

AN AUTOPSY STUDY OF HISTOPATHOLOGIC CHANGES IN THE
URINARY BLADDER TRANSITIONAL EPITHELIUM OF
ATOMIC BOMB SURVIVORS, 1960-83

被爆者の膀胱移行上皮の病理組織学的変化についての
剖検的研究, 1960-83年

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被爆者の膀胱移行上皮の病理組織学的変化についての剖検的研究, 1960-83年

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SUMMARY

In the ABCC-RERF Life Span Study extended sample, 4,499 persons who were the subjects of the Pathology Study of atomic bomb survivors were autopsied 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%), whose urinary bladder epithelia had been preserved satisfactorily to suit the purpose of this study, were selected as the index group. An equal number of control subjects were selected from the nonexposed group, 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 excluded from the study subjects for the index and control groups. These 72 pairs of autopsy cases were pathologically studied for the presence 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 nor the control cases. The risk was relatively higher in the index group than in the control group 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 was small, this was not statistically significant.

要約

ABCC-放影研の寿命調査拡大集団の中で、原爆被爆者の病理学調査の対象で、1960年から1983年の間に剖検調査を行ったのは4,499名であった。推定被曝線量(T65D)100 rad以上を受けた高線量被爆者370例のうちから、本研究目的に沿う膀胱上皮の保存状態が良好な72例(約20%)を抽出してIndex群とした。非被爆群から都市、性、死亡時年齢、死亡年度をIndex群と合致させた者を、同数抽出して対照群とした。ただし、Index群及び対照群ともに、上皮の自己融解の著明な症例及び病理学的に膀胱癌と診断された症例は、調査対象から除外した。これら72組の剖検例について、膀胱上皮の病変、すなわち、過形成、異形成、上皮内癌の有無を病理学的に検索し、その出現頻度をcase-control研究のdesignに基づいて χ^2 検定により、統計的に比較した。

上皮内癌及び高度異形成は、Index群、対照群とも探知されなかった。Index群のリスクは過形成、異形成(軽度及び中等度)の発現率とも対照群に比較して相対的に高率であり、特に乳頭状過形成の相対リスクは4.0であったが、症例の総数が少ないため統計的有意差は認められなかった。

INTRODUCTION

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 (LSS) of A-bomb survivors in Hiroshima and Nagasaki¹ and in their incidence study.² Such a relationship has also been pointed out in a follow-up studies of persons exposed to medical radiation.^{3,4}

In the present study, urinary bladders of A-bomb survivors who were autopsied 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

The 370 autopsy cases (including 108 partial autopsies) of heavily exposed survivors with T65 total doses of 100 rad or more were selected from among the 4,499 autopsy cases resulted from an energetic autopsy procurement program carried out on the some 24,000 deaths occurring from 1960 to 1983 in the LSS-extended sample. Among their preserved urinary bladder materials reviewed, 72 cases were satisfactorily preserved and suitable for this study. These 72 heavily exposed autopsy cases were defined as the index group, and controls were selected at the ratio of 1 to 1 from among the nonexposed autopsy cases in the same fixed population. The controls were selected at random, matched with the index cases by city, sex, age at death (± 5 years), and year of death (1960-64, 1965-69, 1970-74, 1975-83) as 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 not included for both groups.

For reexamination of the pathological findings of the urinary bladder, hematoxylin-eosin stained specimens were prepared. 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.

緒 言

放射線は、ヒトの諸臓器に癌を発生させることが証明されている。膀胱癌と放射線との関連についての研究は、広島・長崎における原爆被爆者の寿命調査¹及び発生率調査²においても明らかである。また、そのような関係は医療用放射線被曝者の追跡調査でも指摘されている。^{3,4}

本研究では、広島・長崎の放影研における原爆被爆者剖検例の膀胱を組織切片により検討して、放射線被曝と膀胱移行上皮の過形成、異形成、上皮内癌などの病変との関連性を調査した。

材料及び方法

1960年から1983年に死亡した者で寿命調査拡大集団に属す約24,000名について強力な剖検調査を行った結果、4,499の剖検例があった。このうちからT65D総線量が100 rad以上の高線量被爆者370例（部分剖検例108を含む）を選んだ。これら既存の膀胱の病理組織標本を検討したところ、本調査の目的に沿う膀胱上皮の保存状態が良好な剖検例は72例であった。この72例の高線量被爆者の剖検例をIndex群とし、同じ固定集団の剖検例で非被爆の症例から1対1の割合で対照例を選んだ。対照例は、Index症例と都市、性、死亡時年齢（ ± 5 歳）、死亡年度（1960-64, 1965-69, 1970-74, 1975-83年）を一致させ膀胱の移行上皮が自己融解していないという条件に合致した症例をランダムに選んだ。Index群と対照群とも、病理学的に膀胱癌と診断された症例は除いた。

膀胱の病理学的所見を再検査するために、hematoxylin-eosin染色標本を作成した。膀胱上皮の病理学的病変については、過形成（限局性、多発性、乳頭状）、異形成（軽度、中等度、高度）と上皮内癌の有無について記録した。病理学的所見の再検査に当たっては、Index群と対照群の区別ができないようblind procedureによった。

Method of Analysis. 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 test based on the case-control study design.

RESULTS

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.

解析方法. 高線量被曝 (Index) 群と対照群とにおいて, 膀胱移行上皮の過形成, 異形成及び上皮内癌の出現頻度を case-control 研究の design に基づいて χ^2 検定によって統計的に比較した.

結 果

調査対象の分布

表 1 に調査対象 72 組 (総計 144 例) の都市別, 性別の分布を示した. Index 群の高線量被曝者の推定被曝線量 (T65D) の平均値は 254.8 rad であった.

TABLE 1 STUDY SUBJECTS

表 1 調査対象

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

Distribution of Urinary Bladder Lesions

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

膀胱病変の分布

両群における膀胱病変の分布を表 2 に示した. ここでは広島と長崎の症例を区別しなかった. なお, 同一例で複数の病変を有している症例が少数あったため, 各々の群での病変数の合計は 72 を超えた.

TABLE 2 URINARY BLADDER LESIONS

表 2 膀胱病変

	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

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

また, 代表的な病変例を図 1-5 に図示した. すなわち, 限局性過形成 (図 1), 多発性過形成 (図 2), 乳頭状過形成 (図 3), 軽度異形成 (図 4), 及び中等度異形成 (図 5) である.

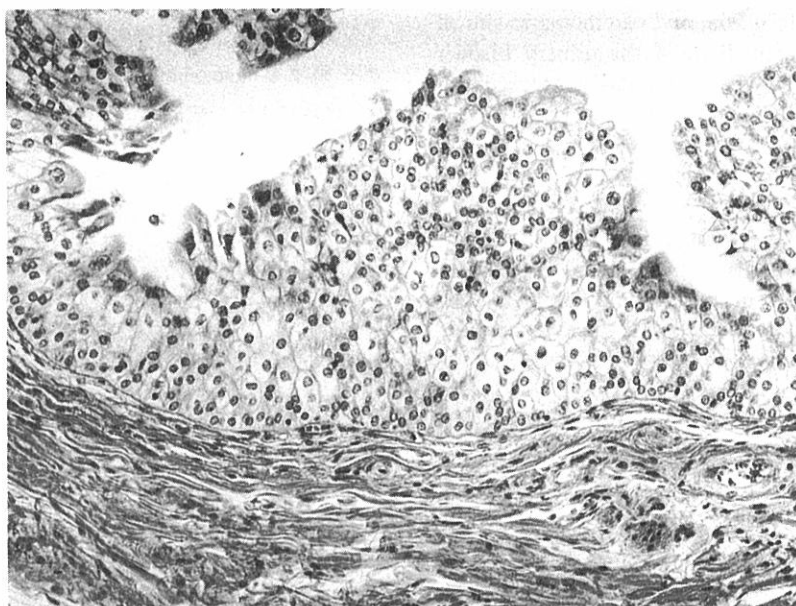


Figure 1. Focal hyperplasia (×50)

図1. 限局性過形成

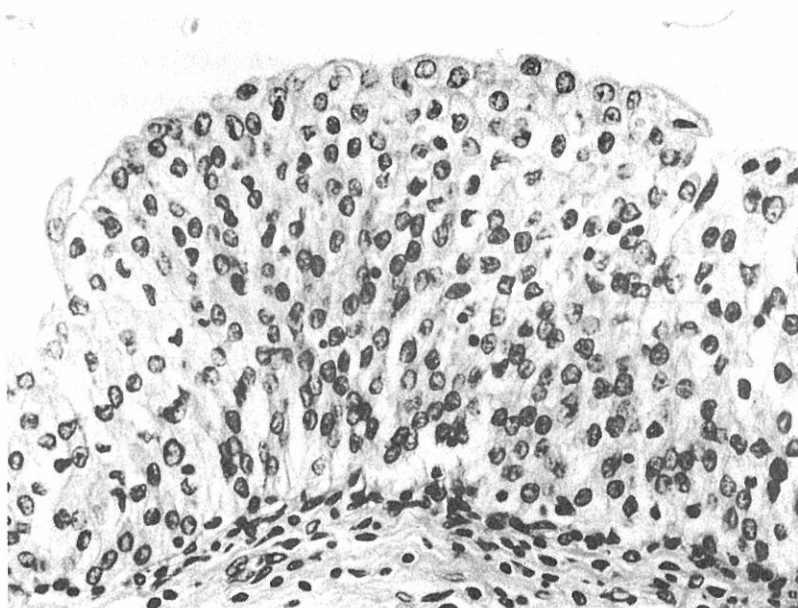


Figure 2. Multifocal hyperplasia (×100)

図2. 多発性過形成

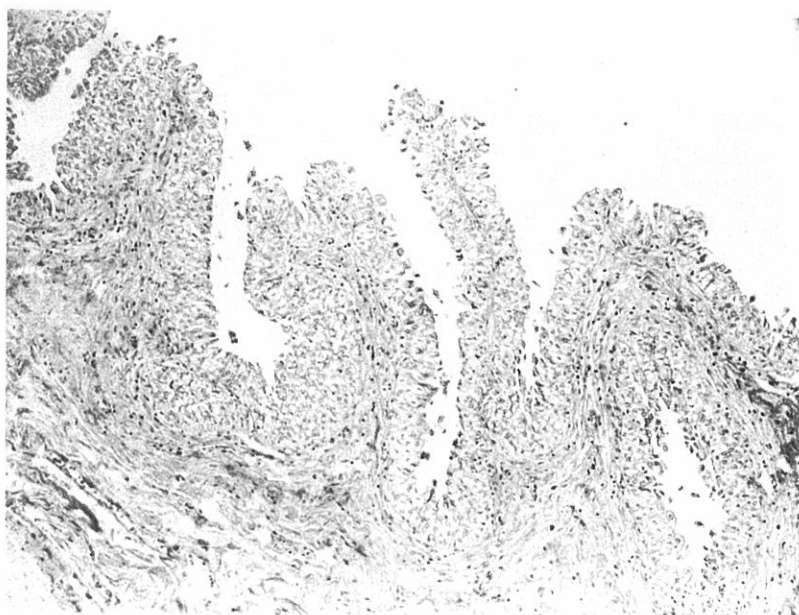


Figure 3. *Papillary hyperplasia* ($\times 25$)

図3. 乳頭状過形成

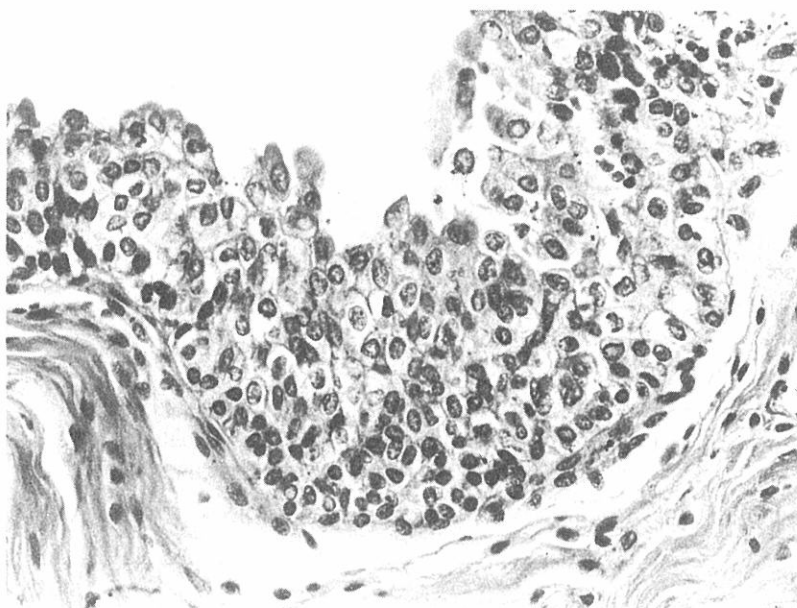


Figure 4. *Mild dysplasia* ($\times 100$)

図4. 軽度異形成

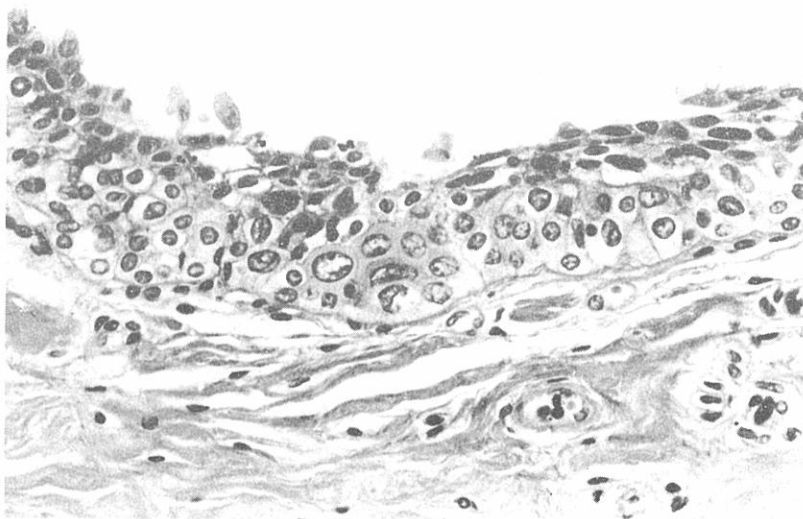
Figure 5. Moderate dysplasia ($\times 100$)

図5. 中等度異形成

Dose Effect

The frequencies of hyperplasia, dysplasia, and carcinoma-in-situ in the heavily exposed (index) group and the control group are compared in Table 3A, B, and C. No cases of carcinoma-in-situ were detected in either group. The index group shows 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.

被曝線量の影響

高線量被曝 (Index) 群と対照群について、過形成、異形成、上皮内癌の発生頻度を比較したのが表3A, B, Cである。両群とも上皮内癌は全く探知できなかった。過形成の頻度はIndex群では対照群に比較し相対リスクは約2.7であり、異形成ではそのリスクは約1.4であったが、症例数が少なく統計的に有意差は認められなかった。

TABLE 3 COMPARISON OF THREE MAJOR PATHOLOGICAL FINDINGS BETWEEN INDEX AND CONTROL

表3 Index 及び対照群間の3種の主要な病理学的所見の比較

A. Hyperplasia (Focal, Multifocal or papillary) 過形成 (限局性, 多発性, 乳頭状)

Control	Index		
	Yes	No	
Yes	4	3	Relative risk: 2.67 $\chi^2[1] = 1.455$ $P > 0.10$ NS
No	8	57	

(Continue 続く)

B. Dysplasia (Mild, moderate or severe)
異形成 (軽度, 中等度, 高度)

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

[] = df. 自由度

C. Carcinoma in situ
上皮内癌

Control	Index	
	Yes	No
Yes	0	0
No	0	72

Table 3D shows a comparison of the above findings by histological type. Hyperplasia was reclassified into three types for comparison i.e., focal, multifocal, 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. Dysplasia was reclassified into mild, moderate, and severe dysplasia and the distributions were compared. 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.

表3Dは、上述の所見について組織型別に比較したものである。過形成については、限局性過形成、多発性過形成、乳頭状過形成の三つに分けて分布を比較した。乳頭状過形成の相対リスクは、対照群に比較して4.0であったが、統計的有意差は認められなかった。限局性過形成の相対リスクは約1.8であったが、有意差はなかった。異形成については、軽度異形成、中等度異形成、高度異形成、の三つに分けて分布を比較した。高度異形成は両群に認められなかった。軽度異形成の相対リスクは約1.3、中等度異形成では2.0であったが、統計的に有意差は認められなかった。

TABLE 3 D. Comparison by Type of Hyperplasia and Dysplasia

表3 D. 過形成及び異形成の組織型による比較

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

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

Multifocal hyperplasia			
Control	Index		Relative risk: 0 $\chi^2[1] = 0$ P>0.10 NS
	Yes	No	
Yes	1	1	
No	0	70	

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

(Continue 続く)

TABLE 3 D. (Continued 続き)

Moderate dysplasia			
Control	Index		Relative risk: 2.00 $\chi^2[1] = 0$ P>0.10 NS
	Yes	No	
Yes	0	1	
No	2	69	

[] = df. 自由度

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 suggested a difference by sex, the occurrence 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.

性別、死亡時年齢別にみた組織学的病変の頻度

表4には、組織病変の頻度を性別、死亡時年齢別に示した。過形成と異形成の頻度を性別に比較してみると、性差が示唆され、限局性過形成の発現率は女子が男子の約5倍で統計的に有意差を認めた。次に死亡時年齢別にみた過形成・異形成の分布を比較してみると、発現率に差は認めがたかった。

TABLE 4 FREQUENCY OF HISTOLOGICAL LESIONS BY SEX AND AGE AT DEATH

表4 組織学的病変の頻度：性及び死亡時年齢別

	Sex			Test of difference	
	Male (%)	Female (%)	Total (%)	$\chi^2 [1]$	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	Sug
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	NS
Papillary	3 (4.1)	2 (2.9)	5 (3.5)	0.154	NS
Dysplasia	15 (20.3)	10 (14.3)	25 (17.4)	0.898	NS
Mild	14 (18.9)	8 (11.4)	22 (15.3)	1.559	NS
Moderate	1 (1.4)	2 (2.9)	3 (2.1)	0.400	NS

	Age at death				Test of difference	
	<59 (%)	60-69 (%)	70+ (%)	Total (%)	$\chi^2 [2]$	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	NS
Focal	4 (7.8)	4 (10.0)	5 (9.4)	13 (9.0)	0.144	NS
Multifocal	1 (2.0)	0 (0.0)	2 (3.8)	3 (2.1)	1.597	NS
Papillary	3 (5.9)	0 (0.0)	2 (3.8)	5 (3.5)	2.337	NS
Dysplasia	7 (13.7)	6 (15.0)	12 (22.6)	25 (17.4)	1.655	NS
Mild	6 (11.8)	5 (12.5)	11 (20.8)	22 (15.3)	1.953	NS
Moderate	1 (2.0)	1 (2.5)	1 (1.9)	3 (2.1)	0.048	NS

[] = df. 自由度

DISCUSSION

The present study using autopsy materials was planned to review the hypothesis that the pathologically observed precancer lesions, i.e., 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, because the risk of urinary bladder tumor has been reported to be significantly high in A-bomb survivors.^{1,2} Using RERF autopsy materials, a review of existing data was made based on the 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.^{5,6} However, it was found that statistically assessable, well-preserved autopsy materials were limited for organs of autopsied cases stored from 1960 to 1983, so that it was decided to review whether 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 frequent in females than in males.

In the present study, cases autopsied 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 conclusions were obtained because the number of cases could not be increased.

考 察

被爆者は膀胱癌のリスクが有意に高いことが報告されているので、^{1,2} 剖検材料を用いる今回の研究は、膀胱上皮の過形成、異形成及び上皮内癌などの前癌病変の出現頻度が高線量被爆者群では対照群に比較し高いかもしれないとの仮説について検討するために計画した。放影研の剖検材料を用い、高線量被曝 (Index) 群と対照群において都市、性、死亡時年齢、死亡年度を合致させた72組を選んで case-control 研究の design に基づいて既存の資料の検討を行った。

本来は膀胱組織の全剖検標本を作成し、Koss ら^{5,6} の膀胱の mapping に関する手法に基づいて病変分布を詳細に記録し、高線量被曝 (Index) 群と対照群について比較検討すべく計画したが、1960年から1983年までの間に保存した剖検例の臓器について良い保存状態の剖検材料が限られていることがわかったので、既存の膀胱の病理組織標本を利用して Index 群の膀胱上皮に前癌病変が多いか否かについて検討することとした。

表3に示したように過形成、異形成の発現率の相対リスクは統計的に有意差は認められなかった。もっと多くの剖検例についての調査が可能であれば、検定力が高まったと思われる。過形成、特に限局性過形成が女子では男子の5倍も認められた理由については十分な説明が見当たらない。

今回の調査は1960年から1983年の間に実施した剖検例を用いたが、放影研の剖検例は死亡から剖検までの時間がかかり長くて膀胱上皮の自己融解している症例が多く、高線量群の約20%しか本調査に利用できなかったため、症例にある種の偏りがあることはいなめない。しかし、このことは Index 群、対照群とも同様な偏りがあると仮定して差し支えないであろう。症例数を大きくすることができなかったため統計的に有意な結論は得られなかった。

T65D, 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 is desirable at present, reanalysis was not made because use of the new dose could not be considered to bring about any significant difference in the results.

高線量被曝群として選んだ今回の対象は、計画時利用可能であった T65D を用いた。現在では新線量システム DS86 を利用することが望ましいが、新線量を用いてもその結果に有意な差異があるとは考えられないので再解析は行わなかった。

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