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Q. OVARY

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Chapter V
Somatic Effects - Cancer

Q. Ovary

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No specific category of radiation-induced ovarian neoplasms in humans was reported in the NAS BEIR I report, although it did refer to a group of miscellaneous neoplasms of other types and sites that reportedly occur in excess after irradiation. However, the human reproductive cells appear to have a relatively low sensitivity to the induction of radiation cancer, compared with other tissues. The 1977 ICRP Report reported that no carcinogenic effects in these organs after irradiation had yet been documented conclusively in humans. However, there have been confirmed reports of carcinoma of the ovary in women who had received radiotherapy for benign conditions of the pelvic organs and in the atomic-bomb survivors of Hiroshima and Nagasaki.

Experimental Studies

There is now reliable experimental literature on the radiation induction of ovarian tumors in mice. A number of important observations emerge, and these relate to the dose-response relationship and the effects of total dose, of dose rate, and of LET. The dose-response relationship for the induction of ovarian tumors appears to have no apparent threshold over the spontaneously high incidence of ovarian adenomas in mice (e.g., 11% control level in LAF mice, 5-15% in RFM mice). The dose-response curve for acute exposure has a very steep curvilinear or sigmoid rise for low radiation doses (about 50 rads) and shows a high susceptibility to radiation neoplasia. In general, the acceleration
and increased induction of tumors result from single acute doses, and may maintain the high levels at a plateau range at higher doses, with a decrease ensuing after 200 rads. The plateau is maintained at 500-600 rads with higher LET, but tends to decline slowly with x irradiation. At low dose rates (e.g., less than 2 rads/day) of continuous gamma irradiation, there is a small increase in incidence, but the response appears to be only slightly curvilinear or sigmoid. At higher dose rates, 112-390 rads/day, the curvilinear or sigmoidal dose response demonstrated was marked, with a plateau thereafter to 390 rads. It is of interest that, provided that the exposure time was held constant in these experiments, the curvilinear response fit a dose-incidence curve in which the incidence varied with the square of the dose.

The experimental radiation studies on ovarian carcinogenesis dealt primarily with tumor induction in mice and demonstrated the following: All cells, both supporting and hormone-secreting elements that comprise the organ, but not the reproductive cells (oocytes and follicular cells), are at risk of neoplastic induction; no single element appears to be more susceptible. The ovary is relatively sensitive to the induction of radiation cancer, and as little as a 50-rad acute exposure can result in a significant increase in the tumor-induction rate. At the lower doses, acute exposure to higher-LET radiation—e.g., higher-energy neutrons and protons—has no greater effectiveness. Higher doses, however, up to 400 rads, maintain a higher incidence plateau, whereas there
is a falloff with x rays. The maximum is reached in the range of 11,12 100-200 rads. There is a dose-rate effect at low doses of continuous gamma irradiation; an increase in dose rate results in an increased yield of tumors. There is a curvilinear dose-response relationship without a threshold in the range of 1.75-112 14 rads/day for total doses up to approximately 400 rads. In general, the dose-response curve appears to be sigmoidal or curvilinear without a threshold, depending on dose rate, LET, and total dose, 15a as well as strain and age. There is a hormone-dependent relationship in ovarian neoplastic transformation after irradiation, possibly mediated by pituitary gonadotropins.

Human Studies

Radiotherapy for Benign Disease. In a retrospective study of 731 gynecologic patients treated with intracavitary radium or external x rays, primarily for uterine fibroids or other benign pelvic disorders, Palmer and Spratt found an excess of 5.4 cases (eight observed versus 2.6 expected) of ovarian cancer. The mean latent period was 10.1 yr. No precise radiation dose estimate could be determined. Air and tissue radiation doses of approximately 2,700 R and 700 R were estimated, but radium dosage was estimated in milligram-hour equivalents. The induction rate could be determined on the basis of x-ray treatment solely, but an estimate of radiation risk per rad could not be ascertained. In their review of five other clinical series, Palmer and Spratt described a total of 3,968 gynecologic patients in whom eight ovarian neoplasms arose
after pelvic irradiation. Precise radiation doses could not be ascertained, and followup periods were generally less than 10 yr.

The 1969 ICRP Report No. 14\(^3\) assessed the data of Court-Brown and Doll\(^17\) and found, in ankylosing-spondylitis patients who developed cancer in heavily irradiated sites, that cancer of the ovary appeared in the subgroup in which the difference between the observed and expected cancer incidences was not statistically significant (four observed, two expected, 1.8 excess cases, and a rate of 0.8 per 1,000 persons).

Smith and Doll\(^18\) reviewed a series of 2,068 gynecologic patients who had been treated with pelvic irradiation for benign metropathia haemorrhagica (benign uterine bleeding). Deaths were recorded at 5 yr or more after radiotherapy. Eight ovarian cancers occurred in the irradiated population (7.66 expected).

**Atomic-Bomb Survivors, Hiroshima and Nagasaki.** In their most recent report on studies of the tumor-registry data on the Japanese atomic-bomb survivors, Beebe and colleagues\(^6\) indicated an increasing rate of induction of ovarian tumors in the exposed Hiroshima population, but not in the Nagasaki survivors. For the 300+ rad kerma exposure group in Hiroshima, the incidence rate per rad kerma was 0.6 ± 0.26\(^*\) excess cancer per 10\(^6\) exposed women per rad during

\(^*\)90% confidence limits.
the 12-yr. followup period, 1959–1970. Considering a ratio of organ dose to kerma dose of 0.36** for an RBE of 1, the risk was \(1.67 \pm 0.72\) excess cancers per \(10^6\) exposed women per rad. For a ratio of organ dose to kerma dose of 0.47 for an RBE of 5, the risk was \(1.28 \pm 0.55\) excess cancers per \(10^6\) exposed women per rad for the 12-yr followup period. The induction rate for the Nagasaki cohort was \(0.04 \pm 0.22\) excess cancer per \(10^6\) women per rad kerma. However, it is probable that the mean latent period for ovarian tumors is longer, and a rise in the radiation induction rate in the atomic-bomb survivors could occur.

**Conclusions.** It is probable that the human ovary is susceptible to cancer induction by radiation, but at a relatively low rate that cannot be determined with any precision from the information now available.

**See Appendix____, page ____.
REFERENCES


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