

RADIATION & YOUR PATIENT



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Too soon to say if soy is a promising adjuvant for radiotherapy

Bryant Furlow

New preclinical findings appear to bolster the case that a mixture of dietary plant estrogens derived from soybeans could prove to be a promising treatment adjuvant, reducing radiation toxicity and even possibly enhancing anti-tumor efficacy. Soy supplementation appears to be safe and headlines about soy compounds will increase cancer patients' interest in the dietary supplements, but clinical trials are needed.

Despite important advances in external-beam radiotherapy targeting that allow higher tumor doses with less irradiation of healthy, nontarget tissues, radiation-associated toxicities continue to limit

radiotherapeutic benefits for many cancer patients through dose limitation and treatment disruptions.¹⁻³ This has sparked a search for radiosensitizing and radiation-protective or mitigating agents that can increase tumor susceptibilities or help protect patients' other tissues from acute and chronic radiation-associated toxicities.^{2,3}

Hillman and colleagues investigated soybean isoflavones as a potential treatment that can both radiosensitize tumors while mitigating radiation toxicity in healthy tissues.^{1,4,5} Soy isoflavones are plant estrogens, first recognized as potential cancer chemopreventive agents by epidemiologists studying dietary intake and cancer risks.^{1,6,7} These naturally occurring drugs are protein tyrosine kinase inhibitors (TKIs), estrogen receptor activators, and antioxidants.^{2,8}

Early studies identified genistein as a particularly interesting soy isoflavone candidate for enhancing radiotherapy in preclinical models by upregulating tumor cell apoptosis (cell-suicide) gene pathways.⁹ Importantly, when administered alone, pure genistein increased lymph node metastasis.^{9,10} But the role of an apparently safer and potentially more efficacious mixture of genistein, daidzein, and other soy phytoestrogens in reducing acute radiotherapy toxicities in lung tissue has been under investigation in recent years.^{1,4,5,9}

Findings from a preclinical model indicate the mixture of soy isoflavones enhances high-intensity (10 Gy) radiotherapy, facilitating tumor destruction while protecting lung tissue in nude mice injected with human non-small cell lung cancer (NSCLC) cells.⁵ Hillman's team administered radiation to the left lung at 12 Gy to mice who received soy isoflavones pre- and postradiation. They found that the mixture alleviated the skin and pulmonary toxicities, such as

acute pneumonitis and chronic fibrosis, associated with radiation treatment to the thoracic area.¹

"We report that supplementation with soy isoflavones pre- and postradiation clearly attenuated skin injury and hair loss caused by radiation, a cogent evidence for the radioprotective effect of soy isoflavones on normal tissues," they noted.¹ "Furthermore, soy isoflavones protected mice from radiation-increased breathing rate. Histologic observation of lung tissues confirmed that soy isoflavones protected normal lung structures against radiation-induced inflammation, damage, and fibrosis."¹

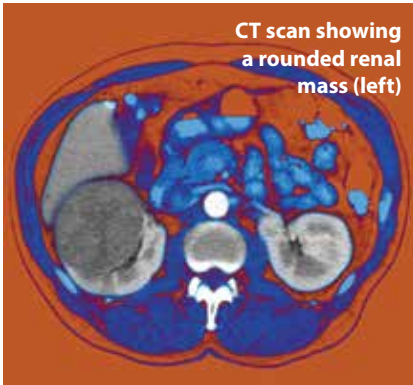
Headlines about preclinical findings are sure to increase patients' interest.

Irradiated lungs in animals that did not receive isoflavones were significantly damaged, showing alveoli-infiltrating inflammatory cells, chronic inflammation, and focal hemorrhages.¹ But irradiated left lungs in mice treated with isoflavones before and after irradiation showed mostly normal bronchioles, alveoli, and blood vessels with minimal inflammatory infiltrate and hemorrhage indicating milder pneumonitis.¹

The findings of this and previous studies by this team of researchers at the Barbara Anna Karmanos Cancer Institute at Wayne State University School of Medicine in Detroit, Michigan, demonstrate that soy isoflavones inhibit radiation-induced up-regulation of survival pathways, resulting in greater cancer destruction in both animal and in vitro studies of lung

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carcinoma, renal cell carcinoma, and prostate cancer.¹ Collectively, the team's findings confirm that soy isoflavones can modulate the inflammatory response to radiation, thereby slowing progressive tissue damage.¹ A phase 1 clinical trial based on the animal study findings is planned but not yet enrolling patients.

Preclinical reports from other research teams suggest possible soy isoflavone mitigation of radiation injuries to hematopoietic, intestinal, and testicular tissues, as well.^{11,12} In a 2013 meta-analysis of data from randomized, controlled clinical trials of soy isoflavones in prostate cancer, researchers suggested soy isoflavones provide a good safety profile and reduced risk of prostate cancer.¹³ (Overall effects on PSA or sex steroid levels were not statistically significant.¹³)

In the meantime, headlines about preclinical findings are sure to increase cancer patients' interest in soy supplementation. Despite the promises, clinical unknowns prevail. Until more clinical trials are completed, the utility of supplemental soy as a radiotherapy

adjuvant is unclear. Efficacies of these and other candidate radioprotective compounds have not yet been studied in combination with concurrent radiochemotherapy or dose escalation.² Therefore, oncology team members must convey to patients that although early, preclinical studies seem promising, and soy generally appears to be safe, whether soy will improve clinical outcomes for patients with lung cancer and other malignancies is still unclear. ■

Bryant Furlow is a medical journalist based in Albuquerque, New Mexico.

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