

PRIMARY LIVER CARCINOMA AND LIVER CIRRHOSIS IN ATOMIC BOMB
SURVIVORS, HIROSHIMA AND NAGASAKI, 1961-75,
WITH SPECIAL REFERENCE TO HB_s ANTIGEN

原爆被爆生存者における原発性肝癌及び肝硬変，特に HB_s 抗原との関係
広島・長崎，1961 - 75年

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In the continued interest of accurately defining the late effects of the atomic bombs, the qualitative and quantitative characteristics of the A-bomb radiation exposure doses are periodically refined. If warranted by future dose assessments, the data reported here will be reanalyzed and subsequently reported.

原爆の後影響を引き続いて正確に究明する目的をもって、原爆放射線被曝線量の質的・量的特質について定期的に改良を加えている。今後線量評価によって、その必要性が起これば、本報の資料を再解析の上、改めて報告する。

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放射線影響研究所(元ABCC)は、昭和50年4月1日に公益法人として発足した。その経費は日米両政府の平等分担とし、日本は厚生省の補助金、米国はエネルギー省との契約に基づく米科学士院の補助金とをもって充てる。

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SUMMARY

During 1961-75, 128 cases of primary liver carcinoma (PLC) in the RERF Life Span Study extended sample and 301 cases of liver cirrhosis in the RERF Pathology Study sample were observed. All cases were assessed for hepatitis B surface antigen (HB_s Ag) using orcein and aldehyde fuchsin staining. The incidence of PLC was 2.0 times higher in Nagasaki than in Hiroshima which was statistically significant, but the prevalence of liver cirrhosis showed hardly any difference between the two cities. Meaningful findings that may possibly explain the higher incidence of PLC in Nagasaki were that the presence of HB_s Ag in the liver of patients without overt liver disease was 2.3 times higher in Nagasaki than in Hiroshima, and the prevalence of liver cirrhosis associated with PLC, especially that of posthepatic cirrhosis with PLC, was almost 2.0 times higher in Nagasaki than in Hiroshima. In both cities a suggestive relationship of radiation dose with the prevalence of liver cirrhosis was noted but not with PLC. We believe that the higher incidence of PLC in Nagasaki is attributable to HB virus infection, though other factors, such as immunological competence affected by radiation, cannot be excluded.

要 約

1961年から1975年までの期間に放射研寿命調査拡大集団中に原発性肝癌が128例，放射研病理調査集団中に肝硬変が301例観察された。全症例にorcein及びaldehyde fuchsin染色を行って，B型肝炎surface抗原(HB_s抗原)を調べた。原発性肝癌の発生率は，長崎の方が広島より2.0倍高く統計学的に有意差があったが，肝硬変の有病率では両市間にほとんど差異がなかった。長崎における原発性肝癌の高発生率を説明すると考えられる有意な所見としては，明白な肝臓疾患のない患者の肝臓におけるHB_s抗原の頻度が，長崎では広島に比べて2.3倍高く，原発性肝癌を伴う肝硬変，特に原発性肝癌を伴う肝炎後性肝硬変の頻度は，広島よりも長崎の方がほとんど2倍高かった。放射線の影響については，両市とも肝硬変の有病率と放射線量との関係が示唆されたが，原発性肝癌と線量との関係は認められなかった。長崎の原発性肝癌の高い発生率は，HBウイルス感染に起因するものと思われてならない。しかし，放射線の影響を受けた免疫能のようなその他の因子は無視できない。

INTRODUCTION

A relationship between ionizing radiation and solid tumors has been found for tumors of the thyroid, breast, and lung from studies of atomic bomb survivors,¹ but there has been no suggestive relationship for liver tumors as a late radiation effect.^{2,3} However, ionizing radiation from such a source as thorotrast has been clinically linked to liver carcinogenesis.⁴ Recently Shikata et al⁵ reported that several methods using the orcein and the aldehyde fuchsin stains in particular could be used to demonstrate the antigen as the surface coat of the HB virus in formalin-fixed paraffin sections. The purpose of the present study was to examine possible relationship between the occurrence of PLC and liver cirrhosis and the presence of HB_s Ag in the Life Span Study (LSS) extended sample.⁶

MATERIALS AND METHODS

The study on PLC consists of all possible cases which occurred during 1961-75 in the LSS extended sample in Hiroshima and Nagasaki. Cases for the study of liver cirrhosis were obtained from autopsied cases in the same sample for the same duration in both cities.

Primary Liver Carcinoma. All possible PLC cases were obtained from the Tumor and Tissue Registries of both cities, and RERF surgical pathology and autopsy files for the period 1961-75. All 128 definite cases, histologically confirmed by the investigators, were stained by hematoxylin-eosin and Masson's trichrome stains and Van Gieson elastic fiber, periodic acid Schiff, and argyrophilic fiber techniques. For assessment of HB_s Ag in tissue, two slides stained by orcein and aldehyde fuchsin, and another two slides for immunofluorescence staining test and its control were prepared.

For the immunofluorescence method the section was incubated with fluorescein isocyanate (FITC)-conjugated antihuman HB_s serum, then rinsed with 0.1M phosphate buffer, pH 7.2, and examined by fluorescence microscopy for deposition of HB_s Ag. An Olympus A-RFL fluorescence microscope equipped with DM500, IF490, BG12, and 0515 filters were used with Kodak high speed Ektachrome film (ASA160).

PLC cases were classified by Edmondson's criteria;⁷ liver cell carcinoma (Grade I, II, III, & IV), bile duct carcinoma, multiple or combined

緒言

原爆被爆者の調査から、電離放射線と充実性腫瘍のうち甲状腺、乳腺及び肺臓の腫瘍については関係のあることが認められているが、¹ 肝臓腫瘍については関係が示唆されていない。^{2,3} しかし、トロトラストのような線源から放出される電離放射線は、肝臓の発現と関係があることが臨床的に認められている。⁴ 志方ら⁵ は最近、特に orcein 及び aldehyde fuchsin 染色を用いる幾つかの方法によって、ホルマリンで固定したパラフィン切片に、HB ウイルス surface 抗原を認めることができたと報告した。本調査の目的は、寿命調査拡大集団⁶ における原発性肝癌及び肝硬変の発生と HB_s 抗原の存在との関係を調べることである。

材料及び方法

原発性肝癌の調査は広島・長崎の寿命調査拡大集団に1961-75年に発生した原発性肝癌と思われる全症例について行った。肝硬変の症例は両市の同期間における同集団の剖検例から得た。

原発性肝癌。 両市の腫瘍登録・組織登録、放影研外科病理記録及び剖検記録から1961-75年における原発性肝癌と思われる全症例を集めた。研究者によって組織学的に確認された128例はすべて、hematoxylin-eosin 及び Masson 三色染色並びに Van-Gieson 弾力線維技法、過ヨウ素酸 Schiff 技法及び好銀線維技法を用いて染色した。組織内の HB_s 抗原を調べるために2枚の標本を orcein と aldehyde で染色し、他の標本2枚は免疫蛍光染色検査用とその対照標本用に作製した。

免疫蛍光法では、切片を fluorescein isocyanate (FITC) 標識抗ヒト HB_s 血清で処理し、燐酸緩衝液 0.1M (pH 7.2) ですすぎ、蛍光鏡検で HB_s 抗原の付着を調べた。DM 500, IF 490, BG 12 及び 0515 フィルター付きオリンパス A-RFL 蛍光顕微鏡をコダック高感度エクタクロームフィルム (ASA 160) と共に使用した。

原発性肝癌の症例は、Edmondson の基準⁷ に従って肝細胞癌 (第1度、2度、3度及び4度)、胆管癌、

primary carcinoma (carcinosarcoma, separate liver cell and bile-duct carcinoma, and hepatobiliary carcinoma), and squamous cell carcinoma. For analysis, hepatobiliary carcinoma was included in the liver cell carcinoma category, as done elsewhere.^{8,9}

Liver Cirrhosis. Retrospectively studied were 301 liver cirrhosis cases autopsied in the LSS extended sample during 1961-75 at RERF. Sections were stained using the same methods as for PLC. Immunofluorescence staining was also used. Liver cirrhosis was classified by both Gall's criteria¹⁰ and Miyake's criteria.¹¹ Gall's criteria are posthepatic, postnecrotic, nutritional, obstructive, pigmentary, and congestive cirrhosis, and Miyake's criteria contain Ko, Ko', Otsu, Otsu', F, and special type. Since there were several cases among types of obstructive, pigmentary, or congestive cirrhosis in the present study, they were grouped as other cirrhosis.

Statistical Methods. Age-sex adjusted prevalence rates of PLC and liver cirrhosis by exposure dose groups were tested for linear increase with dose and homogeneity.¹²

RESULTS

Primary Liver Carcinoma

A total of 77 Hiroshima and 51 Nagasaki PLC cases in the LSS extended sample were examined. Of all PLC cases, liver cell carcinoma including hepatobiliary carcinoma, comprised 80.5% and bile duct carcinoma 18.8%, with only one case (0.78%) of squamous cell carcinoma. Table 1 shows that Grade III+IV type most frequently occurred in Hiroshima and Grade I+II in Nagasaki but no difference was found between the not-in-city (NIC)+0 rad group and 1 rad or more group in both cities. PLC was more common in men than in women; 53 cases in Hiroshima and 34 in Nagasaki were male. The ratio of male to female was approximately 2.1:1. The average PLC incidence per year (Table 2) was 0.76 per 10⁴ among a total of 1,014,397 person-years in Hiroshima and 1.51 per 10⁴ among 336,966 person-years in Nagasaki, the latter being 2.0 times higher. This difference was statistically significant ($P < .001$). The annual incidence rate was classified into six dose groups using the revised estimated dose (T65DR)¹³: NIC, 0, 1-49, 50-99, 100-199, and 200+rad. No relationship between radiation and the incidence of PLC was demonstrated (Table 3 & Figure 1). The average

多発性若しくは混合性原発性癌(癌肉腫, 分離性肝細胞癌及び胆管癌, 肝胆管癌)及び扁平上皮癌に分類した。他の調査^{8,9}同様, 解析の際には肝胆管癌を肝細胞癌に含めた。

肝硬変. 1961-75年の間に放影研で剖検を行った寿命調査拡大集団中の肝硬変301例について遡及的に調査を行った。原発性肝癌の場合と同じ方法を用いて切片を染色した。免疫蛍光染色も用いた。肝硬変はGallの基準¹⁰と三宅の基準¹¹の双方を用いて分類した。前者は肝炎後性, 壊死後性, 栄養性, 閉塞性, 色素性及び鬱血性に, 後者は甲型, 甲'型, 乙型, 乙'型, F型及び特殊型に分類した。本調査では閉塞性, 色素性若しくは鬱血性肝硬変が数例ずつ見られたので, まとめてその他の肝硬変として分類した。

統計学的方法. 年齢一性を補正した被曝線量群別原発性肝癌及び肝硬変の有病率が, 線量及び均質性に対して線形増加を示すか否かを検定した。¹²

結 果

原発性肝癌

寿命調査拡大集団中広島77例, 長崎51例の原発性肝癌を調査した。全症例中肝胆管癌等の肝細胞癌が80.5%, 胆管癌が18.8%を占め, 扁平上皮癌はわずか1例(0.78%)であった。表1から, 広島では第3度+4度の型が, 長崎では第1度+2度の型が最も多いが, 両市とも, 市内にいなかった者(NIC)+0 rad群と1 rad以上の群との間に差異はなかった。原発性癌は女性より男性に多く, 広島では53例, 長崎では34例が男性であった。男性対女性の比は約2.1:1であった。原発性肝癌の年間平均発生率(表2)は広島で計1,014,397人年中10⁴当たり0.76, 長崎では336,966人年中10⁴当たり1.51であり, 長崎が2.0倍高かった。この差は統計学的に有意であった($P < .001$)。改訂推定線量(T65DR)¹³による6つの線量群, すなわち, NIC群, 0 rad群, 1-49rad群, 50-99rad群, 100-199rad群及び200+rad群別に年間発生率を計算したところ, 放射線と原発性肝癌の間に関係は見られなかった(表3及び図1)。原

TABLE 1 DIFFERENTIATION OF PRIMARY LIVER CARCINOMA BY CITY, & SEX

表1 原発性肝癌の組織学的分類, 都市及び性別

Type	Male		Female		Total
	NIC+0 rad	1+rad	NIC+0 rad	1+rad	
Hiroshima					
Liver cell carcinoma					
Grade I + II	10	9	6	1	26
Grade III + IV	15	11	5	2	33
Hepatobiliary	2	1	0	0	3
Squamous cell carcinoma	0	0	1	0	1
Bile duct carcinoma	4	4	5	1	14
Total	31	25	17	4	77
Nagasaki					
Liver cell carcinoma					
Grade I + II	6	11	3	3	23
Grade III + IV	5	7	0	3	15
Hepatobiliary	1	1	1	0	3
Bile duct carcinoma	1	1	3	5	10
Total	13	20	7	11	51
Total both cities	44	45	24	15	128

TABLE 2 ANNUAL INCIDENCE RATE/10⁴ OF PRIMARY LIVER CARCINOMA BY CITY, SEX, AND HISTOLOGIC TYPE, 1961-75表2 原発性肝癌の年間発生率(10⁴ 当たり), 都市, 性及び組織学的型別, 1961-75年

Type of carcinoma	Hiroshima				Nagasaki				Test for city difference
	Cases		Person-years 1961-75	Rate /10 ⁴	Cases		Person-years 1961-75	Rate /10 ⁴	
	No.	%			No.	%			
Male									
Liver cell	45	84.9	395370	1.14	32	94.1	142191	2.25	***
Bile duct	8	15.1		0.20	2	5.9		0.14	
Other	0	0		0.00	0	0		0.00	
Total	53	100.0		1.34	34	100.0		2.39	***
Female									
Liver cell	17	70.8	619027	0.27	9	52.9	194775	0.46	*
Bile duct	6	25.0		0.10	8	47.1		0.41	***
Other	1	4.2		0.02	0	0		0.00	
Total	24	100.0		0.39	17	100.0		0.87	***
Total									
Liver cell	62	80.5	1014397	0.61	41	80.4	336966	1.22	***
Bile duct	14	18.2		0.14	10	19.6		0.30	**
Other	1	1.3		0.01	0	0		0.00	
Total	77	100.0		0.76	51	100.0		1.51	***
Deaths from all causes (proportional mortality)			12449	0.6%			3480	1.4%	

* .01 < P < .05 ** .001 < P < .01 *** P < .001

TABLE 3 ANNUAL INCIDENCE RATE/10⁴ OF PRIMARY LIVER CARCINOMA BY DOSE, SITE, SEX & CITY

表3 原発性肝癌の年間発生率(10⁴ 当たり), 線量, 部位, 性及び都市別

Type of carcinoma	T65 revised dose in rad						Statistical Test	
	NIC	0	1-49	50-99	100-199	200+	L	H
Hiroshima Male								
Liver cell	No.	14	11	15	4	1		Sug
	Rate	1.38	0.81	1.27	3.28	1.01		
Bile duct	No.	1	3	4				
	Rate	0.10	0.22	0.34				
Total	No.	15	14	19	4	1		
	Rate	1.48	1.03	1.61	3.19	1.00		
Female								
Liver cell	No.	6	6	5				
	Rate	0.39	0.26	0.27				
Bile duct	No.	1	4	1				
	Rate	0.06	0.17	0.05				
Total	No.	8	10	6				
	Rate	0.51	0.44	0.32				
Nagasaki Male								
Liver cell	No.	8	4	13	3	1	3	
	Rate	2.26	1.40	2.83	3.64	1.15	3.35	
Bile duct	No.	1	0	1				
	Rate	0.28		0.22				
Total	No.	9	4	14	3	1	3	
	Rate	2.55	1.39	3.05	3.63	1.15	3.35	
Female								
Liver cell	No.	2	2	3	2			
	Rate	0.44	0.63	0.34	2.10			
Bile duct	No.	3	0	4	0	1		
	Rate	0.65		0.44		1.34		
Total	No.	5	2	7	2	1		
	Rate	1.09	0.65	0.79	2.04	1.31		
Cities and Sexes Combined								
Liver cell	No.	30	23	36	9	2	3	.01<P≤.05
	Rate	0.89	0.60	0.83	1.57	0.40	0.61	
Bile duct	No.	6	7	10	0	1	0	
	Rate	0.18	0.18	0.21		0.26		
Total	No.	37	30	46	9	3	3	Sug
	Rate	1.09	0.78	1.05	1.58	0.62	0.66	

L: Linear increase with dose (one-tailed) 線量による線形増加(片側)

H: Homogeneity of dose groups regardless of pattern 型によらない線量群の均一性

age at the time of the bomb (ATB) of patients with PLC was 40.1 years. No relationship was found between age ATB and radiation dose (Table 4). The age of death among subjects with PLC in Hiroshima ranged from 29 to 83 years with an average of 65.3 years, and from 26 to 83 years with an average of 61.7 years in Nagasaki.

原発性肝癌患者の平均原爆時年齢は40.1歳であった。原爆時年齢と放射線量の間には関係が認められなかった(表4)。原発性肝癌患者の死亡時年齢は広島で29-83歳で平均65.3歳, 長崎では26-83歳で平均61.7歳であった。

TABLE 4 RELATIVE RISK (100+/0 rad) OF PRIMARY LIVER CARCINOMA
LIVER CIRRHOSIS BY AGE ATB表4 原発性肝癌及び肝硬変の相対的リスク
(100+ / 0 rad), 原爆時年齢別

Age ATB	T65 revised dose in rad			Relative risk C/A	
	NIC + 0 A	1-99 B	100+ C		
Primary Liver Carcinoma					
10-19	Observed	3	5	0	-
	*Person-years	188230	118893	25575	
	Rate /10 ⁴	0.16	0.42	0.00	
20-34	Observed	17	9	2	1.11
	*Person-years	176055	107359	18446	
	Rate /10 ⁴	0.97	0.84	1.08	
35-49	Observed	33	29	3	1.01
	*Person-years	172367	106617	15650	
	Rate /10 ⁴	1.91	2.72	1.92	
50+	Observed	14	12	1	1.06
	*Person-years	55112	35355	3738	
	Rate /10 ⁴	2.54	3.39	2.68	
Liver Cirrhosis					
0-19	Observed	11	10	6	1.93
	**Subjects	117	102	33	
	Rate %	9.40	9.80	18.18	
20-34	Observed	25	21	2	0.41
	**Subjects	226	179	44	
	Rate %	11.06	11.73	4.55	
35-49	Observed	77	61	13	1.32
	**Subjects	976	702	125	
	Rate %	7.89	8.69	10.4	
50+	Observed	43	25	3	0.59
	**Subjects	1167	1038	139	
	Rate %	3.68	2.41	2.16	

*Person-years (1961-75) from LSS extended sample 寿命調査拡大集団の人年(1961-75年)

**Persons from autopsy sample 剖検例の数

Of the 128 PLC cases, 43 (55.8%) in Hiroshima and 28 (54.9%) in Nagasaki were associated with liver cirrhosis and no discrepancy in incidence rates between cities was noted. The proportion of coexisting cirrhosis in PLC by type was 85.9% for posthepatic cirrhosis, 2.8% for postnecrotic cirrhosis, 5.6% for nutritional cirrhosis, and 4.2% for other cirrhosis. Bile duct carcinoma associated with liver cirrhosis was seen only in two cases (1.5%). No relationship was observed between radiation and the proportion of PLC with liver cirrhosis (Table 5).

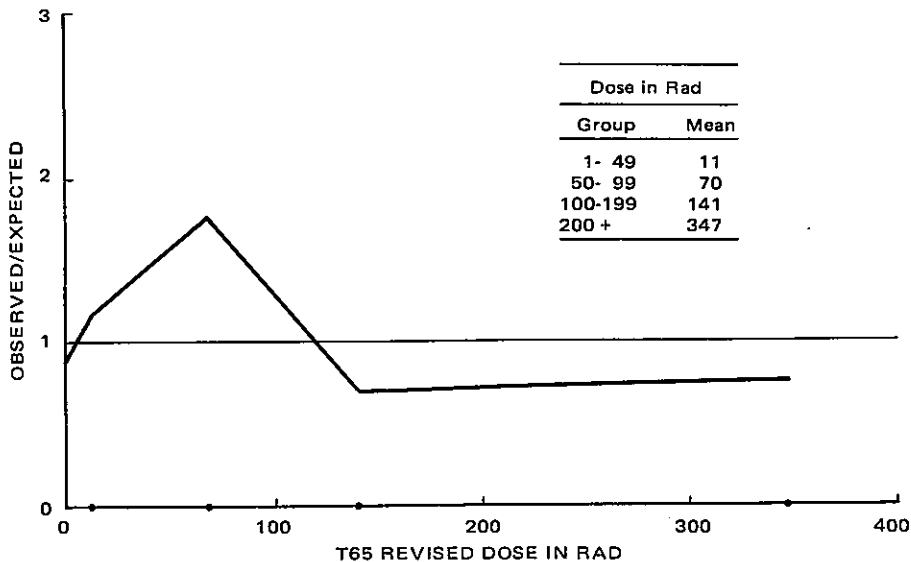
Hepatocytes positive for HB_s Ag were present mainly in the noncancerous areas of the liver, and were unevenly distributed. The cellular

原発性肝癌128例のうち広島で43例(55.8%), 長崎で28例(54.9%)が肝硬変を伴っており, 両市間の発生率に差はなかった。原発性肝癌に肝硬変を伴っている割合を型別に見ると, 肝炎後性肝硬変が85.9%, 壊死後性が2.8%, 栄養性が5.6%, その他が4.2%であった。胆管癌が肝硬変を伴っている例はわずか2例(1.5%)であった。原発性肝癌と肝硬変の併発率と放射線との間には関係は認められなかった(表5)。

HB_s 抗原が陽性の肝細胞は主として肝臓の癌のない部分に見られ, 非均等に分布していた。orcein 及び

FIGURE 1 OBSERVED AND EXPECTED RATIO OF PRIMARY LIVER CARCINOMA
ADJUSTED FOR AGE, CITY, & SEX, BY DOSE

図1 年齢、都市及び性別に標準化した原発性肝癌の観察数対期待数の比、線量別



deposition of orcein and aldehyde fuchsin stains appeared in the cytoplasm but was rarely found near the cytoplasmic membrane. Some Kupffer cells contained orcein-positive material (Figure 2). None of the livers with bile duct carcinoma or squamous cell carcinoma contained orcein-positive material. The percentage of PLC positive for HB_s Ag was 20.0% in Hiroshima and 19.6% in Nagasaki. The percentage of positive HB_s Ag in the livers with PLC accompanied by cirrhosis was 35.5% in Hiroshima and 35.7% in Nagasaki. The rate of positive HB_s Ag seemed unrelated to radiation dose (Table 6).

HB_s Ag was positive in the cytoplasm of tumor cells in four PLC cases. The cytoplasm of some giant cells was positive for HB_s Ag also. The cytoplasm in most tumor cells was diffusely positive and in some the positive material was localized as a granular mass like an inclusion body (Figure 2). Stained nuclei were never found. They were classified as Grade III by Edmondson's criteria. Table 7 suggests that the positive tumor cells could not be attributed to the late effect of A-bomb radiation.

Liver Cirrhosis

There were 225 Hiroshima and 76 Nagasaki liver cirrhosis cases available in the autopsy series in

aldehyde fuchsin 染色の細胞付着は細胞質に見られたが、細胞膜付近にはほとんど見られなかった。Kupffer 細胞の中には orcein 陽性物質を含むものがあつた(図2)。胆管癌や扁平上皮癌のある肝臓は orcein 陽性物質を含んでいなかった。HB_s 抗原に対して陽性の原発性肝癌の率は広島で20.0%、長崎で19.6%であつた。原発性肝癌に肝硬変を伴った肝臓の HB_s 抗原陽性率は広島で35.5%、長崎で35.7%であつた。HB_s 抗原陽性率は放射線量と関係がないように思われる(表6)。

原発性肝癌4例において腫瘍細胞の細胞質内に HB_s 抗原が見られた。幾つかの巨細胞の細胞質も HB_s 抗原陽性であつた。多くの腫瘍細胞の細胞質は瀰漫性に陽性であつたが、一部のものでは陽性物質は封入体様の顆粒塊状に局在していた(図2)。陽性染色された核は見られなかった。これらは Edmondson の基準では第3度に分類された。陽性の腫瘍細胞は原爆放射線の後影響によるものでないことが表7によって示唆される。

肝硬変

広島・長崎の剖検例中広島で225例、長崎で76例の

TABLE 5 PROPORTION OF PRIMARY LIVER CARCINOMA ASSOCIATED WITH LIVER CIRRHOSIS BY CITY, HISTOLOGIC TYPE AND DOSE

表5 肝硬変を伴った原発性肝癌の割合、都市、組織学的型及び線量別

Type of carcinoma		T65 revised dose in rad							
		Total		NIC + 0		1-99		100+	
		No.	%	No.	%	No.	%	No.	%
Hiroshima									
Liver cell	With	42	67.7	25	67.6	16	66.7	1	100.0
	Without	20		12		8		0	
	Total	62		37		24		1	
Bile duct	With	1	7.1	1	11.1	0	0.0	0	0.0
	Without	13		8		5		0	
	Total	14		9		5		0	
Total	With	43	55.8	26	55.3	16	55.2	1	100.0
	Without	34		21		13		0	
	Total	77		47		29		1	
Nagasaki									
Liver cell	With	27	65.9	11	68.8	13	61.9	3	75.0
	Without	14		5		8		1	
	Total	41		16		21		4	
Bile duct	With	1	10.0	0	0.0	1	20.0	0	0.0
	Without	9		4		4		1	
	Total	10		4		5		1	
Total	With	28	54.9	11	55.0	14	53.8	3	60.0
	Without	23		9		12		2	
	Total	51		20		26		5	

Hiroshima and Nagasaki. They consisted of 225 (74.8%) posthepatic cases, 49 (16.3%) postnecrotic, 16 (5.3%) nutritional, and 11 (3.7%) cases of the other types of liver cirrhosis; or 21 (7.0%) of Ko type, 60 (19.9%) of Ko' type, 146 (48.5%) of Otsu type, 45 (14.9%) of Otsu' type, 16 (5.3%) of F type, and 13 (4.3%) of special type. The total number of autopsied cases during 1961-75 was 4,920 (3,857 in Hiroshima and 1,063 in Nagasaki).¹⁴ The prevalence rate of liver cirrhosis was 5.8% in Hiroshima and 7.2% in Nagasaki, showing no difference between the two cities (Table 8). Of the 301 cases of liver cirrhosis, 156 cases were in NIC + 0 rad group, 141 in 1 rad or more, and 4 in the dose unknown group. Classifying them into NIC, 0, 1-49, 50-99, 100-199, and 200+ rad groups, there was a suggestive association between radiation dose and the prevalence of liver cirrhosis in both cities (Table 9 and Figure 3). The association of postnecrotic liver cirrhosis in

肝硬変症例が含まれていた。このうち 225例 (74.8%) が肝炎後性, 49例 (16.3%) が壊死後性, 16例 (5.3%) が栄養性, 11例 (3.7%) がその他の型であり, また, 21例 (7.0%) が甲型, 60例 (19.9%) が甲'型, 146例 (48.5%) が乙型, 45例 (14.9%) が乙'型, 16例 (5.3%) がF型, 13例 (4.3%) が特殊型であった。1961-75年の剖検例総数は4,920 (広島3,857例, 長崎1,063例)であった。¹⁴ 肝硬変の有病率は広島5.8%, 長崎7.2%で, 両市間に差異はなかった (表8)。301例の肝硬変のうち, 156例がNIC + 0 rad群, 141例が1 rad以上群, 4例が線量不明群であった。これらをNIC群, 0 rad群, 1-49rad群, 50-99rad群, 100-199rad群及び200+rad群に分けると, 両市で放射線量と肝硬変の有病率の間に示唆的な関係が見られた (表9及び図3)。両市における壊死後性肝硬変と放射線量

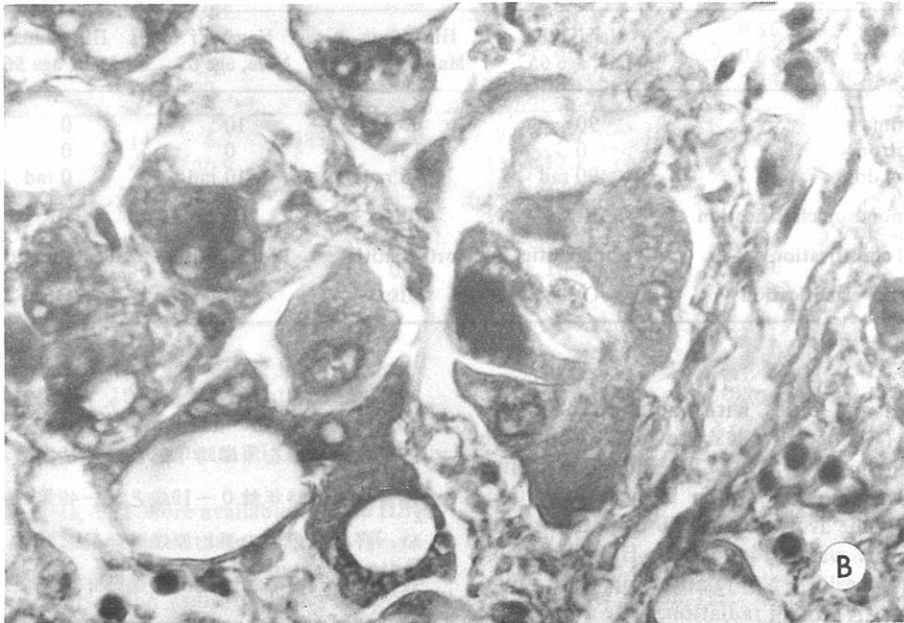
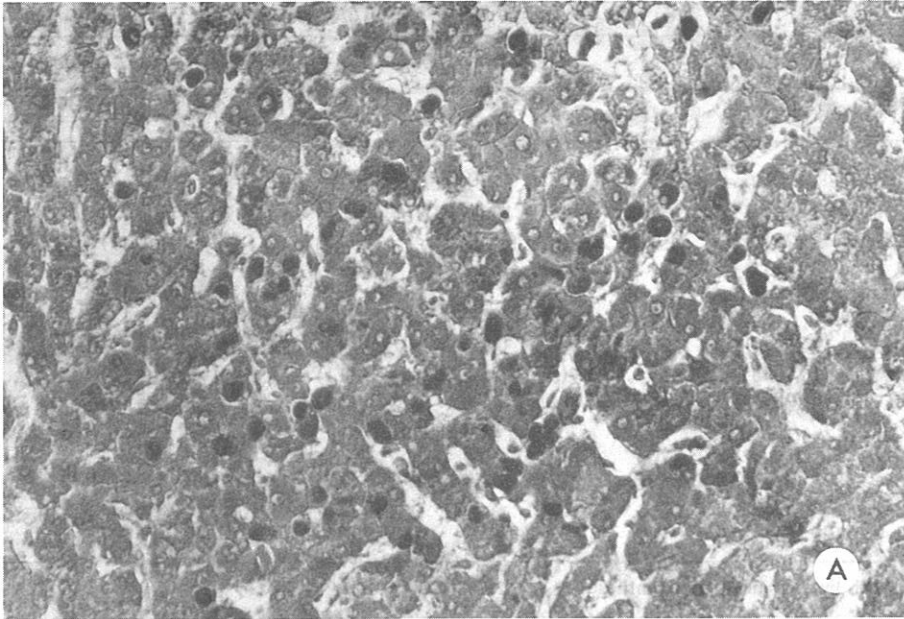


Figure 2 A) Orcein-positive material is visible within the cytoplasm of the hepatic cells in liver cirrhosis; nuclei are unstained. (Orcein stain for HB_s Ag. x100). B) Tumor cells contain HB_s Ag in cytoplasm as shown by the intensity of staining. (Orcein stain for HB_s Ag. x400).

図2 A) 肝硬変における肝細胞の細胞質中に orcein 陽性物質が見られる。核は染色されていない (HB_s 抗原の orcein 染色 100倍)。B) 染色の濃度で明らかなように、腫瘍細胞が細胞質内に HB_s 抗原を含んでいる (HB_s 抗原の orcein 染色 400倍)。

TABLE 6 PROPORTION OF PRIMARY LIVER CARCINOMA CASES WITH POSITIVE HB_s Ag BY DOSE
表6 HB_s 抗原陽性の原発性肝癌の割合、線量別

	Total		NIC + 0		1-99		100+	
	No.	%	No.	%	No.	%	No.	%
Hiroshima								
Positive	11 (11)	20.0 (35.5)	6 (6)	19.4 (37.5)	4 (4)	18.2 (28.6)	1 (1)	100.0 (100.0)
Negative	44 (20)		25 (10)		18 (10)		0 (0)	
Total	55 (31)		31 (16)		22 (14)		1 (1)	
Nagasaki								
Positive	10 (10)	19.6 (35.7)	6 (6)	30.0 (54.5)	3 (3)	11.5 (21.4)	1 (1)	20.0 (33.3)
Negative	41 (18)		14 (5)		23 (11)		4 (2)	
Total	51 (28)		20 (11)		26 (14)		5 (3)	
Total								
Positive	21 (21)	19.8 (35.6)	12 (12)	23.5 (44.4)	7 (7)	16.7 (25.0)	2 (2)	33.3 (50.0)
Negative	85 (38)		39 (15)		42 (21)		4 (2)	
Total	106 (59)		51 (27)		49 (28)		6 (4)	

Cases with liver cirrhosis in parentheses () 内は肝硬変を併発した症例

TABLE 7 POSITIVE HB_s Ag IN PRIMARY LIVER CARCINOMA OF FOUR CASES
表7 HB_s 抗原陽性に見られる原発性肝癌細胞の4症例

	Nagasaki Male, age 65	Hiroshima Male, age 69	Nagasaki Male, age 65	Hiroshima Male, age 56
Gamma	90	63	10	0
Neutron	0	13	0	0
Total dose	90 rad	76 rad	10 rad	0 rad
Edmondson classification	III	III	III	III
Gall classification	Posthepatitic	Posthepatitic	Posthepatitic	Posthepatitic
Miyake classification	Otsu	Otsu	Otsu	Otsu

both sexes and cities with radiation dose was significant ($P < .01$). Table 4 shows the proportion of liver cirrhosis by age ATB and dose. Liver cirrhosis was most common in ages ATB 0-19 and 35-49. The average age ATB of patients with liver cirrhosis was 41.4 years in Hiroshima and 37.4 in Nagasaki. No relationship was found between age ATB and radiation. The average age at death of patients with liver cirrhosis was 63.2 years in Hiroshima and 60.5 in Nagasaki.

Of the 301 cases of liver cirrhosis, 67 (22.2%) were accompanied by PLC, including 59 post-hepatitic, 1 postnecrotic, 4 nutritional, and 3 biliary type. The rate of association with PLC was 2.0 times higher in Nagasaki than in

の関係は男女とも有意であった ($P < .01$)。表4に肝硬変患者率を原爆時年齢及び線量別に示した。肝硬変は原爆時年齢0-19歳と35-49歳の者が最も多い。肝硬変患者の平均原爆時年齢は広島で41.4歳、長崎で37.4歳であった。原爆時年齢と放射線の間に関係は認められなかった。肝硬変患者の平均死亡時年齢は広島で63.2歳、長崎で60.5歳であった。

肝硬変301例のうち67例(22.2%)が原発性肝癌を伴っており、その内訳は肝炎後性59例、壊死後性1例、栄養性4例、肝胆管性3例であった。原発性肝癌

TABLE 8 PREVALENCE RATE/10² OF LIVER CIRRHOSIS BY CITY, SEX, & HISTOLOGIC TYPE, 1961-75表8 肝硬変の有病率(10²当たり), 都市, 性及び組織学的型別, 1961-75年

Histologic type	Hiroshima				Nagasaki				Test for city difference
	Cases		Autopsies 1961-75	Prevalence Rate (%)	Cases		Autopsies 1961-75	Prevalence Rate (%)	
	No.	%			No.	%			
Male									
Posthepatic	112	80.6	1927	5.81	42	72.4	597	7.04	Sug
Postnecrotic	20	14.4		1.04	8	13.8		1.34	
Nutritional	4	2.9		0.21	4	6.9		0.67	
Other	3	2.1		0.16	4	6.9		0.67	
Total	139	100		7.21	58	100		9.72	
Female									
Posthepatic	62	69.8	1930	3.21	9	50.0	466	1.93	Sug
Postnecrotic	17	19.8		0.88	4	22.2		0.86	
Nutritional	6	7.0		0.31	2	11.1		0.43	
Other	1	3.5		0.05	3	16.7		0.64	
Total	86	100		4.46	18	100		3.86	
Sexes Combined									
Posthepatic	174	72.0	3857	4.51	51	67.1	1063	4.80	Sug
Postnecrotic	37	16.4		0.96	12	15.8		1.13	
Nutritional	10	4.4		0.26	6	7.9		0.56	
Other	4	1.2		0.10	7	9.2		0.66	
Total	225	100		5.83	76	100		7.15	
Ko	14	6.2	3857	0.36	7	9.2	1063	0.66	
Ko'	47	20.9		1.22	13	17.1		1.22	
Otsu	121	53.8		3.14	25	32.9		2.35	
Otsu'	28	12.4		0.73	17	22.4		1.60	
F	10	4.4		0.26	6	7.9		0.66	
Specific	5	2.2		0.13	8	10.5		0.66	
Total	225	100		5.83	76	100		7.15	

Hiroshima (Table 10). No relationship was observed between radiation dose and the prevalence of liver cirrhosis with PLC.

Of the 301 cases, 231 were available for the HB_s Ag study. The positive rate was 18.7% in Hiroshima and 18.4% in Nagasaki, suggesting that they were of about the same tendency in both cities. On the other hand positive results were obtained in livers of 39.3% of patients with both liver cirrhosis and PLC in Hiroshima and in 33.3% of those in Nagasaki. Especially, in Nagasaki the positive rate was the highest in liver cirrhosis cases with PLC in the NIC+0 rad group (54.4%). There were 25 (22.5%) positive cases in the NIC+0 rad group and 18 (15.5%) in

を伴った率は長崎の方が広島に比べて2倍高かった(表10)。放射線量と原発性肝癌を伴う肝硬変との間に関係は見られなかった。

301例中231例についてHB_s抗原の検査が可能であった。陽性率は広島18.7%, 長崎18.4%で、両市ともほぼ同じ傾向であることが示唆された。一方、肝硬変と原発性肝癌を併発している肝臓で、陽性を示したのは広島39.3%, 長崎33.3%であった。特に長崎ではNIC+0 rad群における併発例の陽性率が最も高かった(54.4%)。NIC+0 rad群では25例(22.5%), 1 rad以上群では18例(15.5%)の陽性例が見られ

TABLE 9 PREVALENCE RATE/10³ OF LIVER CIRRHOSIS BY RADIATION DOSE, HISTOLOGIC TYPE, SEX, & CITY表9 肝硬変の有病率(10³当たり),放射線量,組織学的型,性及び都市別

Histologic type		T65 revised dose in rad						Statistical test †	
		NIC	0	1-49	50-99	100-199	200+	L	H
Hiroshima Male									
Posthepatic	No.	37	33	28	7	1	3		
	Rate	85.06	50.29	45.81	87.62	16.78	53.44		
Postnecrotic	No.	2	3	9	2	3	0		*
	Rate	4.60	4.63	14.60	26.04	45.97			
Nutritional	No.	0	0	4	0	0	0		
	Rate			6.71					
Total	No.	39	38	41	10	4	3		
	Rate	89.66	57.99	67.06	129.20	65.30	53.33		
Female									
Posthepatic	No.	20	19	14	4	2	3		
	Rate	47.17	31.34	20.72	41.64	40.56	44.10		
Postnecrotic	No.	4	3	7	1	1	1		
	Rate	9.43	4.91	10.45	10.42	20.30	14.05		
Nutritional	No.	1	3	2	0	0	0		
	Rate	2.36	4.87	3.00					
Total	No.	25	25	24	5	3	4		
	Rate	58.96	41.10	35.64	51.85	60.64	58.37		
Nagasaki Male									
Posthepatic	No.	11	4	16	4	3	4		
	Rate	87.30	44.52	67.60	95.93	75.73	100.86		
Postnecrotic	No.	2	1	0	3	0	2		* Sug
	Rate	15.87	13.85		69.12		43.28		
Nutritional	No.	1	1	2	0	0	0		
	Rate	7.94	8.98	8.67					
Total	No.	15	7	20	7	3	6		Sug
	Rate	119.05	77.72	84.60	168.63	77.46	147.40		
Female									
Posthepatic	No.	3	2	3	1	0	0		
	Rate	33.33	26.12	12.64	46.43				
Postnecrotic	No.	1	0	2	1	0	0		
	Rate	11.11		9.75	17.07				
Nutritional	No.	1	0	1	0	0	0		
	Rate	11.11		4.30					
Total	No.	5	2	8	2	1	0		
	Rate	55.56	30.86	33.98	70.11	46.48			
Cities and sexes combined									
Posthepatic	No.	71	53	61	16	6	10		
	Rate	66.05	40.74	35.44	65.51	33.19	52.64		
Postnecrotic	No.	9	7	18	7	4	3		* **
	Rate	8.37	5.04	10.45	26.24	21.05	15.68		
Nutritional	No.	3	4	9	0	0	0		
	Rate	2.79	2.82	5.16					
Total	No.	84	72	93	24	11	13		Sug
	Rate	78.14	51.42	53.57	97.66	59.75	67.19		

* .01 < P ≤ .05 ** .001 < P ≤ .01 † See Table 3 表3を参照

FIGURE 3 RELATIVE RISK OF LIVER CIRRHOSIS BY DOSE & HISTOLOGIC TYPE, CITIES COMBINED

図3 肝硬変の相対的リスク，線量及び組織学的型別，両市合計

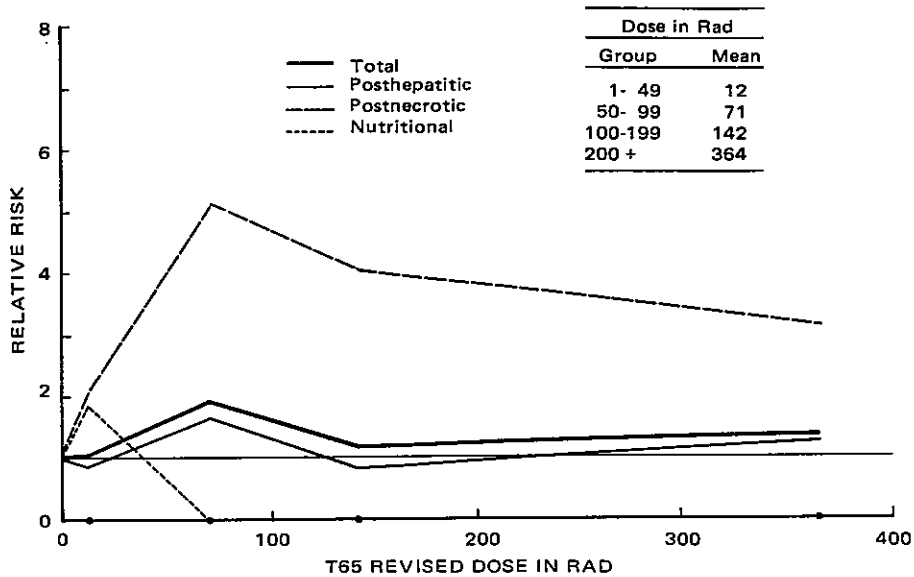


TABLE 10 PROPORTION OF LIVER CIRRHOSIS ASSOCIATED WITH PRIMARY LIVER CARCINOMA BY CITY, HISTOLOGIC TYPE, & DOSE

表10 原発性肝癌を伴った肝硬変の割合，都市，組織学的型及び線量別

Histologic type		T65 revised dose in rad							
		Total		NIC + 0		1-99		100+	
		No.	%	No.	%	No.	%	No.	%
Posthepatic	With	37	21.6	24	22.0	12	22.6	1	11.1
	Without	134		85		41		8	
	Total	171		109		53		9	
Postnecrotic	With	0	0.0	0	0.0	0	0.0	0	0.0
	Without	36		12		19		5	
	Total	36		12		19		5	
Total	With	40	18.1	24	18.9	15	18.8	1	7.1
	Without	181		103		65		13	
	Total	221		127		80		14	
Nagasaki									
Posthepatic	With	22	43.1	9	45.0	10	41.7	3	42.9
	Without	29		11		14		4	
	Total	51		20		24		7	
Postnecrotic	With	1	8.3	1	25.0	0	0.0	0	0.0
	Without	11		3		6		2	
	Total	12		4		6		2	
Total	With	27	35.5	11	37.9	13	35.1	3	30.0
	Without	49		18		24		7	
	Total	76		29		37		10	

TABLE 11 PROPORTION OF LIVER CIRRHOSIS CASES WITH POSITIVE HB_s Ag BY DOSE
表11 肝硬変のHB_s 抗原陽性の割合，線量別

	Total		T65 revised dose in rad					
			NIC + 0		1-99		100+	
	No.	%	No.	%	No.	%	No.	%
Hiroshima								
Positive	29 (11)	18.7 (39.3)	17 (6)	20.7 (42.9)	7 (4)	12.1 (30.8)	5 (1)	45.5 (100.0)
Negative	126 (17)		65 (8)		51 (9)		6 (0)	
Total	155 (28)		82 (14)		58 (13)		11 (1)	
Nagasaki								
Positive	14 (9)	18.4 (33.3)	8 (6)	27.6 (54.5)	4 (2)	10.8 (15.4)	2 (1)	20.0 (33.3)
Negative	62 (18)		21 (5)		33 (11)		8 (2)	
Total	76 (27)		29 (11)		37 (13)		10 (3)	
Total								
Positive	43 (20)	18.6 (36.4)	25 (12)	22.5 (48.0)	11 (6)	11.6 (23.1)	7 (2)	33.3 (50.0)
Negative	188 (35)		86 (13)		84 (20)		14 (2)	
Total	231 (55)		111 (25)		95 (26)		21 (4)	

Cases with primary liver cancer in parentheses ()内は原発性肝癌を伴った症例

TABLE 12 PROPORTION OF HB_s Ag POSITIVE IN LIVER CIRRHOSIS BY AGE ATB
表12 肝硬変のHB_s 抗原陽性の割合，原爆時年齢別

	Total		0-19		20-34		35-49		50+	
	No.	%	No.	%	No.	%	No.	%	No.	%
Hiroshima										
Positive	29	18.7	2	22.2	7	26.9	16	21.3	4	8.9
Negative	126		7		19		59		41	
Total	155		9		26		75		45	
Nagasaki										
Positive	14	18.4	1	7.7	0	.0	11	28.2	2	13.3
Negative	62		12		9		28		13	
Total	76		13		9		39		15	
Total										
Positive	43	18.6	3	13.6	7	20.0	27	23.7	6	10.0
Negative	188		19		28		87		54	
Total	231		22		35		114		60	

the 1 rad or more group (Table 11). The distribution of positive HB_s Ag cases was examined by age ATB; the highest positive rate was noted in the age ATB group 35-49 years and the lowest in 50 years or more (Table 12).

When the liver of patients without overt liver disease matched by sex and age ATB in both cities was examined for HB_s Ag, positive results were found in 5.4% in Hiroshima and 12.5% in

た(表11). HB_s 抗原陽性例の分布を原爆時年齢別にみると，最も陽性率が高いのは原爆時年齢35-49歳の群で，最低は50歳以上の群であった(表12).

明白な肝疾患のない患者の肝臓について両市で性及び原爆時年齢を一致させてHB_s 抗原の有無を調べたところ，陽性は広島が5.4%，長崎が12.5%であっ

FIGURE 4 RELATIONSHIP BETWEEN PRIMARY LIVER CARCINOMA,
LIVER CIRRHOSIS (LC), AND HB_sAg

図4 原発性肝癌、肝硬変及びHB_s抗原の関係

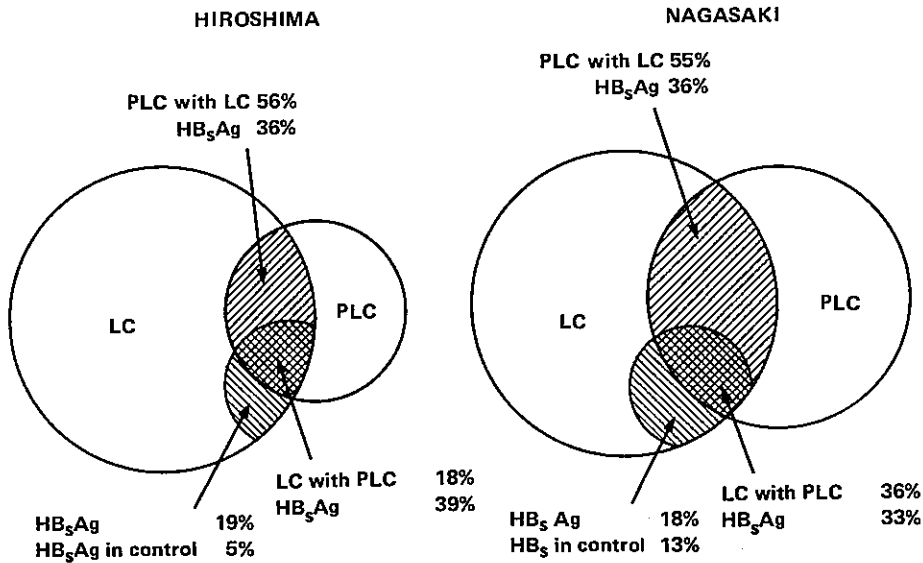


TABLE 13 HB_s Ag POSITIVE RATE IN CONTROLS

表13 対照者のHB_s抗原陽性率

Age ATB	Hiroshima			Nagasaki		
	Total	Positive		Total	Positive	
		No.	%		No.	%
0-9	13	1	7.69	21	3	14.29
10-19	23	1	4.35	33	7	21.21
20-34	21	2	9.52	24	4	16.67
35-49	27	1	3.70	21	1	4.76
50+	18	0	0.00	12	0	0.00
Total	102	5	4.90	111	15	13.51
Age adjusted *		5.37 (indirect) 5.22 (direct)			12.51 12.45	

*Test for city difference, .05 < P < .10
都市間の差の検定

t = 1.81 (H vs N)

Nagasaki. Consequently, HB_s Ag was 2.3 times more common in Nagasaki than in Hiroshima and the lowest positive rate was noted in those aged 50 or more ATB (Table 13).

DISCUSSION

The delayed effects of radiation on the liver include various cloudy swelling of hepatic cells, periportal fibrosis, proliferation of bile ducts,

したがってHB_s抗原は長崎の方が広島よりも2.3倍比率が高く、最も陽性率の低いのは原爆時年齢50歳以上の者であった(表13)。

考 察

放射線が肝臓に及ぼす後影響には肝細胞の種々の混濁腫張、門脈周囲線維症、胆管増殖、肝細胞の

and rapid diffuse necrosis of hepatic cells.^{4,15,16} However, late effects on the liver of A-bomb survivors have not yet been confirmed.^{2,3,17-20} Schreiber et al³ reported a positive association between radiation and the prevalence of liver cirrhosis in a prior study of the ABCC autopsy series, however, in the present study, no effect on the incidence of PLC by radiation but a suggestive association between radiation and the prevalence of liver cirrhosis was noted. The incidence of PLC in the present study was 0.8%. In the pathological autopsy cases in Japan, the rate is approximately 0.7%.²¹ The prevalence of liver cirrhosis in autopsy material is 5.5% in Hiroshima²⁰ and 9.3% in Nagasaki¹⁹ and these rates are almost consistent with those in the present study (5.8% in Hiroshima and 7.2% in Nagasaki). A statistically significant difference in the overall rates of PLC between Nagasaki and Hiroshima has been reported in a prior study² and the present study showed the average incidence per year of PLC was approximately 2.0 times higher in Nagasaki. It is interesting that the higher incidence of PLC in Nagasaki cannot be explained by an increased prevalence of liver cirrhosis, because in the latter there is no clear difference between the two cities.

The positive rate for HB_s Ag was almost 36% in the liver accompanied by liver cirrhosis using PLC samples, and it was almost 36% in the liver accompanied PLC using liver cirrhosis samples in both cities. Furthermore, HB_s Ag occurred at a significantly higher rate (12.5%) in livers without PLC or cirrhosis in Nagasaki than in Hiroshima (5.4%). Kato et al²² reported that the frequency of a positive HB_s Ag reaction in the Adult Health Study sample was about 1.5 times higher in Nagasaki (3.3%) than in Hiroshima (2.0%). Belsky et al²³ reported that the positive hepatitis-associated antigen rate in Nagasaki was almost 1.4 times that in Hiroshima. McGregor et al²⁴ reported also that 2.6% of postmortem sera from 194 ABCC autopsies in Hiroshima were positive for HB_s Ag. Okochi et al²⁵ found a 2.0% positive rate for Australia antigen among voluntary donors in Tokyo and the frequency of Australia antigen in the younger age group was higher than in the older age group. The relatively lower positive rate for HB_s Ag in this study might be explained by a bias in the samples which are composed of relatively older survivors and restricted to those having their permanent address in either city as compared with those of Kanda,²⁶ who reported a positive rate of 54.8%

急速な瀰漫性壊死等がある。^{4,15,16} しかし、原爆被爆者の肝臓における後影響はまだ確認されていない。^{2,3,17-20} Schreiber ら³ は、以前に行った ABCC の剖検例調査で放射線と肝硬変の間に明確な関係があると報告したが、本調査では放射線による原発性肝癌の発生率への影響は認められず、放射線と肝硬変との間に示唆的關係が見られた。本調査では原発性肝癌の発生率は0.8%であった。日本の病理解剖調査では、発生率は約0.7%である。²¹ 剖検材料における肝硬変の有病率は広島で5.5%、²⁰ 長崎で9.3%¹⁹ であり、これらの率は本調査の結果(広島5.8%、長崎7.2%)とほぼ一致する。以前の調査² では、広島と長崎の原発性肝癌の総発生率に統計学的に有意な差があることが報告されており、本調査でも原発性肝癌の年間平均発生率は長崎の方が約2.0倍高かった。肝硬変については両市間で明らかな差がないため、長崎で原発性肝癌の発生率が高いことが肝硬変の有病率増加によると考えられないのは、興味ある所見である。

原発性肝癌の標本を用いた場合、肝硬変を伴った肝臓の HB_s 抗原陽性率は約36%であった、また両市の肝硬変標本における原発性肝癌を伴う例の HB_s 抗原陽性率は約36%であった。更に、原発性肝癌あるいは肝硬変を有していない肝臓においては、HB_s 抗原の頻度は長崎(12.5%)の方が広島(5.4%)よりも有意に高かった。加藤ら²² は、成人健康調査対象者における HB_s 抗原反応の陽性率は長崎(3.3%)の方が広島(2.0%)よりも約1.5倍高いことを報告している。Belsky ら²³ は、肝炎関連抗原の陽性率は長崎では広島の約1.4倍であると報告している。McGregor ら²⁴ も、広島 ABCC における194例の剖検から得られた血清の2.6%に HB_s 抗原が陽性であったと報告している。大河内ら²⁵ は、東京の献血者におけるオーストラリア抗原の陽性率が2.0%であり、その頻度は若年群が高年齢群より高いことを発見した。本調査で HB_s 抗原の陽性率が比較的低いのは、長崎地方の原発性肝癌を有する肝臓の陽性率が54.8%であると報告した神田の調査²⁶ に比べて対象者がかなり高齢の被爆者から成っており、広島・長崎のいず

in livers with PLC in the Nagasaki area. Satoh et al,¹⁹ however, reported a positive rate of 21%.

Thung et al²⁷ and several others²⁸⁻³⁰ have reported that HB_s Ag was found in tumor cells. In our study, HB_s Ag positive tumor cells were detected in 4 of 128 PLC cases. Trevisan et al³¹ reported that in a few cases the tumor cells were positive for core antigen while nontumor cells were negative. Maupas et al³² ascertained serologically that the prevalence of anti-HB core antigen was higher in PLC patients than in controls, ranging from 70% to 95% in the patients and from 20% to 68% in the controls from Asia and Africa and 24% of PLC patients and 4% of controls from the U.S. These findings suggest that HB virus infection might have a close connection with oncogenicity. Williams³³ asserted that the frequency of HB_s Ag detection was greater in the sera of patients living in areas with a higher incidence rate of PLC than those with a lower rate. In general, the reports in several countries^{34,35} reveal that there is a strong correlation between HB_s Ag prevalence and mortality from PLC. In Japan, HB_s Ag was positive in 60% of livers with PLC in Tokushima Prefecture, where the death rate from PLC is the highest.³⁶ It is generally accepted that viral hepatitis is one of the most important antecedent lesions which predisposing to posthepatic or postnecrotic cirrhosis, although the precise relationship between HB virus infection and PLC is uncertain. However, the possibility that HB is a risk factor for PLC has been proposed previously on various occasions. In the international workshop on HB and liver cancer, Ziegler et al³⁷ summarized that susceptibility factors may include risk of exposure to HB virus, age of onset of infection (tolerance), duration of infection, immunological determinants, nutritional status, or virus strain (virulence). And they introduced some studies that provided evidence for HB virus infection in early life in PLC patients indicating perinatal infection from mothers who were carriers. Such a condition was ascertained experimentally by Gyorkey et al³⁸ who reported that a group of monkeys given only HB virus showed no evidence of PLC, or HB virus with diethylnitrosamine (DENA) did not influence the induction period of PLC. However, multifocal PLC apparently developed in the postnecrotic cirrhotic nodule, when juvenile monkeys were given HB virus before the administration of DENA. In the present study, 22% of posthepatic cirrhosis was associated

れかに本籍を有している者に限られているという偏りによるものかもしれない。しかし佐藤ら¹⁹は、陽性率が21%であると報告している。

Thung ら²⁷ 及び若干の研究者²⁸⁻³⁰ は、腫瘍細胞内に HB_s 抗原が認められたと報告している。本調査では、128例の原発性肝癌のうち4例に HB_s 抗原陽性腫瘍細胞が探知された。Trevisan ら³¹ は、2-3の症例において腫瘍細胞は core 抗原が陽性であったが、非腫瘍細胞では陰性であったと報告している。Maupas ら³² は、原発性肝癌患者の抗 HB core 抗原の頻度は対照者より高く、アジア、アフリカの患者が70%-95%でその対照者が20%-68%、米国の患者が24%でその対照者が4%であることを血清学的に確認している。これらの所見は、HBウイルス感染が発癌と密接な関連をもっているかもしれないということを示唆している。Williams³³ は、原発性肝癌の発生率の高い地域に住んでいる患者の血清 HB_s 抗原探知率は、発生率の低い地域の患者より高いことを報告した。一般に幾つかの国の報告^{34,35} では、HB_s 抗原の頻度と原発性肝癌の死亡率との間には強い相関のあることが明らかにされている。日本では、原発性肝癌の死亡率が最も高い徳島県では、原発性肝癌を有する肝臓の HB_s 抗原陽性率は60%であった。³⁶ HBウイルス感染と原発性肝癌との明らかな関係は確認されていないが、ウイルス性肝炎が肝炎後性や壊死後性肝硬変の原因となる最も重要な前駆病変の一つであるということは一般に認められている。しかし、B型肝炎が原発性肝癌のリスク要因である可能性は以前から提唱されてきた。B型肝炎及び肝癌に関する国際ワークショップにおいて、Ziegler ら³⁷ は、罹患要因としてはHBウイルスへの被曝、感染時年齢(耐性)、感染期間、免疫学的決定因子、栄養状態、ウイルス種(菌力)等があると述べた。また、幾つかの調査を紹介し、原発性肝癌患者が早期にHBウイルスに感染していた証拠を示した。これはキャリアであった母親から分娩時に感染したことによるものであった。このことはGyorkey らの実験³⁸ でも確認されており、HBウイルスのみを与えた猿の群は原発性肝癌を示さず、diethylnitrosamine (DENA) とHBウイルスを与えても原発性肝癌の誘発時期に影響を及ぼさなかった。しかし、若年の猿にDEN Aを投与する前にHBウイルスを与えると、壊死後性硬変結節に明らかな多発性原発性肝癌が発現した。本調査では長崎の原発性肝癌の発生率は

with PLC in Hiroshima, and 43% in Nagasaki, despite the fact that the Nagasaki incidence rate of PLC was higher than Hiroshima whereas the prevalence of liver cirrhosis was about the same in both cities. As summarized in Figure 4, the high incidence of PLC in Nagasaki might be attributed to HB virus infection, but further careful studies on other factors such as immunological competence and various mycotoxins are necessary.

広島より高く、肝硬変の有病率は両市ではほぼ等しいにもかかわらず、原発性肝癌を伴った肝炎後性肝硬変は広島で22%、長崎で43%であった。図4にまとめたように、長崎の原発性肝癌発生率が高いのはHBウイルス感染によるものかもしれないが、免疫能や種々の菌類毒素のような他の要因についても更に慎重な調査を行う必要がある。

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