A Review of Forty-Five Years Study of Hiroshima and Nagasaki Atomic Bomb Survivors

II. BIOLOGICAL EFFECTS

Follow-up Studies of Breast Cancer Incidence among Atomic Bomb Survivors

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Breast cancer/Atomic bombing/Radiation/Carcinogenesis/Epidemiology

INTRODUCTION

Although breast cancer rates among Japanese women are normally very low compared to other countries, the excess risk associated with exposure to ionizing radiation, as observed in the Life Span Study Sample (LSS) sample of the Radiation Effects Research Foundation (RERF), Hiroshima and Nagasaki, is fully as high as that seen in medically-irradiated Western populations. This combination of a high radiation-related excess and a relatively low baseline level of risk means that the LSS cohort is especially informative about radiation-induced breast cancer. In this paper we review the results of published studies of breast cancer incidence and mortality among A-bomb survivors, their relationship to findings from studies of other irradiated populations, and their possible implications for radiation-induced cancer in general. We conclude with an overview of current studies, which extend beyond the investigation of risk as a function of radiation dose.

BACKGROUND

Breast cancer incidence among A-bomb survivors

The first study to find an excess breast cancer risk among A-bomb survivors was reported by Wanebo et al.1) in 1967. This was only two years after Mackenzie2) had demonstrated an association with x-ray exposure from multiple chest fluoroscopies used to monitor pneumothorax treatment for tuberculosis in a Nova Scotia sanatorium. Wanebo’s study was limited to the clinical sub-sample of the LSS sample, that is, the subgroup that has been routinely solicited for biennial clinical examinations at the Atomic Bomb Casualty Commission and its successor, the RERF, since 1958. It is of some interest, in view of the numbers in more recent studies, to note that
Wanebo's finding was based on only 27 breast cancer cases diagnosed during the period 1950–66 and, in particular, on only 9 histologically verified cases with estimated exposures over 0.9 Gy T65D<sup>3</sup> tissue Kerma compared with 4.3 cases expected in the absence of a dose response. The report by Mackenzie was based on 13 cases in 271 patients vs. one case in 570 patients who had not been given fluoroscopy; most of the irradiated patients had received cumulative breast tissue doses far higher than all but a very few A-bomb survivors.

McGregor et al.<sup>4</sup>) extended the A-bomb survivor investigation to the entire LSS sample, and reported 231 breast cancers diagnosed during the period 1950–69. Ascertainment was based upon death certificates, autopsy records, the tumor registries of Hiroshima and Nagasaki, and ABCC records. A strong, approximately linear dose response was observed: for all exposure ages combined the estimated excess relative risk at 1 Gy breast tissue dose (see Kerr<sup>5</sup>) was about 1.1 ± 0.26. Of special interest from today's vantage point was the evidence of a downward gradient in risk with increasing age at exposure: the estimated excess relative risks at 1 Gy were approximately 2.5 ± 0.8, 0.7 ± 0.3, 0.18 ± 0.24, and 0.35 ± 0.42 for exposure ages 10–19, 20–34, 35–49, and 50+, respectively. Only one (non-exposed) case was observed among women who were under 10 years of age ATB (i.e., at the time of the bombings), whose maximum age in 1969 was only 34. Also of interest was an apparent lack of dependence among breast cancer cases between radiation dose and time from exposure until cancer diagnosis.

Tokunaga et al.<sup>6</sup>) in extending the LSS sample incidence series through September, 1974, introduced more exhaustive methods of case ascertainment using local sources of diagnostic information such as hospitals and clinics. A total of 360 cases was reported, including only 5 among women under 10 years of age ATB. Highly significant dose responses were found for each of the cohorts 10–19, 20–29, and 30–39 years of age ATB, but there was actually a statistically significant decrease in risk with increasing dose for women exposed between ages 40 and 50. In absolute terms, the observed increase in excess cases per unit dose was approximately the same for survivors exposed during their second, third, and fourth decades of life but, for similar ages at observation for risk, those exposed at younger ages exhibited higher levels of excess risk. For women who developed breast cancer, mean time from exposure until cancer diagnosis was shown to be heavily dependent upon exposure age but independent of radiation dose.

In the third LSS survey, through 1980, Tokunaga et al.<sup>7</sup>) ascertained 564 breast cancer cases in the LSS sample. The most remarkable finding<sup>8</sup>) was a statistically significant dose response for 24 cases diagnosed among women who were under 10 years of age ATB. The relationship was seen even among women under 5 ATB, and provided the first strong evidence that breast cancer can be induced by irradiation of stem cells, well before breast budding. The overall pattern of a decreasing relative risk with increasing age at exposure was thus strengthened, as the earlier pattern was maintained among women over 10 years of age ATB and the dose-related relative risk in the 0–9 ATB group was, if anything, even higher than that in the 10–19 ATB cohort. However, the dose-related deficit observed earlier in the 40–49 ATB group was no longer apparent. Within restricted age-ATB intervals, excess relative risk tended to remain fairly constant over time following exposure; this is another manifestation of the observation, reported in the two earlier LSS surveys, that time from exposure until cancer diagnosis tends to be independent of radiation dose. Regardless of the age at exposure, no excess risk was apparent until ages at
which rates in the non-exposed population become appreciable.

At the time of the third survey, the dosimetric basis for estimation of risk in the LSS sample was being reevaluated, a process which eventually led to the DS86 dosimetry\textsuperscript{9,10} now in place. Based on preliminary information, it was calculated that the new dosimetry would result in an increase of about 30\% in dose-specific estimates of increased risk\textsuperscript{7}.

**Breast cancer incidence in other irradiated populations**

Following Mackenzie's study, which was extended by Myrd\textsuperscript{n} and Hiltz\textsuperscript{11}, Boice and Monson\textsuperscript{12} reported a dose-related excess risk among 1054 patients treated by pneumothorax and monitored with multiple fluoroscopies at a Massachusetts tuberculosis sanitorium; many of them had been treated as teenagers and a decreasing relative risk was observed with increasing exposure age similar to that seen in the LSS sample. More recently, Hrubec et al.\textsuperscript{13} have reported on follow-up through 1980; 58 cancers were observed vs. 35.8 expected based on general population rates, whereas 19 were observed vs. 22.8 expected among women treated by other means. Only 2 cancers were observed among women treated by pneumothorax before age 15, but the relative risk decreased from 3.0 (19 observed vs. 6.3 expected) for treatment beginning at ages 15–19, to 1.5 (25 vs 16.9) at ages 20–29, to barely one (9 vs. 8.2) for treatment beginning at ages 30–39.

Dose-related excess breast cancer risk has also been observed among women treated by X-ray for benign breast disease. Shore et al.\textsuperscript{14}, in the most recent of a series of follow-up studies of a fixed cohort of New York women treated for acute postpartum mastitis\textsuperscript{14,15}, found 56 breast cancers among 601 exposed patients compared to 59 among 1239 non-exposed controls. Eighty-five percent of the women were 20–34 years of age at the time of treatment; 4.5\% were younger and 10.3\% were older. There was no significant difference by exposure age with respect to dose-specific excess relative risk, which was 0.58±0.18 per Gy for breast doses under 7 Gy. No significant differences were found between irradiated and control subjects with respect to time from exposure or study enrollment to breast cancer diagnosis, and relative risk remained roughly constant over time following exposure.

In 1983 Hildreth et al.\textsuperscript{16} reported a 5-fold increased risk of breast cancer among 1201 women who had received X-ray treatment in infancy for an enlarged thymus, as compared to their 2469 non-irradiated sisters. This finding confirmed and strengthened the inference by Tokunaga et al.\textsuperscript{8} of a dose-related excess risk among female A-bomb survivors under age 10 ATB, the more so since more than 90\% of the thymus patients had been less than 6 months of age at the time of their exposures. After another 6 more years of follow-up\textsuperscript{17}, the number of breast cancers increased from 9 to 22 in the irradiated group, and from 4 to 12 in their non-irradiated sisters. The estimated excess relative risk at 1 Gy breast tissue dose was 2.48 (95\% confidence interval 1.1 to 5.2). The first breast cancer was observed 28 years after exposure, and there was no difference between the irradiated and non-irradiated groups with respect to mean age at breast cancer diagnosis.

**A COMPARISON OF PUBLISHED FINDINGS**

A formal analysis in parallel\textsuperscript{18}, using identical age groupings, follow-up intervals, and
regression techniques, obtained markedly higher dose-specific estimates of excess relative risk from the 1950-74 LSS sample data than from the Massachusetts tuberculosis and New York mastitis series, for similar ages at exposure. Absolute measures of excess risk, on the other hand, were reasonably similar. Table 1 is based on that analysis, with a 30% upward adjustment in the LSS sample estimates to make them roughly compatible with the DS86 dosimetry.

Table 1. Estimates of excess relative and absolute risk per Gy breast tissue dose, from Land et al. (18).

<table>
<thead>
<tr>
<th>Series:</th>
<th>Mastitis Patients (15)</th>
<th>Fluoroscopy Patients (12)</th>
<th>LSS Sample, 1950-74 (6)</th>
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<tbody>
<tr>
<td>15–19</td>
<td>27.9 ± 19.8</td>
<td>10–19</td>
<td>8.9 ± 3.1</td>
</tr>
<tr>
<td>20–29</td>
<td>6.3 ± 2.0</td>
<td>20–29</td>
<td>3.8 ± 2.1</td>
</tr>
<tr>
<td>40–44</td>
<td>52.1 ± 21.0</td>
<td>40–44</td>
<td>6.4 ± 15.6</td>
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</tbody>
</table>

A. Excess Absolute risk

<table>
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<tbody>
<tr>
<td>15–19</td>
<td>27.9 ± 19.8</td>
<td>10–19</td>
<td>8.9 ± 3.1</td>
<td>10–19</td>
<td>11.6 ± 4.0</td>
</tr>
<tr>
<td>20–29</td>
<td>6.3 ± 2.0</td>
<td>20–29</td>
<td>3.8 ± 2.1</td>
<td>20–29</td>
<td>3.8 ± 1.1</td>
</tr>
<tr>
<td>40–44</td>
<td>52.1 ± 21.0</td>
<td>40–44</td>
<td>6.4 ± 15.6</td>
<td>40–49</td>
<td>−1.3 ± 0.59</td>
</tr>
</tbody>
</table>

B. Excess relative risk

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>15–19</td>
<td>0.43 ± 0.18</td>
<td>10–19</td>
<td>0.84 ± 0.45</td>
<td>10–19</td>
<td>3.9 ± 1.3</td>
</tr>
<tr>
<td>20–29</td>
<td>0.35 ± 0.16</td>
<td>20–29</td>
<td>0.23 ± 0.16</td>
<td>20–29</td>
<td>1.1 ± 0.38</td>
</tr>
<tr>
<td>30–39</td>
<td>1.57 ± 1.21</td>
<td>30–39</td>
<td>2.3 ± 3.1</td>
<td>30–39</td>
<td>1.8 ± 1.1</td>
</tr>
<tr>
<td>40–44</td>
<td>1.57 ± 1.21</td>
<td>40–44</td>
<td>0.54 ± 1.7</td>
<td>40–49</td>
<td>−0.4 ± 0.18</td>
</tr>
</tbody>
</table>

1 Excess cases per 10^4 women per year per Gy, following assumed minimal latent periods of 20, 15, and 10 years for exposure ages 10–14, 15–19, and 20+, respectively.

2 Excess cancer risk per Gy as a proportion of age-specific baseline breast cancer risk.

3 The published LSS series estimates have been increased by 30% as a rough conversion between the T65D and DS86 dosimetry systems.

It is of some interest that the U. S. National Academy of Science’s 1990 Committee on the Biological Effects of Ionizing Radiation, also known as BEIR V, projected breast cancer risks among populations on the basis of equal dose-specific excess relative risks, an assumption that
seems inconsistent with Tables 1 and 2.

### SOME IMPLICATIONS FOR RESEARCH STRATEGY

The initial finding by Mackenzie\(^2\) was followed by a virtual explosion of new information linking breast cancer risk with exposure to ionizing radiation, and the rate at which new information has appeared continues to increase, as members of the major irradiated study populations who were exposed when they were young reach the ages when breast cancer risk normally contributes significantly to overall mortality and morbidity. It is clear that breast cancer is a major late effect of radiation exposure. Mole\(^2\) has characterized the female breast as "the single organ most susceptible to cancer induction after exposure to ionizing radiation." It is also an organ for which other cancer risk factors have been well characterized. There is considerable variation in risk among countries, and it is intriguing that the major study populations exposed to ionizing radiation are in countries having among the world's lowest and highest baseline breast cancer rates. It is also intriguing to note, from Tables 1 and 2, that at doses well under one Gy, depending upon age ATB, most of the breast cancers observed among the younger (i.e., under 40 ATB) A-bomb survivors probably would not have occurred in the absence of exposure. Among the North American subjects this conceptual "boundary" dose tends to be higher because population rates are higher, but in both populations it is possible to identify groups on the basis of radiation dose and age at exposure in which radiation induction can be confidently assumed for the majority of observed cases, and comparison groups for which radiation causation can be virtually ruled out for practical purposes. Thus it is in theory possible to investigate the extent to which the excess risk associated with radiation exposure may be influenced by the other factors that seem to have so much to do with breast cancer risk in the absence of significant radiation exposure.

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**Table 2.** Comparisons of published estimates of excess relative risk per Gy breast tissue dose from specified studies and newly computed estimates from the 1950-80 LSS series (7).

<table>
<thead>
<tr>
<th>Study</th>
<th>Age at Irradiation</th>
<th>% Excess RR/Gy (95% CI or ± S.D.)</th>
<th>Comparable LSS Estimate(^1)</th>
<th>Age ATB(^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hildreth (17)</td>
<td>&lt;1</td>
<td>248 (107, 517)</td>
<td>560 (192, 1630)</td>
<td>0.9</td>
</tr>
<tr>
<td>Shore (14)</td>
<td>20–40 (mainly)</td>
<td>58 (± 18)</td>
<td>129 (78, 215)</td>
<td>20–39</td>
</tr>
<tr>
<td>Hrubec (13)</td>
<td>&lt;20</td>
<td>164 (38, 382)</td>
<td>273 (170, 439)</td>
<td>10–19</td>
</tr>
<tr>
<td></td>
<td>20–29</td>
<td>40 (−31, 158)</td>
<td>130 (67, 253)</td>
<td>20–29</td>
</tr>
<tr>
<td></td>
<td>30+</td>
<td>151 (−61, 651)</td>
<td>128 (58, 282)</td>
<td>30–39</td>
</tr>
</tbody>
</table>

\(^1\) LSS estimates were increased by 30% as a rough conversion between the T65D and DS86 dosimetry.

\(^2\) At the Time of the Bombings.
For example, the excess relative risks in Tables 1 and 2 suggest that populations normally at low risk of breast cancer are not necessarily, if exposed, at lower risk than other populations of radiation-induced cancer. But also, analysis of time to tumor diagnosis and variation of relative risk over time following exposure suggest that the factors that determine the dependence of baseline rates on age at observation also apply to radiation-induced breast cancer.

Radiation-induced breast cancer appears to be mainly a consequence of exposure before (about) age 40, and risk is especially high following exposure during childhood or adolescence. It is of interest in this connection that the major epidemiological risk factor is age at first full-term pregnancy, and that early age at menarche is a risk factor. Events early in life would seem to play a role in the Japan-United States difference, since rates among Japanese migrants to the United States have tended to remain low, whereas the second and third generations have had rates more similar to those of U.S. whites. The apparent reduction in radiation susceptibility after age 40 observed in most study populations is especially sharp in the LSS series, and this suggests the possibility that radiation exposure might interfere with ovarian function, leading to a protective effect similar to that found after surgical menopause.

There appears to be little or no excess risk until somewhere around age 30, regardless of age at exposure; estimates based on observations near that age are highly unstable because very few cases tend to be observed in either exposed or non-exposed subjects, and for that reason it is perhaps unrealistic to expect to be able to determine “minimal latency periods” for exposures at young ages. There is little evidence that radiation-related excess risk decreases over time following exposure, either absolutely or relative to age-specific baseline rate, although BEIR V modelled relative risk as decreasing over time after reaching a maximum 15–20 years after exposure. There is now fairly strong evidence from the LSS mortality surveys that relative risk among survivors 0–9 ATB, of mortality from all cancers other than leukemia, considered as a group, declined somewhat from the very high, but statistically unstable, value observed when an excess first became apparent. But it is possible that the change reflects a shift in the kinds of cancers observed, from more radiation-susceptible tumors characteristic of childhood and adolescence, to adult-type cancers; inferences based on a single site, like the breast, are free from this complication.

The findings by Tokunaga et al. of a dose-related excess risk among survivors exposed during their first decade of life, and by Hildreth et al. of a similar excess among women exposed to therapeutic X ray during infancy effectively undermined theoretical speculations by Korenman and others that the hormonal stimulation and changes in breast tissue associated with menarche marked the beginning of a period of increased vulnerability to carcinogenic agents, which ended with the menopause. An alternative model, which was proposed by the present authors, is that an early carcinomatous change can be caused in an epithelial cell by radiation at any age, but that the probability that this change may eventually result in clinical breast cancer depends upon the amount of hormonal stimulation following exposure and on the length of time during which that stimulation is present.
CURRENT RERF INVESTIGATIONS OF BREAST CANCER

A number of investigations now nearing completion at RERF are aimed at particular questions raised in the preceding section. The large number of female autopsy cases among the LSS sample, including 216 with tissue kerma exposure of 1 Gy or more, permits an investigation of atypical epithelial hyperplasia in breast tissue obtained at autopsy from high-dose and low-dose survivors, and non-exposed LSS subjects, in whom no breast cancer had been diagnosed. Serial sections have been made and examined from 93 high-dose and 221 low-dose autopsy cases, matched by age ATB and age at death (RERF RP 21-81). Preliminary findings indicate that hyperplasia prevalence increases with increasing dose, and that the dose response, like that for breast cancer, decreases with increasing age ATB. The decline is, however, more regular in that a stronger dose response was found for tissues from women 40–49 ATB than in women exposed at older ages.

Estrogen, prolactin, other hormone levels have been evaluated for breast cancer cases and controls from stored serum samples obtained during clinical examinations around 1970, well before cancer diagnosis, and are being compared for possible associations with risk (RERF RP 11-85). It seems unlikely, however, that the resulting data will prove to be numerous enough to permit inferences about possible interactions between hormone levels and radiation dose.

A case-control interview study (RERF RP 14-79) based on over 200 living cases from the 1950–80 incidence series accessible to interviewers in Hiroshima and Nagasaki, and 580 matched controls, has been performed to investigate the role of established breast cancer risk factors other than radiation, and their possible interaction with radiation dose. Preliminary results indicate that the usual factors, which are mainly related to reproductive history are associated with risk and that, for the most part, the excess risk associated with radiation dose is diminished or increased by these factors in rough proportion to their effects on baseline risk.

Finally, a new breast cancer incidence study, covering the period 1950–1985, is underway (RERF RP 1-90). Case ascertainment relies in part, as it has in the past, on death certificate reporting which in the long term is virtually complete for survivors resident anywhere in Japan. But principal reliance for living cases is placed on ascertainment through the LSS tumor registry which is based on the tissue and tumor registries of Hiroshima and Nagasaki. The registries are being upgraded and expanded with the eventual aim of complete ascertainment for reportable cancers diagnosed in hospitals and clinics located in Hiroshima and Nagasaki and their environs; unlike the experience with earlier breast cancer series, it has become very rare to find new cases from local sources that have not already been gathered by the LSS registry.

A longer-term goal for the LSS registry is ascertainment of incident cases among LSS sample members who no longer live within the reporting areas covered by the Hiroshima and Nagasaki registries. This is of concern especially for the youngest cohorts of female survivors, among whom the excess of radiation-induced breast cancer is most marked. Currently, a residential history database is being constructed for the LSS sample to facilitate utilization of information from local tumor and tissue registries and other possible case-ascertainment sources throughout Japan. Another source is the Japanese Breast Cancer Registry (JBCR), a hospital-based registry under the auspices of the Japanese Breast Cancer Society which is thought to cover about half of all...
cases diagnosed within the past few years. In a comparison with the LSS sample roster of JBCR cases for the period 1978–82, there were 54 cases already included in the LSS registry and another 9 cases among LSS sample members who had migrated from Hiroshima or Nagasaki before their cancers had been diagnosed.

Preliminary results from the 1950–85 LSS sample incidence series include a total ascertainment of 815 breast cancer cases. (This total excludes the 9 JBCR-only cases identified to date, and any new cases from that source that may be added for the period 1983–85). Some of the increase over the previous series (1950–85, 564 cases) is due to an expansion of the LSS sample by including more low-dose Nagasaki survivors; thus some of the new cases would have been included in the earlier series if the LSS sample, as then defined, had included these subjects. Also, as in past series, others of the newly identified cases were diagnosed before the cutoff date of the previous series (December 31, 1980) but had been missed because of delays in the process by which cases are reported to the tumor registries. But 190 of the total cases were diagnosed during 1981–85, as compared to 162 in 1976–80 and 139 in 1971–75. Moreover, 44 new cases were added in the theoretically interesting 0–9 ATB group, making a total of 68, and there were 79 new 10–19 ATB cases, for a total of 232.

In general, the preliminary analyses suggest risk patterns not very different from those adapted from the 1950–80 series and summarized in Table 2. Larger numbers, of course, mean greater statistical stability and narrower confidence limits for the risk estimates. The additional 5 years of follow-up allows more confident estimation of the dependence of excess risk on time after exposure. On the other hand, the DS86 dosimetry has been applied to fewer LSS subjects than the T65D system. This is particularly true for the subjects in the 10–19 ATB cohort, many of whom, because of wartime labor assignments, were exposed in concrete buildings fairly close to the hypocenters, for which dosimetry estimation presents special difficulties. DS86 dose estimates are available for only 185 of the 232 cases in this age group, vs. T65D estimates for 141 out of 150 in the previous series; comparable numbers for other age-ATB cohorts are 66 of 68 vs. 24 out of 24 previously for those 0–9 ATB, 325 of 346 vs. 243 of 247 for those 20–39 ATB, and 166 of 169 vs. 143 of 143 for those over 40 ATB. As a group, the women with unknown DS86 dose have about two-thirds more breast cancer incidence than the low-dose and non-exposed sample members, and in the 0–19 ATB cohort the difference is more than two-fold; this suggests that the average unknown breast tissue dose may be 0.5 Gy or more. Based on dose-response analyses and rate-ratio comparisons it would appear that about 102 of the 742 cases with DS86 dose estimates were caused by radiation, and that another 29 radiation-induced cancers are included among the 79 unknown-dose cases. Moreover, the distribution of excess cases is now definitely skewed toward the younger ages ATB: the estimated excess includes about 57 of the 251 known-dose and 27 of the 49 unknown-dose cases among those 0–19 ATB, about 39 of 325 and 2 of 21 in the 20–39 ATB group, and perhaps 5 of 166 known-dose and 0 of 3 unknown-dose cases in the oldest sub-cohort.

The following preliminary findings seem unlikely to change: There is now little room for doubt that a dose-related excess has occurred among the A-bomb survivors who were exposed as children (i.e., 0–9 ATB). Moreover, that excess is closely comparable in terms of relative risk
to that observed following exposure in the second decade of life, and lags behind it by about 10 years in terms of time since exposure. In general, the excess relative risk per unit dose declines with increasing age ATB, but seems fairly constant over each of the intervals 0–19 and 20–39 ATB. The level of dose response, number of cases, and the length of follow-up is now such that the data set has considerable power for detecting patterns in excess risk over time following exposure, but there is still no strong evidence for substantial variation in excess relative risk over time, for any given age ATB.

**SOME PROJECTIONS AND RECOMMENDATIONS**

A major implication of the preliminary findings described above is that, as far as radiation-related breast cancer is concerned, the LSS cohort experience is now clearly dominated by its youngest members: we estimate that 84 of 131 radiation-induced cancers occurred in women who were under 20 years of age ATB. Based on the numbers of survivors alive at the end of 1985, and on current Japanese breast cancer rates\(^{30}\) and life tables\(^{31}\), about 350, 120, and 10 new cases would be expected during the remainder of life for members of the 0–19, 20–39, and 40+ ATB sub-cohorts, respectively, in the absence of radiation exposure. If current relative risk estimates continue to hold, the corresponding radiation-related excess should be about 140 cases in the youngest group, but only 16 and 0 in the two older groups. Thus, we are unlikely to learn much more from incidence surveys of the LSS cohort about radiation-induced breast cancer risk following exposure at ages greater than 20 or so, but the potential for new information about risk following exposure in childhood and adolescence is very great indeed.

Another implication is that subsidiary studies, like the case-control interview and laboratory studies described in the previous section, should have greater potential than before to evaluate radiation-induced as well as baseline risk in terms of factors other than radiation. This is true simply because, with each new incidence study, the number of radiation-induced cancers in the series can be expected to increase markedly (the increase between 1980 and 1985 was from about 80 to about 130, for example). Although radiation-induced cancers cannot be identified with certainty, probabilistic assessments based on radiation dose and age ATB are effective when numbers are large. It is important, then, that each new incidence study be followed by an interview study of newly identified cases and matched controls, that pathology and other biological specimens be collected and preserved for future study, and that periodic evaluations be made of the extent to which clinical records and stored tissue samples, possibly informative about important determinants of risk, may already be available for newly diagnosed cases.

**REFERENCES**


