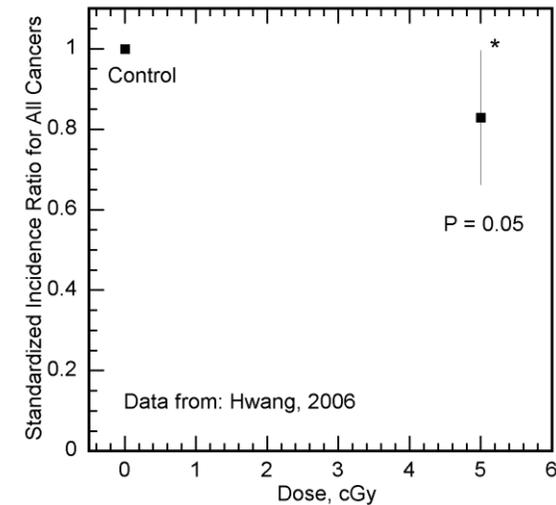
4. Improved survival in non-Hodgkin's lymphoma patients having interspersed 10 or 15 cGy total-body or half-body irradiation (TBI or HBI) for five weeks (total dose 1.5 Gy) between standard radiation treatments to tumor. [Sakamoto, 2004](#).

Survival of Non-Hodgkin's Lymphoma Radiation Therapy Patients



5. Reduced overall cancers in Taiwan apartment residents having ~5 cGy radiation dose from Co-60 contaminated building materials. Data from [Hwang, 2006](#), Table III.

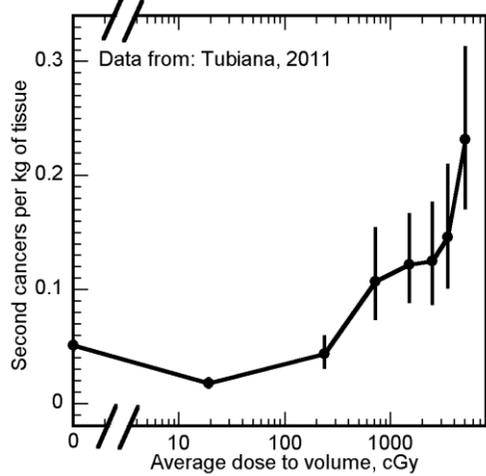
Incidence of All Cancers in Irradiated Taiwan Apartment Residents



Note: In spite of the reported increase of malignancies for a few subsets of data with poor statistics in [Hwang, 2006](#), the overall cancer incidence declines at 5 cGy, as seen in the figure above and in Table III of the publication.

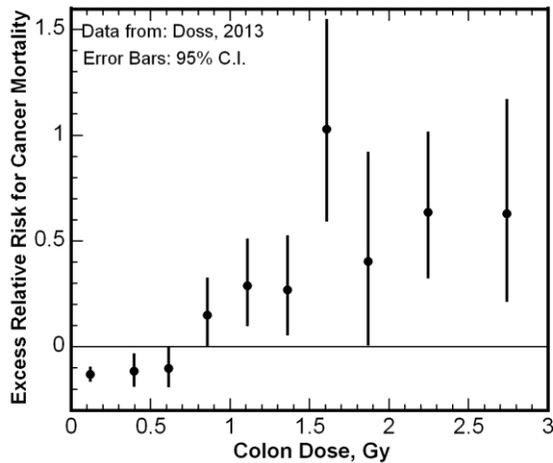
6. Reduced second cancers in radiation therapy patients in regions of body subjected to total dose of ~20 cGy, and threshold dose of >100 cGy for increased second cancers. [Tubiana, 2011](#).

### Second Cancers Following Radiation Therapy



7. Threshold dose of ~50 cGy for increased solid cancer mortality in atomic bomb survivors. Reduction of cancers for lower doses. Analysis of data from [Ozasa, 2012](#) in [Doss, 2013](#).

Solid Cancer Mortality in Atomic Bomb Survivors with correction for -20% bias in baseline cancer rate, and data below 0.3 Gy averaged to a single data point



8. Threshold dose of greater than ~50 cSv for increased leukemias in Hiroshima atomic bomb survivors. Analysis of data from [UNSCEAR 1958](#) in [Cuttler 2014](#).

### Leukemia Incidence in Hiroshima Survivors

