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An Autopsy Study of Histopathological Changes in the Urinary Bladder Transitional Epithelium of Atomic Bomb Survivors, 1960—1983

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ABSTRACT

From the ABCC-RERF Life Span Study extended sample, there were 4,499 cases in the Pathology Study sample of atomic bomb survivors who had come to autopsy in the period 1960—83. Among 370 subjects who were heavily exposed with an estimated dose (T65D) of 100 rad or more, 72 (about 20%) of them, whose urinary bladder epithelia had been preserved satisfactorily to suit the purpose of this study, were sampled as the index group. An equal number of control subjects were selected from the unexposed group individually, matched with the index cases by city, sex, age at death, and year of death. However, cases with marked epithelial autolysis and those pathologically diagnosed as urinary bladder cancer were previously excluded from both the index group and control subjects. These 72 pairs of autopsy cases were pathologically studied for the presence or absence of epithelial lesions of the urinary bladder, namely, hyperplasia, dysplasia and carcinoma-in-situ, and the frequencies of appearance of these lesions were compared statistically by χ^2 test based on a case-control study design.

Carcinoma-in-situ and severe dysplasia were detected in neither the index cases nor the control cases. The risk was relatively higher in the index group than in the control subjects for both hyperplasia and dysplasia (mild and moderate), in particular the relative risk of papillary hyperplasia being about 4.0, but as the total number of cases were small, this was not statistically significant.

Key words: *Urinary bladder, Dysplasia, Hyperplasia, Atomic bomb survivors*

Radiation has been demonstrated to cause cancer in various organs in man. A significant relationship between urinary bladder cancer and radiation has been observed in the Life Span Study of Atomic Bomb Survivors in Hiroshima and Nagasaki[5] and in the Incidence Study[7]. Such a relationship has also been observed in follow-up studies of persons exposed to medical radiation[1, 8].

In the present study urinary bladders of A-bomb survivors who came to autopsy at RERF, Hiroshima and Nagasaki, were examined using sections, with a view to investigating the relationship between radiation exposure and lesions such as hyperplasia, dysplasia and carcinoma-in-situ of the transitional epithelium of the urinary bladder.

MATERIALS AND METHODS

Three hundred and seventy autopsy cases (along with 108 partial autopsy cases) exposed to high T65 total doses of 100 rad or more were selected from among the 4,499 cases that came to autopsy as a result of an energetic autopsy procurement program carried out on the some 24,000 cases of death occurring in the period from 1960 to 1983 in the Life Span Study extended sample. And their preserved urinary bladder materials were reviewed. Seventy-two cases whose urinary bladder specimens were satisfactorily preserved were found suitable for this study. Using these 72 heavily exposed autopsy cases as the index group, control subjects were selected at the ratio of 1 to 1 from among the autopsy cases of the same fixed population who had no radiation exposure. The control subjects were selected at random, matched whith the index cases by city, sex, age at death (±5 years) and year of death, ('60—'64, '65—'69, '70—'74, '75—'83) as

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well as by the condition that the transitional epithelium of the urinary bladder had not undergone autolysis. Cases pathologically diagnosed as urinary bladder cancer were excluded from the index group and the control group.

For reexamination of the pathological findings of the urinary bladder, hematoxylin-eosin stained specimens were prepared. As pathological lesions of the urinary bladder epithelium, hyperplasia (focal, multifocal, papillary), dysplasia (mild, moderate, severe) and carcinoma-in-situ were recorded as to their presence or absence. Blind procedure was employed in reexamining the pathological findings to preclude distinction between index cases and control cases.

The frequencies of appearance of hyperplasia, dysplasia and carcinoma-in-situ of the transitional epithelium of the urinary bladder were compared, between the heavily exposed (index) group and the control group, by χ^2 (chi-square) test based on a case-control study design.

RESULTS

1. *Distribution of study subjects*

Table 1 shows the distribution of the 72 pairs of study subjects (144 in total) by city and sex. The mean estimated dose (T65D) of the heavily exposed survivors of the index group was 254.8 rad.

2. *Distribution of urinary bladder lesions*

The distributions of the urinary bladder lesions of the two groups are shown in Table 2. No separation of Hiroshima and Nagasaki has been made here. The total number of lesions exceed 72 in each group because there were a few cases with more than one lesion.

Typical lesions are illustrated in Fig. 1—5, namely focal hyperplasia (Fig. 1), multifocal hyperplasia (Fig. 2), papillary hyperplasia (Fig. 3), mild dysplasia (Fig. 4) and moderate dysplasia (Fig. 5).

3. *Dose effect*

The frequencies of hyperplasia, dysplasia and carcinoma-in-situ in the heavily exposed (index)

Table 1. Study Subjects

	Number of pairs
Hiroshima	40
Nagasaki	32
Male	37
Female	35
Total	72

Table 2. Urinary Bladder Lesions

	High dose (Index) Group	Control Group
Normal (No lesion)	50	58
Focal hyperplasia	8	5
Multifocal hyperplasia	1	2
Papillary hyperplasia	4	1
Mild dysplasia	12	10
Moderate dysplasia	2	1
Severe dysplasia	0	0
In-situ carcinoma	0	0

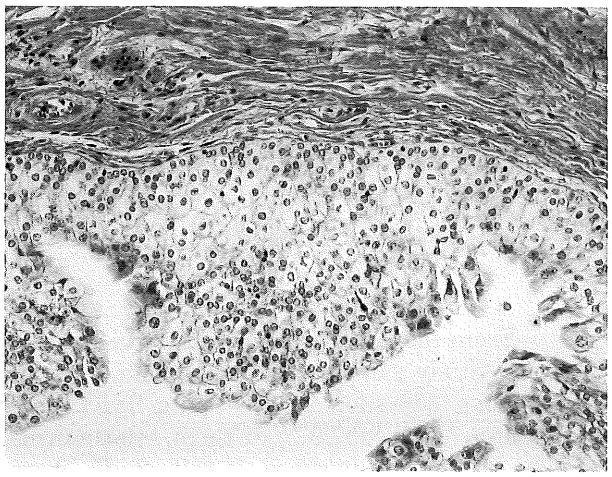

Fig. 1. Focal hyperplasia (H&E stain, × 50)

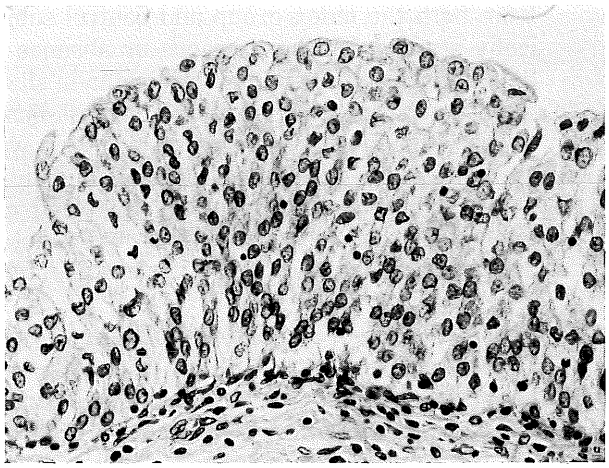

Fig. 2. Multifocal hyperplasia (H&E stain, × 100)

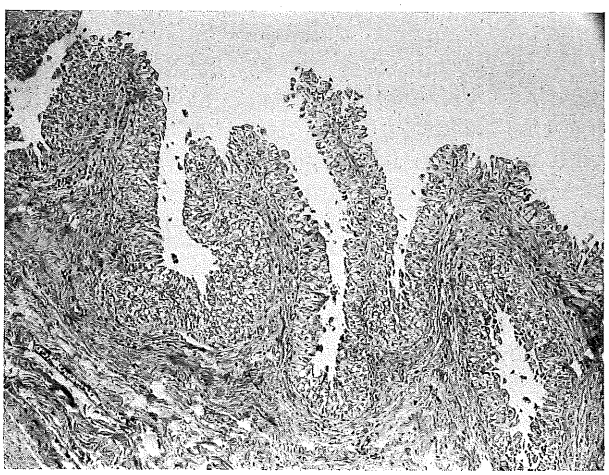

Fig. 3. Papillary hyperplasia (H&E stain, × 25)

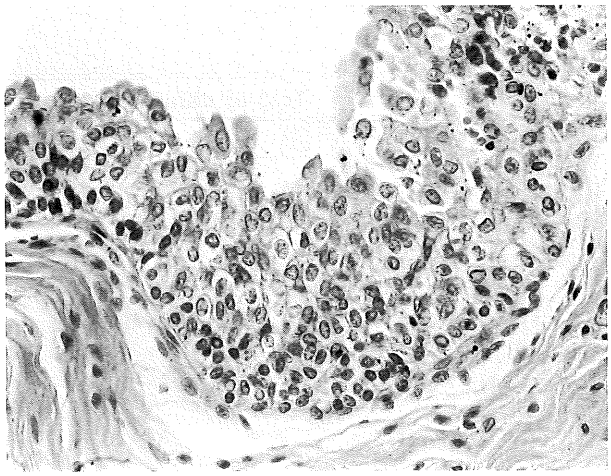

Fig. 4. Mild dysplasia (H&E stain, × 100)

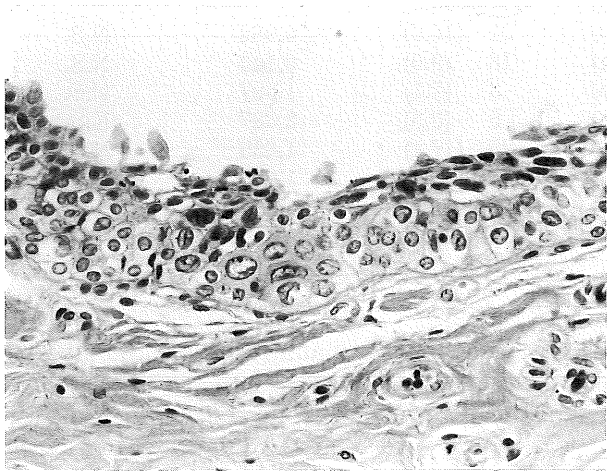

Fig. 5. Moderate dysplasia (H&E stain, × 100)

group and the control group are compared in Table 3-A, B and C. No cases of carcinoma-in-situ were detected in either group. The index group show for hyperplasia a relative risk of about 2.7 and, for dysplasia, a relative risk of about 1.4, as compared with the control group, but no statistically significant differences were observed in view of the small number of cases.

Table 3-D shows a comparison of the above findings by histological type. The distribution of hyperplasia was compared with the lesions divided into three types, i.e., focal hyperplasia, multifocal hyperplasia and papillary hyperplasia. The relative risk of papillary hyperplasia was 4.0, comparing the index group to the control group, but not statistically significant. The relative risk of focal hyperplasia was about 1.8, again not statistically significant. The distribution of dysplasia was compared with the lesions divided into mild dysplasia, moderate dysplasia and severe dysplasia. Severe dysplasia was found in neither group. The relative risk of mild dysplasia was about 1.3 and that of moderate dysplasia, 2.0, but no statistically significant differences were observed.

Table 3. Three Major Pathological Findings Between Index and Control

A. Hyperplasia (Focal, multifocal or papillary)

Control	Index		
	Yes	No	
Yes	5	3	Relative risk: 2.67
No	8	56	$\chi^2[1] = 1.455$
			P: >0.10 N.S.

B. Dysplasia (Mild, moderate or severe)

Control	Index		
	Yes	No	
Yes	4	7	Relative risk: 1.43
No	10	51	$\chi^2[1] = 0.235$
			P: >0.10 N.S.

C. Carcinoma in situ

Control	Index		
	Yes	No	
Yes	0	0	Relative risk:
No	0	72	$\chi^2[1] =$
			P

D. Pathological Findings by Type of Hyperplasia and Dysplasia

Focal hyperplasia

Control	Index		
	Yes	No	
Yes	1	4	Relative risk: 1.75
No	7	60	$\chi^2[1] = 0.364$
			P: >0.10 N.S.

Multifocal hyperplasia

Control	Index		
	Yes	No	
Yes	1	1	Relative risk: 0
No	0	70	$\chi^2[1] = 0$
			P: >0.10 N.S.

Papillary hyperplasia

Control	Index		
	Yes	No	
Yes	0	1	Relative risk: 4.00
No	4	67	$\chi^2[1] = 0.800$
			P: >0.10 N.S.

Mild dysplasia

Control	Index		
	Yes	No	
Yes	4	6	Relative risk: 1.33
No	8	54	$\chi^2[1] = 0.071$
			P: >0.10 N.S.

Moderate dysplasia

Control	Index		
	Yes	No	
Yes	0	1	Relative risk: 2.00
No	2	69	$\chi^2[1] = 0$
			P: >0.10 N.S.

Note: [ ] = df.

Table 4. Frequency of Pathological Findings by Sex and Age at Death

1. Sex

	Sex			Test of difference	
	Male	Female	Total	χ^2 [1]	P
No. of subjects	74 (100.0)	70 (100.0)	144 (100.0)		
Hyperplasia	7 (9.5)	14 (20.0)	21 (14.6)	3.209	Sugg.
Focal	2 (2.7)	11 (15.7)	13 (9.0)	7.415	<.01
Multifocal	2 (2.7)	1 (1.4)	3 (2.1)	0.286	N.S.
Papillary	3 (4.1)	2 (2.9)	5 (3.5)	0.154	N.S.
Dysplasia	15 (20.3)	10 (14.3)	25 (17.4)	0.898	N.S.
Mild	14 (18.9)	8 (11.4)	22 (15.3)	1.559	N.S.
Moderate	1 (1.4)	2 (2.9)	3 (2.1)	0.400	N.S.

2. Age at death

	Age at death				Test of difference	
	−59	60—69	70+	Total	χ^2 [2]	P
No. of subjects	51 (100.0)	40 (100.0)	53 (100.0)	144 (100.0)		
Hyperplasia	8 (15.7)	4 (10.0)	9 (17.0)	21 (14.6)	0.969	N.S.
Focal	4 (7.8)	4 (10.0)	5 (9.4)	13 (9.0)	0.144	N.S.
Multifocal	1 (2.0)	0 (0.0)	2 (3.8)	3 (2.1)	1.597	N.S.
Papillary	3 (5.9)	0 (0.0)	2 (3.8)	5 (3.5)	2.337	N.S.
Dysplasia	7 (13.7)	6 (15.0)	12 (22.6)	25 (17.4)	1.655	N.S.
Mild	6 (11.8)	5 (12.5)	11 (20.8)	22 (15.3)	1.953	N.S.
Moderate	1 (2.0)	1 (2.5)	1 (2.5)	3 (2.1)	0.048	N.S.

Note: ( ) shows percentage, [ ] = df.

4. *Frequencies of histological lesions by sex and age at death*

Table 4 shows the frequencies of the histological lesions by sex and age at death. Comparison of the frequencies of hyperplasia and dysplasia by sex suggested a difference by sex, the incidence of focal hyperplasia being about five times higher in females than in males, which was statistically significant. A comparison of the distributions of hyperplasia and dysplasia by age at death showed no difference in the incidence of hyperplasia or dysplasia in terms of this variable.

DISCUSSION

The present study using autopsy materials was planned in order to review the hypothesis that the pathologically observed precancer lesions hyperplasia, dysplasia and carcinoma-in-situ of the urinary bladder epithelium may occur at higher frequencies in the heavily exposed subjects than in the controls, in view of the fact that the risk of urinary bladder tumor has been reported to be significantly high in atomic bomb survivors. Using RERF autopsy materials, a review of existing data was made based on a case-control study design, selecting 72 pairs of heavily exposed and control subjects matched by city, sex, age at death and year of death.

Originally, it was planned to make a comparative study of the heavily exposed (index) group and the control group by preparing step-cut specimens of urinary bladder tissues and recording the distribution of lesions in detail based on the urinary bladder mapping technique of Koss et al[2, 3]. However, it was found that statistically assessable, well-preserved autopsy materials were limited for organs of autopsied cases stored long from 1960 to 1983, so that it was decided to review whether or not precancer lesions of urinary bladder tumor were frequent in the urinary bladder epithelium of the index group using available existing pathological specimens of the urinary bladder.

As shown in Table 3, no statistically significant differences were observed in the relative risks of hyperplasia and dysplasia. The power of test would be strengthened if it were possible to study a larger number of cases. Sufficient explanation cannot be found as to why hyperplasia, especially focal hyperplasia, is found as much as five times more frequently in females than in males.

In the present study, cases that came to autopsy at RERF from 1960 to 1983 were used, and it cannot be denied that there is a certain bias in these cases. This is because autolysis of the urinary bladder epithelium had occurred in many of them due to the rather long time lapse from death to autopsy and only about 20% of the heavily exposed group could be used. But, the index group and the control group can be assumed to have the same bias. No statistically significant conculusions were obtained because the number of cases could not be increased.

T65D[4], which was available at the time of planning of this study, was used in selecting the subjects of our heavily exposed group. Though use of the new dose system DS86[6] is desireble at present, re-analysis was not made because use of the new dose could not be considered to bring about any significant difference in the results.

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Abbreviation: A-bomb; Atomic bomb,
ABCC; Atomic Bomb Casualty Commission,
RERF; Radiation Effects Research Foundation,
T65D; Tentative 1965 radiation dose (Ref. No.4)
DS86; Dosimetry System 1986 (Ref. No.6)