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Risks Associated with Therapeutic ^{131}I Radiation Exposure

In 1996, Schlumberger et al. (*1*) reported on the effects of therapeutic ^{131}I exposure on pregnancy. The research involved 2,113 pregnancies occurring after 1970 and 258 pregnancies in women who had undergone radioiodine therapy. In that report, the epidemiological data indicated there was an increased risk of miscarriages in women after high doses of radiation to the ovaries from the treatment. Consequently, the authors recommended that women postpone conception for at least 1 y after such treatment (*1*). However, the authors cautioned that this conclusion was based on a small sample of women undergoing "high"-dose radiotherapy and subsequently conceiving a child (96 of 258 pregnancies). High doses include cumulative doses exceeding 3,700 MBq (100 mCi). Such doses approximately equate to a 140-mGy total dose to the ovaries; however, under extraordinary circumstances, total cumulative (fractionated) doses to the ovaries might escalate to approximately 1,000 mGy, as indicated by Garsi et al. (*2*) in an article in this issue of *The Journal of Nuclear Medicine*.

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Garsi et al. (*2*) have completed a larger, follow-up study with more statistical power (2,673 pregnancies) on the effects of therapeutic ^{131}I exposure on pregnancy and the health of offspring. This new study excluded earlier data reported by Schlumberger et al. (*1*) because of the inability to validate the older data set. Garsi et al. (*2*) reported that the new, more rigorous data set showed that miscarriages were not significantly more frequent in women treated with radioiodine in the year before conception. In addition, the incidences of stillbirths, preterm births, low birth weight, congenital malformations, and neonatal death during the first year of life were not significantly different for women who received radioiodine therapy and those who did not. Finally, the incidences of thyroid or any other types of cancer were similar in children born before and those born after a mother's exposure to radioiodine. The authors concluded that there is now no epidemiological evidence to indicate that radioiodine therapy before conception has any adverse consequences for pregnancy or offspring (*2*). There are several reasons why this latest conclusion is not surprising, including the reality that there are thresholds for consequences of radiation exposure and the fact that biologic mechanisms can protect organisms.

Unfortunately, there is a belief that exposure to all radiation, including that from radioiodine therapy, will have a negative impact on biologic systems. This belief is the linear no-threshold (LNT) relationship, and it is a model that predicts risk on the basis of the idea that risk is linearly proportional to dose, without a threshold. The LNT model is based on the following assumptions: every dose, no matter how low, carries with it some risk; risk per dose unit is constant and independent of dose rate; risk is additive and can increase only with an increased dose; and biologic variables are of no importance. However, many examples do not support this LNT concept at low doses or low dose rates (*3–5*). Consequently, the use of an LNT model for the prediction of radiation risk in pregnancy and the expectation of detrimental effects at all doses may be inappropriate. The results reported by Garsi et al. (*2*) support this contention, even after relatively high cumulative doses (>1,000 mGy) to the ovaries.

Dose estimation for various organs and tissues is complicated for therapeutic ^{131}I exposure. The highest exposures are to the thyroid or any metastasized thyroid cancers. Lower exposures occur systemically because radioiodine initially is weakly dispersed throughout the body before becoming concentrated in thyroid tissue. In addition, either dose protraction (lower dose rate) during radioiodine therapy can occur over hours and days or multiple therapies can be given over extended periods of months or years (high cumulative fractionated doses). These treatment situations will have effects on cells different from those of single acute high-dose exposures, from which detrimental effects might be expected. Garsi et al. (*2*) reported that estimated doses to the ovaries during radioiodine treatment might be as high as 1,000 mGy under extraordinary situations. For example, thyroid cancer metastases in the vicinity of the ovaries can lead to an escalation of the total cumulative dose. However, under normal circumstances, when most radioiodine uptake is concentrated in the thyroid, doses to normal tissue, including the ovaries, are approximately

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100–150 mGy (*2*). For this dose range, there is strong evidence to indicate that there is a threshold for detrimental effects of radiation, particularly with respect to DNA damage (*3,4*). In other words, at doses above this threshold, radiation has a negative impact, whereas below this threshold, the effects are absent or positive. In general, doses exceeding the threshold elicit cellular emergency defense mechanisms that attempt to rapidly minimize extensive DNA damage and ensure cell survival. However, these defense systems are known to be error-prone and, consequently, to increase risks such as DNA mutation and cancer development (*3,6*). Conversely, at doses below the threshold, alternative biologic response mechanisms are activated; these mechanisms are error-free and eliminate DNA alterations caused by the low-dose radiation exposure. These processes can restore the genome to normal, with no associated genetic risk. The net beneficial effect of low-dose radiation exposure has been given many names, including the adaptive response, hormesis and, more recently, activated natural protection (*7*). Because biologic mechanisms respond differently to high doses and to low doses, it cannot be assumed that the risk at all doses is proportional to the total cumulative dose.

In simple models, cells exposed to low doses of radiation (1–100 mGy) can undergo an adaptive response and become resistant to the DNA-damaging effects of high doses. It was shown that the frequency of chromosomes damaged by high doses of radiation, as measured by micronucleus formation or mutation, could be significantly reduced by first allowing the cells to adapt with low-dose radiation exposure (*3–5*). This evidence indicates the activation of mechanisms to allow for a greater DNA repair capacity. It is interesting that exposure to radioiodine therapy induced a similar adaptive response in vivo in patients (*8*). Lymphocytes collected from patients after therapy developed an adaptive response and subsequently had less radiation-induced DNA damage, as measured by micronucleus formation, than pretherapy lymphocytes. Therefore, low-dose radiation from the radioiodine therapy induced a mechanism in patients' cells that either eliminated genetically damaged cells or improved the overall DNA repair capacity of the lymphocytes. Both of these processes have been shown to occur in normal human cells in response to low doses of radiation (*3,4,6,9*).

A reduction in the frequency of transformation (cancer risk) and an increase in the latency period for cancer have also been demonstrated after low-dose radiation exposure. Single doses of γ-radiation of 1–100 mGy reduced the frequency of in vitro spontaneous transformation by 3-fold (*3*). The same observation was made for mammographic-energy x-rays at acute exposures, from 1 mGy up to 300 mGy (*10*). These results demonstrate that transformation risk is not proportional to dose and that the probability of developing cancer can be reduced by inducing a mechanism that eliminates unstable, preneoplastic cells. It is interesting that a single exposure to doses similar to those expected from radioiodine treatment can also extend the latency period for some cancers (*3,11*). In other words, even if the frequency of transformation does not change, cancer mortality can be significantly delayed (increased longevity) (*11*). These findings lend credence to the view that low-dose medical exposures may actually increase life expectancy, even if the probability of developing disease is unchanged.

In summary, there remains a belief that all radiation is detrimental, despite strong biologic and epidemiologic evidence to the contrary. Studies have shown no evidence for significantly increased cancer mortality in patients undergoing radioiodine therapy or other diagnostic exposures, even in cancer-prone individuals (*12*). There is no convincing evidence that doses below 100 mGy produce significant increases in cancer risk or adverse pregnancy outcomes, such as congenital malformations (*13*). Therefore, it is important to maintain a balanced perspective with respect to the risks and benefits of medical radiation exposures. Reports that warn of increased risk on the basis of assumptions and calculations from high-dose extrapolation (LNT relationship) and not actual data should be viewed with caution, considered hypothetical, and even considered potentially detrimental if improperly used for medical advice. Garsi et al. (*2*) have provided clear clinical evidence to show that there are no known effects of radioiodine therapy on pregnancy outcomes or the health of offspring. This information should be used by physicians to make informed decisions and help patients understand that after this type of therapy, normal pregnancy outcomes can be expected.

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