

# LUNG CANCER AT AUTOPSY IN ATOMIC BOMB SURVIVORS AND CONTROLS, HIROSHIMA AND NAGASAKI 1961-70

原爆被爆者および対照者の剖検における肺癌，広島・長崎，1961-70年

## I. AUTOPSY FINDINGS AND RELATION TO RADIATION

### 1. 剖検所見ならびに放射線との関係

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JAPANESE NATIONAL INSTITUTE OF HEALTH OF THE MINISTRY OF HEALTH AND WELFARE

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## SUMMARY

Cancer of the lung is increased in persons exposed to chemicals, long term radiation, lung irritants, and other substances. Previous studies indicated there might be an increase of lung cancer in atomic bomb survivors in Hiroshima and Nagasaki. Lung cancer was present in 204 of 3778 autopsies on radiation exposed survivors and controls performed during 1961-70. Using the WHO classification, 32% were epidermoid, 19% small cell anaplastic, 29% bronchogenic adenocarcinoma, 9% bronchiolo-alveolar, and 11% other types of carcinoma. Small cell anaplastic carcinomas were definitely increased in irradiated persons compared to controls (relative risk 3.9;  $P < .05$ ). Epidermoid and bronchogenic adenocarcinoma showed increased risk but this was not statistically significant. In this entire series, 89% were 60 years old or older, 67% were in men with male/female ratios of 2.4:1 for epidermoid, 3.9:1 for small cell anaplastic, and 1.3:1 for bronchogenic adenocarcinoma. No data were available for a study of the possible effect of internal irradiation. It was evident that analysis for the carcinogenic effect of external irradiation at the time of the bomb could not be made without simultaneous consideration of cigarette smoking and occupational effects. An analysis of the effect of these factors on the interpretation of whole-body irradiation as a cause of lung cancer is reported separately.

## 要 約

肺癌は，化学薬品，長期放射線被曝，肺刺激剤およびその他の物質の被曝で増加する。以前の調査では，広島および長崎における原爆被爆者に肺癌の増加があるのではないかと示唆された。1961-70年の間に実施した被爆者と非被爆対照者の剖検3778例中に肺癌を204例認めた。世界保健機関の分類に従うと表皮癌32%，小細胞型退行性癌19%，気管支原性腺癌29%，細気管支肺胞癌9%およびその他の癌11%であった。放射線照射を受けた者における小細胞型退行性癌は，対照者に比べて明らかに増加していた（相対的危険率3.9； $P < .05$ ）。表皮癌および気管支原性腺癌の発生危険率の増加も認められたが，これは統計的には有意ではなかった。全例中の89%が60歳以上で，67%が男子であった。男子と女子との比率は，表皮癌が2.4:1，小細胞型退行性癌が3.9:1，および気管支原性腺癌が1.3:1であった。放射線内部照射による影響の可能性を検討するための資料は入手できなかった。原爆時の放射線外部照射についての解析を行なうにあたって，喫煙および職業の影響も同時に考慮しなければならないことは明らかである。これらの因子が肺癌の原因としての全身放射線照射の解釈に及ぼす影響についての解析結果は別に報告する。

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## INTRODUCTION

It appears to be well established that there is an increased incidence of lung cancer when radiation-emitting substances such as radon and its radioactive daughters enter the lungs and are present there for long periods of time. Numerous reports have documented the carcinogenic effect of chronic alpha-particle bombardment of the lung substance from inhaled material in miners in the European and North American continents.<sup>1-10</sup> In Japan, Yamada<sup>11</sup> described the pathologic findings in lung cancer in workers chronically exposed to mustard gas, a radiomimetic agent. In both the miners exposed to radioactive dust and the workers in the mustard gas factory the carcinogenic agent was in persistent and intimate contact with the bronchial epithelium. Histologically, the increase in lung cancer in the above studies was noted to be due to increases in the small cell anaplastic and squamous cell types of carcinoma.

Surveys of populations exposed to externally applied radiation have been less numerous than those dealing with inhaled radioactive substances and the attendant data has been less conclusive. In their survey of mortality among patients treated with external irradiation for ankylosing spondylitis, Court Brown and Doll<sup>12</sup> found an increase in tumors of several organs, including the lungs. However, histological typing of the lung tumors was not performed in their study and therefore histologic comparison could not be made with the studies mentioned above. Simpson and Hempelmann<sup>13</sup> conducted a 27-year follow-up of a large group of children given thoracic X-irradiation for enlarged thymus and though thyroid carcinoma was markedly increased and leukemia and bone tumors were observed, no pulmonary tumors were found. Fifteen years after the Bikini atomic explosion accidentally exposed a number of Marshall Islanders to radioactive fallout, no pulmonary neoplasms were reported although an increase in thyroid cancer was documented.<sup>14</sup>

Animal studies in general have supported the findings of the carcinogenic effect of inhaled radioactive particulate material observed in miners.<sup>15-17</sup> As for external irradiation, high-dose X-irradiation applied to the thorax of hamsters has resulted in malignant change in from 2% to 12% of the animals.<sup>18,19</sup> In mice, X-irradiation and fast neutron application have not been associated consistently with an increase in pulmonary cancer.<sup>20,21</sup> Gross et al<sup>19</sup> attributed an increase in pulmonary tumors in rats to the synergistic effect of radiation and the endemic pulmonary inflammation common to many rodent colonies. Thus it appears the particular type of animal used as well as potentially additive factors such as chronic inflammation are important factors

## 緒言

ラドンおよびその放射性娘物質のような放射性物質が肺に侵入して長期間そこに存在する場合には、肺癌の発生率が増加することが証明されているようである。欧米の鉱夫において、吸入した物質による肺組織の慢性的 $\alpha$ 粒子衝撃が発癌性影響を与えていることについては多くの報告がある。<sup>1-10</sup> 日本では、山田<sup>11</sup>が、擬放射性物質であるマスタード・ガスに長期間さらされた労働者の肺癌の病理学的所見について報告した。放射性塵芥にさらされた鉱夫およびマスタード・ガス工場の労働者においては、いずれも発癌因子と気管支上皮とが持続的に密接な関係をもっていた。上記諸調査における肺癌の増加は、組織学的には小細胞退行性型および扁平上皮細胞型の癌の増加によることが報告されている。

体外から放射線照射を受けた人口集団に関する調査は、放射性物質の吸入に関するそれよりも少なく、付随資料による確証も乏しい。Court Brown および Doll<sup>12</sup>は、強直性脊椎炎の治療のために体外より放射線照射を受けた者の死亡率について調査を行ない、肺を含むいくつかの臓器の腫瘍が増加していることを認めている。しかし、これらの調査では肺腫瘍の組織学的分類は行なわれていないので、上記の諸調査との組織学的比較を行なうことができなかった。Simpson および Hempelmann は、胸腺肥大のために胸部X線治療を受けた子供の大規模な集団について27年間の追跡調査を行ない、甲状腺癌の著しい増加や白血病および骨腫瘍の増加を認めたが、肺腫瘍の増加は認めていない。<sup>13</sup> Bikiniの原爆実験でマーシャル群島住民多数が放射性降下物に被曝して15年を経た現在、甲状腺癌の増加が報告されているが、<sup>14</sup> 肺腫瘍の増加についての報告はない。

概して、動物実験は、鉱夫に認められた放射性微細物質の吸入がもたらす発癌性影響を裏づけている。<sup>15-17</sup> ハムスターの胸廓に高線量のX線の体外照射を行なった結果、2%から12%に悪性変化が生じた。<sup>18,19</sup> マウスでは、X線照射および速中性子照射と肺癌増加との間には、一貫した関連は認められていない。<sup>20,21</sup> Grossら<sup>19</sup>は、ネズミに肺腫瘍が多いのは、多くのげっ歯類によくみられる風土性肺浸潤と放射線との相乗作用の影響のせいであるとしている。したがって、肺における悪性腫瘍の放射線誘発実験では、動物の種類ならびに慢性炎症などの潜在的

in experimental radiation-induced pulmonary malignancies.

The survivors of the atomic bombs constitute the largest source available for study of the effects of single, whole-body exposure to radiation in humans. In Hiroshima and Nagasaki the delayed effects of radiation are being studied in survivors and controls selected as members of a fixed population, the JNII-ABCC Life Span Study (LSS) sample. An increased risk for leukemia, thyroid cancer, salivary gland tumors, and perhaps lymphoma and breast cancer has been found among the more heavily irradiated individuals.<sup>22-26</sup> Several reports have indicated that there probably is an increase of lung cancer in the survivors.<sup>27-29</sup> Wanebo et al,<sup>30</sup> studied the cases accumulated through 1966 and reported that lung cancer was increased in frequency among heavily irradiated survivors. However, in the 51 cases of the ABCC-JNII Adult Health Study sample in which tissue sections were available for microscopic review, no increase in any particular histologic type could be demonstrated. They found a relationship between lung cancer and radiation dosage when the diagnosis was based on death certificates, and only a consistent but not statistically significant relationship when based on autopsy confirmed cases. In a study of 200 autopsied cases of lung carcinoma in Hiroshima and Nagasaki Mansur et al,<sup>31</sup> stated that the relative frequency of the various histologic types was comparable with reports from other countries. Among the 200 autopsies there were 63 which were suitable for evaluation of radiation exposure. There was a slight but statistically significant increase in lung carcinoma in those receiving 128 rad or more at the time of the bomb (ATB) when all histologic types and both sexes were combined. No increase was found when the male population alone was examined, nor was there any significant increase in any separate histologic type of lung carcinoma.

Since the last ABCC report, additional cases of lung cancer in the LSS sample have come to autopsy and an epidemiologic investigation of smoking and occupational exposure has been completed. This report gives the findings in 204 autopsies by histologic type as related to the radiation dose in rad. The description and interpretation of the epidemiologic survey will be reported separately.

## METHODS AND MATERIALS

**Population.** The LSS population is a fixed sample consisting of approximately 100,000 persons who were living in Hiroshima or Nagasaki at the time of the 1950 National census. It is composed of four comparison groups selected by distance from the

付加因子が重要な要因であるように思われる。

原爆被爆生存者はヒトに対するただ1回の全身被曝の影響に関する調査の対象としては最大の集団である。広島・長崎においては、選択された被爆者および対照者を対象として予研-ABCC寿命調査の固定集団の放射線の後影響についての調査が行なわれている。強度の被曝者には、白血病、甲状腺癌、唾液腺腫瘍に、また、おそらくリンパ腫と乳癌にも危険率の増加が認められている。<sup>22-26</sup> 若干の報告では、被爆者にはおそらく肺癌の増加があると思われると述べられている。<sup>27-29</sup> Waneboら<sup>30</sup>は、1966年までに収集された症例について検討を加え、強度被曝者に肺癌の頻度の高かったことを報告した。しかし、ABCC-予研成人健康調査対象者のうち、顕微鏡検査のための組織片が入手されている51例においては、特定の組織型に増加は認められなかった。死亡診断書に基づく診断の場合には、肺癌と放射線量との間に関係が認められ、剖検によって確認された例でも一致した所見が認められたが、統計的に有意な関係はなかった。Mansurら<sup>31</sup>は、広島・長崎の肺癌剖検例200例に関する調査において、各組織型の相対的頻度が外国の調査結果に類似していると述べた。200の剖検例のうち、放射線被曝の評価に適したものは63例であった。各組織型と男女を合計した場合、原爆時に128 rad以上を受けた者の肺癌は、わずかながら統計的に有意な増加を示した。男子集団のみについての調査では増加は認められず、また、個々の組織型別にみても有意の増加はなかった。

前回の報告以来、寿命調査対象者に発生した肺癌の剖検数がふえ、また喫煙歴や放射線の職業被曝に関する疫学的調査も完了している。本報告では、204例の剖検例における所見を組織型別に放射線量(rad単位)に関連して示す。疫学調査の結果については別に報告する。

## 方法および材料

**調査集団:** 寿命調査集団は、1950年度国勢調査時に広島または長崎に居住していた約10万人の対象者から構成されている固定集団である。また、原爆時に爆心地か



bomb hypocenter ATB; 1) an inner proximally exposed group of 27,800 survivors who were within 2000 m from the hypocenter; 2) an outer proximally exposed group of 16,600 survivors who were from 2000 to 2499 m from the hypocenter; 3) a distal exposed group of 27,800 survivors who were from 2500 to 10000 m from the hypocenter; and 4) a group of 27,800 persons who were not in either city ATB. Groups 3 and 4 were matched to Group 1 by age and sex. Subsequently the radiation exposure dose for each survivor was estimated in rad based on air decay curves and shielding factors following special surveys and investigations at ABCC and at the Oak Ridge National Laboratory.<sup>32,33</sup> The dose in rad (T65D) is the simple sum of the gamma and neutron radiation dose. No data were available for a study of the possible effect of internal irradiation ATB although it is generally believed that in these cases this probably was not a significant factor. In approximately 5% of the members of the sample a dose could not be estimated because of peculiar shielding configurations and in the tables they are listed as "no estimate." The study is based on all autopsied cases of primary lung cancer observed in the JNH-ABCC LSS population, Hiroshima and Nagasaki in the 10-year-period 1961-70.<sup>34</sup>

Most of the autopsies were performed at ABCC but many were performed by pathologists at the universities and hospitals of the two cities. The number of autopsies in this study from each city (Hiroshima 156; Nagasaki 48) approximates the ratio of 3:1 for the population of the two cities in the LSS sample.

**Selection of Material.** Because of various biases in selection of cases, autopsy material accumulated by ABCC prior to 1961 has limited value for the study of radiation exposure effects and was not included in this study. The protocols and slides from all autopsies coded with a diagnosis of primary lung cancer in the years 1961-70 were reviewed. Decision as to whether any particular case qualified for this study was based on the gross description and microscopic picture without knowledge of the patient's exposure status. Two cases with microscopic changes characteristic of pulmonary tumorlets were not included in the study because of their uncertain position in relation to lung cancer. Particular attention was focused on cases with an additional extra-pulmonary primary carcinoma to rule out the possibility that lung metastases were being mistaken for a primary lung cancer. Six cases were rejected because they had an associated malignancy of a histologic type so similar to that of the pulmonary tumor that evidence for primary lung cancer was equivocal. Three cases were excluded because no biopsy or surgical material was available to establish the diagnosis and no lung cancer was

らの距離によって選ばれた次の四つの比較群から構成されている。すなわち、(1) 爆心地から2000 m以内で被爆した内近距離群の27,800人、(2) 2000 mから2499 mで被爆した外近距離群の16,600人、(3) 2500 mから10,000 mの距離にいた遠距離被爆者の27,800人および(4) 原爆時にいずれの市にもいなかった27,800人である。第3群および第4群の対象者は第1群の対象者と年齢および性をもとにして組み合わせた。その後各被爆者の受けた被曝線量は、ABCCおよびOak Ridge National Laboratory (ORNL) による特別の研究で空中崩壊曲線および遮蔽因子をもとにして推定された。<sup>32, 33</sup> Rad単位の暫定推定線量 (T65D) は、ガンマ線量および中性子線量の単純和である。原爆放射線の内部照射によって起こると考えられる影響を調査するための資料は入手されていないが、おそらくこれは有意な因子ではないであろうと考えられている。調査集団の約5%は、特別な遮蔽状態のため線量推定が行われず、表には「推定値のないもの」として記入されている。この調査は、1961-70年の10年間に広島および長崎の寿命調査集団に認められた原発性肺癌の全剖検例をもとにして行なわれたものである。<sup>34</sup>

剖検の大部分はABCCで行なわれたが、両市の大学および病院の病理学者によって行なわれたものも多い。本調査における両市の剖検例数(広島156例、長崎48例)は寿命調査集団における両市を対象群構成者の比率である3:1に近似している。

**資料の選定:** 剖検例選択にいろいろの偏りがあったため、1961年以前に収集したABCCの剖検資料は放射線被曝の影響を研究するには価値があまりないので、本調査には含めなかった。1961-70年の間に原発性肺癌と診断された全剖検例の剖検記録および標本スライドを検討した。特定の剖検例が本調査対象として適格であるかどうかの決定は、肉眼的所見および顕微鏡的所見によって行なわれ、対象例の被爆状態は伏せておいた。肺癌に特有の微細な顕微鏡的变化の認められた2例は、肺癌との位置的関係が不明確であったため、本調査の対象に含めなかった。肺以外に別の原発性癌のある例については、肺転移癌を原発性肺癌と取り違える可能性を防止するため特に注意を払った。6例では、別の悪性腫瘍の併存が認められ、その組織型が肺腫瘍のそれと非常によく似ていて、認められた肺癌が原発性のものである証拠が明確でなかったため、対象から除外した。また別の3例は、臨床所見をもとに肺癌の治療を受けていたが、診断を確立するための生検または外科材料が入手されておらず、

found at autopsy although they had been treated for lung cancer based on clinical findings. A total of 204 autopsies with primary lung cancer were accepted for this study. Examination of records showed that none had received radiation therapy prior to the onset of the lung cancer.

**Histologic Classification of Tumors.** The WHO histologic classification of lung tumors<sup>35</sup> was used. All sections from the lung tumors were reviewed by at least two pathologists who did not know radiation exposure status, smoking or occupational history, age, sex, or other clinical data relating to the patient. In most cases the lungs fixed in formalin were available for reexamination and for selection of additional blocks for histologic study.

**Epidemiologic Information.** The lungs and lung sections were examined for evidence of active tuberculosis as well as for old, healed scars consistent with healed tuberculosis. Subsequently the clinical history of each patient was also examined for evidence of tuberculosis. Chronic or old healed tuberculosis was diagnosed if there was clinical evidence of tuberculosis more than 3 years before death and old or healed pulmonary granulomatous disease consistent with tuberculosis at autopsy. If a clinical history was not available, the diagnosis was made if acid fast bacilli were found in old caseous foci.

Additional data were obtained from the protocols including date of onset and duration of disease. Sites of metastasis were verified by examination of histologic sections. The significance of the lung cancer was reevaluated as to whether it was the underlying disease or was not related to the cause of death. All information was entered on code sheets and submitted for statistical evaluation. Analyses were made based on data already in the computer including age, sex, date of death, place of death, radiation exposure, etc. The description and methods of analyses of the smoking and occupation survey are reported separately.<sup>36</sup>

## RESULTS

During the 10-year period 1961-70, 10,412 persons in the LSS sample died. Autopsies were performed on 3778 of these persons of whom 204 had a confirmed diagnosis of lung cancer. In 190 of the patients, lung cancer was the underlying (principal) disease while in 14 patients the lung cancer was small and found incidentally during autopsy. The male/female ratio was 0.72:1 for the entire LSS study population, 1.07:1 for the entire autopsy series and 2:1 for lung cancer.

剖検時に肺癌も認められなかったもので、それらも除外した。本調査では、原発性肺癌の認められた計 204 例の剖検例を対象とした。記録を調べてみると、肺癌発生以前に放射線療法を受けた者は 1 例もなかった。

**腫瘍の組織学的分類：**WHO の定めた肺癌の組織学的分類<sup>35</sup>を用いた。対象者の被爆状態、喫煙歴、年齢、性その他の臨床資料について知らされていない少なくとも 2 人の病理医が、肺腫瘍から採取された切片のすべてを検討した。大部分の例の肺はホルマリンで固定されていて、再検討および組織検査のために組織ブロックを選択して追加することが可能であった。

**疫学的資料：**肺および肺切片材料を調べて活動性結核の徴候ならびに治癒した結核を示す古い癒痕の有無を確かめた。次いで、各対象者の臨床歴をもとに結核の有無を調べた。死亡 3 年以上前に結核の臨床的徴候があり、剖検時に結核を裏づける古いまたは治癒した肺肉芽腫性疾患があった場合は、慢性結核または古い治癒した結核と診断した。臨床歴が得られていない場合でも古い乾酪性病巣に抗酸菌が認められた場合には結核の診断を下した。

そのほかに、剖検記録から、発病年月日および罹病期間などの資料をも入手した。転移の部位は組織切片検査により確認した。肺癌が原死因であるか死因に関係ないかについて再評価を行なった。資料はすべて符号化用紙に記入され、統計的評価に付された。年齢、性、死亡年月日、死亡場所、放射線被曝、など、すでに電子計算機に入っている資料に基づいて解析を行なった。喫煙および職業に関する解析結果については別に報告する。<sup>36</sup>

## 結 果

1961-70 年の 10 年間に寿命調査対象者のうち 10,412 人が死亡した。そのうち、3778 例の剖検が行なわれ、204 例に肺癌の診断が確定されている。患者の 190 例では、肺癌が原死因であり、14 例では肺癌は小さく、剖検により付随的に発見されたものであった。寿命調査集団全体の男女構成比率は 0.72:1 であり、全剖検例での比率は 1.07:1 であり、また肺癌の比率は 2:1 であった。

**Histological Types of Lung Cancer.** The distribution of the confirmed lung cancers by sex and histologic type is listed in Table 1. Epidermoid carcinoma was most frequent in males and bronchogenic adenocarcinoma most frequent in females. Epidermoid and small cell anaplastic carcinoma together accounted for 57% (77/136) of the cancers in men and 40% (27/68) in women. Bronchogenic adenocarcinoma was found in 24% of the men and 38% of the women. Bronchiolo-alveolar carcinoma was found in 7% of the men and in 15% of the women. The male/female sex ratios for these tumors was; 2.4:1 for epidermoid carcinoma, 3.9:1 for small cell anaplastic carcinoma, 1.3:1 for bronchogenic adenocarcinoma, and 0.9:1 for bronchiolo-alveolar carcinoma. When calculated in terms of percent for each sex or by rate per 1000 autopsies performed for each sex, epidermoid carcinoma and small cell anaplastic carcinoma were significantly more frequent in males than in females ( $P < .01$  and  $P < .001$  respectively) but there was no statistically significant difference in frequency by sex for any of the other histologic types of lung cancer. Tumors with any epidermoid or small cell anaplastic characteristic comprised 52% of the lung cancers. No carcinoid, bronchial gland tumors, papillary surface tumors, "mixed" tumors, carcinosarcomas or primary lung sarcomas were found in this autopsy series.

**肺癌の組織型:** 表1には、確認された肺癌の性別および組織型別分布を示す。類表皮癌は男子において最も多く、気管支原性腺癌は女子において最も多かった。類表皮癌および小細胞型退行性癌の合計は男子の癌の57% (77/136)、女子の癌の40% (27/68)を占めた。気管支原性腺癌は男子の24%、女子の38%に認められた。気管支肺腺癌は男子の7%、女子の15%に認められた。これらの腫瘍の男女比は、類表皮癌では2.4:1、小細胞型退行性癌では3.9:1、気管支原性腺癌では1.3:1、および気管支肺腺癌の場合は0.9:1であった。性別百分率または剖検1000件当たりの有病率では、類表皮性癌および小細胞型退行性癌の率は女子よりも男子において有意に高い頻度(それぞれ $P < .01$ および $P < .001$ )に認められたが、その他の組織型による性別頻度には統計的に有意な差は認められなかった。類表皮性または小細胞性退行性型は肺癌の52%を占めていた。今回の剖検調査では、類癌腫、気管支腺腫、乳頭表皮腫瘍、"混合"腫瘍、癌肉腫または原性肺肉腫は認められなかった。

TABLE 1 DISTRIBUTION OF 204 LUNG CANCERS BY HISTOLOGIC TYPE AND SEX, LSS AUTOPSY SERIES, HIROSHIMA AND NAGASAKI, 1961-70

表1 寿命調査集団中の剖検における肺癌 204例の分類: 組織型および性別, 広島・長崎, 1961-70年

Group	WHO Classification Histological Type	Male		Female		Total	
		No.	%	No.	%	No.	%
I	Epidermoid	46	33.8	19	27.9	65	31.9
II	Small cell anaplastic	31	22.8	8	11.8	39	19.1
III-1	Bronchogenic adenocarcinoma	33	24.3	26	38.2	59	28.9
III-2	Bronchiolo-alveolar Adenocarcinoma	9	6.6	10	14.7	19	9.3
IV	Large cell carcinoma	4	2.9	3	4.4	7	3.4
V	Combined epidermoid and adenocarcinoma	5	3.7	0		5	2.5
XI	Unclassified*	8	5.9	2	2.9	10	4.9
Total		136	100.0	68	100.0	204	100.0

Test of significance by sex and type  $\chi^2 = 13.206$   $df = 6$   $P < .05$

\*This group included the following histological types of cancer: Epidermoid + large cell anaplastic — 2 cases; Epidermoid + small cell anaplastic — 3 cases; Small cell anaplastic + bronchogenic adenocarcinoma — 3 cases; and two cases of undifferentiated carcinoma which could not be classified into any of the other categories. この群には、次の組織型の癌が含まれる: 類表皮性+大細胞型退行性=2例, 類表皮性+小細胞型退行性=3例, 小細胞型退行性+気管支原性腺癌=3例, および他のいずれの群にも分類できなかった未分化の癌2例。

**Radiation Effects.** The prevalence rates of lung cancer in the LSS autopsy series by dose for the 10-year-period 1961-70 is given in Table 2. There was no significant difference in lung cancer rate for those who received less than 1 rad ATB (col E) and those who were not in either city ATB (col F). Comparison of the lung cancer rate for those who received 200 rad or more ATB (col A) with the rate for those who received less than 1 rad showed a two-fold increase in rate ( $P < .05$ ) for the high dose group in both cities together. Table 3 gives the same information by city with little difference in the relative risk ( $\geq 200$  rad vs  $< 1$  rad) but a suggestive difference of  $P < .1$  for Hiroshima only. There was no significant difference in the lung cancer rate by sex (Table 4) although the rate was higher for those in the high dose group.

Table 5 lists the crude prevalence rates for lung cancer in the LSS autopsy series by histologic type and radiation dose. The small cell anaplastic type was the only type which showed a significant increase for those exposed to 200 rad or more. The prevalence rate was approximately four times higher in the heavily exposed group than in the group who received less than 1 rad. All three of the individuals with estimated exposure levels of more than 400 rad had small cell anaplastic lung carcinomas.

**放射線の影響:** 1961-70年の10年間における寿命調査集団の剖検において認められた肺癌の線量別有病率は表2に示した。原爆時1 rad未満の放射線を受けた者(E欄)および原爆時両市にいなかった者(F欄)では、肺癌有病率に有意な差はない。原爆時200 rad以上を受けた者(A欄)と1 rad未満を受けた者との肺癌有病率の比較では、両市を合わせた高線量群の率( $P < .05$ )が2倍の増加を示している。表3には同じ資料を市別に示した。相対的危険率にはほとんど差はない( $\geq 200$  rad 対  $< 1$  rad)が、広島だけの場合は統計的に有意な差( $P < .10$ )が示唆された。高線量被曝群では肺癌有病率は男女ともに高かったが、全体としては性別に有意の差はなかった(表4)。

表5には、寿命調査集団の剖検で認められた肺癌の粗有病率を組織型別および被曝線量別に示した。200 rad以上の線量に被曝した者に有意の増加を示したのは、小細胞型移行性のものだけであった。強度被曝群では、有病率は1 rad未満群よりも約4倍高かった。推定被曝線量が400 rad以上であった3例は、ことごとく小細胞移行性型であった。

TABLE 2 PREVALENCE RATE OF LUNG CANCER IN LSS AUTOPSY SERIES BY DOSE, HIROSHIMA AND NAGASAKI, 1961-70

表2 寿命調査集団中の剖検における肺癌の有病率：線量別，広島・長崎，1961-70年

	No Estimate	T65 Total Dose (rad)					Not in City	Total
		200+	100-99	50-99	1-49	<1		
		(A)	(B)	(C)	(D)	(E)	(F)	
Autopsies	58	127	120	182	1271	1196	824	3778
Lung cancer	4	13	5	11	68	61	42	204
Crude prevalence rate (per 1000)	69.0	102.4	41.7	60.4	53.5	51.0	51.0	54.0
Standardized prevalence rate* (per 1000)	88.9	93.9	48.4	60.2	54.3	50.2	49.8	.
Relative risk	1.8	1.9	1.0	1.2	1.1	1.0	.	.

Test of significance: Crude prevalence rate: A-B  $\chi^2 = 4.800$  df=1  $P < .05$

Test of significance: Standardized prevalence rate: A-E  $\chi^2 = 5.406$  df=1  $P < .05$

\*Adjusted by sex and age ATB

TABLE 3 PREVALENCE RATE OF LUNG CANCER IN LSS AUTOPSY SERIES BY DOSE AND CITY,  
HIROSHIMA AND NAGASAKI, 1961-70

表3 寿命調査集団中の剖検例における肺癌の有病率：線量および都市別，  
広島・長崎，1961-70年

	No Estimate	T65 Total Dose (rad)					Not in City	Total
		200 +	100-199	50-99	1-49	<1		
HIROSHIMA								
Autopsies	32	82	83	130	936	1049	650	2962
Lung cancer	2	8	5	8	54	50	29	156
Crude prevalence rate	62.5	97.6	60.2	61.5	57.7	47.7	44.6	52.7
Standardized prevalence rate*	87.2	91.9	58.0	65.8	59.0	46.7	44.1	-
Relative risk	1.9	2.0	1.2	1.4	1.3	1.0	-	-
NAGASAKI								
Autopsies	26	55	37	52	335	147	174	816
Lung cancer	2	5	0	3	14	11	13	48
Crude prevalence rate	76.9	90.0	0	57.7	41.8	74.8	74.7	-
Standardized prevalence rate*	56.0	136.3	-	38.7	38.9	75.1	62.8	-
Relative risk	0.7	1.8	-	0.5	0.5	1.0	-	-

\* Adjusted by sex and age ATB

TABLE 4 PREVALENCE RATE OF LUNG CANCER IN LSS AUTOPSY SERIES BY DOSE AND SEX,  
HIROSHIMA AND NAGASAKI, 1961-70

表4 寿命調査集団中の剖検例における肺癌の有病率：線量および性別，  
広島・長崎，1961-70年

	T65 Total Dose (rad)						Not in City	Total
	No Estimate	200+	100-199	50-99	1-49	<1		
MALE								
Autopsies	43	63	68	88	625	632	430	1949
Lung cancer	3	8	3	7	43	41	30	135
Crude prevalence rate (per 1000)	69.8	127.0	44.1	79.5	68.8	64.9	69.8	69.3
Standardized prevalence rate (per 1000)*	97.6	118.3	59.0	76.9	69.1	64.2	67.7	-
Relative risk	1.5	1.8	0.9	1.2	1.1	1.0	-	-
FEMALE								
Autopsies	15	64	52	94	646	564	394	1829
Lung cancer	1	5	2	4	25	20	12	69
Crude prevalence rate (per 1000)	66.7	78.1	38.5	42.6	38.7	35.5	30.5	37.7
Standardized prevalence rate (per 1000)*	79.7	67.9	37.2	42.4	38.6	35.2	30.7	-
Relative risk	2.3	1.9	1.1	1.2	1.1	1.0	-	-

\* Adjusted by age ATB



TABLE 5 CRUDE PREVALENCE RATE\* FOR LUNG CANCER IN LSS AUTOPSY SERIES BY HISTOLOGIC TYPE AND DOSE, HIROSHIMA AND NAGASAKI, 1961-70

表5 寿命調査集団中の肺癌の粗有病率：組織型および線量別，広島・長崎，1961-70年

Morphologic Type		T65 Total Dose (rad)				Not in City	Total	Test (A+C)
		No Estimate	200+	1-199	<1			
Autopsies		58	127	1573	1196	824	3778	
Epidermoid	No.	2	3	30	17	13	65	
	Rate	34.5	23.6	19.1	14.2	15.8	17.2	P>.10
	Relative risk	2.4	1.7	1.3	1.0	-		
Small cell anaplastic	No.	0	5	14	12	8	39	
	Rate	-	39.4	8.9	10.0	9.7	10.3	P<.05
	Relative risk	-	3.9	0.9	1.0	-		
Bronchogenic adenocarcinoma	No.	2	4	21	19	13	59	
	Rate	34.5	31.5	13.4	15.9	15.8	15.6	P>.10
	Relative risk	2.2	2.0	0.8	1.0	-		
Bronchiolo-alveolar adenocarcinoma	No.	0	0	11	6	2	19	
	Rate	-	-	7.0	5.0	2.4	5.0	
	Relative risk	-	-	1.4	1.0	-		
Large cell carcinoma	No.	0	0	3	3	1	7	
	Rate	-	-	1.9	2.5	1.2	1.9	
	Relative risk	-	-	0.8	1.0	-		
Combined and unclassified**	No.	0	1	5	4	5	15	
	Rate	-	7.9	3.2	3.3	6.1	4.0	
	Relative risk	-	2.4	1.0	1.0	-		

\* Rate per 1000 autopsies

\*\* Groups V and XI WHO Classification

TABLE 6 CRUDE PREVALENCE RATE\* OF LUNG CANCER BY HISTOLOGIC TYPE AND AGE AT DEATH, LSS AUTOPSY SERIES, HIROSHIMA AND NAGASAKI, 1961-70

表6 寿命調査集団における肺癌の粗有病率：組織型および死亡時年齢別，広島・長崎，1961-70年

Histologic Type		Age at Death					Total
		<50	50-59	60-69	70-79	80+	
Autopsies		367	384	1013	1260	754	3778
Epidermoid	No.	1	4	25	24	11	65
	Rate	2.7	10.4	24.7	19.1	14.6	17.2
Small cell anaplastic	No.	2	2	11	20	4	39
	Rate	5.5	5.2	10.9	15.9	5.3	10.3
Bronchogenic adenocarcinoma	No.	2	6	25	21	5	59
	Rate	5.5	15.6	24.7	16.7	6.6	15.6
Bronchiolo-alveolar adenocarcinoma	No.	0	3	5	7	4	19
	Rate	-	7.8	4.9	5.6	5.3	5.0
Large cell carcinoma	No.	0	2	2	2	1	7
	Rate	-	5.2	2.0	1.6	1.3	1.9
Combined and unclassified types**	No.	0	1	7	6	1	15
	Rate	-	2.6	6.9	4.8	1.3	4.0
Total	No.	5	18	75	80	26	204
	Rate	13.6	46.9	74.0	63.5	34.5	54.0

\* Rate: per 1000 autopsies

\*\* Groups V and XI WHO Classification

**Smoking Factors and Occupational Exposure.** Analysis of smoking history and occupational exposure as factors affecting the prevalence of lung cancer in irradiated persons in the LSS autopsy series is reported in a separate paper.<sup>36</sup> It was concluded that the data indicate a probable association between lung cancer and ionizing radiation ATB independent of smoking. In this group there was no occupational exposure effect related to radiation.

**Age Factors.** Table 6 gives the crude prevalence rate for lung cancer by age at death and histologic type. Of the 204 patients, 181 (89%) were 60 years old or older and only 5 were below age 50. This age distribution in general held for all histologic types. However, in terms of prevalence rates, both bronchiolo-alveolar and large cell carcinoma were most frequent in the age decade 50-59.

Table 7 gives the prevalence rates for lung cancer by dose and age ATB. Only one person was below age 20 ATB and he received less than 1 rad. There were 24 between age 20 and 39 ATB and 156 between ages 40 and 59 ATB who developed lung cancer. The relative risk for those exposed to 200 rad or more compared to those who received 1 rad for these two age groups was 2.4 and 2.3 respectively. None of the 23 persons who were 60 years old or older ATB received radiation doses of 200 rad or more.

**Metastatic Sites.** Table 8 gives the metastases in percent to 12 specific anatomic sites for each histologic type of lung cancer. The liver (35%) and adrenal glands (32%) were the most frequent sites for metastasis followed by brain (26%), heart (24%), vertebrae (21%), kidneys (21%) and ribs (20%). The tendency to metastasize to a particular site appeared to be influenced by histologic type. For example, only 11% of epidermoid carcinomas metastasized to the adrenal glands while other types metastasized to the adrenals much more frequently. The frequency of bronchiolo-alveolar adenocarcinoma metastasis to the liver, adrenals, and brain was similar to that for the other types of lung cancer but consistently lower for metastasis to other sites. The small cell anaplastic and bronchogenic adenocarcinoma types of lung cancer showed a definite tendency for higher rates of metastases to any given anatomic site.

In 23 lung cancers there were no metastases to lymph nodes or any other tissue. Twelve of the cancers were epidermoid carcinomas, two were small cell anaplastic carcinoma, two were bronchogenic

喫煙因子および職業的被曝： 寿命調査集団の被曝者の剖検で認められた肺癌の有病率に影響を与える因子としての喫煙歴および職業的被曝の解析については、別の報告<sup>36</sup>で述べる。原爆による電離放射線被曝と肺癌の間には、喫煙歴の有無にかかわらず、ある程度関係のあることが示唆された。同じ調査群においては、職業的放射線被曝の影響はみられなかった。

年齢因子： 表6は、肺癌の粗有病率を死亡時年齢と組織型別とによって示したものである。204例のうち、181例(89%)は60歳以上であり、5例のみ50歳未満であった。この年齢分布はおおむねすべての組織型において認められた。しかし、50-59歳では気管支肺胞性腺癌および大細胞型癌の有病率が最も高かった。

表7には肺癌の有病率を線量別および原爆時年齢別に示した。原爆時年齢が20歳以下の症例は1例のみで、その被曝線量は1 rad以下であった。なお、20-39歳の症例は24例、40-59歳は156例であった。この二つの年齢群中200 rad以上の線量を受けた症例の比較では、相対的危険率はそれぞれ2.4と2.3であった。原爆時60歳以上であった23例には、200 rad以上の線量を受けた者はなかった。

転移の部位： 表8は、12の特定の解剖学的部位への転移を、各組織型別に百分率で示したものである。最も転移の多い部位は肝臓(35%)および副腎(32%)であり、次いで脳(26%)、心臓(24%)、脊椎(21%)、腎臓(21%)および肋骨(20%)の順であった。特定の部位へ転移する傾向は、明らかに組織型によって影響されるようであった。たとえば、類表皮癌では11%が副腎へ転移したのみであったが、その他の型の副腎への転移の頻度はより高かった。気管支肺胞腺癌の肝臓、副腎、および脳への転移は、肺癌の他の型のものとほぼ同程度であったが、その他の部位への転移の頻度は他のものよりも一貫して低かった。小細胞型移行性癌および気管支原性腺癌の二つの型の肺癌は、いずれの部位へも高い率で転移する傾向が明らかに認められた。

23例の肺癌では、リンパ腺へも他の組織へも転移は認められなかった。これらのうち、12例は類表皮癌、2例は小細胞型移行性癌、2例は気管支原発性腺癌、6例は気

adenocarcinomas, six were bronchiolo-alveolar adenocarcinomas and one was an unclassified histologic type. In 18 of these 23 cases, the tumor was limited to one lung. Ten of these were present only in one pulmonary lobe and these tumors were among those which were considered not to be the principal underlying disease leading to death. Only metastasis to the liver ( $P < .05$ ) showed an association between site of metastasis and radiation dose ATB (Table 9).

**Association with Tuberculosis.** Table 10 shows the frequency of chronic or old healed pulmonary tuberculosis in the lung cancer patients by histologic type of cancer. The lowest percentage is seen in the small cell anaplastic type of lung cancer. Tuberculosis was present in 646 (17.1%) of the 3778 autopsies in the LSS series and in 36 (17.6%) of the 204 autopsies with lung cancer. No statistical selection ( $P > .10$ ) was found for radiation exposure ATB and the presence of chronic or healed tuberculosis in these cases of lung cancer when examined by histologic type of cancer.

**Bronchial Epithelial Alterations.** Table 11 lists the observed alterations in bronchial epithelium by histologic type of lung cancer. There was squamous metaplasia (11 cases), carcinoma in situ (4 cases) or both (3 cases) in the bronchi of 18 (8.8%) of the 204 cases of lung cancer. When these epithelial changes were examined by radiation exposure dose ATB, no significant relation ( $P > .10$ ) was found.

**Associated Malignancies.** Twenty-one of the individuals in this study were found to have at least one other cancer in addition to lung cancer (Table 12). Two of these had two additional cancers. Twelve persons had significant second primary cancers, (i.e., invasive cancers which frequently are a cause of death,) and nine had second primary cancers which usually remain localized. In the first group the mean age was 73 and in the second it was 64. There are too few cases for analysis by histologic type although, as seen in Table 12, there is a suggestion that some types tend to be associated. In the first group, the lung cancer was the underlying disease in 11 of the 12 autopsies and carcinoma of the stomach was the principal disease in the 12th case (Case #3).

管支肺腺癌, 1例は未分類型であった。23例中18例では腫瘍は一方の肺に限定されていた。そのうち, 10例では腫瘍は一つの肺葉のみに認められ, 主要な原死因性疾患とは考えられなかった。これらの例を原爆時の被曝線量別(表9)に調べた場合においては, 肝臓への転移のみに線量との関係が認められた( $P < .05$ )。

**結核との関係:** 表10は, 肺癌患者における慢性または治癒した古い肺結核の頻度を癌の組織型別に示す。頻度の最も低かったのは小細胞型移行性癌であった。結核は, 寿命調査の剖検3778例中646例(17.1%)および肺癌204剖検例中36例(17.6%)に認められた。組織型別では, 原爆時の被曝線量および慢性または治癒した結核の有無に関しては, 統計的の差異は認められなかった( $P > .10$ )。

**気管支上皮の変化:** 表11は, 気管支上皮に認められた変化を組織型別に示したものである。肺癌204例中18例の気管支に扁平上皮化生(11例), 潜在癌(4例)またはその両者の併存(3例)が認められた。これらの上皮性変化および原爆時の被曝線量には有意の関係は認められなかった( $P > .10$ )。

**関連ある悪性腫瘍:** 本調査対象群中21例では, 肺癌以外の癌が少なくとも一つあったことが認められた(表12)。これらのうち2例には癌がさらに二つ認められた。12例には, 有意な二次的原発性癌, すなわちしばしば死因となる浸襲性癌が認められ, 9例には通常限局性を維持する二次的原発癌が認められた。最初の群では平均死亡時年齢は73歳であり, 次の群では64歳であった。組織型別に解析を行なうには例数が少なすぎるが, 表12にみられるようにある型のものでは関連性を示す傾向が示唆された。最初の群において, 12例の剖検例中11例では肺癌が原死因であり, 残りの一例(症例3)は胃癌が原死因であった。

TABLE 7 PREVALENCE RATES FOR LUNG CANCER BY RADIATION DOSE AND AGE ATB, LSS AUTOPSY SERIES, HIROSHIMA AND NAGASAKI, 1961-70

表7 寿命調査集団中の肺癌有病率：線量および原爆時年齢別，広島・長崎，1961-70年

	No Estimate	T65 Total Dose (rad)					Not in City	Total
		200+	100-199	50-99	1-49	<1		
Age ATB: 20-39								
Autopsies	14	25	24	28	175	175	134	575
Lung cancer	-	3	-	2	7	7	5	24
Crude prevalence rate	-	120.0	-	71.4	40.0	40.0	37.3	41.7
Standardized prevalence rate*	-	97.5	-	74.3	40.0	39.9	36.9	-
Relative risk	-	2.4	-	1.9	1.0	1.0	-	-
Age ATB: 40-59								
Autopsies	27	74	74	112	773	723	505	2288
Lung cancer	4	10	4	9	55	41	33	156
Crude prevalence rate	148.2	135.1	54.1	80.4	71.2	56.7	65.4	68.2
Standardized prevalence rate*	146.8	130.5	54.9	80.8	72.5	56.6	64.6	-
Relative risk	-	2.3	1.0	1.4	1.3	1.0	-	-
Age ATB: 60+								
Autopsies	11	15	13	32	265	240	146	722
Lung cancer	-	-	1	-	6	12	4	23
Crude prevalence rate	-	-	76.9	-	22.6	50.0	27.4	31.9
Standardized prevalence rate*	-	-	79.2	-	22.6	47.0	26.7	-
Relative risk	-	-	1.7	-	0.5	1.0	-	-

\* Adjusted by sex

Note: Lung cancer was found in one of 193 autopsies on persons less than 20 years of age ATB and in that case the radiation dose was less than 1 rad.

注：原爆時年齢20歳以下の193剖検例中1例に肺癌を認めたが，その被曝線量は1 rad以下であった。

TABLE 8 METASTATIC SITES IN 204 LUNG CANCER BY HISTOLOGIC TYPE, LSS AUTOPSY SERIES, HIROSHIMA AND NAGASAKI, 1961-70

表8 寿命調査集団中における肺癌204例の転移部位：組織型別，広島・長崎，1961-70年

Site of Metastasis	Examined	Histologic Type of Lung Cancer											
		Epidermoid		Small Cell Anaplastic		Bronchogenic Adenocarcinoma		Bronchiolo-alveolar Adenocarcinoma		Large Cell Anaplastic		Combined and Unclassified	
		%	No.	%	No.	%	No.	%	No.	%	No.	%	No.
Heart and Pericardium	204	25	16/65	33	13/39	37	22/59	0	0/19	0	0/7	53	8/15
Esophagus	201	19	12/63	13	5/39	10	6/58	0	0/19	0	0/7	15	2/13
Liver	201	22	14/63	49	19/39	40	23/58	32	6/19	14	1/7	47	7/15
Pancreas	202	2	1/63	18	7/39	19	11/59	5	1/19	0	0/7	13	2/15
Adrenals	201	11	7/63	38	15/39	50	29/58	32	6/19	43	3/7	20	3/15
Kidneys	202	13	8/63	20	8/39	34	20/59	10	2/19	0	0/7	33	5/15
Thyroid	202	3	2/63	13	5/39	15	9/59	0	0/19	0	0/7	20	3/15
Brain	193	17	10/59	24	9/38	32	18/56	22	4/18	57	4/7	33	5/15
Ribs	204	12	8/64	24	9/38	16	9/55	11	2/19	17	1/6	13	2/15
Vertebrae	199	8	5/64	32	12/38	34	19/56	11	2/19	14	1/7	13	2/15
Mediastinum	202	17	11/64	15	6/39	17	10/58	11	2/19	29	2/7	20	3/15
Supraclavicular lymph nodes	200	6	4/63	8	3/39	11	6/57	5	1/19	14	1/7	7	1/15

TABLE 9 METASTASES IN 204 LUNG CANCERS BY SITE AND RADIATION DOSE, LSS AUTOPSY SERIES, HIROSHIMA AND NAGASAKI, 1961-70

表9 寿命調査集団中の肺癌 204例における転移：部位および線量別，広島・長崎，1961-70年

Site of Metastasis	T65 Total Dose (rad)				Total	$\chi^2$ Test A=B=C	
	No Estimate	200+	1-199	<1 & NIC			
		(A)	(B)	(C)			
Heart & Pericardium	25.0 (1/4)	38.5 (5/23)	76.5 (26/84)	36.9 (38/103)	34.3 (70/204)	.819	NS
Esophagus	0 (0/4)	15.4 (2/13)	9.8 (8/82)	14.7 (15/102)	12.4 (25/201)	1.097	NS
Liver	50.0 (2/4)	61.5 (8/13)	25.9 (21/81)	37.9 (39/103)	34.8 (70/201)	7.355	P<.05*
Pancreas	0 (0/4)	7.7 (1/13)	9.8 (8/82)	12.6 (13/103)	10.9 (22/202)	.545	NS
Adrenals	25.0 (1/4)	30.8 (4/13)	34.6 (28/81)	29.1 (30/103)	31.3 (63/201)	.626	NS
Kidneys	0 (0/4)	23.1 (3/13)	15.9 (13/82)	26.2 (27/103)	21.3 (43/202)	2.898	NS
Thyroid	0 (0/4)	15.4 (2/13)	11.0 (9/82)	7.8 (8/103)	9.4 (19/202)	1.080	NS
Brain	0 (0/4)	23.1 (3/13)	23.2 (19/82)	28.9 (28/97)	25.9 (50/193)	.601	NS
Ribs	0 (0/4)	15.4 (2/13)	19.0 (15/79)	14.0 (14/100)	15.7 (31/197)	.748	NS
Vertebrae	25.0 (1/4)	23.1 (3/13)	21.3 (17/80)	19.6 (20/102)	20.6 (41/199)	.131	NS
Mediastinum	25.0 (1/4)	15.4 (2/13)	14.5 (12/83)	18.6 (19/102)	16.8 (34/202)	.589	NS
Supraclavicular lymph nodes	25.0 (1/4)	0 (0/13)	7.3 (6/82)	8.9 (9/101)	8.0 (16/200)	1.316	NS

NS = P>.10

TABLE 10 CHRONIC AND HEALED PULMONARY TUBERCULOSIS IN 204 LUNG CANCER AUTOPSIES BY HISTOLOGIC TYPE, LSS AUTOPSY SERIES, HIROSHIMA AND NAGASAKI, 1961-70

表10 寿命調査集団中の肺癌 204剖検例における慢性肺結核および治癒した肺結核：組織型別，広島・長崎，1961-70年

Histologic Type	Total	Chronic and Healed Tuberculosis	
		No.	%
Epidermoid	65	11	16.9
Small cell anaplastic	39	5	12.8
Bronchogenic adenocarcinoma	59	10	16.9
Bronchiolo-alveolar adenocarcinoma	19	5	26.3
Large cell carcinoma	7	0	-
Combined & unclassified	15	5	33.3
Total	204	36	17.6

TABLE 11 BRONCHIAL EPITHELIAL CHANGES IN 204 LUNG CANCER CASES BY HISTOLOGIC TYPE OF CANCER, LSS AUTOPSY SERIES, HIROSHIMA AND NAGASAKI, 1961-70

表11 寿命調査集団中の肺癌 204例における気管支表皮性変化：組織型別，広島・長崎，1961-70年

Histologic Type	Total	Bronchioepithelial Change					
		Squamous Metaplasia		Carcinoma In Situ		Both	
		No.	%	No.	%	No.	%
Epidermoid	65	7	10.8	2	3.1	2	3.1
Small cell anaplastic	39	0	-	1	2.6	0	-
Bronchogenic adenocarcinoma	59	3	5.1	0	-	0	-
Bronchiolo-alveolar adenocarcinoma	19	0	-	0	-	0	-
Large cell carcinoma	7	1	14.3	0	-	0	-
Combined & unclassified	15	0	-	1	6.7	1	6.7
Total	204	11	5.4	4	2.0	3	1.5



TABLE 12 MULTIPLE PRIMARY MALIGNANCIES ONE OF WHICH IS LUNG, LSS AUTOPSY SERIES,  
HIROSHIMA AND NAGASAKI, 1961-70

表12 寿命調査集団中の剖検例における多発性原発性悪性腫瘍の一つが肺癌であった例,  
広島・長崎, 1961-70年

	Sex	Age	Histologic Type	
			Lung Cancer	Other Cancer
A. Significant Second Primary Cancer				
1	M	82	Epidermoid	Adenocarcinoma, stomach
2	M	79	Epidermoid	Adenocarcinoma, stomach
3	M	63	Epidermoid	Adenocarcinoma, stomach
4	F	79	Epidermoid	Adenocarcinoma, stomach
5	F	82	Epidermoid	Adenocarcinoma, rectum (occult carcinoma, thyroid)
6	F	66	Epidermoid	Epidermoid, cervix
7	M	78	Small cell anaplastic	Adenocarcinoma, rectum
8	F	81	Small cell anaplastic	Adenocarcinoma, stomach
9	M	67	Bronchogenic adenocarcinoma	Adenocarcinoma, stomach
10	F	78	Bronchogenic adenocarcinoma	Adenocarcinoma, thyroid; Adenocarcinoma, colon
11	F	65	Bronchogenic adenocarcinoma	Epidermoid, cervix
12	M	56	Combined epidermoid and adenocarcinoma	Epidermoid, larynx
B. Localized Second Primary Cancer				
1	F	57	Small cell anaplastic	Occult carcinoma, thyroid
2	M	68	Small cell anaplastic	Occult carcinoma, thyroid
3	M	70	Small cell anaplastic	Occult carcinoma, thyroid
4	M	69	Small cell anaplastic	Transitional cell carcinoma, urinary bladder
5	F	62	Small cell anaplastic	Carcinoid, rectum
6	M	59	Bronchogenic adenocarcinoma	Occult carcinoma, thyroid
7	F	61	Bronchogenic adenocarcinoma	Occult carcinoma, thyroid
8	F	63	Bronchogenic adenocarcinoma	Occult carcinoma, thyroid
9	F	69	Bronchiolo-alveolar adenocarcinoma	Occult carcinoma, thyroid

A. Significant second primary cancer - An invasive primary cancer arising in a site other than lung. Except for case 3 (gastric cancer) lung cancer was the underlying disease for all cases in this group.

B. Localized second primary cancer - A slow growing localized histologically malignant tumor with little potential for distal metastasis. None of the second tumors in this group were biologically significant.

A. 有意の第2原発性癌—侵襲性の原発性癌で肺以外の部位に発生した。症例2(胃癌)を除いてこの群に属する全例では、肺癌が原疾患であった。

B. 限局性第2原発性癌—成長のおそい限局性で組織学的に悪性で遠隔部位への転移の危険性の少ない腫瘍。この群に属する第2腫瘍にはいずれも生物学的有意性はなかった。

## DISCUSSION

Prior to 1961, less than 10% of the deaths in the LSS sample were autopsied and there was a strong selection bias in that the main effort was directed at obtaining autopsies on persons close to the hypocenter, on persons who had had radiation sickness symptoms, on persons with certain death certificate diagnoses such as leukemia, etc. In 1961 the autopsy procurement system was changed and trained autopsy contactors solicited permission for autopsy on all members of the LSS sample. As a result of their vigorous efforts, the autopsy rate for the LSS sample rose to 35% to 45% in the period 1961-70. However, permission for autopsy still was more easily obtained for some categories of patients than others. This was especially true for heavily irradiated survivors, members of the Adult Health Study sample, persons dying of a hematologic disease (equated by lay people with "atom bomb disease") etc.

Death certificates are obtained regularly on more than 98% of persons in the LSS sample who die. These are used as one test of bias in the autopsy sample. Table 13 gives the autopsy rate by radiation dose for all deaths in the LSS sample and for those with a death certificate diagnosis of lung cancer. There is definite selection ( $P < .001$ ) for radiation in obtaining autopsy permission in the LSS sample but not for radiation in obtaining permission when the death certificate lists lung cancer. Table 14 gives the death certificate detection rate by radiation dose for lung cancer. This is the percent of lung cancers found at autopsy which were also listed on the death certificate. The analysis is based on 184 rather than 204 autopsy confirmed lung cancers because 20 were not clinically recognizable and therefore could not be expected to be listed on death certificates. The statistical test of this data indicates that death certified and autopsy confirmed lung cancers were not selected by radiation dose for inclusion in the autopsy series.

It should be noted in Tables 13 and 14 that the autopsy rate for persons with death certificate diagnosis of lung cancer and for persons with autopsy confirmed death certificate diagnosis of lung cancer is higher for those who received 200 rad or more ATB than for those who received less than 1 rad. The autopsy rate is 82% (9/11) vs 52% (33/63) for the high and low dose persons with death certificate diagnosis of lung cancer and the death certificate detection rate is 62% (8/13) vs 48% (27/56) when the death certificate diagnosis of lung cancer is confirmed by autopsy. These differences are not statistically significant although they do suggest that the more heavily irradiated

## 考 察

1961年以前には、寿命調査集団における死亡例の10%未満が剖検されたにすぎず、また爆心地に近かった者、放射線疾患の症状のあった者、白血病のような特定の死亡診断書のあった者などの剖検を行なうことに主力を傾注していたために、剖検の選択に強い偏りがあった。1961年には、剖検入手の方法が変更され、訓練された剖検連絡員が寿命調査集団中の死亡例の剖検承諾を求めることになった。かれらの積極的な努力により1961-70年の間に寿命調査集団中の剖検率は、35%から45%へと上昇した。しかし、承諾はやはりある特定の症例群において他のそれにおけるよりも得られやすかった。この事實は、特に強度被曝者、成人健康調査対象者および血液疾患患者（一般に言われている「原爆症」に相当するもの）の死亡例において認められた。

寿命調査集団中の死亡者の98%以上については死亡診断書が定期的に入手されている。これらは剖検例中の偏りを調べるための検定に使用されている。表13は寿命調査対象者中の全死亡者および死亡診断書が肺癌となっている者の剖検率を線量別に示す。寿命調査対象者の剖検許可を求めるにあたり、線量については明らかに選択( $P < .001$ )が行なわれているが、死亡診断書が肺癌となっている者の許可を求める場合には線量による選択は行なわれていない。表14には死亡診断書による肺癌の発見率を線量別に示した。これは剖検において認められた肺癌例中死亡診断書にも同じ記載がなされていたものの百分率を示す。20例では肺癌が臨床的に認められなかったもので、死亡診断書に記載されるはずがないため、解析は204例の確認剖検例についてではなく、184例について実施された。この資料の統計的検定の結果、死亡診断書に記載され、剖検によって確認された癌症例を剖検集団に含めるため放射線量による選択が行なわれなかったことがわかる。

表13および14から死亡診断書の所見が肺癌となっている例および死亡診断書の所見が肺癌であってそれが剖検によって確認された例の剖検率は、200 rad以上の線量を受けた者のほうが1 rad以下の者よりも高いことは注目し値する。死亡診断書所見が肺癌であった高線量および低線量被曝者の剖検率は82% (9/11) 対 52% (33/63) であって、死亡診断書所見が肺癌であって剖検によって確認されたものの発見率は62% (8/13) 対 48% (27/56) であった。これらの差は統計的に有意ではないが、肺癌

survivors who are suspected of having lung cancer are more likely to have autopsy and that their clinical diagnosis is more likely to be correct.

の疑いのある強度被曝者の場合には剖検を受ける傾向があり、その臨床診断もより正しい可能性が大である。

TABLE 13 AUTOPSY RATE BY RADIATION DOSE FOR ALL DEATHS IN THE LSS SAMPLE AND THOSE WITH A DEATH CERTIFICATE DIAGNOSIS OF LUNG CANCER, HIROSHIMA AND NAGASAKI, 1961-70

表13 寿命調査集団中の全死亡例および死亡診断書所見が肺癌となっていたものの線量別剖検率，広島・長崎，1961-70年

T65 Total Dose	Deaths*	Autopsies	Autopsy Rate (%)	Test for Difference of Autopsy Rate by Dose ( $\chi^2$ test)
A. All Deaths				
No estimate	148	58	39.2	$\chi^2 = 70.808$ df = 4 P < .001
200+ rad	270	127	47.0	
1-199	3920	1573	40.1	
<1	3442	1196	34.7	
Not in City	2632	824	31.3	
Total	10412	3778	36.3	
B. Lung Cancer as Underlying Cause of Death on the Death Certificate				
No estimate	6	3	50.0	$\chi^2 = 7.473$ df = 4 P > .10
200+	11	9	81.8	
1-199	105	61	58.1	
<1	63	33	52.4	
Not in City	57	24	42.1	
Total	242	130	53.7	

\* A - Total number of deaths

B - Number of deaths with a death certificate diagnosis of lung cancer

TABLE 14 DEATH CERTIFICATE DETECTION RATE FOR LUNG CANCER BY RADIATION DOSE BASED ON AUTOPSY CONFIRMATION, LSS AUTOPSY SERIES, HIROSHIMA AND NAGASAKI, 1961-70

表14 寿命調査集団中における肺癌の剖検による確認と死亡診断書での発見率：線量別，広島・長崎，1961-70年

T65 Total Dose	Lung Cancer		Detection* Rate (%)	Test for Difference of Detection Rate by Dose
	At Autopsy	On Death Certificate		
	(a)	(b)		
No estimate	4	2	50.0	$\chi^2 = 4.768$ df = 4 P > .10
200+ rad	13	8	61.5	
1-199	75	49	65.3	
<1	56	27	48.2	
Not in City	36	18	50.0	
Total	184	104	56.5	

\* Detection rate:  $b/a \times 100$

Note: 20 lung cancers found at autopsy were deleted because they were not clinically recognizable or detectable. Subsequently lung cancer was given as the principal diagnosis at autopsy in 6 of these cases. None were deleted in the 200 rad or more group. There were 9 in the 1-199 rad group, 5 in the less than 1 rad group and 6 in the NIC group that were deleted.

The distribution of lung cancers by histologic type in this series is similar to that reported by Christiansen<sup>37</sup> and by Herman and Crittenden<sup>38</sup> who used a histologic classification similar to the WHO classification. The average age at death in our series appears somewhat higher than that found by Miyaji<sup>39</sup> in his report on lung cancer in Japan.

An increased risk of lung cancer was found for those individuals exposed to 200 rad or more ATB. Although the relative risk was increased for epidermoid, bronchogenic adenocarcinoma, and for combined and unclassified carcinomas (Table 5), only the relative risk of 3.9 for small cell anaplastic carcinoma was statistically significant ( $P < .05$ ). Since smoking has been associated with an increased risk for this type of lung cancer as well as others, it is obviously essential that the contribution of smoking to the increased risk of developing lung cancer should be examined before accepting radiation as the cause for the A-bomb survivors' increased risk. In the epidemiologic study of smoking and radiation,<sup>36</sup> the increased risk for small cell anaplastic carcinoma disappeared evidently because of the small number of cases involved. However, the data indicated that for all lung cancers, there probably was a radiation effect independent of smoking.

Some recent reports<sup>40,41</sup> suggest that patients with chronic tuberculosis have an increased risk for developing lung cancer. In this autopsy series there was no evidence for such an increased risk. In addition there was evidently no relation between radiation exposure and tuberculosis because tuberculosis was approximately equally distributed among the various radiation dosage groups.

Chronic pulmonary infections and intrapulmonary fibroses of various types have been implicated as a related factor in the development of a special form of lung cancer, the so-called "scar carcinoma."<sup>42-45</sup> This type is not recognized in the WHO classification. In the LSS autopsy series there were 13 lung cancers which would meet the generally accepted criteria for "scar carcinoma." Only one was found in a survivor who had been exposed to 200 rad or more ATB. Five of these tumors were small, localized and without metastasis.

本調査での癌症例の組織型別の分布は、WHO分類と同様のものを使用した。Christiansen<sup>37</sup>ならびに Herman と Crittenden<sup>38</sup>の報告した分布に似ていた。本調査における死亡時平均年齢は宮地<sup>39</sup>の日本における肺癌に関する報告のそれより幾分高かったようである。

原爆時 200 rad 以上の線量を受けた者における肺癌の危険率は増加していた。しかし、類表皮腺癌、気管支原性腺癌および混合型と未分類癌(表5)の相対的危険率は増加していたが、小細胞型移行性癌の相対的危険率 3.9 のみが統計的に有意( $P < .05$ )であった。喫煙がこの型をはじめ他の型の肺癌の危険性の増加と関係があるとされているので、原爆被爆者における危険性の増加が放射線に起因すると認める前に、喫煙による肺癌発生の危険率増加への寄与を調べることが重要であることは明白である。喫煙と放射線についての疫学的調査<sup>36</sup>においては、小細胞型移行性癌の危険率の増加は、対象症例が少ないために、不明瞭である。しかし、全肺癌をみると、喫煙とは無関係に、いくらかの放射線影響は示唆された。

最近の報告<sup>40,41</sup>では慢性結核の患者において肺癌の発生する危険率が増加していることが示唆されている。本調査では、そのような危険率の増加の所見は認められなかった。さらに、結核は各被曝群間にほぼ等しい割合で発生していたので、放射線被曝と結核との間に関係はないようであった。

慢性肺感染や各種肺内線維症は特別の型の肺癌であるいわゆる「瘢痕性癌」の発生に関係ある要因とされている。<sup>42-45</sup> この型はWHOの分類には認められていない。寿命調査剖検例には「瘢痕性癌」の基準として認められているものに該当する肺癌が13例あった。原爆時 200 rad またはそれ以上の線量を受けた被爆者では1例のみにこの癌が認められた。また、5例では腫瘍の大きさは小さく、限局されていて転移はなかった。

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# APPENDIX

## 付録

### LIST OF LUNG CANCER CASES

肺癌症例のリスト

MF No.	Autopsy No.	Tissue Dx.	MF No.	Autopsy No.	Tissue Dx.	MF No.	Autopsy No.	Tissue Dx.
		1			2			3
		1			2			3
		2			3			3
		1			7			1
		7			1			3
		6			1			1
		1			3			3
		2			6			1
		1			1			4
		3			3			1
		7			4			1
		3			2			1
		2			3			1
		1			1			3
		5			3			2
		1			5			3
		1			1			1
		2			1			1
		4			1			5
		1			3			7
		2			1			4
		2			2			3
		3			2			2
		3			1			1
		1			5			3
		7			3			1
		1			1			5
		7			1			2
		2			2			2
		2			1			3
		1			2			3
		1			3			4
		3			4			1
		3			1			1
		2			3			3
		3			2			1
		7			2			4
		1			3			2
		3			3			1
		7			5			4

MF No.	Autopsy No.	Tissue Dx.	MF No.	Autopsy No.	Tissue Dx.	MF No.	Autopsy No.	Tissue Dx.
		3			1			3
		2			4			1
		3			3			1
		2			2			6
		4			4			1
		1			3			1
		3			1			1
		2			1			2
		3			4			3
		3			1			3
		3			1			6
		4			1			3
		2			1			3
		3			1			3
		4			2			2
		3			6			3
		3			3			5
		4			1			1
		2			3			3
		2			7			3
		1			4			1
		1			3			3
		2			1			3
		7			4			3
		1			2			1
		2			3			2
		3			4			1
		4			2			2

Tissue Dx.

1. Epidermoid
2. Small Cell Anaplastic
3. Bronchogenic Adenocarcinoma
4. Bronchiolo-alveolar Adenocarcinoma
5. Large Cell Carcinoma
6. Combined Epidermoid and Adenocarcinoma
7. Unclassified Type of Carcinoma