TECHNICAL REPORT
RERF TR 14-78
業 績 報 告 書

BREAST CANCER AMONG ATOMIC BOMB SURVIVORS
RELATIONSHIP OF PROGNOSIS TO PATHOLOGIC FINDINGS

原 爆 被 爆 者 の 乳 癌
予 後 と 病 理 学 的 所 見 と の 関 連 に つ い て

MASAYOSHI TOKUNAGA, M.D. 徳永正義

放影研
RERF

RADIATION EFFECTS RESEARCH FOUNDATION
財団法人 放 射 線 影 響 研 究 所

A cooperative Japan - United States Research Organization
日 米 共 同 研 究 機 関

ACKNOWLEDGMENT

謝　辞

See page 16.
16ページ参照

RERF TECHNICAL REPORT SERIES
放影研業績報告書集

The RERF Technical Reports provide the official bilingual statements required to meet the needs of Japanese and American staff members, consultants, and advisory groups. The Technical Report Series is in no way intended to supplant regular journal publication.

放影研業績報告書は，日米専門職員，顧問，諮問機関の要求に応えるための日英両語による公式報告記録である．業績報告書は決して通例の誌上発表論文に代わるものではない．

The Radiation Effects Research Foundation (formerly ABCC) was established in April 1975 as a private nonprofit Japanese Foundation, supported equally by the Government of Japan through the Ministry of Health and Welfare, and the Government of the United States through the National Academy of Sciences under contract with the Department of Energy.

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国学士院の補助金とをもって充てる．

放影研 RERF RADIATION EFFECTS RESEARCH FOUNDATION
財団法人 放射線影響研究所

Research Project 研究課題 7-74

BREAST CANCER AMONG ATOMIC BOMB SURVIVORS; RELATIONSHIP OF PROGNOSIS TO PATHOLOGIC FINDINGS

原爆被爆者の乳癌 予後と病理学的所見との関連について

MASAYOSHI TOKUNAGA, M.D.(徳永正義)*

Department of Pathology
病理部

** The Second Department of Pathology, School of Medicine, Kagoshima University*
鹿児島大学医学部第二病理学教室

SUMMARY

Three hundred and sixty cases of breast cancer were collected from among the 63,000 female members of the RERF extended Life Span Study sample which includes atomic bomb exposed women and controls of Hiroshima and Nagasaki. The relationship of these breast cancer cases to A-bomb radiation was sought, and in studying 5-year survival, the following conclusions were obtained concerning its relationship to histopathological findings: 1) The prognosis of the 50+ rad high dose group is the best, followed by the nonexposed group and the low dose group; 2) The apparently better survival may be due, at least in part, to the fact that this group is heavily weighted in favor of those who were younger at the time of the bomb; 3) There is no specificity of the histologic type of breast cancer in the survivors by dose; 4) Nor, is any significant difference observed in the distribution of tumor size and histological grade; 5) Cellular reaction is significantly marked at the stroma of carcinoma tissue in the high dose group; 6) Immune reaction is considered to be strong at the affected site of breast cancer in the high dose group and this can be regarded as a finding suggestive of good prognosis; 7) Further extended studies are therefore warranted.

INTRODUCTION

More than 30 years after the A-bombs, leukemia, thyroid cancer, lung cancer, and breast cancer are reported as malignant neoplasms related to

要 約

広島および長崎の被爆女性とその対照例を含む放影研の拡大寿命調査集団63,000名の女性の中から360例の乳癌症例を収集した．これらの乳癌症例の原爆放射線との関連を求めるとともに，5年間の予後について調べた結果，病理組織学的所見に関連して次のような結論が得られた．1) 50 rad 以上の高線量被曝者群の予後が最も良く，次に非被曝者群，さらに低線量被曝者群と続く．2) 50 rad 以上の高線量被曝者群の生存率が他に比べて良いようにみえるのは，原因の一部としておそらくこの群が被爆時に若年であった者が多く，統計的に偏っていることによるものと思われる．3) 被爆者の乳癌の病理組織型には被曝線量による特異性はない．4) 腫瘍の大きさ，組織学的悪性度の分布にも被曝線量による有意な差はみられない．5) 高線量被曝者群において癌腫組織の間質に細胞反応が有意に強くみられた．6) 高線量被曝者の乳癌では，局所での免疫反応が強いと考えられ，これはその予後が良いことを示唆する所見とみなされる．7) したがって今後さらに広範な調査が必要である．

緒 言

原爆に被爆してから30年余りを経て，広島および長崎の原爆被爆者において電離放射線と関係のある

Approved 承認 10 July 1978

Printed 印刷 October 1978

ionizing radiation in the A-bomb survivors of Hiroshima and Nagasaki.[1] In particular, Wanebo et al[2] in 1967 reported the incidence of breast cancer both clinically and pathologically to be high in females exposed to high doses. McGregor et al[3] made a pathological study of the incidence of breast cancer during 1950-69 on the fixed population of the ABCC (now RERF) extended Life Sapn Study (LSS) sample, and found the incidence of breast cancer significantly increased with increase of exposure dose. The present author and associates studied breast cancer incidence in A-bomb exposed females of Hiroshima and Nagasaki in the period 1950-74, on the same fixed population as McGregor et al[3] but with the period extended, and pointed out that the risk of breast cancer showed a statistically linear increase with radiation exposure dose.[4]

The present paper describes a study using the same materials in an attempt to determine the biological effects of ionizing radiation on A-bomb survivors, the survival rate of breast cancer patients, and the relationship between the pathomorphological findings of breast cancer and prognosis by exposure dose.

MATERIALS AND METHOD

The breast cancer cases selected for study were collected from the Tumor and Tissue Registries of Hiroshima and Nagasaki, Schools of Medicine of Hiroshima and Nagasaki University, RERF, and the departments of pathology and surgery of public and municipal hospitals in the two cities. All subjects are included in the extended LSS sample which is composed of approximately 110,000 members based on Japanese exposed survivors resident in either Hiroshima or Nagasaki at the time of the 1950 National Census, and nonexposed matched controls. It is so constructed that the findings obtained can readily be used for epidemiological review. There are approximately 63,000 females in this sample including 47,600 who were within 10,000 m from the hypocenter in Hiroshima or Nagasaki at the time of the bomb (ATB) and 15,400 not-in-city (NIC) subjects who migrated into the two cities after the bombs. The breast tissue dose has been calculated for most of these subjects.[5] Among the cases selected, 360 were diagnosed as breast cancer during 1950-74 and these became the study subjects. They were classified by exposure dose (T65D) into the NIC+0 rad nonexposed group (NIC+0 rad group), 1-49 rad exposed group (1-49 rad group), 50 rad

悪性腫瘍として，白血病，甲状腺癌，肺癌，乳癌[1]が報告されている．1967年にWanebo ら[2]は，特に乳癌の発生率が臨床的にも病理学的にも高線量被曝女性に高いことを指摘している．McGregor ら[3]はABCC（現放影研）の拡大寿命調査集団（LSS）という固定人口集団を対象として1950—69年の期間における乳癌発生の病理学的調査を行い，乳癌発生率が被曝線量の増加に伴い有意に増加することを見いだしている．著者らはMcGregor ら[3]と同じ固定人口集団ではあるが期間を延長し，1950—74年間の広島および長崎の被爆女性における乳癌発生の調査研究を行い，被曝放射線量の増加に伴い乳癌発生危険率が統計学的に直線的上昇を示していることを指摘した．[4]

本論文では，同じ検索材料を用いて，電離放射線が被爆者に与える生物学的影響，乳癌患者の生存率，および乳癌の病理形態学的所見と予後との関係を被曝線量別に検討する．

材料および方法

調査のための乳癌症例は，広島・長崎の腫瘍登録ならびに組織登録，広島大学および長崎大学の医学部，放影研，さらに両市の公・市立病院の病理部および外科から収集した．対象者全員を含む放影研の拡大寿命調査集団とは，1950年の国勢調査時に広島あるいは長崎に在住していた日本人被爆者およびこれと対照の非被爆者，合計約110,000名から構成されている．この調査集団から得られた所見は容易に疫学的検討が行えるように設定されている．これらの中で女性は約63,000名で，これは原爆時（ATB）に広島および長崎の爆心地から10,000m以内にいた者約47,600名，および原爆後両市に転入した原爆時市内にいなかった者（NIC）約15,400名の女性例を含んでおり，これらの大部分については推定乳腺組織被曝線量が計算されている．[5] 以上の選別された症例のうち1950—74年間に乳癌と診断された症例は360例であり，これらを研究対象とした．被曝線量（T65線量）で分類して，NIC＋0 radの非被曝者群（NIC＋0 rad群），1—49 radの被曝者群（1—49 rad群），および50 rad以上の被曝者群（50＋ rad群），さらに

and over exposed group (50+ rad group), and exposure dose unknown group (UNK group).

By koseki (official family record) check of all study cases, the prognosis after the lapse of 5 years or more as of 31 May 1977 was ascertained for 321 (89%) of the 360 cases. Among them, 187 had died and death certificates were available. From this investigation, the observed survival rates were calculated by the methods of Kurihara and Takano,[6] and Axtell[7] and relative survival rates were calculated by obtaining the expected survival rates by dose group using their table of year- and age-specific expected survival rates in Japan.[8] Observed survival rates were calculated for the three dose categories and for age ATB; comparisons were based on survival rates at 5 years.

Histopathological reexamination was possible for 234 of the 360 cases. These cases were classified by histologic type according to the criteria of the Nihon Nyugan Kenkyu Kai (Japan Breast Cancer Research Society)[9] and compared by three dose groups: NIC+0 rad group, 1-49 rad group, and 50+ rad group. Size of tumor, histologic grade, and degree of cellular reaction were evaluated in addition to histopathologic type and compared with the 5-year survival rate by dose group. Histologic grading was done by the methods of Bloom and Richardson[10] and Champion and Wallace.[11] Scores were assigned to the three findings of tubule formation, nuclear morphology, and mitotic figures by the extent of each and the sum of scores was considered to be the histologic grade, divided into grades I-III. Photographs of each are shown in Figure 1 ABC. Inflammatory lymphocytic infiltration in the tumor tissues can be regarded as a defensive reaction of the living body against tumor tissues. This was used to study whether it was related in any way to the prognosis of the patient by examining the distribution by dose group of the grades of lymphocytic infiltration, divided into the three grades of mild, moderate, and marked (Figure 1 DEF), and a comparative study was made with the 5-year survival rate of each. A similar study was made of the forms of lymphocytic infiltration divided into three classifications, according to the method of Harry et al[12] (i.e., Peri – infiltration in the peripheral area of the tumor; Inter – infiltration in the interspaces of the tumor nests; and Intra – infiltration in the interspaces of the tumor cells).

被曝線量不明群(UNK群)に分けて検討した.

全検索症例の戸籍照合により,1977年5月31日現在で360例中321例(89%)は5年以上経過しての予後が確認されている.そのうち187例が死亡し,その死亡診断書を入手した.この調査から,栗原,高野[6]およびAxtell[7]の方法により実測生存率を計算するとともに,日本における年次別,年齢別期待生存率の表[8]を利用して,被曝線量別の期待生存率を求め相対生存率も算出した.実測生存率は三つの線量群別および原爆時年齢別に求め,その比較は5年の生存率を基に行った.

360例中病理組織学的に再検査が可能な症例が234例あった.これらの症例について日本乳癌研究会[9]の分類基準に従って組織型分類を行い,三つの被曝線量群(すなわち,NIC+0 rad群,1—49 rad群,および50+ rad群)別に比較した.病理組織型のほかに腫瘍の大きさ,組織学的悪性度,細胞反応の程度を評価し,被曝線量群別に5年生存率と比較した.組織学的悪性度はBloomおよびRichardson[10]や,Championおよび Wallace[11]の方法に従った.管腔形成,核の形態および核分裂像の3所見につき,それぞれの程度により評価値を与え,その合計をI—III度の組織学的悪性度とみなした.それぞれの写真を図1ABCに示す.腫瘍組織における炎症性細胞浸潤は,腫瘍組織に対する生体側の防衛反応の一つとみなされる.これが患者の予後と関連性を有するかどうかを検討するためにとりあげたものである.その方法として,細胞浸潤の程度を軽度(図1D),中等度(図1E),高度(図1F)の3段階に分け,被曝線量群別にその分布を調べそれぞれの5年生存率と比較検討した;また,細胞浸潤の様式についてもHarryら[12]の方法に準じてPeri(腫瘍周囲への細胞浸潤),Inter(腫瘍胞巣間への浸潤)およびIntra(腫瘍細胞間への浸潤)の3種類に分けて同様に検討した.

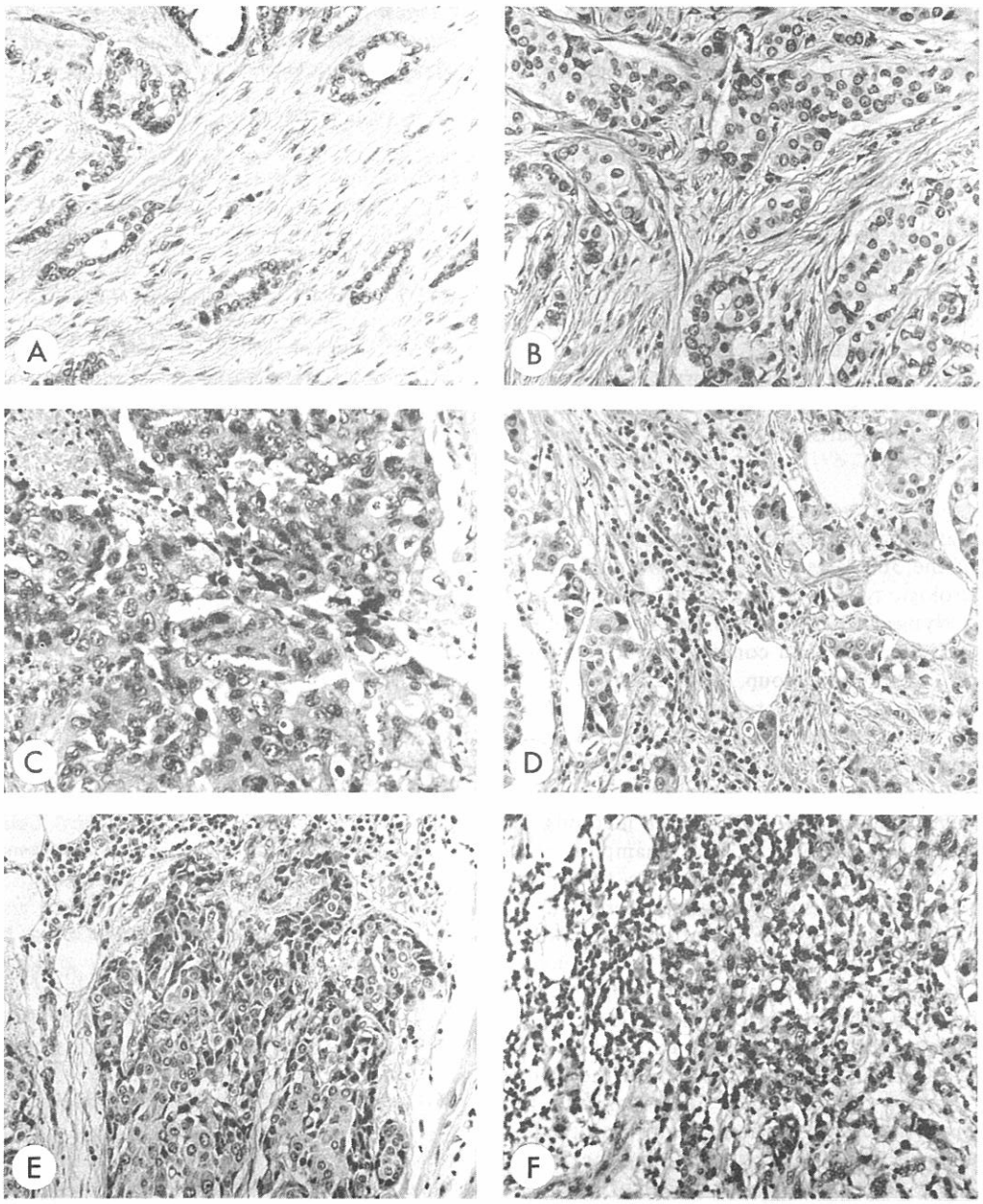


FIGURE 1. HISTOLOGICAL FINDINGS. A: Grade I, showing well differentiated tubule formation, regular size and staining of the nucleus and very rare mitotic figures. B: Grade II, showing moderate nuclear pleomorphism and few mitotic figures. C: Grade III, showing marked nuclear pleomorphism and many mitotic figures. D: Mild lymphocytic infiltration in interspaces of the tumor nests (INTER). E: Moderate lymphocytic infiltration in peripheral area of the tumor (PERI). F: Marked lymphocytic infiltration in interspaces of the tumor cells (INTRA).

図1　組織学的所見．A：悪性度Ⅰ，進んだ管腔形成の分化，核の正常の大きさと染色，きわめて少数の核分裂像が見られる．B：悪性度Ⅱ，中等度の核多形成と少数の核分裂像が見られる．C：悪性度Ⅲ，顕著な核多形成と多数の核分裂像が見られる．D：腫瘍胞巣間への軽度のリンパ球浸潤（INTER）．E：腫瘍周囲への中等度のリンパ球浸潤（PERI）．F：腫瘍細胞間への高度のリンパ球浸潤（INTRA）．

RESULTS

A study of the 360 cases of breast cancer divided into four groups by estimated breast tissue exposure dose determined the yearly incidence per 100,000 female population (Table 1). Whereas the frequency in the NIC+0 rad group of 23.02 cases was not very different from 24.62 in the 1-49 rad group, the frequency was 58.29 in the 50+ rad group. The distribution of these frequencies shows statistically significant difference by dose group even on the cases reviewed histologically (χ^2=52.72, P<0.002).

結　果

360例を推定乳腺組織被曝線量により4群に分けて検討すると，女性人口100,000人当たりの乳癌年間発生頻度が明らかになった（表1）．NIC＋0 rad群の23.02人という発生頻度は，1－49 rad群の24.62人と大差ないのに対し，50＋ rad群では58.29人であった．組織学的に検査された症例にも，発生頻度の分布状態には統計学的に有意な差がみられた（$\chi^2 = 52.72$, $P < 0.002$）．

TABLE 1 BREAST CANCER INCIDENCE RATE BY TISSUE DOSE
表1　乳癌発生率，組織線量別

Dose group	Person years at risk	Total Study cases	Cases of path. Review
NIC+0	829738	191 (23.02)	118 (14.22)
1-49	402045	99 (24.62)	62 (15.42)
50+	104651	61 (58.29)	47 (44.91)
Unknown	28931	9 (31.11)	7 (24.20)
Total	1365365	360 (26.37)	234 (17.14)

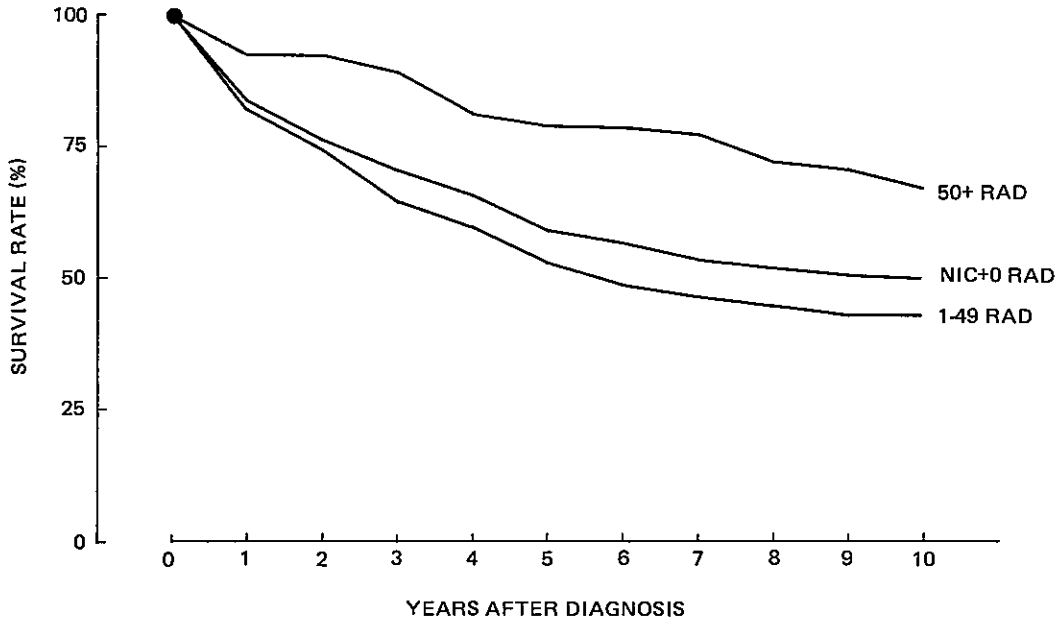
( ) Incidence rate, cases/100,000 women/year
（）は発生率を示す，年間100,000人（女子）当たりの症例

Figure 2 shows the curves of the trends of the observed survival rates from 1 to 10 years after diagnosis of breast cancer in the various dose groups. The 5-year survival rates were 58.6% in the NIC+0 rad group, 52.2% in the 1-49 rad group, and 78.5% in the 50+ rad group, and the 10-year survival rates were 49.1 %, 42.2%, and 66.6%, respectively. The curve for the 50+ rad group shows the most favorable survival followed by the NIC+0 rad group (Table 2). The survival rate of the 1-49 rad group was the poorest. The relative estimated 5-year survival rate, was 63.6% in the NIC+0 rad group, 56.0% in the 1-49 rad group, and 81.4% in the 50+ rad group. It is evident that the relative survival rate is also very good in the 50+ rad group. The distribution of cases and observed survival rates by age ATB and dose group are shown in Table 3. Though the 50+ rad group comprised the smallest number of persons, the distribution is higher in the younger age ATB groups (0-19, 20-29) and lower in the older age ATB groups (40-49, 50+). The 5-year survival rates in general gradually decreased with increase of age ATB in the NIC+0 and 1-49 rad groups, but this trend is not apparent in the 50+ rad group.

図2は，乳癌診断時より1年から10年に至る各群における実測生存率の推移曲線を示す．5年生存率はNIC＋0 rad群で58.6%，1－49 rad群で52.2%，50＋ rad群で78.5%であり，10年生存率はそれぞれ49.1%，42.2%，66.6%であった．50＋ rad群の曲線が最も高い生存率を示し，次がNIC＋0 rad群である（表2）．1－49 rad群の生存率が最も悪い．相対推定5年生存率は，NIC＋0 rad群で63.6%，1－49 rad群で56.0%，50＋ rad群で81.4%であり，相対生存率においても50＋ rad群の生存率が非常に良いことが明らかである．原爆時年齢別および線量群別にみた症例分布状態と実測生存率を表3に示した．50＋ rad群の対象者数は最も少数であるにもかかわらず，その症例分布状態は原爆時に若年であった群（0－19歳，20－29歳）に高く，高年群（40－49歳，50＋歳）では低かった．5年生存率は一般にNIC＋0 rad群および1－49 rad群では原爆時年齢の増加に伴い徐々に減少したが，50＋ rad群ではこの傾向は明白ではない．

FIGURE 2 OBSERVED SURVIVAL RATES 1-10 YEARS AFTER DIAGNOSIS OF BREAST CANCER

図２　乳癌診断時より１－10年後の実測生存率



The case distribution of the histologic types by dose group in the 234 cases on which pathologic examination was possible is shown in Table 4, but no statistically significant difference is evident (χ^2=10.119, 0.265<P<0.202). Compared with the NIC+0 rad group, the medullary tubular type and the special type are more frequent, and the papillotubular type and the scirrhous type are less freuqent in the 1-49 rad group. The special type is rather frequent in the 50+ rad group.

The 5-year survival rates by histologic type in the dose groups are shown in Table 5. Whereas the rate was 100% for the noninfiltrating type, 58.7% for the papillotubular type, 42.8% for the medullary tubular type, and 61.3% for the scirrhous type in the NIC+0 rad group, the 5-year survival rate in the 50+ rad group was generally favorable with the exception of the scirrhous type, though the number of cases was small. Particularly noteworthy is the 5-year survival rate of 100% indicated for the medullary tubular type.

病理学的検査が可能であった234例における組織線量群別の病理組織型症例分布は表４に示す通りであるが，統計学的に有意な差はみられない（χ^2 =10.119, 0.265< P < 0.202）．NIC＋０rad 群に比較して１－49 rad 群では髄様腺管型と特殊型が多く，乳頭腺管癌および硬癌が少ない．また50＋ rad 群では特殊型がやや多い．

各群における組織型別５年生存率を表５に示すが，NIC＋０rad 群では非浸潤癌が100%，乳頭腺管癌が58.7%，髄様腺管癌が42.8%，硬癌が61.3%であるのに対し，50＋ rad 群では症例数は少ないが硬癌を除き全体に５年生存率が良い．注目すべきことは，髄様腺管癌が100%の５年生存率を示していることである．

TABLE 2 BREAST CANCER 5-YEAR SURVIVAL RATES BY TISSUE DOSE
表 2　乳癌の 5 年生存率，組織線量別

Dose group	Study cases	5-year survivor	5-year survival rate		
			Observed	Expected	Relative
NIC+0	191	113	58.6	92.2	63.6
1-49	99	52	52.2	93.2	56.0
50+	61	48	78.5	96.4	81.4
Unknown	9	3	65.7		
Total	360	216	59.6		

TABLE 3 BREAST CANCER 5-YEAR SURVIVAL RATES BY AGE ATB AND TISSUE DOSE
表 3　乳癌の 5 年生存率，原爆時年齢および組織線量別

Age ATB	Dose group								
	NIC+0			1-49			50+		
	Cases	%	Rate	Cases	%	Rate	Cases	%	Rate
0-19	34	18	76.2	20	20	64.8	25	41	83.0
20-29	44	23	64.2	21	21	64.3	17	28	88.4
30-39	49	26	50.6	21	21	66.0	13	21	53.8
40-49	38	20	55.0	22	22	38.9	2	3	100.0
50+	26	13	42.1	15	15	13.3	4	6	75.0
Total	191	100		99	100		61	100	

TABLE 4 BREAST CANCER BY HISTOLOGICAL TYPE AND TISSUE DOSE
表 4　乳癌，病理組織型および組織線量別

Type	Dose group								Total		Sakamoto[20]	
	NIC+0		1-49		50+		Unk.					
Noninfiltrating	3	3%	2	3%	2.	4%	0		7	3.0%	90	3.5%
Papillotubular	27	23	8	13	9	19	3		47	20.0	543	21.3
Medullary tubular	27	23	23	37	11	23	3		64	27.4	528	20.7
Scirrhous	53	44	20	32	20	43	1		94	40.2	1201	47.1
Special types	8	7	9	15	5	11	0		22	9.4	187	7.3
Total	118	100	62	100	47	100	7		234	100	2549	100

As an index of the stage of disease at the time of diagnosis the distribution of the tumor sizes by dose groups (Table 6) showed that tumors of 0-1.9 cm were rather numerous and those of 2.0-4.9 cm were infrequent in the 1-49 rad group. There were few of 5.0 cm or more in the 50+ rad group. However, these differences were not statistically significant (χ^2=2.867, 0.736<P<0.558).

乳癌診断時の病期の指標として，各群での腫瘍の大きさの分布をみると（表 6），1－49 rad 群では 0－1.9cmの症例がやや多く，2.0－4.9cmが少ない．50＋ rad 群では 5 cm以上が少ない．しかしこれらの差異は統計学的に有意でない（χ^2 = 2.867, 0.736< P < 0.558）.

TABLE 5 BREAST CANCER 5-YEAR SURVIVAL RATES BY HISTOLOGICAL TYPE AND TISSUE DOSE

表 5　乳癌の 5 年生存率，病理組織型および組織線量別

Type	Dose group					
	NIC+0		1-49		50+	
	Cases	Rate	Cases	Rate	Cases	Rate
Noninfiltrating	3	100	2	100	2	100
Papillotubular	27	58.7	8	72.2	9	77.8
Medullary tubular	27	42.8	23	43.3	11	100
Scirrhous	53	61.3	20	65.6	20	64.5
Special Type	8	87.5	9	44.4	5	80.0

TABLE 6 BREAST CANCER 5-YEAR SURVIVAL RATES BY TUMOR SIZE AND TISSUE DOSE

表 6　乳癌の 5 年生存率，腫瘍の大きさおよび組織線量別

Size	Dose group								
	NIC+0			1-49			50+		
	Cases	%	Rate	Cases	%	Rate	Cases	%	Rate
0-1.9 cm	31	25	64.5	21	33	66.7	14	28	64.3
2.0-4.9	59	47	64.4	24	38	62.5	25	50	80.0
5.0+	35	28	42.9	19	29	21.1	11	22	72.7
Total	125	100		64	100		50	100	

As for the relation between tumor size and prognosis in the NIC+0 rad group and the 1-49 rad group, the 5-year survival rates of the cases whose tumor size was 5 cm or more were considerably poorer than for those of less than 5 cm. On the other hand, it is noteworthy that the prognosis in cases with large-sized tumors is by far more satisfactory than with small-sized tumors of 2 cm or less in the 50+ rad group, and also is better than in the NIC+0 rad group and the 1-49 rad group.

The distribution of the cases by histological grade and dose group with 5-year survival rates are shown in Table 7. Among the three dose groups, cases of histological grade I, the lowest grade, were the least frequent and grade II the most frequent in the 1-49 rad group, while on the contrary, grade I was the most frequent and grade II the least frequent in the 50+ rad group. However, these differences are not statistically significant ($\chi^2=6.86$, $0.199<P<0.136$). The

また腫瘍の大きさと予後との関係については，NIC＋0 rad 群および 1－49 rad 群では 5 cm以上の症例の 5 年生存率が 5 cm以下の症例よりかなり悪い．一方，50＋ rad 群では腫瘍が大きい症例の予後が 2 cm以下の小腫瘍群例よりも，また NIC＋0 rad 群や 1－49 rad 群よりもはるかに良好であるのが注目される．

組織学的悪性度の症例数分布および各群の 5 年生存率を表 7 に示す．1－49 rad 群では，低悪性度とされる悪性度 I の症例数が 3 群のうち最も少なく，II が多い．また 50＋ rad 群では逆に I が多く II が少ない．しかしながら，これらの差異は統計学的に有意でない（$\chi^2=6.86$，$0.199<P<0.136$）．それぞれの 5 年

TABLE 7 BREAST CANCER 5-YEAR SURVIVAL RATES BY HISTOLOGICAL GRADE AND TISSUE DOSE

表7　乳癌の5年生存率，組織学的悪性度および組織線量別

Grade	Dose group								
	NIC+0			1-49			50+		
	Cases	%	Rate	Cases	%	Rate	Cases	%	Rate
Grade I	65	55	70.9	26	42	59.8	30	64	75.7
Grade II	44	37	42.4	32	52	51.3	13	28	76.6
Grade III	9	8	55.5	4	6	0	4	8	100
Total	118	100		62	100		47	100	

TABLE 8 BREAST CANCER 5-YEAR SURVIVAL RATES BY DEGREE OF CELLULAR REACTION AND TISSUE DOSE

表8　乳癌の5年生存率，細胞浸潤の程度および組織線量別

Degree	Dose group								
	NIC+0			1-49			50+		
	Cases	%	Rate	Cases	%	Rate	Cases	%	Rate
Mild	48	56	56.4	27	66	45.8	0	0	0
Moderate	32	37	44.8	12	29	54.5	21	70	68.4
Marked	6	7	75.0	2	5	50.0	9	30	100
Total	86	100		41	100		30	100	

5-year survival rate was the highest for grade I followed by grades III and II in the NIC+0 rad group, but the prognosis was better in the 50+ rad group than in any other groups regardless of histological grade. It is of particular interest that a 5-year survival rate of 100% is observed even for grade III.

Table 8 shows the degree of cellular reaction and the 5-year survival rate in each dose group. Whereas mild cellular reactions account for the majority in the NIC+0 rad group and 1-49 rad group with 56% and 66%, respectively, moderate to marked cellular reactions account for all of the cases in the 50+ rad group, there being no mild cases. These differences between the groups are statistically significant ($\chi^2=38.739, P<0.001$).

Prognosis in the dose groups does not necessarily parallel the degree of cellular reaction, but a tendency is seen for the prognosis to be generally satisfactory in the cases where the reaction is

生存率はNIC＋0 rad群では悪性度Ⅰが良く，次いでⅢ，Ⅱと続くのに対し，50＋ rad群では悪性度に関係なくいずれも他群より予後が良い．ことに悪性度Ⅲでも100%の5年生存率を示していることは興味深い．

表8は各群における細胞浸潤の程度とそれぞれの5年生存率を示す．NIC＋0 rad群および1－49 rad群では，軽度が56%と66%で過半数を示すのに対し，50＋ rad群では，軽度の症例はなく，中等度から高度の細胞浸潤を認める例によって占められている．これらの各群での差は統計学的に有意である（$\chi^2=38.739$, $P<0.001$）．

各群の予後は必ずしも細胞浸潤の程度と平行しないが，細胞浸潤程度が強い症例の予後が一般に良好で

TABLE 9 BREAST CANCER 5-YEAR SURVIVAL RATES BY TYPE OF CELLULAR REACTION AND TISSUE DOSE
表 9　乳癌の 5 年生存率，細胞浸潤様式および組織線量別

Type	Dose group								
	NIC+0			1-49			50+		
	Cases	%	Rate	Cases	%	Rate	Cases	%	Rate
Peri	32	37	60.9	15	37	41.7	11	37	70.0
Inter	50	58	48.9	26	63	52.0	17	57	81.3
Intra	4	5	100	0	0	-	2	6	100
Total	86	100		41	100		30	100	

marked, and this tendency is especially pronounced in the 50+ rad group. Most of these cellular reactions are comprised of lymphocytes together with plasma cells.

The forms of cellular reaction generally show similar distribution of cases in all dose groups as shown in Table 9. No special relationship can be seen in the differences of these reaction forms between the dose groups (χ^2=2.526, 0.736<P<0.558).

DISCUSSION

With regards the relationship between ionizing radiation from the atomic bomb and female breast cancer, increased risk of breast cancer with increase of exposure dose was reported in both the early study of Wanebo et al[2] (1958-66) on the development of breast cancer in the A-bomb survivors and the study of McGregor et al[3] (1950-69) using the extended LSS sample as the study population. The present author and associates[4] also found in a 1950-74 study using the same study population that the risk of breast cancer is markedly affected by increase of breast tissue dose, noting in particular that whereas the risk increased to a limited extent with increase of dose from 0 to 60 rad (the rate being approximately 135%) the increase was much more marked from 70 to 140 rad (the rate being approximately 220%). In the present study the author reviewed the examination data of 360 cases of Hiroshima and Nagasaki divided into the NIC+0 rad group of 191 cases, the 1-49 rad group of 99 cases in whom the effect of radiation can be regarded as weak, the 50+ rad exposed group of 61 cases, and the dose unknown group of 9 cases, and

ある傾向がみられ，特に50＋ rad 群で顕著である．これらの細胞浸潤の大部分はリンパ球ならびに形質細胞である．

表 9 に示すように，細胞浸潤様式は各群とも同様の症例分布を示している．これらの浸潤様式の相違には，各群における格別の関連性は見いだし得ない（χ^2 = 2.526, 0.736< P < 0.558）．

考　察

原子爆弾による電離放射線と女性乳癌との関連については，被曝放射線量の増加に伴って乳癌発生危険率が上昇することが原爆被爆者における乳癌発生に関する Wanebo ら[2]による初期の研究（1958—66年），および拡大寿命調査集団を母集団とした McGregor ら[3]による研究（1950—69年）で報告されている．著者ら[4]も同一母集団による1950—74年の期間の調査で，乳腺組織被曝線量の増加に伴い乳癌発生危険率は顕著な影響を受けること，特にその増加率は 0—60 rad までの線量で約135%であり比較的緩やかであるのに対し，70—140 rad 群では約 220%のより顕著な増加率であることを認めている．今回，広島・長崎の 360例の検索材料を用い，NIC＋0 rad 線量被曝者群191例，放射線の影響が弱いとみなされる 1—49 rad 線量被曝者群 99例，さらに50 rad 以上の線量被曝者群61例および線量不明群 9 例に分けて検討を加えたが，前回と同様の所見を得ている．

obtained findings similar to those obtained previously. That is, a significant difference is evident in the incidence by radiation dose per 100,000 women population per year, showing the development of breast cancer in exposed women is related to radiation dose (Table 1).

すなわち，女性人口100,000人年当たりの被曝線量別発生頻度に有意の差が明らかであり，被爆者女性乳癌の発生が放射線量に関係あることを示している（表1）．

As in other cases of a relationship between irradiation and development of breast cancer in humans, a high incidence of breast cancer in women who repeatedly underwent fluoroscopic examination in pneumothorax for the treatment of tuberculosis was reported by MacKenzie[13] in 1965 and Cook et al[14] in 1974. Recently Boice and Monson[15] found that breast cancer occurred at a high frequency in lactating patients with mastitis following radiotherapy. Thus, it is noteworthy that the presence of a relationship between medical X-ray and development of breast cancer has been accepted as an irrevocable fact.[16]

放射線照射と乳癌発生のその他の人体例は，結核治療のための気胸術の際に透視検査を繰り返し受けた女性に乳癌発生率の高いことが1965年 MacKenzie[13] により，また1974年に Cook ら[14] により報告された．また最近 Boice および Monson[15] は，授乳期乳腺炎に対する放射線治療後の患者に乳癌が高頻度に発生することを認めている．このように医療用放射線と乳癌発生の関係は，決定的事実として認められ注目を受けている．[16]

Our survey of the 5-year survival rate of A-bomb exposed breast cancer cases, indicated that the survival rate was much higher in those exposed to 50+ rad than in the nonexposed and those exposed to low doses of less than 50 rad. The apparently better survival rate in the 50+ rad group compared to the NIC and 1-49 rad groups is based on the 5-year survival, admittedly not an ideal interval, considering the biological behavior of breast cancer, but 10-year survival based on these data is even less satisfactory because of the small number of cases involved. However, as shown in Table 2, the 5-year survival rates of the NIC+0 rad group as the nonexposed control group and the 1-49 rad group were much poorer than the rates reported by other investigators in Japan. According to the report of Sato et al,[17] the 5-year survival rate of breast cancer patients in general was 73.6% and the figures reported by the Japan Breast Cancer Research Society[18] were 4,158 cases among 6,103 common type breast cancer cases, or 68%. The poor 5-year survival rate in the NIC+0 rad group and 1-49 rad group may in part be ascribable to different methods of diagnosis and treatment, inasmuch as the methods used were not necessarily uniform because the cases for this study were collected from various institutions, including the university hospitals, other large institutional hospitals, and hospitals in general in the cities. Further, the cases studied included 16 (8.4%) based only on the death certificate diagnosis in the NIC+0 rad

本論文で原爆被爆者乳癌症例の5年生存率についての検討を試みた結果，50 rad 以上での被曝者は非被曝者や49 rad 以下の低線量被曝者に比べて生存率が非常に良いことが明らかにされた．NIC群および0－49 rad 群に比較すると，50＋ rad 群の生存率は明らかに良いが，この生存率とは5年生存率に基づくものである．5年生存率は確かに乳癌の病態を考慮すると理想的な間隔ではないものの，これらのデータに対して10年生存率を用いることは，関係症例数が少ないためより一層満足のゆくものではないのである．しかし，表2に示すように，非被曝者対照としてのNIC＋0 rad 群および1－49 rad 群の5年生存率は日本の他の研究者の報告にある5年生存率よりきわめて悪い．すなわち，佐藤ら[17]の報告によると一般乳癌患者の5年生存率は73.6%であり，日本乳癌研究会[18]によると通常型乳癌6,103例中4,158例で68%という数字を得ている．NIC＋0 rad 群と1－49 rad 群での5年生存率が悪い理由として，当検索症例の収集が両市の大学病院から一般市中病院まで種々の施設よりなされたため，用いた方法が必ずしも統一されておらず，診断および治療方法に幾分違いがあったためと考えられよう．さらに，検索症例の中には死亡診断書の診断のみの例がNIC＋0 rad 群で16例（8.4%），

group, 9 (9.1%) of the same in the 1-49 rad group, 1 (1.6%) in the 50+ rad group, and 1 (11.1%) in the dose unknown group. Nonetheless, the observed 5-year survival rate of 78.5% in the 50+ rad group, taking this factor into consideration, may be regarded as very good. Additionally, in the 50+ rad group the apparent better survival may be due, at least in part, to the fact that this group is heavily weighted in favor of those of younger age ATB. Also, the possibility should not be neglected that cancer consciousness is high among the A-bomb survivors, and there is the additive effect of social factors, such as having more opportunities to receive medical care. However, it cannot be said, on observing the distribution of tumor sizes as an index of the disease stage at the time of diagnosis, that the diagnoses were made earlier for the 50+ rad group. Sakamoto et al[19] studied tumor sizes and 10-year survival rates and reported that for tumors less than 2 cm in size 10-year survival was 76.7%, but in the present study the 5-year survival for tumors less than 2 cm in size was 64%-66%. On the other hand, whereas the 5-year survival rate for tumors 2 cm or more in size was poor in the NIC+0 rad group and 1-49 rad group, the rate was very good in the 50+ rad group. Thus, the relationship between tumor size and prognosis reported by others was observed among the A-bomb exposed cases. It appears there is a need to conduct further studies at the tissue level to clarify this point.

By histological grade also, it is noteworthy that for those classified as high grade the prognosis was good in the 50+ rad group. Compared with the other groups, the survival rate seems better in this group even for those whose disease stage and histological grade were poor. As for the distribution of the cases in the dose groups by histological grade, compared with the NIC+0 rad group, grade II cases were more frequent in the 1-49 rad group; and grade II cases were less frequent and grade I cases more frequent in the 50+ rad group. This also might have brought about the good survival rate in the 50+ rad group and the lowering of the survival rate in the 1-49 rad group. However, the good prognosis of the 50+ rad group cannot be fully explained only by such a histological study of cancer tissues themselves as described above. Therefore, the defense factors of the host in the tumor-host relationship will also have to be studied.

1－49 rad 群で9例（9.1%），50＋ rad 群で1例（1.6%），UNK群で1例（11.1%）含まれていることにも起因していると考えられる．それにもかかわらず，この因子を考慮してみても，50＋ rad 群での実測5年生存率の78.5%は非常に良いとみなされよう．さらに，50＋ rad 群の生存率が他に比べて良いように見えるのは，原因の一部としておそらくこの群が原爆時に若年であった者が多く，統計学的に偏っていることによるものと思われる．また，原爆被爆者の癌に対する意識程度が高いとか，医療に接する機会が多いなどの社会的因子が加わり生存率が良くなった可能性も否定できない．しかし乳癌診断時の病期の指標としての腫瘍の大きさの分布をみると，50＋ rad 群がより早期に診断されているとは言えない．坂元ら[19]は，腫瘍の大きさと10年生存率の検討を行い，2 cm以下の10年生存率は76.7%であったと報告しているのに対し，本検索例では2 cm以下の5年生存率は64%－66%である．一方，2 cm以上の5年生存率はNIC＋0 rad 群や1－49 rad 群で悪いのに対し，50＋ rad 群では非常に良い．このように原爆被爆症例では，他の研究者により報告された腫瘍の大きさと予後との関連がみられた．そこでこの点を明らかにするため，今後は各種の組織レベルでの検討が必要となるわけである．

組織学的悪性度別にみても，50＋ rad 群では悪性度が高いと分類される症例群の予後が良いことが注目される．すなわち50＋ rad 群では他群に比べると，病期や組織学的悪性度の悪いものでもその生存率が良くなっていると思われる．また，組織学的悪性度の各群における症例分布はNIC＋0 rad 群に比べ1－49 rad 群では悪性度Ⅱが多く，50＋ rad 群ではⅡが少なくⅠが多い．このことも50＋ rad 群では良好な生存率となり1－49 rad 群では生存率の低下を示す結果をもたらす可能性が考えられる．しかし，上述のように癌組織そのものの組織学的検討のみからは50＋ rad 群の良好な予後は十分に説明し得ない．したがって，腫瘍－宿主関係における宿主側の防衛因子の検討も必要となろう．

About the only study made on inhibition of immune reaction in the human body by radiation exposure is that reported by Kanemitsu et al[21] who investigated the influenza antibody productivity in A-bomb survivors. No study has yet been made concerning radiation carcinogenesis and immune competence of the living body or regarding the immune competence of cancer carriers.[22]

In the present study an attempt was made to estimate the immune competence of cancer carriers against cancer by studying the cellular reaction at the site of breast cancer, but contrary to expectation, the cellular reaction appeared more strongly in the 50+ rad group than in the nonexposed group and the group exposed to less than 50 rad, and it was further shown that the 5-year survival rate in this dose group was good. One possible explanation for the better survival rate of breast cancer cases in the 50+ rad group, is that local cellular reaction against cancer is stronger in this group than in the nonexposed (NIC+0 rad) and those exposed to less than 50 rad.

Medullary carcinoma with lymphoid infiltration is well known as a special type of breast cancer evoking a strong cellular reaction against cancer tissues. Three cases of this type were found in the present study, all nonexposed and still alive after 4 years and 3 months, 5 years and 10 months, and 14 years, respectively, after diagnosis and surgery. The cellular reaction described in this report may be regarded as a reaction to cancer tissues regardless of histologic type, and since most of the infiltrating cells are lymphocytes with the inclusion of some plasma cells, the reaction probably can be regarded as some type of an immune reaction of the carrier. However, why was the cellular reaction more prominent in the 50+ rad group? One possible reason may be that radiation-induced breast cancer may evoke a stronger antigenicity to tumor than endocrine-induced breast cancer, but this cannot be substantiated at the present time.

Shimosato et al[23] made a detailed histopathological study of the events that occur in human cancer tissues undergoing successful treatment by radiotherapy and reported that a lymphoid cell reaction can be seen transiently in the cancer tissues simultaneously with the degeneration and dissolution of cancer cells.

放射線被曝による人体での免疫反応の抑制に関する研究は，原爆被爆者のインフルエンザ抗体産生能を調査した金光ら[21]の報告にみられる程度であり，放射線発癌と生体の免疫能や担癌生体の免疫能に関する研究はいまだ行われていない.[22]

本研究では，乳癌局所での細胞反応を調べることにより，担癌生体の癌に対する免疫能を推測することを試みたが，予想に反して50＋ rad 群では非被曝者群や49 rad 以下の被曝者群よりも細胞反応が強くみられ，5年生存率が良いことも明らかになった．すなわち，50＋ rad 群における乳癌の生存率が他群よりも良いと考え得られる理由の一つは，癌に対する局所細胞反応が非被曝者（NIC＋0 rad）や49 rad 以下（1－49 rad）の被曝者よりも強いことである．

癌組織に対する強い細胞反応のみられる特殊型乳癌としてリンパ様浸潤を伴う髄様癌がよく知られている．本検索例の中にこの型は3例みられ，すべて非被爆者でありそれぞれ診断および手術後4年3か月，5年10か月，および14年を経過し生存中である．本論文で示している細胞反応は，組織型を問わず癌組織への反応としてとらえられるであろうし，浸潤細胞の大部分がリンパ球であり，一部に形質細胞を含むことから担癌生体の免疫反応の何らかの型とみなしてもよいと考えられる．しかし，なぜ50＋ rad 群に高度に細胞反応がみられたのか．その考えられる理由の一つとして放射線誘導乳癌が内分泌誘導乳癌に比べ腫瘍抗原性をより強く発揮することが考えられるが，現今では実証し得ない．

下里ら[23]は，放射線療法により効果的な治療を受ける人癌組織に発生する事象について病理組織学的に詳細に検討し，癌細胞の変性融解と時期を同じくして一過性に癌組織内にリンパ球様細胞反応がみられることを示した．さらに下里らは，動物実験による

Adding to the results of animal experiments, they regard this lymphoid cell reaction to be a finding suggesting the involvement of the immune mechanism of the host against the cancer cells in addition to the direct injury of cancer cells by radiation in the successful treatment of carcinoma by radiotherapy.

More than the fact that these cellular reactions are characteristic of tissues especially when exposed to a high dose of about 3000 rad in one day, it may be possible to regard the lymphocytic reaction seen in breast cancers among A-bomb survivors as a pathologic finding suggesting a cellular immune reaction against the cancer cells. To support this, however, experimental studies concerning therapy will have to be made using animals with radiation-induced cancers. The above results suggest the possibility that radiation not only has a cancer-inducing effect but also is involved in the cellular immune reaction against cancer tissues in the living body.

Examination of lymph nodes was made on only a small number of cases, and though a study was made of the presence or absence of metastasis and the forms of reaction, it was not to an extent that permits discussion of the findings in relation to prognosis.

成績をも加えて，このリンパ球様細胞反応は放射線療法を用いた癌腫の効果的治療において，放射線の癌細胞への直接障害に加えて，癌細胞に対する宿主側の免疫機構の関与を示唆する所見であると考えている．

また，これらの細胞反応は，特に3000 rad 位いの高線量を1日に被曝した際の組織の特徴であるということは事実であるが，原爆被爆者乳癌においてみられたリンパ球反応についても，癌細胞に対する細胞性免疫反応を示唆する病理学的所見とみなすことも可能かと考えられる．しかしながら，このことを裏付けるには放射線発癌動物による治療に関する実験的研究が必要となろう．以上の成績は放射線が発癌性の作用を及ぼすばかりでなく，生体の癌組織に対する細胞性免疫反応にも関与している可能性を示唆している．

なお，リンパ節の検査は少数例においてのみなされ，転移の有無，反応様式について検討を加えたが，予後に関して所見を論ずるに至っていない．

REFERENCES
参考文献

1. BEEBE GW, KATO H: A review of thirty years study of Hiroshima and Nagasaki atomic bomb survivors. II. Biological effects. E. Cancers other than leukemia. J Radiat Res (Tokyo) 16 (Suppl):97-107, 1975

2. WANEBO CK, JOHNSON KG, SATO K, THORSLUND TW: Breast cancer after exposure to the atomic bombings of Hiroshima and Nagasaki. N Engl J Med 279:667-71, 1968

3. McGREGOR DH, LAND CE, TOKUOKA S, LIU PI, WAKABAYASHI T, BEEBE GW: Breast cancer incidence among atomic bomb survivors, Hiroshima and Nagasaki, 1950-69. J Natl Cancer Inst 59:799-811, 1977

4. 徳永正義，浅野正英，徳岡昭治，西森一正，J. E. Norman：広島・長崎における被爆者乳癌に関する研究．日病会誌66(補)：38，1977
(TOKUNAGA M, ASANO M, TOKUOKA S, NISHIMORI I, NORMAN JE: Study of breast cancer in the atomic bomb survivors of Hiroshima and Nagasaki. Nihon Byori Gakkai Kaishi-Trans Soc Path Jpn)

5. JONES TD, AUXIER JA, CHEKA JS, KERR GD: In-vivo dose estimates for A-bomb survivors shielded by typical Japanese houses. Health Phys 28:367-81, 1975

6. 栗原 登，高野 昭：癌の治癒率の計算方法について－相対生存率の意義と算出法．癌の臨床11：628－632，1965
(KURIHARA M, TAKANO A: Calculation method of cancer cure rate – Significance and calculation method of relative survival rate. Gan no Rinsho-Jpn J Cancer Clin)

7. AXTELL LM: Computing survival rates for chronic disease patients. JAMA 186:1125-28, 1963

8. 栗原 登，高野 昭：相対生存率の算出に用いる期待生存率．癌の臨床22(8): 295－6，1976
(KURIHARA M, TAKANO S: Expected survival rate used in the calculation of relative survival rate. Gan no Rinsho-Jpn J Cancer Clin)

9. JAPAN MAMMARY CANCER SOCIETY: General rule for clinical and histological record of mammary cancer. Part II. Histological classification of mammary cancer. Jpn J Surg 5:175-85, 1975

10. BLOOM HJG, RICHARDSON WW: Histological grading and prognosis in breast cancer; A study of 1409 cases of which 359 have been followed for 15 years. Br J Cancer 11:359-77, 1957

11. CHAMPION HR, WALLACE IWJ: Breast cancer grading. Br J Cancer 25:441-8, 1971

12. HARRY LI, BRENT HD, EDWARD P: The immune response at the tumor site in lung carcinoma. Cancer 38:2296-309, 1976

13. MACKENZIE I: Breast cancer following multiple fluoroscopies. Br J Cancer 19:1-8, 1965

14. COOK DC, DENT O, HEWITT O: Breast cancer following multiple chest fluoroscopy. Can Med Assoc J 3:402-12, 1974

15. BOICE JD Jr, MONSON RR: Breast cancer in women after reported fluoroscopic examinations of the chest. J Natl Cancer Inst 59:823-32, 1977

16. UPTON AC, BEEBE GW, BROWN JM, QUIMBY EH, SHELLABARGER C: Report of NIC ad hoc working group on the risks associated with mammography in mass screening for the detection of breast cancer. J Natl Cancer Inst 59:481-93, 1977

17. SATO E, KUMAGAI N, ABE R: Significant prognostic factors in breast cancer of Japanese women; Special reference to nuclear grade and sinus histiocytosis. Tohoku J Exp Med 120:135-49, 1976

18. 小堀鷗一郎，草間 悟：乳癌の組織学的進展と予後．臨床成人病 4：395－404，1974
(KOBORI O, KUSAMA S: Histologic development and prognosis of breast cancer. Rinsho Seijinbyo-J Adult Dis)

19. 坂元吾偉，管野晴夫，井川洋二，梶谷 鐮，久野敬二郎，深見敦夫，木下 巌，堀 雅晴：乳癌の組織型と生存率．癌の臨床 18：453－460，1972
(SAKAMOTO G, KANNO H, IKAWA Y, KAJITANI K, HISANO K, FUKAMI A, KINOSHITA I, HORI M: Histologic type and survival rate of breast cancer. Gan no Rinsho-Jpn J Cancer Clin)

20. 坂元吾偉，管野晴夫，深見敦夫，久野敬二郎：乳腺の小葉癌．癌の臨床 22：449－56，1976
(SAKAMOTO G, KANNO H, FUKAMI A, HISANO K: Lobular cancer of the mammary gland. Gan no Rinsho-Jpn J Cancer Clin)

21. KANEMITSU M, MORITA K, FINCH SC, KATO H, ONISHI S: Serological response of atomic bomb survivors following Asian influenza vaccination. Jpn J Med Sci Biol 19:73-84, 1966

22. BEEBE GW, HAMILTON HB: Review of thirty years study of Hiroshima and Nagasaki atomic bomb survivors. III. Future research and health surveillance. J Radiat Res (Tokyo) 16 (Suppl):149-64, 1975

23. SHIMOSATO Y, OBOSHI S, BABA K: Histological evaluation of effects of radiotherapy and chemotherapy for carcinomas. Jpn J Clin Oncol 1:19-35, 1971

ACKNOWLEDGMENT

謝　辞

Appreciation is expressed to former ABCC Chiefs of Pathology Dr. Arthur Steer and Dr. Murray D. Angevine, former ABCC and former RERF Chief of Epidemiology and Statistics Dr. Gilbert W. Beebe, and RERF Acting Chief of Pathology Dr. Tsutomu Yamamoto for the motivation to begin this study.

Appreciation is also expressed to Assistant Chief of Pathology Dr. Masahide Asano (RERF Department of Pathology, Nagasaki), Professor Shoji Tokuoka (Hiroshima University School of Medicine, Department of Pathology), Professor Haruo Ezaki (Hiroshima University School of Medicine, Department of Surgery), Professor Issei Nishimori (Nagasaki University School of Medicine, Atomic Disease Institute, Department of Pathology), Professor Yasukuni Tsuji (Nagasaki University School of Medicine, Department of Surgery), Dr. Toshiro Wakabayashi (RERF, Department of Epidemiology and Statistics), and Dr. James E. Norman (formerly of RERF, Department of Epidemiology and Statistics, now at the National Academy of Sciences, Washington, D.C.) for their guidance and encouragement in the course of collection of cases and conduct of the study.

Many diagnostic data were made available by the Tumor Registries of the Hiroshima and Nagasaki City Medical Associations, and by the Tissue Registries of the Hiroshima Prefectural Medical Association and the Nagasaki City Medical Association. Sincere appreciation is due to these organizations as well as to the institutions that participated in the tumor and tissue registry programs.

Further, appreciation is expressed to the doctors of pathology and surgery at Hiroshima University and Nagasaki University and at the public and private hospitals in the two cities for providing cases and extending cooperation in the review of specimens and otherwise.

Lastly, appreciation is expressed to Professor Eiichi Sato for his kind review of the manuscript.

本研究を始める動機を与えて下さった前ABCC病理部長の Arthur Steer 博士，および Murray D. Angevine 博士，Gilbert W. Beebe 前ABCC，前放影研疫学統計部長ならびに山本 務放影研病理部部長代理に感謝したい．

また，症例収集および研究推進に当たりご指導ご鞭撻を賜わった浅野正英副部長（放影研，長崎，病理部），徳岡昭治教授（広島大学医学部，病理学教室），江崎治夫教授（広島大学医学部，外科学教室），西森一正教授（長崎大学医学部，原爆後障害医療研究施設病理部門），辻 泰邦教授（長崎大学医学部，外科学教室），若林俊郎博士（放影研，疫学統計部），James E. Norman 博士（前放影研，疫学統計部，現在ワシントン市の米国学士院）に感謝する．

多くの診断資料は，広島市および長崎市医師会の腫瘍登録および広島県医師会と長崎市医師会の組織登録から入手した．腫瘍登録および組織登録に参加した病医院のみならずこれら両市の医師会にも深甚の謝意を表する．

さらに症例の提供ならびに標本の再検査などにご協力頂いた広島大学および長崎大学，ならびに両市の公私立病院の病理や外科の先生方に感謝する．

最後に，佐藤栄一教授のご校閲にお礼を申し上げたい．