Soy and Breast Cancer

Protection May Vary by Dose and Age

Soy foods, rich in plant estrogens, have been embraced by American women seeking relief from menopause without the breast cancer risk associated with synthetic hormones. Because Asian women consume soy-based diets but have a low incidence of breast cancer, it has been suggested that soy prevents cancer, perhaps by reducing estrogen levels. Asian women living in Asia have serum estrogen levels as much as 40% lower than U.S. women and demonstrate a fivefold lower risk of developing breast cancer.

The link between soy and cancer prevention is far from conclusive, though, as Kerrie B. Bouker and Leena Hilakivi-Clarke of Georgetown University's Lombardi Cancer Center in Washington, DC, demonstrate with their summary of research on soy's effects on the breast [*EHP* 108:701–708]. The researchers suggest that for postmenopausal women in the United States, soy may actually have estrogenic effects.

USDA Agricultural Research Service

Soy potential uncertain. Several factors may influence whether plant estrogens such as those found in soy have estrogenic or antiestrogenic effects.

Soy's assumed anticancer potential is associated with its rich supply of phytoestrogens, particularly genistein. A number of *in vitro* studies have shown genistein to suppress estrogenic activity, possibly by inhibiting estrogen-metabolizing enzymes. Animal experiments and studies with human breast cancer cells have demonstrated genistein's capacity to repress cell growth. Yet *in vivo* and *in vitro* models have also shown genistein to be estrogenic. Genistein is structurally similar to steroidal estrogens and binds to estrogen receptors. Like estrogen, it also helps build bone density, improves lipid profiles, and may reduce the risk of heart disease.

The paradox of genistein's estrogenic and antiestrogenic properties may be related to dose. Studies show that doses higher than can be achieved only by consuming soy-based foods provide protection against breast cancer similar to the drug tamoxifen. At doses achievable by consuming foods high in soy, genistein stimulates the growth of human breast cancer cells. However, a study of postmenopausal American women given 38 grams of soy protein isolate daily for 5 months (the amount they would get in a high-soy diet) showed no changes.

Genistein's effect also may depend on a woman's age during exposure. Rat studies show that *in utero* exposure to genistein but not to soy increases the risk of breast cancer. Another vulnerable stage for genistein exposure appears to be the years following menopause; animal studies with ovariectomized mice (a model of postmenopause) suggest that genistein increases breast cancer risk. However, no increase in risk is seen in animals exposed during their reproductive stage, and rats exposed to genistein before puberty show low breast cancer risk.

Asian women, however, eat a soy-based diet throughout pregnancy without raising their daughters' risk. Bouker and Hilakivi-Clarke speculate that Asian women's protection stems from their lifelong exposure. They also suggest that other components of soy such as saponins and phytic acids may temper genistein's estrogenic effects in humans.

The researchers theorize that genistein's varying effects may be a function of women's estrogen levels. When levels are low, as before puberty, genistein may act as an estrogen. Animal and human studies suggest that estrogen exposure before puberty paradoxically reduces breast cancer risk. The researchers also suggest that the phytoestrogen promotes the proliferation of mammary cells in women of all ages, but that because older women may already have malignant cells in their breasts, they're more likely to develop cancer.

In light of evidence suggesting that genistein may promote cancer, Bouker and Hilakivi-Clarke call for more studies of its effects. They believe explanations for the phytoestrogen's dual nature are close at hand. **–Cynthia Washam**

Inhalation of Radiation

Low Doses Yield High Risks

Through studies of large groups exposed to radiation, epidemiologists try to quantify the relationship between doses received and resulting carcinogenic effects. Such information is used in the establishment of radiation protection standards. Many radiation exposures today, particularly those of workers in certain types of nuclear facilities, occur when radioactive materials are taken inside the body. But except for a few cases, few human epidemiological studies of the health effects of internal exposures have been conducted. So a team of investigators led by epidemiologist Beate Ritz of the University of California at Los Angeles launched a retrospective study of former nuclear employees to assess the long-term health effects of radiation exposures primarily due to the inhalation of airborne radioactive materials [EHP 108:743–751]. They found that low internal radiation doses may increase the risk of certain cancers.

The researchers quantified the doses to nearly 2,300 workers who had worked at various times between 1950 and 1994 at Rocketdyne/Atomics International, a nuclear research and development facility in Simi Valley, California. The investigators relied primarily on data derived from analysis of specific radionuclides in worker urine and feces samples. They also perfomed external measurements of the radiation emitted by the radioactive materials in the subjects' bodies.

In conducting their analyses, Ritz and colleagues separated the workers into four groups, depending on the dose they were estimated to have received. The four groups ranged from those who were not exposed at all to those receiving a maximum dose of 30 millisieverts or more. A comparison of the adjusted rate-ratios for cancers among these groups showed that the workers who received the highest doses died at a substantially higher rate from leukemias and lymphomas than did those who were not exposed. The same relationship was true for workers who died from cancers of the mouth, throat, esophagus, and stomach. Substantiating these observations was the fact that workers in the zero-dose range had the lowest rates of death and those within the two intermediate dose ranges had progressively higher rates of death with increasing dose. Again, this was true both for leukemias and lymphomas and for cancers of the mouth, throat, esophagus, and stomach. The researchers also examined lung, bladder, kidney, and prostate cancer incidence, but found no elevations in mortality rates. Although the link to increased leukemias and lymphomas had been reported in two earlier studies, the relationship to mouth, throat, and esophagus cancers had not previously been reported for workers exposed to internally deposited radionuclides in this low-dose range.

Still, due to the small number of cases in each cancer group, the authors are careful to acknowledge that their estimates are imprecise.

MTBE's Effects

A Sensitives Issue

In response to the 1990 Clean Air Act, oxygenators such as MTBE (methyl tertiary butyl ether) were added to fuels in concentrations up to 15% in order to reduce carbon monoxide pollution. It was only when acute health complaints—an increase in headaches, nausea, and eye, nose, and throat irritations—surfaced following this increase in MTBE use that researchers began to study the possible health effects of the compound. Earlier studies had looked at the effect of pure MTBE on healthy individuals. However, a study by Nancy Fiedler and colleagues at the University of Medicine and Dentistry of New Jersey–Robert Wood Johnson Medical School in Piscataway, New Jersey, is the first to study controlled exposures of individuals to MTBE in gasoline vapor at concentrations that mimic real-life exposures such as refueling or driving situations [*EHP* 108:753–763].

The researchers compared the symptoms, psychophysiologic reactions, and neurobehavioral performance of two experimental groups during exposure to four controlled exposure conditions: clean air, regular gasoline fumes, and fumes of gasoline containing either 11% or 15% MTBE. Researchers compared one group of 12 individuals selected based on their self-report of symptoms associated with MTBE exposure with another group of 19 control individuals without self-reported sensitivities.

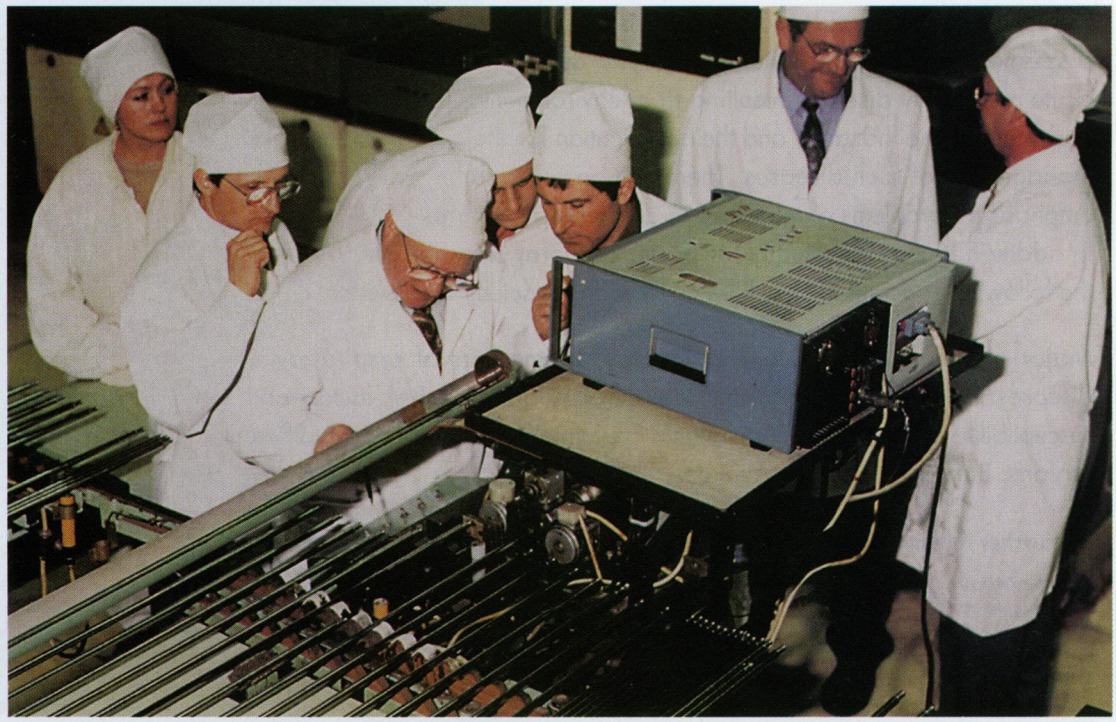
The exposures occurred one week apart and took place in a controlled-environment facility. After a 5-minute relaxation period known as the baseline period, subjects were exposed for 15 minutes to one of the four exposure conditions. After each exposure, subjects rated their experience of 42 different symptoms associated with MTBE and solvent exposure, anxiety, depression, and breathing problems. They also rated the testing environment on factors that might have affected their symptom reports, and completed odor questionnaires assessing the intensity of and irritation caused by the gasoline odor in the room at the time. The subjects took a computerized driving test to test the effects of MTBE on functions such as reaction time and peripheral vision. Researchers measured psychophysiologic responses, finger temperature, finger pulse volume, and the percentage of carbon dioxide in exhaled breath (an indicator of hyperventilation), and the measures were compared to those taken during the baseline period. Before departing each day, subjects were asked to guess which exposure condition they had experienced during that session.

The researchers found that, compared with the control group, the group of sensitives reported significantly more total symptoms when exposed to gasoline with 15% MTBE than when exposed to gasoline with 11% MTBE, plain gasoline, or clean air, although there were no significant differences in neurobehavioral performance or psychophysiologic responses. The self-reported sensitives group also reported higher total symptoms than the control group during every exposure condition, as well as during the baseline period before any exposures. Researchers believe the latter finding suggests heightened sensitivity among this group, regardless of exposure.

The researchers observed no significant differences among the two groups in symptoms, neurobehavioral performance, or psychophysiologic responses when exposures to gasoline with 11% MTBE were compared with exposures to regular gasoline and clean air. According to this study, these results do not support a dose response to MTBE. And, even though the self-reported sensitives did report increased symptoms during exposure to the gasoline with 15% MTBE, the researchers found that the exposure did not impair performance or cause psychophysiologic changes. They also found that neither group could accurately identify specific exposure conditions. At the very best, they could distinguish only between clean air and gasoline exposures.

According to the researchers, it is possible that MTBE, when mixed with gasoline, produces a different effect than that observed with exposure to pure MTBE. They also concede the possibility that using longer exposure periods or conditions that reflect ongoing exposure while driving may show greater effects on performance. To better understand reported health effects, the researchers say, direct testing of subgroups reporting unexpected symptoms in response to low-level exposures may be necessary. **–Jennifer Medlin**

They also caution that these findings need to be confirmed by further follow-up of the present group. Nonetheless, each such study is important because it contributes information about the potential carcinogenicity of specific radionuclides prevalent in the nuclear materials work environment. **–Dade W. Moeller**



Radkowsky Thorium Power Corporation

Something in the air. People who work with nuclear materials, such as these fuel rod assembly workers, may be at increased risk for developing certain cancers due to inhalation of airborne radioactive matter.