

HISTOLOGICAL REVIEW OF BREAST CANCER IN
ATOMIC BOMB SURVIVORS, HIROSHIMA AND NAGASAKI

原爆被爆者の乳癌の組織学的研究，広島・長崎

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SUMMARY

A group of pathologists from the United States and Japan reviewed breast cancer material of women exposed to the atomic bombs in Hiroshima and Nagasaki and controls. The purpose of the review was to verify the diagnoses, establish a base of confirmed cases for epidemiologic study, and provide a reference for other pathology review.

Compared to the control group, matched through the Life Span Study extended sample, there were no differences in distribution of tumor type and tumor size. There were also no differences in histological type by age or radiation dose. The peak age for cancer to develop was the same in the exposed and control groups. The type of radiation had no effect on histological type. Atypical changes or residual proliferative lesions were not found in women exposed to radiation but free from cancer. On the basis of this study, it was concluded that radiogenic breast cancer does not differ histologically from spontaneously occurring cancer in Japanese women.

要約

日米の病理学者グループは広島・長崎で放射線に被曝した女性とその対照群の乳癌標本を検討した。検討の目的は診断を確認し、疫学的検討のために、確認された症例の基盤を設定し、その他の病理学的検討に対する参考に資することであった。

寿命調査拡大集団の対照群と比較すると、腫瘍の型や大きさの分布に差異はなかった。組織型にも、年齢や被曝線量による差異はみられなかった。発癌年齢のピークは被爆群、対照群ともに同じであった。放射線の線質は組織型に影響を及ぼさなかった。被曝はしたが癌が発現しなかった女性には、非定型変化や残存増殖性病変はみられなかった。この研究により、日本人女性においては放射線誘発性乳癌は組織学的には、自然発生の乳癌と相違しないという結論が得られた。

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INTRODUCTION

A series of epidemiologic studies, beginning in 1968, have indicated a significantly higher incidence of breast cancer in Japanese women exposed to A-bomb radiation than in comparable women not exposed.¹⁻⁷ These studies have consistently revealed that risk of breast cancer increases linearly with radiation dose, at least for tissue doses below 200 rad, and that the greatest risk (absolute and relative) occurs in women who were exposed at age 10-19, and who received more than 100 rad. In contrast to the data on radiation-induced leukemia, increases in radiation dose appears not to reduce the latent period for breast cancer to develop, which is at least 10 years, but only serves to increase the incidence. Further, there is no significant difference in the slope of the dose-response curves for Hiroshima and Nagasaki, even though the Hiroshima A-bomb emitted neutron and gamma radiation while the Nagasaki bomb emitted gamma radiation only.

Previous histological review was conducted on a small number of cases,³ but the number has increased to the extent that studying the effect of radiation on breast tissue seemed most important. Consequently, arrangements were made for a binational group of pathologists to review the available histological material from these breast cancer patients in order to verify and compare them with nonirradiated breast cancer patients.

MATERIALS AND METHODS

All available histological material from breast cancer cases identified among members of the RERF Life Span Study (LSS) extended sample was reviewed. The LSS extended sample includes approximately 63,000 women, of whom 47,600 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 cities after the bombs.⁸ The breast tissue dose in rad has been calculated for most of the exposed subjects.^{9,10} The histological material was collected from the Tumor and Tissue Registries of Hiroshima and Nagasaki, the Schools of Medicine of the Hiroshima and Nagasaki Universities, RERF files, and many hospitals located throughout the two cities.^{1,2,4} The control group consisted of those NIC ATB or those in the cities but with 0 rad exposure.

緒言

1968年に始まった一連の疫学的研究によって、原爆放射線に被曝した日本人女性における乳癌の発生率は非被曝対照群よりも有意に高いことが示された。¹⁻⁷ これらの研究によって、乳癌のリスクは少なくとも組織線量200rad以下では放射線量とともに直線的に増加すること、そしてリスク(絶対的及び相対的)は10~19歳で100rad以上に被曝した女性で最大であることが一貫して明らかになった。放射線誘発性白血病の資料とは対照的に、放射線量が増加しても乳癌が発現するまでの最低10年間の潜伏期間が短くなることはなく、単にその発生率が高くなるだけである。更に、広島型原爆は中性子とガンマ線を放出したが、長崎型はガンマ線しか放出しなかったにもかかわらず、広島と長崎では線量-反応曲線の傾斜に有意差はない。

従来の組織学的検討は少数の症例に対して行われたが、³ その症例数は増加し、放射線の乳腺組織への影響の研究は最重要と考えられるようになった。その結果、日米の病理学者グループは被曝者における乳癌例の組織学的材料を確認し、被曝していない乳癌例と比較検討を行った。

材料及び方法

放影研寿命調査(LSS)拡大集団のうちで乳癌と診断された症例から、入手可能な組織学的材料がすべて検討された。LSS拡大集団には約63,000人の女性が含まれ、そのうち47,600人は被曝時広島又は長崎で爆心地から10,000m以内にいたが、15,400人は非被曝者で、原爆後に市内に移住したものである。⁸ Radで表された乳腺組織線量はほとんどの被曝者について算定されている。^{9,10} 組織学的材料は広島・長崎の腫瘍登録、組織登録、広島大学医学部、長崎大学医学部、放影研ファイル及び両市内の多数の病院から集められた。^{1,2,4} 対照群は被曝時市内にいなかった者と、市内にいたが被曝線量が0radだった者から成っている。

Among the cases reviewed, 172 surgical and 8 autopsy cases in Hiroshima and 41 surgical and 2 autopsy cases in Nagasaki were reported for the years 1950-74.³ There were an additional 60 surgical cases from Hiroshima and 20 from Nagasaki during 1975-78.

The World Health Organization (WHO) Tentative Histological Classification of Breast Tumors (1978) was modified and combined for this binational study so that results could be converted to either the WHO or the Japanese Breast Cancer Society format. Modifications included the addition of three subtypes, "papillotubular," "medullary tubular," and "scirrhous type," under the categories "invasive ductal carcinoma" and "invasive ductal carcinoma with predominantly intraductal component." The "papillary carcinoma" of the WHO classification was deleted since these cases are included in the "papillotubular" subtype. In classifying tumors of mixed type, the predominant pattern was used if it represented more than 50% of the lesion. In addition, a new category (Cannot Subclassify Further) was established for the cases that could not be subclassified. This allowed inclusion of those cases for which there was no consensus among the pathologists about subtype or for which there was no predominant pattern.

Rules and diagnostic criteria by the Japanese Breast Cancer Society¹¹ and the WHO revised classification,¹² were followed in classifying the lesions. Since the combined classification and rules were adopted during the preliminary meeting held in the US, the US participants became familiar with them at that time.

In addition to identified breast cancer cases, a pilot study was undertaken to review breast tissue, without clinically evident cancer, obtained from women examined under the ABCC-RERF Autopsy Program and with estimated breast tissue dose of 100 rad or more. A total of 56 women were included in the pilot study. Samples were examined for atypical or residual hyperplastic or proliferative lesions.

The five Japanese pathologists initially reviewed the slides over three days and the three American pathologists conducted their independent review at a later date. The two groups then met to resolve any controversies and to discuss their findings.

今回検討された症例のうち、1950～74年の広島の外科学病理例172、剖検例8、及び長崎の外科学病理例41、剖検例2がこれまでに報告されている。³ 1975～78年の間に更に外科学病理例が広島で60、長崎で20追加された。

世界保健機関(WHO)乳腺腫瘍の暫定組織分類(1978年)を、診断がWHO又は日本乳癌研究会のいずれの形式にも変換できるように、この日米共同研究のために修正し統合した。その修正のうちには「浸潤性乳管癌」及び「乳管内成分優位の浸潤性乳管癌」の範ちゅう内で「乳頭腺管型」、「髓様腺管型」及び「硬癌」の三つの亜型の追加が含まれる。WHOの分類の「乳頭癌」は「乳頭腺管型」に含まれているので削除した。混合型腫瘍を分類する際に、優勢な型が病変の50%以上を占めていればそれを用いた。加えて、亜型に分類不可能な症例のために、新しい範ちゅう(これ以上細分類不可能)が設けられた。これには亜型について病理学者の合意が得られない症例や優勢な型がない症例が含まれる。

病変を分類するに当たり、日本乳癌研究会規定による診断基準¹¹とWHO改訂分類¹²に従った。統合された分類及び規定は、米国での予備会議で採用されたため、米国側出席者はその時点でこれらを熟知した。

診断された乳癌例に加えて、ABCC-放影研剖検調査の下で剖検を受け、推定乳腺組織線量100rad以上で、乳癌の臨床的徴候が認められなかった女性の乳腺組織を検討するため、試験的調査が行われた。合計56人の女性が試験的調査の対象になった。標本については非定型病変、残存性過形成病変、増殖性病変の検査が行われた。

まず、日本の病理学者5人が3日間にわたり標本を検討し、次いで米国の病理学者3人が独自の検討を行った。その後、両グループは会合をもち、論点を解決し、所見を討議した。

Except for the pilot study, all material was reviewed without knowledge of exposure status or estimated dose. The final diagnosis represents a consensus of the participating pathologists. Cases for which no consensus was gained regarding the histological type or subtype at the first review were restudied and openly discussed. There were two cases for which an agreement could not be reached.

Information about laterality, size of breast cancer, age at diagnosis, age ATB, and history of radiation exposure was obtained from RERF files. There were a few cases for which slides were not available to the reviewers at the time of the review.

RESULTS

Of the 316 cases reviewed (245 in Hiroshima and 71 in Nagasaki), 300 (290 surgical and 10 autopsy) or 95% were accepted for final analysis. These included 149 exposed cases (1 rad or more) and 152 control cases* (0 rad or nonexposed). There were 107 patients from Hiroshima and 42 from Nagasaki in the exposed group, and 131 patients from Hiroshima and 21 from Nagasaki in the Control group.

The 16 cases excluded from the final analysis are shown in Table 1. There were no non-epithelial tumors, except for one case of primary malignant lymphoma of the breast found in a control patient. No cases of male breast cancer were observed.

Tumor Size. In the exposed group, the average tumor size in largest dimension was 3.39 cm in Hiroshima (76 cases) and 2.57 cm in Nagasaki (29 cases). In the control group, the average size was 3.72 cm in Hiroshima (99 cases) and 2.82 cm in Nagasaki (12 cases). Although there was no difference in tumor size between the two groups in each city, the average size was larger in Hiroshima for both groups. It was not possible to relate tumor size to radiation dose in individual patients.

Age Distribution. Table 2 shows the average age ATB and at diagnosis by exposure group. The average age ATB and at diagnosis was less in

試験的調査を除き、材料はすべて被爆状態や推定線量を伏せて検討された。最終診断は出席病理学者の一致した意見を示すものである。第一回検討で組織型や亜型に関して合意が得られなかった症例は再び検討され、率直に討議された。合意が得られなかった症例が2例あった。

乳癌の側方性や大きさ、診断時年齢、被爆時年齢及び放射線被曝歴に関する情報は放影研のファイルから入手した。検討時に標本が入手できなかった例も幾つかあった。

結果

検討された316例(広島245, 長崎71)のうち、300例(外科病理例290, 剖検例10)、すなわち95%が最終分析に供された。この中には被爆例が149例(1 rad以上)と対照例*(0 rad又は非被爆者)が152例含まれていた。被爆群は広島の患者107人、長崎の患者42人、対照群は広島の患者131人、長崎の患者21人であった。

最終分析から除かれた16例は表1に示されている。対照群中、乳腺の原発性悪性リンパ腫の1例を除いて、非上皮性腫瘍はなかった。男性乳癌例はみられなかった。

腫瘍の大きさ。 被爆群では、最大径の平均値は広島で3.39cm(76例)、長崎で2.57cm(29例)であった。対照群での平均値は広島で3.72cm(99例)、長崎で2.82cm(12例)であった。いずれの都市においても両群間に腫瘍の大きさに差はなかったが、大きさの平均値は両群において広島の方が大であった。個々の患者について腫瘍の大きさと放射線量を関係づけることは不可能であった。

年齢分布。 表2は被爆の有無別の被爆時及び診断時の平均年齢を示す。被爆時及び診断時の平均年齢

*One patient was considered twice because of bilateral breast cancer.

1人の患者は左右両方とも乳癌のため2例として取り扱った。

TABLE 1. CASES NOT CONFIRMED HISTOLOGICALLY

表1 組織学的に乳癌と確認できなかった症例

Master File Number	Diagnosis
	No evidence of cancer. Healed biopsy scar.
	No primary site. Section of nerve showing perineural tumor extension. Consistent with breast cancer.
	No breast tissue. Lymph node has metastatic cancer.
	Papillomatosis. No primary site in sections reviewed. Lymph node has metastatic cancer, primary site unknown, presumed breast.
	No evidence of tumor. Lymph node. No breast tissue present.
	Fat necrosis in breast. No tumor present.
	No evidence of tumor. Lymph node. No breast tissue present.
	In situ gastric carcinoma. No breast tissue present.
	Malignant lymphoma in breast. No breast cancer.
	No primary site. Cancer consistent with breast in lymph node. No breast tissue present.
	No cancer, benign, atypical papillomatosis of breast.
	Carcinomatosis. Impossible to determine primary site.
	Benign, papillomatosis of breast.
	Benign, papillomatosis of breast.
	Lymph node with metastatic tumor, presumed primary in breast.
	Lymph node with metastatic tumor, presumed primary in breast.

TABLE 2. AVERAGE AGE ATB AND AT DIAGNOSIS BY CITY AND EXPOSURE

表2 都市別、被爆の有無別の被爆時及び診断時平均年齢

Age	Nagasaki		Hiroshima	
	Exposed	Control	Exposed	Control
ATB	22.98	26.57	28.60	29.81
Diagnosis	47.05	51.57	51.24	51.54
Difference	24.07	25.00	22.64	21.73

Nagasaki than that in Hiroshima, possibly because the female population tended to be younger in Nagasaki than in Hiroshima. The difference between average age ATB and at diagnosis is essentially the same in all groups.

Distribution of Histological Type. Table 3 presents the distribution of histological type. There was no significant difference in the distribution between the exposure groups or the

が広島より長崎で低かったのは恐らく、広島の女性集団よりも長崎の女性集団の方が年齢が低い傾向があったためであろう。被爆時平均年齢と診断時平均年齢の差は、すべての群において、本質的には同じである。

組織型の分布。表3は組織型の分布を示す。被爆・非被爆群間、両都市間で分布に有意差はなかった。

TABLE 3. BREAST CANCER CASES BY HISTOLOGICAL TYPE, EXPOSURE, AND CITY

表3 被爆の有無，都市別の組織型別乳癌症例数

Classification	Exposed		Control		Total	
	Hiroshima	Nagasaki	Hiroshima	Nagasaki	Exposed	Control
1. Noninvasive						
a. Intraductal carcinoma	1 (0.9)	1 (2.3)	2 (1.5)		2 (1.3)	2 (1.3)
b. Lobular carcinoma in situ						
2. Invasive						
a. Invasive ductal carcinoma						
0. Cannot subclassify further	14 (13.0)	7 (16.0)	17 (13.0)	4 (19.0)	21 (14.0)	21 (14.0)
1. Papillotubular	4 (3.7)	1 (2.3)	4 (3.0)	1 (4.7)	5 (3.3)	5 (3.3)
2. Medullary tubular	20 (18.0)	9 (21.0)	20 (15.0)	1 (4.7)	29 (19.0)	21 (14.0)
3. Scirrhou	47 (44.0)	17 (40.0)	63 (48.0)	13 (62.0)	64 (43.0)	76 (50.0)
b. Invasive ductal carcinoma with predominant intraductal component						
0. Cannot subclassify further						
1. Papillotubular	10 (9.3)	5 (12.0)	12 (9.2)	2 (9.5)	15 (10.0)	14 (9.2)
2. Medullary tubular	1 (0.9)		1 (0.8)		1 (0.6)	1 (0.7)
3. Scirrhou			2 (1.5)			2 (1.3)
c. Invasive lobular carcinoma	4 (3.7)				4 (2.6)	
d. Mucinous carcinoma	1 (0.9)	1 (2.3)	5 (3.8)		2 (1.3)	5 (3.3)
e. Medullary carcinoma			2 (1.5)*			2 (1.3)
f. Tubular carcinoma	1 (0.9)**				1 (0.6)	
g. Adenoid cystic carcinoma						
h. Secretory (juvenile) carcinoma	1 (0.9)				1 (0.6)	
i. Apocrine carcinoma						
j. Carcinoma with metaplasia						
1. Squamous type						
2. Spindle cell type						
3. Cartilaginous and osseous type						
4. Mixed type		1 (2.3)			1 (0.6)	
k. Other			2 (1.5)†			2 (1.3)
3. Paget's disease						
a. In situ carcinoma only	1 (0.9)		1 (0.8)		1 (0.6)	1 (0.7)
b. With invasive carcinoma	2 (1.8)				2 (1.3)	
Total	107	42	131††	21	149	152

Percent of total in parentheses. ()内は合計の%

* *Controversial case, one case of medullary carcinoma was considered by some pathologists to be an invasive ductal carcinoma.*

問題の症例。1例の髄様癌については、浸潤性乳管癌だとする病理学者もある。

** *Controversial case, tabulated as tubular although some pathologists considered it an invasive ductal carcinoma.*

問題の症例。腺管癌として記載されているが浸潤性乳管癌だとする病理学者もある。

† *Includes signet ring cell carcinoma and malignant lymphoma of breast.*

乳房の印環細胞癌と悪性リンパ腫を含む。

†† *Includes one case of bilateral cancer, each breast considered separately.*

両側性癌の1例を含む。乳房の数で示した。

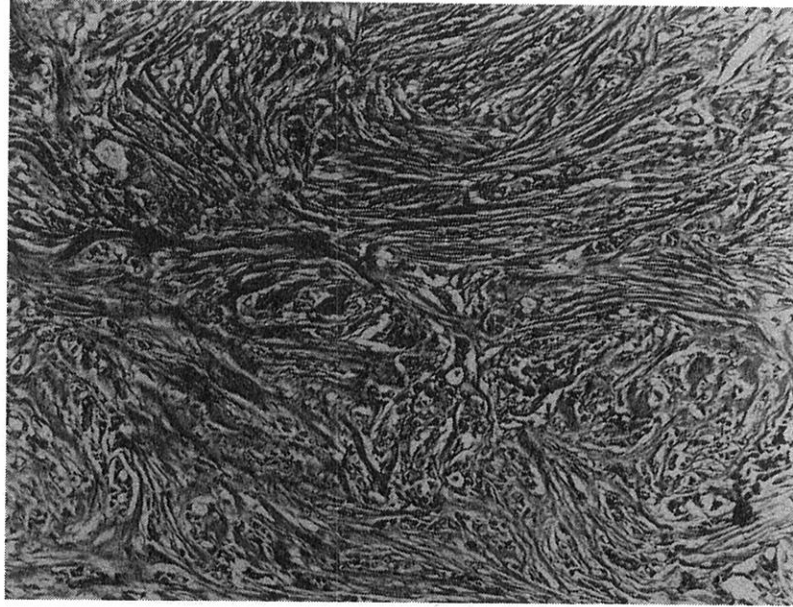


Figure 1. Common scirrhous carcinoma of breast showing bundles of thick collagen separated by tumor cells. H & E. $\times 100$

図1 腫瘍細胞によって分割された厚い膠原線維束を示す硬癌。H & E. $\times 100$

two cities. The scirrhous type of invasive ductal carcinoma was most common. There were four cases of invasive lobular carcinoma and one case of secretory carcinoma, the latter being rare in Japan. In both exposure groups, 14% of the cases could not be subclassified, although there was unanimous agreement that these were invasive ductal carcinomas.

An example of the common scirrhous type of carcinoma is shown in Figure 1, and other types are illustrated in Figures 2-5.

No significant differences by exposure group were observed in the distribution of histological type according to age at diagnosis (Table 4), age ATB, or duration from age ATB to diagnosis.

Relationship of Histological Type to Radiation Dose. Table 5 shows the relationship between tissue dose and histological type. There was no difference in the distribution by tissue dose or histological type.

Pilot Study of Noncancerous Breast Tissue. Review of noncancerous breast tissue from

硬性浸潤性乳管癌が最も一般的であった。浸潤性小葉癌が4例、分泌癌が1例みられたが、後者は日本ではまれである。被爆・非被爆群いずれにおいても、浸潤性乳管癌であると合意を得られたものの、細分類は不可能であった症例が14%あった。

一般的な硬性癌の1例を図1に、その他の型は図2-5に示した。

被爆・非被爆群間で、診断時年齢(表4)、被爆時年齢及び被爆から診断までの期間によって、組織型分布に有意差はみられなかった。

組織型と放射線量との関係。表5に組織線量と組織型との関係を示す。組織線量及び組織型別で分布に差異はなかった。

非乳癌組織の試験的調査。100rad以上に被曝した

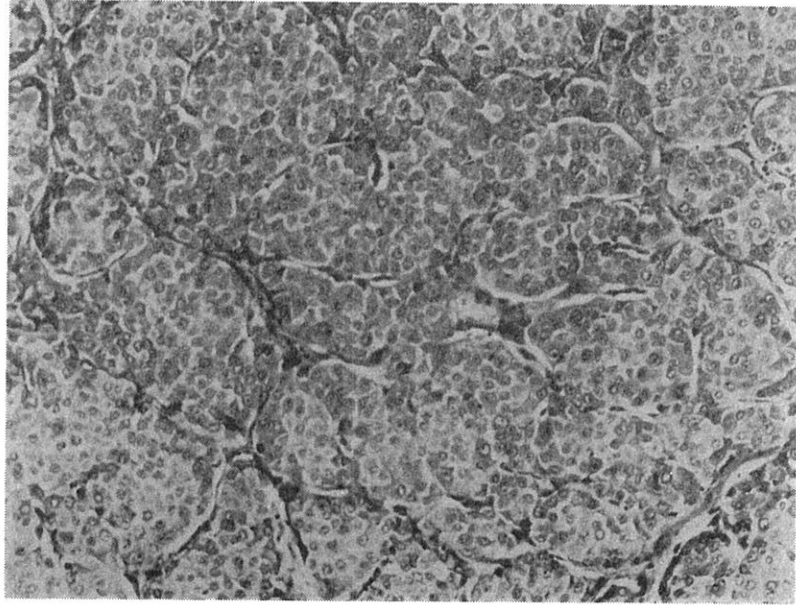


Figure 2. Medullary tubular type consisting of compact nests of tumor cells separated by capillaries. H & E. $\times 100$

図2 毛細血管によって分離された緻密腫瘍細胞巣から成る髄様腺管癌，H&E. $\times 100$

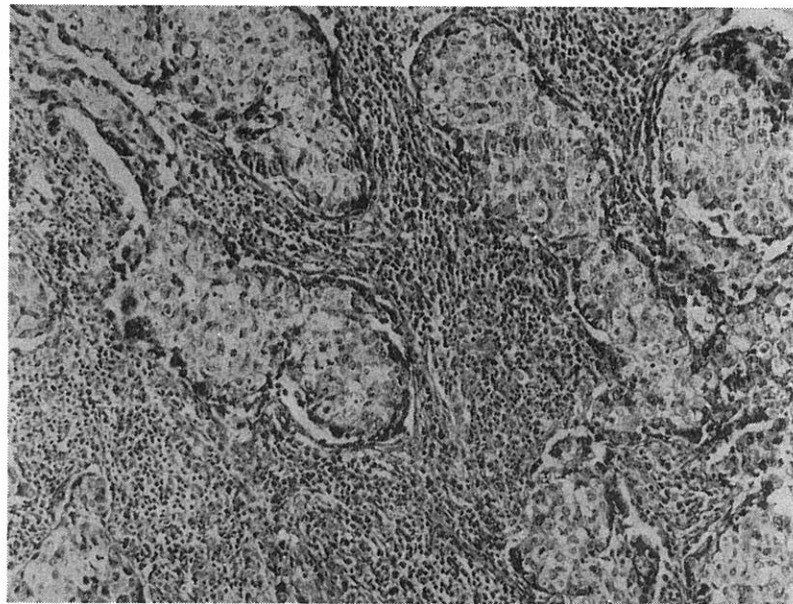


Figure 3. Medullary tubular type showing isolated clusters of tumor cells with intervening lymphocytes. H & E. $\times 100$

図3 介在リンパ球を伴う腫瘍細胞の集束を示す髄様腺管型，H&E. $\times 100$

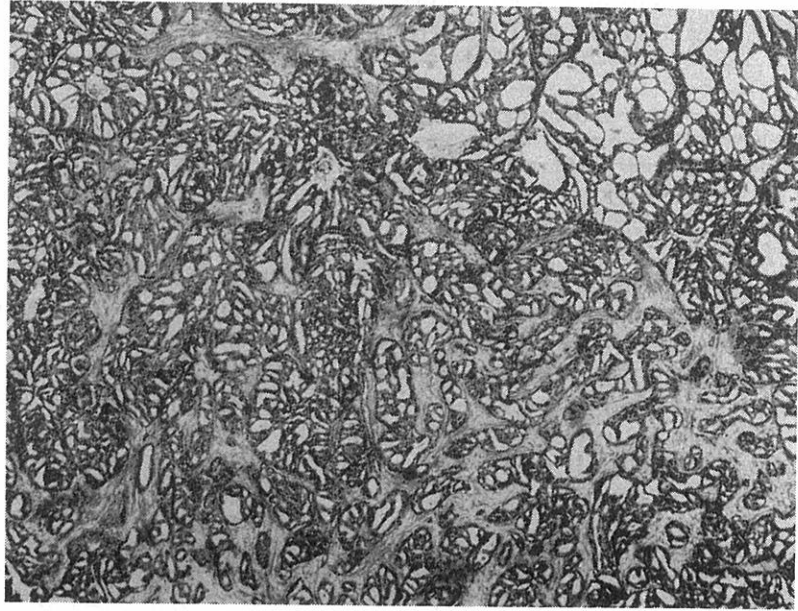


Figure 4. Papillotubular type invasive, according to the classification of the Japanese Mammary Cancer Society this pattern is called papillotubular. H & E. $\times 25$

図4 浸潤性乳頭腺管型, 日本乳癌学会の分類によれば, この型は乳頭腺管型と呼称される.
H & E. $\times 25$

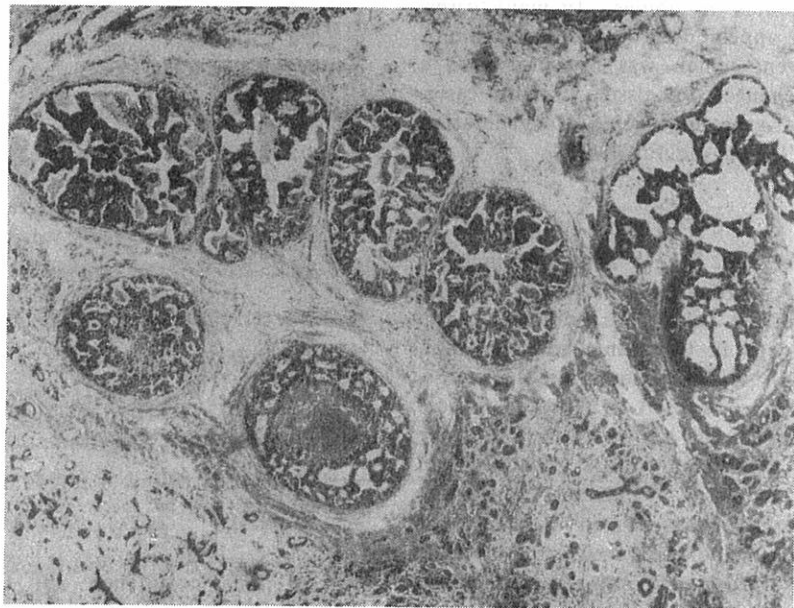


Figure 5. Papillotubular type, predominantly intraductal. H & E. $\times 40$

図5 乳管内優位の乳頭腺管型. H & E. $\times 40$

TABLE 4. BREAST CANCER BY HISTOLOGICAL TYPE, AGE AT DIAGNOSIS, AND RADIATION EXPOSURE
表4 診断時年齢及び放射線被曝の有無別の組織型別乳癌症例数

Histological type*	Age at Diagnosis							
	Exposed				Control			
	< 39	40-59	60+	Total	< 39	40-59	60+	Total
1a	1 (3.7)	1 (1.1)	0	2 (1.3)	1 (5.6)	1 (1.2)	0	2 (1.3)
2a0	7 (25.9)	10 (11.0)	4 (13.8)	21 (14.1)	2 (11.1)	14 (16.3)	5 (10.4)	21 (13.8)
2a1	1 (3.7)	1 (1.1)	3 (10.3)	5 (3.4)	1 (5.6)	1 (1.2)	3 (6.3)	5 (3.3)
2a2	5 (18.5)	18 (19.4)	6 (20.7)	29 (19.5)	1 (5.6)	13 (15.1)	7 (14.6)	21 (13.8)
2a3	7 (25.9)	44 (47.3)	13 (44.8)	64 (43.0)	11 (61.1)	41 (47.7)	24 (50.0)	76 (50.0)
2b1	5 (18.5)	9 (9.7)	1 (3.4)	15 (10.1)	1 (5.6)	10 (11.6)	3 (6.3)	14 (9.2)
2b2	0	1 (1.1)	0	1 (0.7)	0	0	1 (2.1)	1 (0.7)
2b3	0	0	0	0	1 (5.6)	0	1 (2.1)	2 (1.3)
Other	1	9	2	12	0	6	4	10
Total	27	93	29	149	18	86	48	152

Percent of total in parentheses. 括弧内は合計に占める百分率

*See Table 3 for classification. 分類は表3を参照

women exposed to 100+ rad revealed atrophy but no residual or atypical hyperplastic lesions either in the ducts or lobules. In many cases, however, there appeared to be a degeneration of stromal collagen, which was interpreted as a fibroelastotic change. Fat tissue, in many cases, also appeared to be undergoing a degeneration similar to that seen in malnutrition.

DISCUSSION

Epidemiologists and others have convincingly documented the carcinogenic effects of ionizing radiation on breast tissue. In addition to the observations made in Hiroshima and Nagasaki, women treated with X-irradiation for postpartum mastitis or exposed to repeated fluoroscopic examinations are known to have a higher incidence of subsequent breast cancer than nonirradiated controls.¹³⁻¹⁷ In fact, the risk per rad for breast cancer in women irradiated for postpartum mastitis or exposure to multiple fluoroscopy is higher than the risk per rad to bone marrow or the thyroid.¹⁶ This would seem to indicate that breast tissue is more susceptible to radiation-induced cancer than either the thyroid gland or bone marrow. Extensive studies of laboratory animals have

女性の非乳癌組織を検討したところ、萎縮がみられたが、乳管にも小葉にも残存性過形成又は非定型過形成病変はみられなかった。しかしながら、多くの症例で基質膠原線維の変性がみられたが、それは線維弾性の変化であると解釈される。脂肪組織も多くの場合、栄養障害にみられるのと同様の変性を経ているようであった。

考 察

疫学者らは、電離放射線の乳房組織への発癌効果を説得力ある資料をもって確認している。広島・長崎での観察所見に加えて、分娩後乳腺炎に対してX線照射治療を受けた女性、又は再三透視検査を受けた女性は非照射対照者よりも癌発生率が高いことが知られている。¹³⁻¹⁷ 実際に、分娩後乳腺炎に対してX線照射を受けた女性、又は再三透視検査を受けた女性の1 rad当たりの乳癌リスクは1 rad当たりの骨髄や甲状腺に対するリスクよりも高い。¹⁶ このことは、乳腺組織は甲状腺や骨髄よりも放射線誘発性癌への感受性が高いことを示すと思われる。実験動物

TABLE 5. DISTRIBUTION OF PATHOLOGICALLY CONFIRMED BREAST CANCER BY HISTOLOGICAL TYPE

表5 病理学的に確認された乳癌の組織型別被曝線量別分布

Diagnostic Classification	Exposure Dose in Rad						Total	%
	NIC*	0	1-9	10-99	100+	Unk.		
1. Noninvasive								
a. Intraductal carcinoma	1	2	0	1	0	0	4	1.3
b. Lobular carcinoma in situ	0	0	0	0	0	0	0	0
2. Invasive								
a. Invasive ductal carcinoma								
0. Cannot subclassify further	8	13	4	5	11	1	42	14.0
1. Papillotubular	3	1	2	2	1	1	10	3.3
2. Medullary tubular	7	13	6	15	6	3	50	16.6
3. Scirrhou	25	52	20	21	19	3	140	46.5
b. Invasive ductal carcinoma with predominant ductal component								
0. Cannot subclassify further	0	0	0	0	0	0	0	0
1. Papillary tubular	5	9	5	7	3	0	29	9.6
2. Medullary tubular	1	0	1	0	0	0	2	0.7
3. Scirrhou	1	1	0	0	0	0	2	0.7
c. Invasive lobular carcinoma	0	0	1	2	1	0	4	1.3
d. Mucinous carcinoma	0	5	1	0	1	0	7	2.3
e. Medullary carcinoma	0	1	0	0	0	0	1	0.3
f. Tubular carcinoma	0	0	0	0	0	0	0	0
g. Adenoid cystic carcinoma	0	0	0	0	0	0	0	0
h. Secretory carcinoma	0	0	0	0	1	0	1	0.3
i. Apocrine carcinoma	0	0	0	0	0	0	0	0
j. Carcinoma with metaplasia								
1. Squamous type	0	0	0	0	0	0	0	0
2. Spindle cell type	0	0	0	0	0	0	0	0
3. Cartilaginous and osseous type	0	0	0	0	0	0	0	0
4. Mixed type	0	0	0	0	1	0	1	0.3
k. Other	1	1	0	0	0	0	2	0.7
3. Paget's disease								
a. In situ carcinoma only	1	0	1	0	0	0	2	0.7
b. With invasive carcinoma	0	0	1	0	1	0	2	0.7
Total Classified	53	98	42	53	45	8	299	99.3
No agreement as to type	0	1	0	1	0	0	2	0.7
Total	53	99	42	54	45	8	301	100.0

*Not in either city at the time of the bombing. 原爆時両市内にいなかった

also supported the conclusion that ionizing radiation is carcinogenic for breast tissue.^{18,19}

Because of the importance of breast cancer material from women exposed to A-bomb radiation, a binational group of pathologists was

を用いた大規模な研究も、電離放射線は乳腺組織に対して発癌効果をもつという結論を支持するものである。^{18,19}

原爆放射線を受けた女性の乳癌標本は重要であるので、日米両国の病理学者に広島・長崎の標本を検討

called upon to review the material in Hiroshima and Nagasaki and to verify the diagnoses. In developing an acceptable classification of histological types as a basis for review, it was agreed to use a combined WHO-Japanese Breast Cancer Society classification so as to compare the results with other international studies following the WHO format and with previous studies conducted in Japan.

As a part of the analysis, the distribution of different histological types of breast cancer was compared against several variables, and the distribution was essentially the same by exposure group. In fact, it did not differ from the expected distribution for Japanese women.²⁰

The histological distribution was the same for both cities, even though the Hiroshima A-bomb emitted neutron and gamma radiation while that in Nagasaki emitted only gamma radiation. Thus, it seems that type of radiation had no significant effect on histological type of carcinoma.

Breaking down the histological distribution by age at diagnosis (<40, 40-60, and 60+) revealed no differences in either exposed or control group. Furthermore, the distribution was not affected by considering the age ATB or duration from age ATB to age at diagnosis.

On the basis of this and previous studies, it was concluded that radiogenic breast cancer does not differ histologically from spontaneously occurring breast cancer in Japanese women. This does not imply, however, that differences do not exist, but rather that any differences were not discerned by using the current histological classification.

Our observations are essentially similar to those reported in a review of breast cancer in women irradiated for postpartum mastitis by Dvoretzky et al.²¹ Except for an increased desmoplastic response to the cancer in their control group, which was not observed in our study, breast cancer in these exposed women did not differ from that in our subjects for the usual histological variables. However, in the present review, other changes were observed in the collagen, which are believed to be the result of A-bomb irradiation.

し、診断を確認するよう要請した。組織型分類を満足のゆくものにするために、その診断がWHOの分類に従うほかの国際的研究や、日本での過去の研究と比較できるように、WHOと日本乳癌研究会の分類を統合したものを研究に利用することが同意された。

分析の一環として、乳癌の異なる組織型別の分布を幾つかの変数を用いて比較したが、その分布は被爆群と非被爆群で本質的には同じであった。実際に、その分布は日本人女性の期待分布と異なっていなかった。²⁰

広島上空で炸裂した原爆は中性子とガンマ線を放出し、長崎ではガンマ線のみであったにもかかわらず、組織学的分布は両市で同じであった。このように、放射線質は癌の組織型に有意な影響を及ぼさないようである。

診断時年齢別(40歳以下、40～60歳、60歳以上)にみても、組織学的分布は被爆群と非被爆群において差異はなかった。更に被爆時年齢や、被爆から診断までの期間別にみても、その分布は影響を受けなかった。

本研究と過去の研究によって、日本人女性においては放射線誘発性乳癌と自然発生乳癌には組織学的な違いはないと結論された。しかしながら、このことは、違いが存在しないということではなくて、現行の組織分類を用いては違いが識別できなかったということの意味するものである。

我々が得た観察結果は、Dvoretzkyら²¹による分娩後乳腺炎に対して放射線照射を受けた女性の乳癌の検討の中で報告されているものと本質的には同じである。我々の研究では観察されなかったが、彼らの対照群に認められた癌に対する線維形成性反応の増強を除いて、彼らの被曝した女性における乳癌は、通常の組織学的変型に関しては我々の対象群と違いはなかった。しかしながら、今回の検討では膠原線維にはほかの変化が観察され、それは原爆被爆の結果によるものと思われる。

Because irradiation does not reduce the age at which breast cancer develops in Japanese women despite increased incidence and because radiogenic breast cancer does not differ histologically from spontaneous breast cancer, it is suggested that radiation increases the susceptibility of breast tissue to those factors (such as endocrine, etc.) that have been implicated as the cause of spontaneous breast cancer. This suggestion is in keeping with observations on laboratory animals that hormonal factors tend to modify radiation-induced breast cancer. For instance, in rats, ovariectomy following irradiation reduces the incidence of breast cancer while treatment with diethylstilbestrol increases the incidence in certain strains.^{18,19}

The results of the pilot study of noncancerous human breast tissue exposed to 100+ rad revealed no residual atypical or epithelial proliferative lesions in either lobules or ducts. In contrast, the participating pathologists were impressed by the extreme degree of atrophy as well as a definite fibroelastotic change that occurred in the stroma, usually around the ducts. A similar change was observed in some of the irradiated women with breast cancer. In addition, a degeneration of fat tissue similar to that occurring in malnutrition, irradiation, or cachexia was noted. In this regard, changes in the connective tissue surrounding the lesions were also noted in women irradiated for postpartum mastitis.²¹ Perhaps stromal changes, if they can be better defined, may prove to be a marker for radiation exposure.

被曝によって日本人女性の乳癌発生率は高くなるが、乳癌の発現年齢は引き下がらないことと、放射線誘発性乳癌は自然発生の乳癌と組織学的には異ならないことにより、放射線により、乳腺組織は自然発生の乳癌の原因と考えられている要因(内分泌等)への感受性が高くなることが示唆される。このことは、実験動物を用いたホルモンの要因が放射線誘発性乳癌を変化させやすいという観察結果と一致する。例えば、ラットでは放射線照射後卵巣を摘出すると乳癌発生率が減少するが、diethylstilbestrolを用いて処理すると、ある種のラットでは発生率の増加がみられる。^{18,19}

100rad以上に被曝したヒトの非乳癌組織の試験的調査では、小葉にも乳管にも残存性非定型又は上皮性増殖病変はみられなかった。それとは対照的に、検討に参加した病理学者たちは、通常乳管周辺の基質に発生した明白な弾性線維の変化だけでなく極度な萎縮にも驚いた。一部の被曝女性の乳癌に同様の変化が観察された。加えて、栄養障害、放射線被曝又は悪液質において発生すると同様の脂肪組織の変性がみられた。これに関連して、分娩後乳腺炎に対して放射線照射を受けた女性には病変周囲の結合組織の変化も観察されている。²¹ 基質変化の定義が更によくなれば、基質変化は恐らく放射線被曝の指標となるであろう。

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量的・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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