Profiles of non-cancer diseases in atomic bomb survivors

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Introduction

Half a century has elapsed since the atomic bombing of Hiroshima and Nagasaki. Prior to this exposure of a human population to atomic bomb radiation, little had been known about the effect of radiation exposure in humans. Epidemiological studies of the late effects of atomic bomb radiation exposure spanning a period of nearly half a century have yielded a wealth of information, and, in particular, have demonstrated the association between atomic bomb radiation and the increased occurrence of leukaemia and cancer. These studies have not only clearly shown an increased incidence of disease or mortality in association with exposure, but have also presented in detail the relative risk, absolute risk, attributable risk and lifetime risk estimate of various cancers (1-7).

On the other hand, examination of the relationship between atomic bomb radiation exposure and diseases other than cancer, except for a few instances, have been inconclusive in spite of long-term observations (1, 3). The exception is the report by Shimizu et al. (8) on non-cancer mortality in the Life Span Study by the Radiation Effects Research Foundation (RERF) in which a significant increase in mortality from non-cancer diseases was found in association with atomic bomb radiation exposure. Because of problems related to accuracy of death certificate data, however, this finding must be confirmed by incidence studies, prevalence studies or case control studies based on clinical data. A number of studies are now under way along these lines.

The question of whether there is a relationship between atomic bomb radiation and cardiovascular diseases (CVD), which account for about half of the causes of death in the developed countries including Japan, is undoubtedly an important one. Among neoplasms, leukaemia and cancer have been subjected to extensive studies, but information on benign tumour is insufficient at present. Chronic liver diseases also must be studied in more depth.

This paper will mainly present recent findings at the Radiation Effects Research Foundation (RERF) concerning CVD, uterine myoma, hyperparathyroidism, and chronic liver diseases.

Material and methods

A number of study cohorts (9) were developed by the Atomic Bomb Casualty Commission (ABCC), the predecessor of RERF, mainly for the purpose of determining the effects of atomic bomb radiation in humans (Fig. 1).

At time of the 1950 Japanese national census, 284 000 atomic bomb survivors were enumerated as living in all parts of Japan, and, from among these individuals, a Master Sample was developed consisting of 195 000 survivors living in Hiroshima and Nagasaki. Based upon this Master Sample, the Life Span Study (LSS) population of 93 000 exposed and 27 000 controls, a total of 120 000 subjects, was selected, and extensive mortality follow-up of this population has continued since 1950.

Fig. 1

Cohorts of atomic bomb survivors studied by the Atomic Bomb Casualty Commission (ABCC) and the Radiation Effects Research Foundation (RERF)

| Cohorts of survivors des bombardements atomiques ayant fait l'objet d'une étude la Commission chargée des victimes de la bombe atomique/Fondation pour la recherche sur les effets des rayonnements |
| A-bomb survivors (284 000) – Survivants des bombardements atomiques (284 000) |
| 1950 Census – Recensement de 1950 |
| Master sample – Echantillon total (195 000) |
| Life Span Study (LSS) (120 000) – Étude sur la longévité (120 000) |
| 1958 |
| Adult Health Study (AHS) (20 000) – Étude sur la santé des adultes (20 000) |
| 1958 |

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At the same time, the Adult Health Study (AHS) population was selected as a sub-sample of the LSS population. This sample had originally consisted of 5,000 subjects exposed within 2 km of the hypocentre who had experienced acute radiation symptoms, 5,000 subjects likewise exposed within 2 km of the hypocentre but without acute radiation symptoms, 5,000 subjects exposed beyond 3 km from the hypocentre, and 5,000 subjects who had not been in either Hiroshima or Nagasaki at time of the bombing, for a total of 20,000 subjects. Members of this population have undergone biennial physical examinations since 1958, and they are now in the 19th cycle of examinations (1, 2, 9, 10). Approximately two-thirds of this cohort are female. Cooperation of the survivors in this examination programme has been extremely high, and the participation rate has been maintained at about 80% (1). Information available through these examinations include interval history, physical findings, laboratory determinations, clinical diagnoses, etc. Ascertainment of deaths among the AHS population, as well as the larger LSS cohort, is virtually 100% complete through the unique Koseki (family registration) system of Japan. Death certificate information is obtained for deceased subjects, and, in addition, autopsy findings are also available for a portion of the subjects. These data are processed using computers. Clinical diagnoses are encoded according to the International Classification of Diseases (ICD) (Seventh, Eighth and Ninth Revisions) (10).

The method of analysis for the incidence study of non-cancer diseases in the AHS population has been described in detail in the report of Wong et al. (10) but will be reviewed briefly below. A total of 19 non-cancer diseases including coronary heart disease (CHD), stroke, uterine myoma and chronic liver disease (chronic hepatitis and cirrhosis) were selected for analysis. Subjects found to have the disease selected for study when the follow-up began were taken to be prevalence cases, and were excluded from calculation of the incidence. Subjects who were disease-free at the time the follow-up began were used as the population at risk in the follow-up period until time of onset of disease, or death, or the most recent examination. The incidence rate was calculated by the person-year method, and individual radiation exposure doses were based on the DS86 (Dosimetry System 1986) estimates (11). Disease incidence rates were compared by dose categories, and tested statistically to determine whether the incidence was significantly increased by exposure.

In addition, for certain diseases, such as hyperparathyroidism, prevalence studies based on follow-up observations for two years were conducted.

Results
Cardiovascular diseases (atherosclerosis)
Data from observations covering 32 years (1958-1990) in the AHS population were available for examination of the incidence of myocardial infarction (MI). During this period, 163 males and 125 females, a total of 288 subjects, were identified as new cases of MI. Since such risk factors as blood pressure and total serum cholesterol levels are undoubtedly associated with the occurrence of MI, incidence rates were compared by dose groups and tested after adjusting for blood pressure and cholesterol, as well as sex, age and city. As can be seen in Fig. 2, which shows the dose response for the incidence of MI, there was a significant increase in MI incidence in the heavily exposed survivors. It was, however, difficult to determine from this analysis whether the dose response conformed to the linear, quadratic or threshold model, even though there appeared to be an increase in the incidence only among those who received doses higher than 2 Gy (12). The estimated relative risk (RR) at 1 Gy was 1.17 (P = 0.02, 95% confidence interval: 1.01-1.36), which was far smaller than the RR for cancers. The excess was most significant among those who were less than 40 years old when exposed. No difference was seen in the dose response by sex, time since exposure, or city.

By using Cox regression analyses including various risk factors, such as age, sex, blood pressure and cholesterol, it was found that exposure dose still remained a significant factor, although the association was less than with age, sex, or blood pressure, which suggested that atomic bomb radiation may be involved in the occurrence of MI.

Fig. 2
Dose response for risk factor adjusted incidence of myocardial infarction (men and women, 1958-90, Adult Health Study, Hiroshima and Nagasaki)
Relation dose-réponse pour l'incidence de l'infarctus du myocarde ajusté en fonction des facteurs de risque (hommes et femmes, 1958-90, Etude sur la santé des adultes, Hiroshima et Nagasaki)

Bars indicate 65% confidence interval of relative risk - Les barres verticales représentent les intervalles de confiance à 95% du risque relatif.

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In addition to MI incidence, various endpoints of atherosclerosis, such as the incidence of cerebral infarction (13, 14), the prevalence of aortic arch calcification (15), the prevalence of isolated systolic hypertension (16) and pulse wave velocity (17) have also been analysed to maintain consistency in the study results, and all endpoints showed a positive dose response, which supports the possibility of a real association between radiation exposure and atherosclerosis (Table 1).

Among the various CVD risk factors available for analysis, serum cholesterol and psychological factors were examined for possible association with radiation. It was found that cholesterol levels tended to be higher among the heavily exposed survivors (18) and that long-term anxiety persisted in the more proximally exposed survivors (19). The possibility that these risk factors may be involved in the increased occurrence of CVD among atomic bomb survivors cannot be dismissed (Table 1).

Benign tumours
(a) Uterus. Fig. 3 shows the results of incidence studies for uterine myoma, a benign tumour of the uterus, based upon observations covering the 28-year period from 1958 to 1986. A remarkable dose response is seen between the incidence of uterine myoma and atomic bomb radiation exposure. The estimated RR at 1 Gy was 1.46 (P<0.001, 95% confidence interval: 1.27-1.70), the excess in disease cases per 10^4 person-year Gy was 24.4, and the attributable risk of radiation in survivors with doses of 0.001 Gy or more was 20% (10).

(b) Parathyroid gland. An association between atomic bomb radiation exposure and hyperparathyroidism was first reported by Fujinara et al. (20). According to that report, in the two-year period 1986-1988, serum calcium levels in excess of 10.5 mg/dl were noted in 42 among 3948 AHS participants in Hiroshima with DS86 estimates. In further detailed

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**Table 1**

Atomic bomb radiation and atherosclerosis: summary of ABCC/RERF studies

<table>
<thead>
<tr>
<th>Endpoints - Critères</th>
<th>Study design - Type de l'étude</th>
<th>Direction</th>
<th>Association</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-cancer mortality -</td>
<td>M</td>
<td>↑</td>
<td>Weak - Faible</td>
</tr>
<tr>
<td>Mortalité autre que par cancer</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Myocardial infarction -</td>
<td>I</td>
<td>↑</td>
<td>Weak - Faible</td>
</tr>
<tr>
<td>Infarctus du myocarde</td>
<td></td>
<td></td>
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<tr>
<td>Cerebral infarction -</td>
<td>I</td>
<td>↑</td>
<td>Weak - Faible</td>
</tr>
<tr>
<td>Infarctus cérébral</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Calcification of aortic arch -</td>
<td>P</td>
<td>↑</td>
<td>Weak - Faible</td>
</tr>
<tr>
<td>Calcification de la crosse aortique</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Isolated systolic hypertension -</td>
<td>P</td>
<td>↑</td>
<td>Weak - Faible</td>
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<tr>
<td>Hypertension systolique isolée</td>
<td></td>
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<tr>
<td>Pulse wave velocity - Augmentation de la fréquence du pouls</td>
<td>P</td>
<td>↑</td>
<td>Weak - Faible</td>
</tr>
<tr>
<td>Serum cholesterol - Cholestérol sérique</td>
<td>G</td>
<td>↑</td>
<td>Weak - Faible</td>
</tr>
<tr>
<td>Anxiety - Anxiété</td>
<td>P</td>
<td>↑</td>
<td>Weak - Faible</td>
</tr>
</tbody>
</table>

M: Mortality - Mortalité; I: Incidence - Présence; P: Prevalence - Présence; G: Growth curve analysis - Analyse de la courbe de croissance.

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*A prevalence study of uterine myoma is now underway for AHS participants in Hiroshima using ultrasonography as a screening test. Preliminary analysis indicates results similar to the findings of the incidence study.*
studies of these 42 individuals by parathyroid hormone determinations, thallium technetium subtraction scanning, etc., 19 (3 males and 16 females) were found to have primary hyperparathyroidism. The prevalence rate of hyperparathyroidism was demonstrated to increase with radiation dose (p<0.001) after adjusting for sex and age at the bombing. The estimated RR at 1 Gy was 4.1 (95% confidence interval: 1.7-14). There was also evidence that the effect of radiation was greater for individuals who were younger at the time of the bombing. For example, the RR at 1 Gy for those exposed at age 5 was 11 (95% confidence interval: 1.8-23.5). Furthermore, 9 individuals received surgical treatment, 7 were found to have adenoma, and 2 were found to have hyperplasia as the etiology. Among the benign tumors for which the association with atomic bomb radiation exposure has been clearly shown, it was parathyroid adenoma that showed the most remarkable association with radiation.

Molecular studies are under way at RERF to elucidate the pathogenic mechanism for this condition.

(c) Thyroid gland. Nagataki et al. (21) conducted a prevalence study of benign tumors of the thyroid gland among AHS participants in Nagasaki, and found a significant dose response in the prevalence of solid nodules of the thyroid. The solid nodules had not been examined histologically, but many of them probably were adenoma, and a relationship between adenoma and radiation exposure was suggested.

Chronic liver diseases
The results of incidence studies based on observations for a 28-year period, 1958-1986, are shown in Fig. 4. A significant dose response was found between chronic liver diseases and atomic bomb radiation exposure.

Fig. 4
Dose response for incidence of chronic liver disease (men and women, 1958-86, AHS, Hiroshima and Nagasaki)


The estimated RR at 1 Gy was 1.14 (p = 0.006, 95% confidence interval: 1.04-1.27), the excess disease cases per 10^4 person-year Gy was 7.5, and the attributable risk among those exposed to 0.001 Gy or more was 8% (10).

To examine the possibility that hepatitis C virus infection may be related to the increased occurrence of chronic liver diseases among atomic bomb survivors, hepatitis C virus antibody titre determinations are now in progress for AHS participants.

Other non-cancer diseases
Fig. 5 presents a summary of the results of incidence studies that examined the association between non-cancer diseases and radiation exposure. No particular association with radiation has been found for any disease other than those mentioned above (10, 12).

Discussion
Cardiovascular diseases (atherosclerosis)
Concerning the association between radiation and CVD, historically, the cardiovascular system had been regarded to be relatively insensitive to ionizing radiation until the mid-1960's (22, 23). Subsequently, however, numerous reports appeared on the development of such conditions as pericarditis, myocarditis, and conduction abnormalities following mediastinal radiation for malignant tumors, and there now is broad recognition of the effect of ionizing radiation upon the heart (24). Nevertheless, the association between ionizing radiation and the various endpoints of atherosclerosis, such as coronary heart disease (CHD) and stroke, as well as the issue of the pathogenesis, remains to be established (24, 25). It has been found in animal experiments, however, that ionizing radiation can induce vascular lesions (26-29) and, furthermore, many case reports describe the occurrence of CHD following radiotherapy for Hodgkin's disease and breast cancer (30-36). In addition, a few reports on follow-up studies of patients who received radiotherapy have recently appeared (36-45). There also are case reports describing the occurrence of cerebral infarction following radiotherapy to the neck region (46-54), and of peripheral vascular disease of the lower extremities following radiotherapy to the pelvic region (55, 56). A detailed discussion of these studies was presented in a review paper by Kodama (57).

In summary, the results published in the literature indicate that the occurrence of atherosclerotic diseases secondary to radiotherapy is highly likely. A heavy exposure of 20-60 Gy is delivered in radiotherapy, however, and the results cannot necessarily be extrapolated to other populations exposed to lower levels of radiation, such as the atomic bomb survivors.
Fig. 5
Relative risk for incidence of non-cancer diseases
Risque relatif pour l'incidence des maladies non cancéreuses

<table>
<thead>
<tr>
<th>Disease</th>
<th>Relative risk at 1 Gy</th>
<th>Estimated relative risk at 1 Gy</th>
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</thead>
<tbody>
<tr>
<td>Myocardial infarction - Infarctus du myocarde</td>
<td></td>
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<tr>
<td>Hypertension - Hypertension</td>
<td></td>
<td></td>
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<tr>
<td>Hypertensive heart disease - Cardiopathies hypertensives</td>
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<td></td>
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<tr>
<td>Aortic aneurysm - Anevrisme aortique</td>
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<tr>
<td>Cataract - Cataracte</td>
<td></td>
<td></td>
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<tr>
<td>Gastric ulcer - Ulcère gastrique</td>
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<td></td>
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<tr>
<td>Duodenal ulcer - Ulcère duodénal</td>
<td></td>
<td></td>
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<tr>
<td>Chronic liver disease - Hépatopathies chroniques</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cholelithiasis - Lithiase biliaire</td>
<td></td>
<td></td>
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<tr>
<td>Calculus of kidney and ureter - Lithaise des reins et de l'urètre</td>
<td></td>
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<tr>
<td>Uterine myoma - Myome utérin</td>
<td></td>
<td></td>
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<tr>
<td>Cervical polyp - Polypes conivixes</td>
<td></td>
<td></td>
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<tr>
<td>Hyperplasia of prostate - Hyperplasie prostateux</td>
<td></td>
<td></td>
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<tr>
<td>Dementia - Démence</td>
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</tbody>
</table>

A number of epidemiological studies of populations exposed to relatively low levels of radiation have been reported in the literature. For example, Matanoski et al. (58) followed a total of 30,084 radiologists in the United States over a period of up to 50 years to determine whether the causes of death among this group showed any difference from those for internists or ophthalmologists. They found that deaths due to CVD were significantly higher among the group of radiologists who had started medical practice in the period 1920-1929, in comparison to their colleagues in other fields of medicine, and it was suggested there was a relationship between radiation and CVD deaths. However, the report by Court et al. (59), in which 25,732 British radiologists were followed up for as long as 60 years, demonstrated no increase in CVD deaths among radiologists. Furthermore, Darby et al. (60) found no increase in CVD deaths in a follow-up study, spanning a period of 29-48 years, involving 14,554 ankylosing spondylitis patients treated with X-rays. Thus, the results concerning the association between relatively low levels of radiation exposure and CVD are inconsistent.

The question of whether there is any late effect of atomic bomb radiation exposure upon CVD had received attention from the early period since this condition, in addition to cancer, is an important disease in Japan due to its high mortality and morbidity. However, the focus of studies of the late effects of atomic bomb radiation exposure had been directed at leukaemia and cancer, because effects were demonstrated in these conditions from the early period, and studies with regard to CVD were relatively limited (57).

The issue of whether there are late effects of exposure to atomic bomb radiation upon CVD mortality in the ABCC-RERF LSS cohort has been addressed periodically in the Technical Report Series of the Foundation. No suggestive evidence of any association between atomic bomb radiation exposure and mortality from stroke or other CVD was seen up to LSS Report 5 (61), which summarized the results of the study for the period 1950-1966. However, LSS Report 6 (62), which analysed the data for the period 1950-1970, noted for the first time an effect of radiation upon mortality from CVD among females. CVD mortality in females during this study period was found to be increased in all dose groups exposed to 0.1 Gy or more based on the T65D (Tentative 1965 Dosimetry system). This increase was particularly remarkable in the group exposed to 0.5 Gy or more. Although this trend was not confirmed in the subsequent LSS Report 9, Part 2, by Kato et al. (63), which analysed the data for the period 1950-1978, increased mortality from diseases other than cancer was demonstrated in the group exposed to 2 Gy or more.

Shimizu et al. (64) recently assembled a report on non-cancer mortality in the LSS cohort for the period 1950-1985 based on the DS86 dose estimates, and showed clearly increased mortality from circulatory diseases in heavily exposed survivors. Specifically, increased non-cancer mortality was demonstrable after 1958 at high doses of 2 or 3 Gy and over, among those under age 40 at time of the bombing. Particularly, among the non-cancer diseases, CVD and digestive diseases showed excess mortality in the high dose groups. For CVD, both
stroke and heart diseases showed increased mortality at high doses. However, the excess RR for non-cancer mortality was much smaller than that for cancer.

As described above, it is almost certain that non-cancer mortality is increased among atomic bomb survivors, and highly probable that there is an increase of CVD, which accounts for a considerable portion of non-cancer diseases. However, it is well known that mortality data, particularly information related to non-cancer diseases, suffer from problems of accuracy. Carter et al. (64), Ron et al. (65) and others have examined the issue of accuracy of death certificate diagnoses using the ABCC-RERF autopsy series. The sensitivity and positive predictive value of death-certificate diagnoses were found to be 67% and 40%, respectively, for stroke and 34% and 52%, respectively, for heart diseases, which indicated that the death certificate did not accurately reflect the cause of death. The situation differs, however, depending upon which disease is examined, and the sensitivity and positive predictive values for all cancers were 76% and 91%, respectively, indicating that the death certificate is relatively accurate in all cancers.

Death-certificate information for CVD, unfortunately, must be considered to be less accurate, and incidence studies and prevalence studies based upon clinical observations are needed to confirm the results of mortality studies.

Only a few studies have been undertaken in the AHS in the past, however, concerning the association between CVD incidence and atomic bomb radiation exposure, and, moreover, they were limited to CHD and stroke (13, 14, 66, 67).

Among the studies of CVD in the AHS that have been continued since the early period, Johnson et al. (65, 67) found no association between atomic bomb radiation exposure and the incidence of CHD or stroke in the period 1958-1964. Robertson et al. (13), in their study covering the 16-year period 1958-1974, observed for the first time a suggestive increase (0.05<p<0.10) of stroke and CHD in heavily exposed females in Hiroshima, and this trend was particularly remarkable in females who were under 50 years of age at time of the bomb.

Kodama et al. (14) subsequently extended the period of observation to cover the 20-year period 1958-1978, and demonstrated a significant increase of stroke incidence with radiation exposure dose in females in Hiroshima. There also was a significant excess incidence of CHD in Hiroshima females. Examination of the increased incidence of CVD in females of Hiroshima by time of observation showed that the increase was significant after 1969, and, moreover, this was remarkable in those who had been under age 40 at time of the bomb. Since these diseases occur in association with arteriosclerosis, the long latency until their occurrence is understandable, as is the demonstration of radiation effects in the more radiation-sensitive younger age group, but it is difficult to explain why the effect occurred mainly in females. It was felt that this finding must be confirmed by extending the period of observation and improving the method of data collection.

On the issue of MI incidence, a recent analysis of the data for the 32 years from 1958 to 1990 confirmed the significant increase in MI incidence among the heavily exposed survivors seen in previous studies, and the estimated RR at 1 Gy was 1.17 (P=0.02, 95% confidence interval: 1.01-1.36), with the excess being most significant among those who were less than 40 years old when exposed (12). No difference, however, was seen in the radiation effect by sex, time since exposure, or city, and the previously observed increase limited to Hiroshima females was no longer present. But the excess of MI in atomic bomb survivors was very small in comparison with cancer, and may have been the result of some bias. Therefore, to maintain consistency in the study results, analyses were conducted of various endpoints of atherosclerosis, such as the incidence of cerebral infarction (13, 14), the prevalence of aortic arch calcification (15, 68), the prevalence of isolated systolic hypertension (16), and pulse wave velocity (17), and all endpoints were found to show a positive association with radiation dose. This seems to indicate that there almost certainly is an increase of CVD among atomic bomb survivors.

However, since all risk factors associated with lifestyle had not necessarily been adjusted for, it was difficult to conclude that the increase of MI among survivors was an effect of radiation. Further studies are needed to confirm whether direct effects of radiation are present.

Benign tumours
(a) Uterine myoma. An increase in uterine myoma among atomic bomb survivors was first suggested by Sawada et al. (68) in AHS Report 6. This was confirmed in the incidence study based upon observations covering a period of 28 years by Wong et al. (10). No report, however, has been found in the open literature describing any association of uterine myoma and radiation. Although a weak effect of radiation has been noted in cervical cancer mortality among atomic bomb survivors, no radiation effect is apparent for uterine cancer (4, 5). Since uterine myoma is not a fatal disease, a greater frequency of examinations would naturally improve the possibility of detection. The likelihood of medical attention being sought more frequently by heavily exposed survivors cannot be ruled out, so that a greater frequency of examinations, rather than an actual effect of radiation, may conceivably have caused uterine myoma to artificially appear to be increased. In fact, 40% of the diagnoses of myoma had been made as a result of gynaecological
examinations at ABCG-REF, and another 40% had been detected at outside medical institutions (19).

To exclude the possibility that bias was responsible for the increase of uterine myoma seen among atomic bomb survivors, ultrasonographic studies of all female AHS participants are under way in Hiroshima to determine the prevalence of uterine nodules. The results of preliminary analysis continue to indicate a strong radiation effect even after elimination of as much bias as possible. Uterine myoma appears to be almost certainly increased among atomic bomb survivors, but it presently cannot be concluded as being a radiation effect because of the lack of any such report from studies of other exposed populations. Further detailed analyses including the role of confounders as well as molecular approaches are needed.

(b) Parathyroid adenoma. Several studies have been reported in the literature concerning the occurrence of hyperparathyroidism after radiotherapy. In prospective studies, Tisell et al. (69) reported the prevalence of hyperparathyroidism among 444 persons after radiotherapy to be 17.5% in males and 34.5% in females at an absorbed parathyroid dose of 14 Gy or more. More recently, Cohen et al. (70) reported that the incidence of hyperparathyroidism among 4287 patients who received radiotherapy during childhood for benign conditions in the head and neck was 2.9 times higher for people under the age of 40 years and 2.5 times higher for people in the 40 to 60 year age group compared to that among the general population.

The association of atomic bomb radiation and hyperparathyroidism was first reported by Fujiwara et al. (20). Exposures to atomic bomb radiation in that study population ranged from 0 to 5.6 Gy and the mean dose was 0.4 Gy. Even though these exposure levels were lower, the results of this study are consistent with those reported by Tisell et al. and Cohen et al. The estimated RR at 1 Gy was found to be quite high, at 4.1 (95% confidence interval: 1.7-14), and there was also evidence that the effect of radiation was greater for individuals who were younger at the time of the bombing. This was a biologically plausible finding. Most of the cases of hyperparathyroidism had adenoma. Among the benign tumours found to be associated with atomic bomb radiation, parathyroid adenoma has been demonstrated to show the strongest relationship with exposure.

Molecular studies are now in progress at RERF to determine the pathogenic mechanism for this condition.

(c) Other benign tumours. Other studies of the AHS population include the report of Nagataki et al. (21) in which thyroid adenoma was found to be increased among atomic bomb survivors. Ron et al. (71) conducted a study of benign gastro-intestinal tumours in the LSS cohort and reported an association of benign stomach tumours with radiation dose, but no dose response was found for benign tumours of the colon or rectum. Tokunaga et al. (72) reported that ovarian benign tumours were increased in association with dose in the ABCG-REF autopsy series, and Yoshimato et al. (73) found a similar increase of thyroid adenoma in the autopsy series.

Although fewer studies have been conducted than for cancer, an obvious association with radiation for various adenomas is emerging.

Chronic liver diseases

Whether the liver is a radiation-sensitive organ has been under debate (74, 75). Increased mortality from liver cirrhosis in association with radiation has been reported in the German throraxt study (76). In studies at RERF, the report on non-cancer mortality in the LSS by Shimizu et al. (8) described an increase in mortality from digestive diseases, in which liver cirrhosis seems to play an important role. The accuracy of death-certificate diagnosis for liver cirrhosis, however, is rather poor, and the sensitivity and positive predictive value of death-certificate diagnosis was 47% and 48%, respectively (64, 65). Therefore, the results of the mortality study of liver cirrhosis likewise need to be confirmed through incidence studies and prevalence studies based upon clinical data.

The results of the incidence study based on 28 years of observation from 1958 to 1986 for the AHS population showed a significant dose response for chronic liver disease incidence in association with atomic bomb radiation. Further, the estimated RR at 1 Gy was 1.44, the excess disease cases per 10^4 person-year Gy was 7.9, and the attributable risk of radiation among those exposed to 0.001 Gy or more was 8%.

Previous studies on liver diseases in the AHS population had shown radiation effects for liver cirrhosis (77, 78). In the recent incidence study, chronic hepatitis and cirrhosis had been combined in the analysis, but since the proportion of chronic hepatitis is probably greater, there likely is not only an excess occurrence of cirrhosis but also of chronic hepatitis among atomic bomb survivors.

The possibility that the increased occurrence of chronic liver diseases among the survivors may be due to hepatitis virus infection cannot be ruled out. Previous hepatitis B virus studies of members of the AHS population had shown no clear association with radiation (79). To examine the possible involvement of hepatitis C virus infection, hepatitis C virus antibody titre determinations are now in progress for AHS participants.
Summary

This article summarizes the results of a recent study of atomic bomb radiation and non-cancerous diseases in the AHS (Adult Health Study) population by the REFF (Radiation Effects Research Foundation) along with a general discussion of previous studies.

The association of atomic bomb radiation and CVD was examined by incidence studies and prevalence studies of various endpoints of atherosclerosis, such as MI, stroke, aortic arch calcification, isolated systolic hypertension, and pulse wave velocity, and, although the excess was small, all endpoints indicated an increase of CVD in the heavily exposed group. Because of the consistency of the results, it is almost certain that CVD is higher among atomic bomb survivors. However, all CVD risk factors associated with lifestyle had not necessarily been adjusted for in studies to date, and it is difficult at present to conclude that the increase in CVD among survivors was a direct effect of radiation.

Recent studies have demonstrated almost certainly that uterine myoma is more frequent among atomic bomb survivors. It cannot, at present, be concluded that uterine myoma is caused by radiation, because there are no reported studies of other exposed populations. Further analyses including the role of confounding factors as well as molecular approaches are needed to verify this radiation effect.

The relationship between atomic bomb radiation exposure and hyperparathyroidism can now be said to have been established in view of the strong dose response, the agreement with results of studies of other populations, the high risk in the younger survivors, and the biological plausibility. Future studies by molecular approaches, etc., are needed to determine the pathogenic mechanism.

Among other benign tumours, a dose response has been demonstrated for tumours of the thyroid, stomach and ovary. Although fewer studies have been conducted than for cancer, a clear association between radiation and various benign tumours is emerging.

Concerning the association between atomic bomb radiation exposure and chronic liver diseases, the recent incidence study of members of the AHS population demonstrated a significant dose response. Both chronic hepatitis and cirrhosis were suggested as being associated with exposure. The possibility that the increased occurrence of chronic liver diseases among the survivors may be due to hepatitis virus infection cannot be excluded, and the results of the ongoing hepatitis C virus antibody titre studies are awaited.

Résumé

profil des maladies non cancéreuses chez les survivants de bombardements atomiques

Le présent article résume les résultats de l'étude récente faite sur l'irradiation due aux bombardements atomiques et les maladies non-cancéreuses dans l'étude de la santé des adultes (AHS) à la Fondation pour la recherche sur les effets des rayonnements et fait en même temps un bilan général des études précédentes.

L'association de l'irradiation due aux bombardements atomiques et des maladies cardio-vasculaires a été examinée par des études portant sur l'incidence et la prévalence de différents critères de l'athérosclérose, comme les infarctus du myocarde, les accidents vasculaires cérébraux, la calcification de la crosse aortique, l'hypertension systolique isolée et l'augmentation de la fréquence du pouls et, bien que l'excès fût faible, tous les indicateurs montraient un accroissement des maladies cardio-vasculaires dans le groupe qui avait été lourdement exposé. Du fait de la cohérence des résultats obtenus, il est pratiquement certain que les maladies cardio-vasculaires ont augmenté chez les survivants des bombardements atomiques. Toutefois, tous les facteurs de risque des maladies cardio-vasculaires liés au mode de vie n'ont pas forcément fait l'objet d'un ajustement dans les études effectuées à ce jour, et il est difficile à l'heure actuelle de conclure que l'augmentation des maladies cardio-vasculaires chez les survivants est une conséquence directe de l'irradiation.

Des études récentes ont montré presque certainement que le myome utérin a augmenté chez les survivants des bombardements atomiques. On ne peut toutefois pas en conclure à l'heure actuelle que le myome utérin est une conséquence de l'irradiation, à cause de l'absence de ce type de mention dans les études portant sur d'autres populations exposées. De nouvelles analyses y compris le rôle des facteurs de confusion, ainsi que des approches moléculaires, sont nécessaires pour vérifier cette conséquence de l'irradiation.

On peut désormais dire que la relation entre l'exposition aux rayonnements due aux bombardements atomiques et l'hyperparathyroïdie est établie compte tenu de la forte relation dose-réponse, de la concordance avec les résultats des études faites sur d'autres populations, du risque élevé couru par les plus jeunes survivants et de la plausibilité biologique. Il faut entreprendre de nouvelles études basées sur l'approche moléculaire pour déterminer le mécanisme pathogène.

Parmi d'autres tumeurs bénignes, une relation dose-réponse a été prouvée pour la thyroïde, l'estomac et l'ovaire. Bien que l'on ait entrepris moins d'études que dans le cas du cancer, l'association entre rayonnements et diverses tumeurs bénignes se dégage nettement.

En ce qui concerne l'association entre l'exposition aux rayonnements due aux bombardements atomiques et les hépatopathies chroniques, l'étude récente de l'incidence concernant des membres de la population de l'étude sur la santé des adultes a montré une relation dose-réponse importante. Il a été suggéré que l'hépatite chronique comme la cirrhose étaient associées à l'exposition. La possibilité que l'augmentation de l'apparition des hépatopathies chez les survivants soit due à une infection par le virus de l'hépatite ne peut être exclue, et on attend les résultats des études en cours pour déterminer le titre en anticorps dirigés contre le virus de l'hépatite C.
References/Referências
