

INCIDENCE OF STROKE AND CORONARY HEART DISEASE
IN THE ADULT HEALTH STUDY SAMPLE, 1958-78

成人健康調査集団における脳血管疾患及び
虚血性心疾患の発生率, 1958 - 78年

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A Cooperative Japan - United States Research Organization
日米共同研究機関

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

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

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SUMMARY

Approximately 16,000 study subjects in the Adult Health Study sample who had received examination at least once during the 20 years (1958-78) in Hiroshima or Nagasaki and were found to have neither stroke nor coronary heart disease (CHD) at the initial examination were studied for the incidence of stroke and CHD and the relationship of these to atomic bomb radiation exposure. Their secular trends were also studied.

Findings suggestive of a relationship between stroke and radiation exposure among Hiroshima females were first discovered for the years 1969-73, that is, 24-28 years after A-bomb exposure. In general, this association is supported by the present analysis. Stroke incidence continued to decrease during the present report's period of observation. Analysis by type showed that cerebral infarction and cerebral hemorrhage both decreased, but the decrease of the latter is especially remarkable. The trend to decrease is observed in both sexes and in both cities.

A relationship between CHD and radiation exposure was, as noted for stroke, first observed only in Hiroshima females for the years 1969-73, but from this analysis it appears that the trend began earlier and the association is getting

要 約

広島・長崎の成人健康調査において、20年間(1958—78年)に最低1回の診察を受け、初診時に脳血管疾患、又は虚血性心疾患の認められなかった約16,000名について、脳血管疾患及び虚血性心疾患の発生率を求め、放射線被曝との関連性、年次推移等について検討した。

脳血管疾患と放射線被曝との関連を示唆する所見は、被爆後24～28年経過した1969—73年に初めて広島の女性に認められた。この関連性は、今回の解析でも概して認められている。脳血管疾患の発生率は、今回の観察期間中減少を続け、病型別にも脳梗塞、脳出血ともに減少しているが、脳出血に特に減少が著しい。減少の傾向は男女とも、広島・長崎ともに見られた。

虚血性心疾患と放射線被曝との関連は、脳血管疾患と同様に、1969—73年に広島の女性のみ初めて認められたが、今回の解析ではこの傾向はそれより早期から出現していることが示唆され、時の経過と

stronger with the passage of time. Analysis by type showed myocardial infarction (MI), but not angina pectoris, to be related to radiation exposure. The incidence rate for CHD, especially for MI, was almost constant during the observation period, it being 1.2/1,000 person-years on the average. Comparing by sex, the incidence rate was constant in males. In females, the pattern varied with time. There appear to be no between-city differences in secular trends – essentially constant.

Continued observation is believed to be necessary to ascertain whether the above findings, especially those suggesting direct or indirect effect of radiation, represent real trends.

INTRODUCTION

The diagnoses in the Adult Health Study (AHS) sample have been classified and documented according to the International Classification of Disease (ICD) code and preserved, but the numbers of cases of some types of diseases are difficult to grasp accurately in the tables used in the AHS report for examination cycles 6-11. This is particularly so for those diseases that are relatively highly lethal, and prevalence alone is a poor measure of the disease burden in a cohort. In addition, since many physicians are involved in the diagnosis of an illness because long-term observations are being made, there is a tendency for a lack of consistency to develop in the application of diagnostic criteria. Naturally, there are some analyses of diseases in which these factors create more of a problem than in others. Taking these factors into consideration, the incidence of two major diseases, stroke and CHD, was determined by review of medical records (after establishing diagnostic criteria). A study was made of each of their relationships to radiation exposure and their respective secular trends.

A relationship between sublethal radiation exposure and incidence of cardiovascular disease (CVD) has not yet been established.¹ Regarding stroke, no relationship between stroke mortality and radiation exposure is evident in the period 1950-78 in the ABCC-RERF Life Span Study.² In the AHS sample, no relationship was found in a study of the period 1958-64,³ but a study of the period 1958-74 by Robertson et al.⁴ revealed findings suggesting a relationship to radiation exposure, but only for Hiroshima females.

ともに関連性はより強くなっていることが観察された。病型別に見ると、心筋梗塞には放射線との関連性が認められたが、狭心症には認められなかった。虚血性心疾患、特に心筋梗塞の発生率は今回の観察期間中ほとんど変化なく、平均1.2/1,000人年であった。性別に見ると、男性では不変であったが、女性には経時的にかなりの変動が見られた。都市別では、経時的変化にほとんど差がなかった。

以上の所見、特に放射線の直接的又は間接的な影響を示唆する所見については、これが真の傾向であるか否かを確かめるため、今後も観察の継続が必要と思われる。

緒言

成人健康調査受診者の診断名は、国際疾病分類(ICD)コードに従って分類、記録、保存されているが、同調査の第6～11診察周期の報告に用いた表では、ある種の疾患の症例数は、的確に把握し難い。これは特に、比較的致命率の高い疾患において言えることで、有病率のみではコホート内の疾患傾向が適切に示されない。更に、長期間の観察が行われているため、多数の医師が疾患の診断に関与しており、診断基準の適用には均一性に欠ける傾向がある。そして解析上、これらの因子がより問題となる疾患が当然認められる。以上の点を考慮に入れて、脳血管疾患、虚血性心疾患の二大疾患に関して、(一定の診断基準を設けて)医学記録の検討を行い、発生率を決定した。各疾患の放射線被曝との関連性、年次推移について解析した。

致死量以下の放射線被曝と心臓血管疾患発生との関連性はまだ確定されていない。¹ 脳血管疾患について見ると、ABCC-放影研寿命調査においては、1950-78年の間では同疾患の死亡率と放射線との関連は認められていない。² 成人健康調査集団においては、1958-64年にかけての調査では関連性は示されなかったが、³ Robertsonら⁴による1958-74年の調査は、広島の女性にのみ被曝との関係を示唆する所見を明らかにした。

Similarly, in a CHD study based on the AHS sample, no relationship was noted for the period 1958-64,⁵ but a study of the period 1958-74⁴ showed, as for stroke, a relationship to radiation exposure, but only for Hiroshima females. An electrocardiographic study suggested effects of radiation exposure in Hiroshima males proximally exposed to the A-bomb,⁶ but the study is weak insofar as the observation period was short. Many reports of research elsewhere describe increased incidence of CHD following radiation therapy. Brosius et al,⁷ in particular, report making a detailed study and finding a significant increase in frequency of stenosis and obstruction of the coronary artery following radiation therapy. However, as mentioned before, previous ABCC/RERF reports concerning the relationship between CVD and radiation exposure lack consistency. Accordingly, the study by Robertson et al⁴ has been extended to include the years 1975-78 and the whole matter reanalyzed.

Many reports have been made on the secular trend of CVD in various parts of the world. The secular trend of stroke incidence was studied for the AHS sample,^{3,8} which, like another report,⁹ has shown a definite trend to rapidly decrease. A similar trend to decrease is observed for mortality.^{9,10} Recently the CHD mortality has been showing a slight trend to decrease.¹⁰ With the extension to the years 1975-78 it is possible now to examine the trends in incidence rates for stroke and CHD as observed in the AHS sample for the 20-year period, 1958-78.

MATERIALS AND METHODS

The AHS sample was composed of 19,961 subjects in 1958 when it was selected.¹¹ The number who were examined at least once during the period of this study was 16,738, and 16,144 were available for CVD incidence determination.

In order not to miss any stroke and CHD cases, all participants in the AHS with past findings on clinical diagnosis reports by physicians, electrocardiogram (ECG), death certificate or autopsy which suggest CHD were subjected to medical chart review.

As a review had already been completed for about 3,500 cases by 1974,^{4,8} the approximately

同様に、成人健康調査集団に基づく虚血性心疾患調査では、1958—64年間には関連性は示されなかったが、⁵ 1958—74年⁴には脳血管疾患と同様、被曝との関連が広島的女性にのみではあるが認められた。また以前心電図による調査で、広島の近距離被曝の男性に放射線被曝の影響が示唆されたが、⁶ これには観察期間が短かったという難点がある。他の研究報告には、放射線治療後の虚血性心疾患の増加に関する論文が多い。特にBrosiusら⁷は、詳細な検討の結果、放射線治療後の冠動脈の狭窄、閉塞の有意な増加を報告している。しかし、上述のように心臓血管疾患と放射線被曝の関連性についてのABCC-放影研のこれまでの報告は一貫性に乏しい。したがって、Robertsonら⁴の研究を1975—78年を含むよう延長し、全体を再解析した。

心臓血管疾患の年次推移についても、世界各地から多数の報告がある。成人健康調査集団における脳血管疾患発生率の年次推移も検討されたが、^{3,8} ある報告⁹と同様明らかに急激な減少傾向を示している。死亡率においても同様に減少傾向が観察されている。^{9,10} 虚血性心疾患の死亡率は最近やや減少傾向にある。¹⁰ 1975—78年まで調査期間を延長することによって、1958—78年の20年間に成人健康調査集団に認められた脳血管疾患及び虚血性心疾患の発生率の年次推移を調べることが可能である。

対象及び方法

成人健康調査の対象者は1958年の設定時には19,961名であった。¹¹ 今回の研究期間中に少なくとも1回診察を受けた者の数は16,738名で、このうち16,144名が心臓血管疾患発生率決定に利用できた。

この受診者の中から脳血管疾患、虚血性心疾患を漏れなく取り上げるために、現在までの医師による臨床診断報告、心電図所見、死亡診断書、更に病理解剖で虚血性心疾患を示唆する所見を有するすべての症例について医学記録の再検討を行った。

1974年までの約3,500の症例については既に検討が

800 cases in whom the two diseases were newly noted as suggestive findings during 1975-78 were reviewed using the same method as in the previous report. The diagnostic criteria for both stroke and CHD, described in past RERF reports^{4,8,12} were applied without change. Stroke was reviewed by further classifying the disease type into cerebral hemorrhage (CH), cerebral infarction (CI), and subarachnoid hemorrhage (SAH) according to the classification of the Japan Stroke Research Team¹³ and the ICD of the World Health Organization (WHO).¹⁴ CHD was categorized into MI and angina pectoris (AP) according to the WHO ICD.¹⁵ The accuracy of diagnosis was classified into four grades as previously, but only the two grades of "definite" and "probable" were employed in this analysis.

One of the authors (KK), who reviewed the medical records for the present study, had also participated in the review for the period 1958-74. Thus, differences due to review method should be minimal.

The incidence rate for CVD was obtained by calculating person-years from the first examination to the onset of disease, death, or to the last examination date, for all subjects. Comparisons of city, sex, and age-adjusted incidence rates among exposure dose groups were made, and tests for linearly increasing trends were carried out. In order to observe secular trends, annual age-adjusted incidence rates were compared, adjustments being made using the Mantel-Haenszel method.¹⁶

RESULTS

There were 16,144 subjects who had undergone examination more than once during the 20 years between the first examination and 31 December 1978 who did not have CVD prior to the initial examination. Among these the number of stroke cases (definite and probable combined) developing during the interval totaled 758 in all; 430 males and 328 females (Table 1). Classifying by type, 117 were CH, 584 CI, and 57 were SAH and others of unknown type. The number of CHD cases (definite and probable combined) was 312 in total; 183 males and 129 females (Table 1). Classifying by type, the numbers were 276 MI and 128 AP.

完了しているので、^{4,8}今回は、1975-78年間に新たに両疾患の示唆された約800例を前回と同一の方法で検討した。診断基準は、脳血管疾患、虚血性心疾患共に、これまでに放影研より報告されているもの^{4,8,12}をそのまま使用した。脳血管疾患は、更に日本脳卒中研究班¹³及び世界保健機関(WHO)の国際疾病分類¹⁴に従って、病型を脳出血、脳梗塞、及びクモ膜下出血に分けて検討した。虚血性心疾患については、WHOの同分類¹⁵に従って心筋梗塞及び狭心症に分類した。診断の確実性についても、今までどおり4段階に分けて、“確実”、“ほぼ確実”の2群のみ今回の解析の対象とした。

今回、医学記録検討を行った著者の1名(児玉)は、1958-74年調査の同作業に参加しているため、検討方法の差はほとんどないものと思われる。

心臓血管疾患発生率は、受診者全員に対し、最初の診察の日から発病、死亡あるいは最終診察の日までの人年を計算することによって得られた。都市、性、及び年齢訂正発生率が被曝線量群間で比較し、直線増加傾向の検定を行った。年次推移の観察では、Mantel-Haenszel法¹⁶を用いて訂正した年間の年齢訂正発生率について比較を行った。

結 果

第1診察周期から1978年12月31日までの20年間に1回以上受診し、初診時に心臓血管疾患を有していなかった者は16,144名であった。このうち期間中に発生した脳血管疾患症例数(確実及びほぼ確実例の合計)は計758例で、男性が430名、女性が328名であった(表1)。病型別には、脳出血117例、脳梗塞584例、クモ膜下出血57例で、残りは不明であった。虚血性心疾患は計312例(確実及びほぼ確実例合計)で、男性183名、女性129名であった(表1)。病型別には、心筋梗塞276例、狭心症128例であった。

TABLE 1 NUMBER OF SUBJECTS, PERSON-YEARS, AND NUMBER OF CVD, STROKE, AND CHD CASES

表1 対象者数, 人年数, 並びに心臓血管疾患, 脳血管疾患及び
虚血性心疾患症例数

City	Sex	Subjects	Person-years	Incidence cases		
				CVD	Stroke	CHD
H	T	11107	159022	712	586	244
	M	4017	55197	391	322	138
	F	7090	103825	321	264	106
N	T	5037	72009	207	172	68
	M	2099	29120	131	108	45
	F	2938	42889	76	64	23
Both	T	16144	231031	919	758	312
	M	6116	84317	522	430	183
	F	10028	146714	397	328	129

Relationship to Radiation

As mentioned earlier, clinical history, ECG findings, death certificates, and autopsy materials were used to determine the incidence of CHD. Attendance records for clinical examinations (and hence clinical history and ECG tracings) and death certificate information does not differ by exposure dose. However, the autopsy rate tends to be high in the high dose group, especially among Hiroshima females.^{4,17} Because of this, the incidence of disease may be inflated in the high dose group relative to the other groups. In order to eliminate this potential bias from our analysis in studying radiation effects, those cases diagnosed on the basis of autopsy materials alone were excluded from the analysis. As a result, 474 cases of stroke and 190 cases of CHD became the subjects of study. The person-years and number of CVD cases occurring and the incidence rate are shown by exposure dose in Tables 2 and 3, respectively.

Stroke shows a weak tendency to increase with dose, when city and sex are combined, but, comparing by city and sex, a significant increase in rate is seen only among Hiroshima females. High incidence is observed in Nagasaki males in the 100-199 rad group, but no such relationship is noted in Hiroshima males or Nagasaki females.

Observed on the whole, CHD shows an even weaker tendency than stroke to increase with

放射線との関連性

前述のように、虚血性心疾患発生率決定のため、臨床病歴、心電図所見、死亡診断書及び剖検資料が使用された。臨床診察記録(つまり、臨床病歴及び心電図記録)と死亡診断書の情報には、被曝線量による偏りはない。しかし、剖検率は高線量群で高い傾向があり、特に広島的女性にその傾向が著しい。^{4,17} このため、疾患発生が高線量群では、他の群と比較して高くなる可能性がある。そこで、放射線の影響を検討するに当たり、今回の解析ではこの潜在的な偏りを除くため、剖検のみに基づく診断例を解析から除外した。その結果、脳血管疾患474例、虚血性心疾患190例が解析の対象となった。線量別の人年数及び心臓血管疾患発生数と発生率を、表2及び3にそれぞれ示した。

脳血管疾患は、都市及び性を組み合わせた場合は、線量とともに若干増加する傾向が見られるが、都市、性別に比較すれば、広島的女性にのみ発生率に有意な増加がある。長崎の男性の100-199 rad群に高い発生率が観察されるが、広島の男性、長崎の女性にはこのような関連性が認められない。

虚血性心疾患全体では、脳血管疾患よりもまだ弱い

dose. Comparing by sex and city, as is the case for stroke, this tendency is strongest among Hiroshima females, for whom a statistically significant increase in incidence occurs due to the occurrence of one or two additional cases in the 400+rad group. This tendency is not noted among Hiroshima males, nor among Nagasaki males and females.

が、線量とともに増加する傾向を示す。都市、性別に見ると、脳血管疾患と同様広島的女性にこの傾向が最も強いが、これは400+rad群において1~2例多く症例が発生しており、その結果発生率が統計的に有意な増加を示しているためである。広島男性、長崎では男女共にこの傾向は認められない。

TABLE 2 NUMBER OF PERSON-YEARS AT RISK AND NUMBER OF STROKE AND CHD CASES BY RADIATION DOSE, CITY, AND SEX

表2 観察人年数、及び脳血管疾患、及び虚血性心疾患の症例数、放射線量、都市及び性別

Sex		T65 Dose in rad								Total
		0	1-9	10-49	50-99	100-199	200-299	300-399	400+	
Total										
Male	Person-years	21824	4194	10948	6067	7907	3992	2228	2895	60055
	Stroke	90	21	53	19	47	16	5	15	266
	CHD	31	13	25	17	13	7	3	5	114
Female	Person-years	38620	7934	23658	11742	12190	6782	3264	4204	108394
	Stroke	63	12	63	22	13	17	7	11	208
	CHD	22	4	20	8	9	2	3	8	76
Total	Person-years	60444	12128	34606	17809	20097	10774	5492	7099	168449
	Stroke	153	33	116	41	60	33	12	26	474
	CHD	53	17	45	25	22	9	6	13	190
Hiroshima										
Male	Person-years	14246	4099	8562	3837	4249	1905	1128	1749	39775
	Stroke	69	21	46	16	25	10	3	9	199
	CHD	21	12	24	12	7	5	2	3	86
Female	Person-years	27082	7551	19803	8766	6134	3156	1839	2551	76882
	Stroke	48	12	58	16	10	9	5	9	167
	CHD	17	4	20	6	7	1	3	6	64
Total	Person-years	41328	11650	28365	12603	10383	5061	2967	4300	116657
	Stroke	117	33	104	32	35	19	8	18	366
	CHD	38	16	44	18	14	6	5	9	150
Nagasaki										
Male	Person-years	7578	95	2386	2230	3658	2087	1100	1146	20280
	Stroke	21	0	7	3	22	6	2	6	67
	CHD	10	1	1	5	6	2	1	2	28
Female	Person-years	11538	383	3855	2976	6056	3626	1425	1653	31512
	Stroke	15	0	5	6	3	8	2	2	41
	CHD	5	0	0	2	2	1	0	2	12
Total	Person-years	19116	478	6241	5206	9714	5713	2525	2799	51792
	Stroke	36	0	12	9	25	14	4	8	108
	CHD	15	1	1	7	8	3	1	4	40

TABLE 3 AGE-ADJUSTED INCIDENCE OF CVD, STROKE, AND CHD PER 1,000 PERSON-YEARS BY RADIATION DOSE, CITY, AND SEX

表3 1,000人年当たりの心臓血管疾患, 脳血管疾患, 及び虚血性心疾患の年齢訂正発生率, 放射線量, 都市及び性別

City	Sex	T65 Dose in rad								Test Positive Trend
		0	1-9	10-49	50-99	100-199	200-299	300-399	400+	
Cardiovascular Disease										
Hiroshima	Male	5.4	7.0	7.0	5.9	5.8	8.9	5.4	6.4	NS
	Female	2.2	2.3	3.3	2.1	3.0	3.3	4.9	6.4	***
Nagasaki	Male	3.3	4.9	3.4	3.6	6.8	3.7	2.5	7.3	Sug
	Female	1.6	0.0	1.1	2.2	0.77	2.8	1.3	2.2	NS
Total		3.0	3.5	3.9	3.2	3.8	4.5	3.6	5.4	**
Stroke										
Hiroshima	Male	4.6	5.2	5.1	3.7	5.2	5.9	3.1	5.3	NS
	Female	1.7	1.7	2.6	1.7	1.7	2.9	3.0	4.5	**
Nagasaki	Male	2.6	0.0	2.9	1.3	6.5	2.7	1.6	5.8	Sug
	Female	1.3	0.0	1.1	1.6	0.58	2.5	1.3	1.6	NS
Total		2.5	2.5	3.1	2.1	3.1	3.5	2.3	4.1	*
Coronary Heart Disease										
Hiroshima	Male	1.4	3.1	2.7	2.9	1.5	3.1	2.3	1.9	NS
	Female	0.62	0.55	0.93	0.65	1.2	0.33	1.7	3.1	***
Nagasaki	Male	1.3	4.7	0.42	2.1	1.7	0.93	0.76	2.1	NS
	Female	0.44	0.0	0.0	0.59	0.42	0.30	0.0	1.2	NS
Total		0.85	1.3	1.2	1.3	1.1	1.0	1.2	2.1	*

The relative risk of stroke, defined as the ratio of the age-adjusted incidence in the 100+ rad group to that in the 0-9 rad group, is high for Hiroshima females and Nagasaki males. No increased risk is observed for Hiroshima males and Nagasaki females. However, the finding in the case of Nagasaki males is due to the especially high risk in the 100-199 rad group (Table 4). The relative risk for the 200+ rad group is 1.2, showing no statistically significant difference. There is an increased relative risk (2.3) of CHD only among Hiroshima females (Table 4).

0-9 rad 群の発生率に対する 100 rad 以上群の年齢訂正発生率の比である相対危険度も, 脳血管疾患では広島的女性, 長崎の男性に高い。広島男性, 長崎女性には危険度の増加は認められない。しかし, 長崎男性の所見は, 実は 100-199 rad 群の危険度が特に高いためである(表4)。200 rad 以上群の相対危険度は 1.2 で統計的有意差はない。虚血性心疾患では, 広島的女性にのみ相対危険度の増加(2.3)が見られる(表4)。

TABLE 4 RELATIVE RISK (100+ VS 0-9 RAD) OF STROKE AND CHD, BY CITY AND SEX

表4 脳血管疾患及び虚血性心疾患の相対危険度(100+対0-9 rad)都市及び性別

City	Sex	Stroke	CHD
Hiroshima	Male	1.1	1.1
	Female	1.5 ^{Sug}	2.3*
Nagasaki	Male	1.8*	1.0
	Female	1.1	1.1

Needless to say, the diagnosis of AP is based on subjectively determined symptoms. Accordingly, if the tendency to seek medical attention or to complain of symptoms is stronger in the high dose group than in the low dose group among survivors, an observed relation with dose would not represent the true situation. Therefore, CHD was studied as classified into MI (with relatively little bias) and AP (with much greater possibility of bias). The results are shown in Table 5, and contrary to expectation, the only evidence for an association with radiation dose is for MI in Hiroshima females.

狭心症の診断は、言うまでもなく自覚症状に基づくものであり、被爆者において医学的治療を求めたり、症状を訴える傾向が低線量群よりも高線量群で強いならば、観察された線量との関係は実態を示しているとは言えない。そこで、虚血性心疾患を心筋梗塞(偏りが比較的少ない)と狭心症(偏りの可能性はるかに大)に分類して検討した。結果は表5に示すとおり、予測に反し、広島的女性に心筋梗塞において放射線量との関連が見られただけである。

TABLE 5 AGE-ADJUSTED CHD INCIDENCE PER 1,000 PERSON-YEARS BY RADIATION DOSE, CITY, SEX, AND TYPE OF CHD

表5 1,000人年当たりの虚血性心疾患の年齢訂正発生率, 放射線量, 都市, 性及び病型別

City	Sex	T65 Dose in rad								Test Positive Trend
		0	1-9	10-49	50-99	100-199	200-299	300-399	400+	
Myocardial Infarction										
Hiroshima	Male	1.5 (22)	3.1 (12)	2.1 (19)	2.6 (11)	1.7 (8)	2.5 (4)	1.2 (1)	1.2 (2)	NS
	Female	0.51 (14)	0.42 (3)	0.72 (16)	0.32 (3)	0.71 (4)	0.33 (1)	1.7 (3)	2.6 (5)	**
Nagasaki	Male	1.0 (8)	0.0 (0)	0.82 (2)	1.8 (4)	1.7 (6)	0.91 (2)	0.71 (1)	2.1 (2)	NS
	Female	0.27 (3)	0.0 (0)	0.0 (0)	0.52 (2)	0.22 (1)	0.30 (1)	0.0 (0)	0.0 (0)	NS
Total		0.75 (47)	1.1 (15)	0.97 (37)	1.1 (20)	0.98 (19)	0.89 (8)	1.0 (5)	1.4 (9)	NS
Angina Pectoris										
Hiroshima	Male	0.58 (9)	1.9 (8)	1.3 (12)	0.95 (4)	0.60 (3)	1.8 (3)	1.2 (1)	1.8 (3)	NS
	Female	0.44 (12)	0.13 (1)	0.51 (11)	0.43 (4)	0.89 (5)	0.0 (0)	0.0 (0)	0.49 (1)	NS
Nagasaki	Male	0.38 (3)	3.8 (1)	0.0 (0)	1.1 (3)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	NS
	Female	0.26 (3)	0.0 (0)	0.0 (0)	0.34 (1)	0.21 (1)	0.0 (0)	0.0 (0)	1.0 (2)	NS
Total		0.43 (27)	0.68 (10)	0.58 (23)	0.64 (12)	0.48 (9)	0.35 (3)	0.22 (1)	0.94 (6)	NS

() indicates number of cases () は症例数

Since associations with dose for these diseases are confined to Hiroshima females, it is of interest to examine how these associations change with time. As may be noted from Table 6, the relative risks for Hiroshima females to suffer strokes are not at all consistent for the four time periods examined. On the other hand, for CHD the association with dose is increasing with the passage of time.

これらの疾患に対する線量との関連性は、広島的女性にのみ認められるので、時間とともにその関連性がどのように変化していくかを調査することは興味深い。表6から明らかなように、広島的女性が脳血管疾患に罹患する相対危険度は、四つの調査期間で全く一貫していない。一方、虚血性心疾患と線量との関連性は、時の経過とともに増加している。

TABLE 6 RELATIVE RISK (100+ VS 0-9 RAD) OF CVD, STROKE, AND CHD FOR HIROSHIMA FEMALES BY PERIOD

表6 広島的女性における心臓血管疾患、脳血管疾患、及び虚血性心疾患の相対危険度(100+対0~9 rad), 診断周期別

Disease	Total	Period			
		1958-63	1964-68	1969-73	1974-78
Cardiovascular Disease	1.8**	1.4	1.3	3.1**	2.0
Stroke	1.5 ^{Sug}	1.5	0.97	3.7**	0.72
Coronary Heart Disease	2.3*	0.78	2.2	3.0	4.4*

When relative risks are observed by age at the time of the bomb (ATB) in Hiroshima females, the risks are observed to be the greatest for both stroke and CHD among those who were young ATB (Table 7).

広島的女性について相対危険度を被爆時年齢別に観察すると、危険度は、脳血管疾患、虚血性心疾患共に若年被爆者において最も大きい(表7)。

TABLE 7 RELATIVE RISK (100+ VS 0-9 RAD) OF CVD, STROKE, AND CHD FOR HIROSHIMA FEMALES BY AGE ATB

表7 広島的女性における心臓血管疾患、脳血管疾患及び虚血性心疾患の相対危険度(100+対0~9 rad), 被爆時年齢別

Disease	Total	Age ATB			
		<30	30-39	40-49	50+
Cardiovascular Disease	1.8**	4.3**	1.4	1.6	1.5
Stroke	1.5 ^{Sug}	3.2	0.95	1.7	1.2
Coronary Heart Disease	2.3*	6.0*	2.1	1.7	1.5

Secular Trends for Stroke and CHD Incidence

In observing secular trends, there is a possibility in the first cycle of mistaking those who already had the disease with those who developed the disease during the cycle. Also there is a possibility in the last cycle of failing to identify those who have developed the disease. Therefore, in this analysis, secular trends during 1960-76 were studied, excluding the two years of cycle 1 and the two years of the last cycle.

Stroke incidence shows a decreasing trend from cycle 2. By type, CI and CH both decreased in incidence, but the tendency to decrease was greater in the latter (Figure 1).

Regarding stroke, the differences between cities in trends are minimal (Figure 2).

A tendency for stroke rates to decrease in the early cycles has been noted for both sexes (Figure 3), but in recent cycles these rates have leveled off or are even increasing. The picture is similarly confused for the four oldest age-groups ATB (Figure 4).

脳血管疾患、虚血性心疾患発生率の年次の推移

年次推移を見る場合、最初の診察周期は以前からの有病者を同期間中の発病者と誤認し、また最後の周期は発病者の確認が漏れる可能性があるため、今回の解析では、第1周期の2年間、最後の周期の2年間を除き1960-76年間の推移を検討した。

脳血管疾患発生率は第2周期以後減少が見られ、病型別には脳梗塞、脳出血共に発生率が減少しているが、その減少傾向は後者の方が大きい(図1)。

両都市間の年次推移における差異は、脳血管疾患に関しては非常に小さい(図2)。

脳血管疾患発生率は、初期の周期において男女共減少傾向にあるが(図3)、後期の周期では横ばい状態になるか、むしろ増加している。被爆時年齢が高い4群についての年次推移も同様に不定である(図4)。

FIGURE 1 SECULAR TRENDS OF STROKE INCIDENCE BY TYPE

図1 脳血管疾患発生率の年次推移、病型別

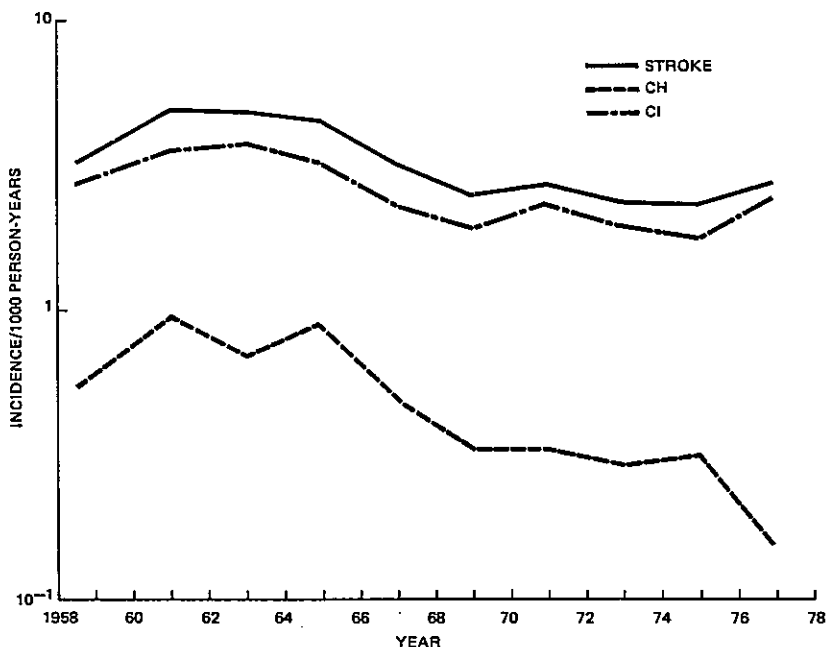


FIGURE 2 SECULAR TRENDS OF STROKE AND CHD INCIDENCE BY CITY

図2 脳血管疾患及び虚血性心疾患発生率の年次推移，都市別

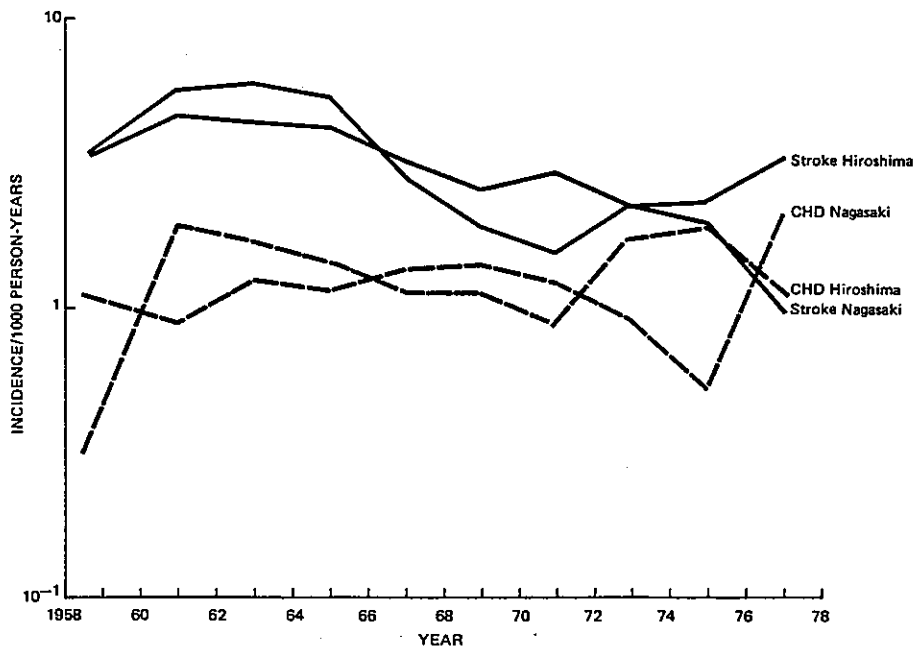


FIGURE 3 SECULAR TRENDS OF STROKE AND CHD INCIDENCE BY SEX

図3 脳血管疾患及び虚血性心疾患発生率の年次推移，性別

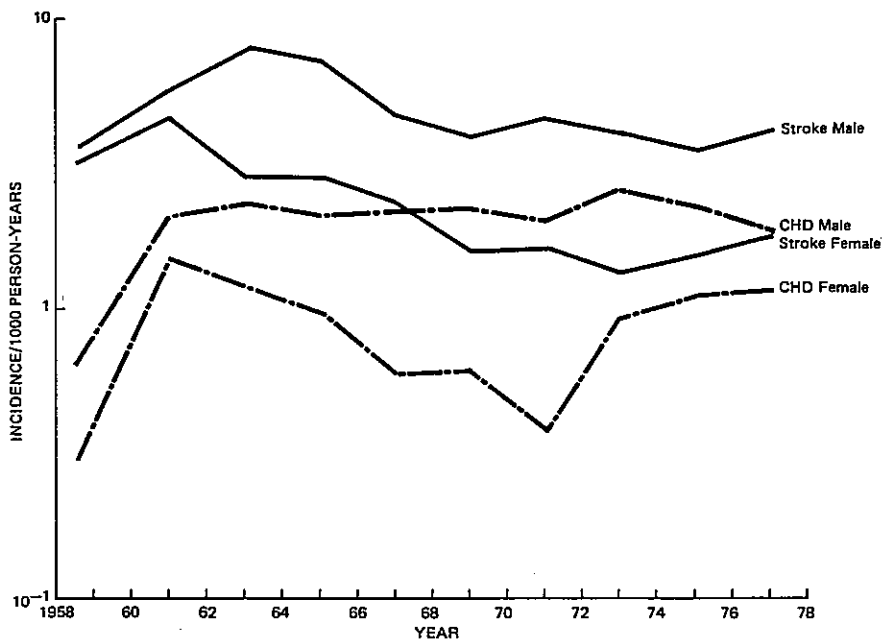
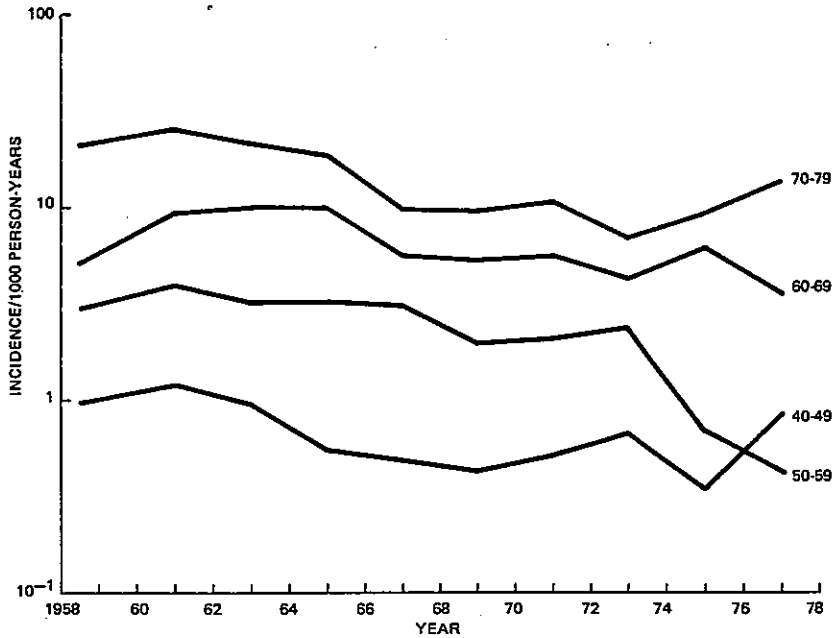


FIGURE 4 SECULAR TRENDS OF STROKE INCIDENCE BY AGE ATB

図4 脳血管疾患発生率の年次推移, 被爆時年齢別



The secular trends for the incidence of CHD in total, and of MI in particular, show hardly any change after 1961-62, the mean annual incidence in the study period being 1.2/1,000 (Figure 5). The secular trend of the incidence of AP shows a peak in 1963-64 then a subsequent uneven course (Figure 5).

Since it does not seem proper to include AP when discussing secular trends of CHD, because there is a strong possibility of having missed AP cases in the present medical records review, review of secular trends was made by sex, city, and age only for MI (Figure 6). Comparison between the two cities showed that the incidence rates behave essentially the same way and show no obvious general trend. The mean annual incidence rates for Hiroshima and Nagasaki during the observation period were 1.2/1,000 and 1.1/1,000, respectively, indicating little difference between the two. The MI incidence rate for males is somewhat higher than that for females for the entire period and a trend for the rate to gradually increase is suggested. In females the pattern is more erratic with little evidence of a secular increase (Figure 7).

虚血性心疾患発生率の年次の推移は、全体で、また特に心筋梗塞で、1961-62年以降ほとんど変動がなく、観察期間の年間平均発生率は、1.2/1,000である(図5)。狭心症の年次推移は、1963-64年にピークに達した後は一定した傾向を示していない(図5)。

今回の医学記録の検討では、狭心症の症例を見逃している可能性が非常に大きいため、虚血性心疾患の年次推移を論ずる場合は、狭心症を含めるのは妥当でないと思われ、性、都市及び年齢別の検討は心筋梗塞に限定して行った(図6)。両都市間の比較では、発生率は本質的に同様に推移し、明瞭な一般的傾向は見られない。観察期間中の広島、長崎の年間平均発生率は、それぞれ1.2/1,000及び1.1/1,000で、両都市間にはほとんど差異がない。男性の心筋梗塞発生率は、全期間を通じて女性より幾分高く、漸増の傾向が示唆されている。女性においては経時的増加をほとんど示さず、パターンはより不規則である(図7)。

FIGURE 5 SECULAR TRENDS OF CHD INCIDENCE BY TYPE

図5 虚血性心疾患発生率の年次推移, 病型別

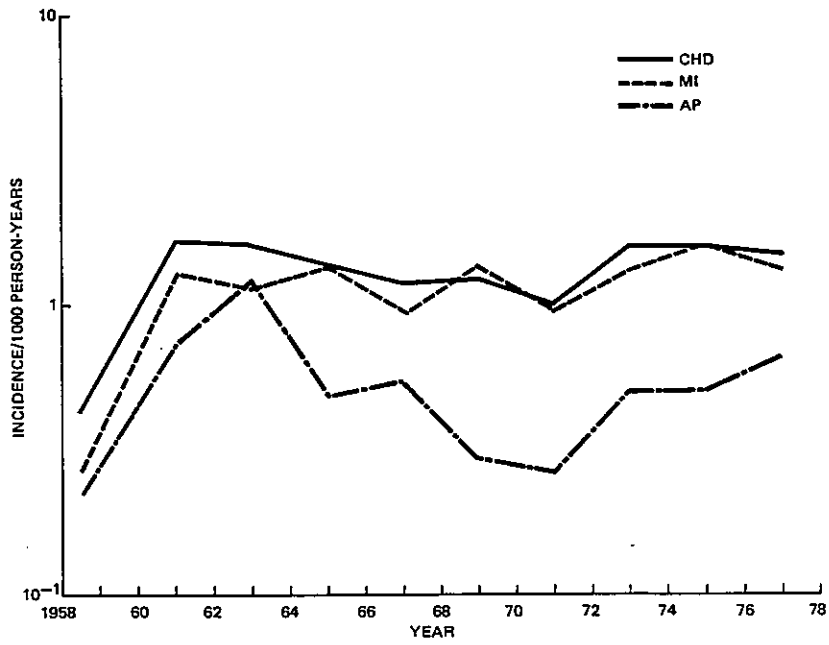


FIGURE 6 SECULAR TRENDS OF MYOCARDIAL INFARCTION INCIDENCE BY CITY

図6 心筋梗塞発生率の年次推移, 都市別

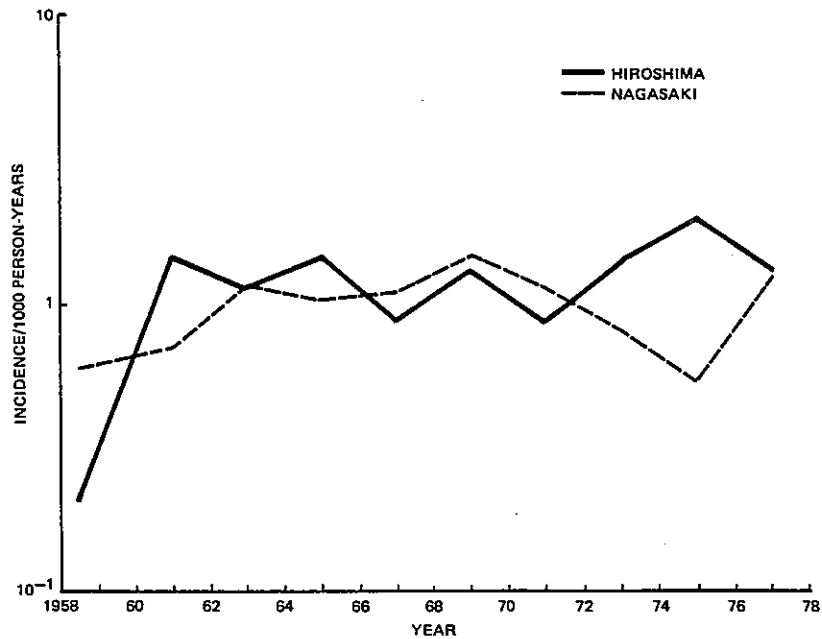
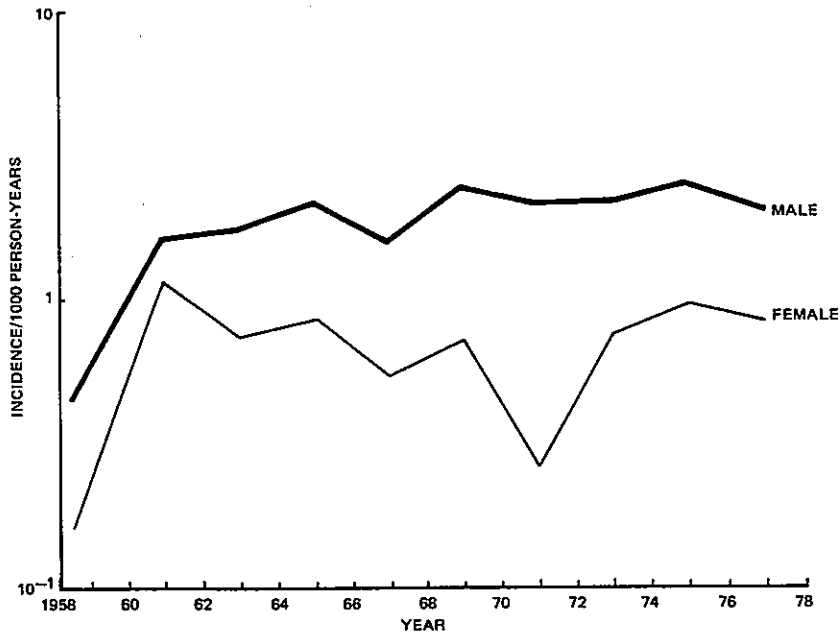


FIGURE 7 SECULAR TRENDS OF MYOCARDIAL INFARCTION INCIDENCE BY SEX

図7 心筋梗塞発生率の年次推移, 性別



The data are insufficient to permit a graphical analysis by age, except for those 60-69 and 70-79, the two oldest age-groups ATB, where perhaps there is a tendency for increase in the 70-79 group (Figure 8).

DISCUSSION

Whether diseases attributable to arteriosclerosis appear only, and in large number, as a result of radiation exposure has been a matter of great interest.¹

In the United States, it was observed¹⁸ that mortality from CVD in aged radiologists has been higher than that from cancer, and it has been reported¹⁹ that small vessel disease of the central nervous system develops some time after head radiation therapy. Stroke due to stenosis or obstruction of the carotid artery and the vertebral artery following neck radiation therapy has been reported.²⁰ There are many reports^{7,21-34} on the development of CHD after irradiation of the mediastinum. Brosius et al,⁷ in particular, have confirmed by autopsy that the frequency of conditions such as stenosis and obstruction of the coronary artery in these cases is definitely higher than in a control group.

被爆時年齢が年長の60-69歳及び70-79歳の2群(70-79歳群では, 増加傾向を示すと思われる)を除いては, 年齢別の解析を行うにはデータが不十分である(図8)。

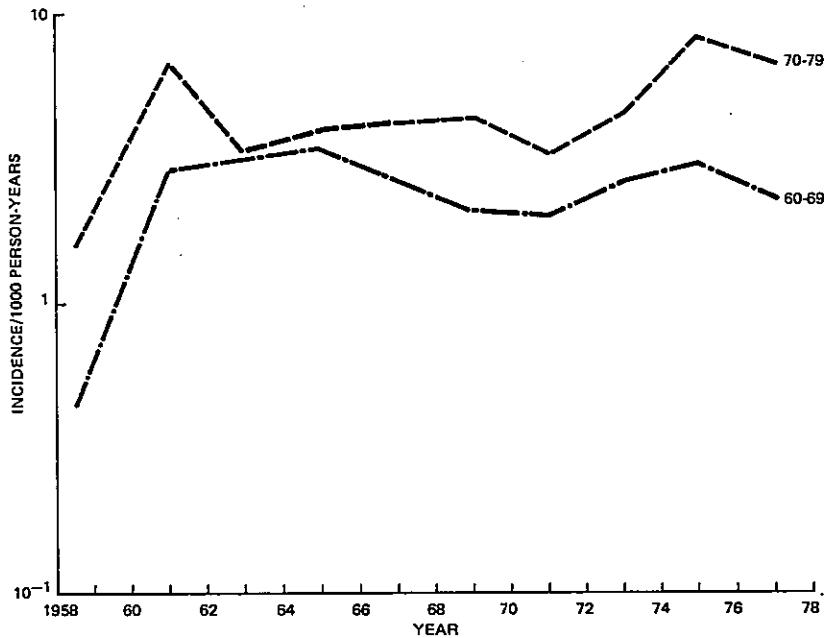
考 察

動脈硬化が原因となる疾患が放射線被曝によってのみ, そして数多く出現するかどうかについては, これまでに大きな関心が寄せられてきた。¹

米国では, 高齢の放射線科医の心臓血管疾患による死亡率が癌よりも高いという観察がなされ,¹⁸ また頭部放射線治療後, 中枢神経系の small vessel disease が後になって発生するとの報告もある。¹⁹ 頸部放射線治療後の頸動脈及び椎骨動脈の狭窄, 閉塞による脳血管疾患についても報告されている。²⁰ 縦隔への放射線照射後の虚血性心疾患の発生については, 多数の報告がある。^{7,21-34} 特に Brosius ら⁷ は, 剖検により冠動脈の狭窄, 閉塞の頻度が, 対照群と比し明らかに高いことを確認している。

FIGURE 8 SECULAR TRENDS OF MYOCARDIAL INFARCTION INCIDENCE BY AGE ATB

図8 心筋梗塞発生率の年次推移, 被爆時年齢別



A significant increase in CVD among A-bomb survivors was not found in early studies,^{2,3} but Robertson et al⁴ have reported findings suggesting a relationship between CVD and radiation exposure in Hiroshima females. However, it is to be pointed out in regard to this finding that an apparent effect may have been observed because the autopsy rate is comparatively high in the high radiation dose group, it being especially high among Hiroshima females. Therefore, in the present study, cases of CVD revealed only at autopsy were excluded from the sample to eliminate this potential source of bias. The observation period for the study was extended to 1978, 33 years after the A-bomb. The relationship to radiation was still observed in Hiroshima females, however.

It is well known that CVD increases after menopause.³⁵ It has been observed³⁶ that among exposed females, onset of menopause begins earlier than the norm. The fact that in this study radiation effects were noted only among females suggests the possibility of a relationship with menopause. Study of AHS females is now under way to determine whether there is early onset of menopause among A-bomb survivors. It may also be possible that Hiroshima females exposed to high doses have an unusual

原爆被爆者における心臓血管疾患の有意な増加は、初期の調査では認められていなかったが、^{2,3} Robertson ら⁴は、広島的女性に同疾患と放射線被曝との関連を示唆する所見を報告している。しかしこの所見については、高線量群で剖検率が比較的高く、特に広島的女性に著しいので見掛け上影響が現れた可能性があることを指摘しなければならない。そこで、今回は、偏りの可能性を除くため、剖検のみによって明らかになった心臓血管疾患例は除外した。観察期間を被爆後33年の1978年まで延長したが、やはり広島的女性に放射線との関連性が認められた。

心臓血管疾患が閉経後増加することはよく知られている。³⁵ 被爆女性で閉経が標準より早期に起こったことが観察されている。³⁶ 今回の調査で女性にのみ放射線の影響が見られたのは、閉経時期との関係が考えられる。成人健康調査集団の女性について、被爆者に早期閉経が認められるかどうか現在検討中である。高線量に被曝した広島的女性において、心臓血管疾患の既知の危険因子が異常に組み合わせ

combination of known risk factors for CVD which is responsible for the association. Examinations were made of blood pressure, serum cholesterol, and the smoking habits of Hiroshima females (Table 8). Only the smoking habit seems to be associated with dose; however, the excess number of smokers in the high dose group is so small that it is unlikely that an unusual concentration of risk factors in the high dose group can explain the association of CVD and radiation exposure among Hiroshima females.

It is not known why the effects reported here have been discovered only in Hiroshima and not in Nagasaki. Possibly, this is due to the difference between Hiroshima and Nagasaki in quality of A-bomb radiation, as has been reported previously. Specifically, it is to be noted that the neutron dose was higher in Hiroshima than in Nagasaki.³⁷ The fact that findings indicating the relation of dose to development of CVD were detected for the first time after the elapse of 24-28 years from the bombing suggests that even if the progress of arteriosclerosis is accelerated by radiation, its progress is still relatively slow and that it still takes considerable time before it becomes manifest as a disease. Further, as there is generally a long interval between onset of arteriosclerosis and death, it should be true that incidence studies would demonstrate an association with radiation dose (if it exists) before mortality studies using the same sample size. It is possible that these trends might be confirmed by the Life Span Study, by autopsy studies and others.

Whatever the case, it is very important to confirm whether the radiation effects observed demonstrate a true trend, and also to discover whether radiation effects will appear in the males of Hiroshima and males and females of Nagasaki. Thus, continuation of observations into the future is necessary.

It is a well-known fact that both the incidence and mortality rates for stroke in Japan have been on the decline.^{3,8-10} This was supported by the findings of this study. There has also been a decrease in CI and CH, the decrease being particularly marked in CH. This is probably due largely to improvements in the Japanese life-style.³⁸ Evidence from the first 11 examination cycles of the AHS shows clearly that cholesterol

さって、それが放射線との関連に関与している可能性がある。なので、広島女性の血圧、血清コレステロール、喫煙習慣を調査した(表8)。喫煙だけが線量と関連性があるように思われるが、高線量群における喫煙者数の過剰は非常に少ない。したがって、高線量群に危険因子が異常に集中していることが、広島女性の心臓血管疾患と放射線被曝の関連性を説明するとは考えられない。

以上のような放射線被曝の影響がなぜ広島のみ認められ、長崎に認められないのか不明である。以前に報告されたように、これは広島、長崎の原爆放射線の質の差異に起因している可能性が考えられる。特に、中性子線量が長崎よりも広島で高いことには留意すべきである。³⁷ 被爆後24~28年経過して初めて心臓血管疾患発生と線量の関係を示唆する所見が認められたという事実は、放射線による動脈硬化の促進があるにしても、比較的緩慢であり、疾患として現れるには、かなりの時間がかかることを示している。また、動脈硬化の発生から死亡までの期間は一般に長いので、放射線量との関連は(もしあるならば)同規模の調査集団を用いた死亡率調査より早期に、発生率調査で明らかになるはずである。今後、寿命調査、剖検などによりこの傾向が確かめられるかもしれない。

いずれにせよ、今回認められた放射線の影響が真の傾向であるのか、また広島の男性、並びに長崎の男性及び女性に今後影響が出現するのかどうかを確認することは、非常に重要であり、今後とも観察の継続が必要である。

日本における脳血管疾患は、発生率、死亡率共に減少してきていることはよく知られている。^{3,8-10} 今回の観察でもこれは裏付けられ、脳梗塞、脳出血共に減少してきているが、脳出血の減少が特に顕著に認められた。これは、恐らく主として日本人の生活習慣の改善による影響であろう。³⁸ 成人健康調査の

TABLE 8 AGE-ADJUSTED DISTRIBUTION AND MEANS OF SYSTOLIC BLOOD PRESSURE, SERUM CHOLESTEROL, AND SMOKING HABIT BY RADIATION DOSE, HIROSHIMA FEMALE

表8 広島的女性における収縮期血圧, 血清コレステロール, 及び喫煙習慣の年齢訂正分布と平均値, 放射線量別

T65 Dose in rad		Systolic blood pressure (mmHg)					Age- adjusted mean	Test
		<110	110-139	140-179	180+	Total		
Total	No. %	1031 20.5	2720 54.1	944 18.8	331 6.6	5026 100.0	127.3	
0-9	No. %	21.6	54.1	18.4	6.0	2208 100.0	126.9	
10-99	No. %	19.5	53.6	19.1	7.7	1892 100.0	128.2	Sug
100-199	No. %	21.4	53.1	20.0	5.2	407 100.0	126.1	
200+	No. %	20.7	58.2	15.8	5.0	519 100.0	125.5	

		Serum cholesterol (mg/100 ml)					Age- adjusted mean	Test
		<125	125-179	180-219	220+	Total		
Total	No. %	436 11.5	2124 56.3	906 24.0	310 8.2	3776 100.0	166.8	
0-9	No. %	12.3	56.4	24.2	7.1	1660 100.0	165.3	
10-99	No. %	11.4	56.2	23.5	8.9	1451 100.0	166.8	Sug
100-199	No. %	9.8	59.3	21.3	9.6	303 100.0	168.2	
200+	No. %	10.3	53.3	27.1	9.5	362 100.0	170.7	

		Smoking habit			Total	Test
		Nonsmokers	Cigarettes per day			
			<20	20+		
Total	No. %	3484 84.9	546 13.3	73 1.8	4103 100.0	
0-9	No. %	87.6	10.9	1.5	1824 100.0	
10-99	No. %	83.4	14.9	1.7	1532 100.0	***
100-199	No. %	83.3	13.9	2.8	319 100.0	
200+	No. %	79.8	17.6	2.8	428 100.0	

levels have been increasing with time among participants. Since for the Japanese, cholesterol level is negatively correlated with stroke, especially CH, this would be an important factor in the decline. Further, as blood pressure levels have been demonstrating a decreasing trend in the past, this also may have played a great role in reducing stroke. However, a tendency for blood pressure levels to increase has been observed recently among AHS participants in the under 50 age-group, and it is feared that stroke will increase in frequency again in the future.

Judging from the mortality rate, CHD has been decreasing slightly during recent years.¹⁰ Our study revealed that the incidence of MI among males showed hardly any change during the observation period, but in females it decreased for a period and recently has begun to increase again. Whether this is a true trend further observation will be required to decide.

The incidence of AP showed a peak in 1963-64 and has displayed an uneven course subsequently. This was quite different from that of MI. The diagnosis of AP is based on a patient's complaints, namely, the presence of chest pain. Cases naturally will be missed unless the patients complain on their own or the examining physician makes a point of asking about chest pain or ascertains this by using a questionnaire. In 1963-64 when the secular trend of AP first reached its peak, a questionnaire survey regarding chest pain was conducted and many AP cases were found. Among these cases are many whose diagnosis of AP was confirmed by a physician, having taken a detailed medical history, or having administered an exercise test.

The RERF Department of Medicine in Hiroshima at the time of the present study had three American physicians, all of whom were cardiologists. Moreover, all three of the Japanese physicians who arrived to serve in the Department were also cardiologists. So, of course, these physicians inquired with regard to past history of chest pain as a regular part of their clinical examinations. Other physicians in the Department naturally would have been influenced by them, so there is a strong possibility that attention to heart disease was generally increased and more AP cases were detected than would have been detected otherwise.

11回に及ぶ診察周期で、受診者のコレステロール値が時とともに増加していることを明確に示している。日本人の場合、コレステロール値は脳血管疾患、特に脳出血と負の相関関係にあるので、これは、上記の減少傾向の重大な要因である。また、血圧は過去において下降傾向にあったため、これも脳血管疾患の減少に大きく寄与したと思われる。しかし、成人健康調査の50歳未満の受診者に近年血圧の上昇傾向が見られ、将来本疾患の再び増加することが危惧される。

死亡率で見ると、虚血性心疾患は最近やや減少してきている。¹⁰ 今回の調査によると、心筋梗塞の発生率は、観察期間中男性にはほとんど変動が認められないが、女性では、一定期間減少し最近増加してきている。これが真の傾向かどうか明らかにするためには今後の観察を必要とする。

狭心症発生率は1963-64年をピークに、その後は一定していない。これは、心筋梗塞の発生率と全く異なる。狭心症の診断は患者の訴え、つまり胸痛の有無にかかっている。患者が自発的に訴えるか、診察の医師が必ず胸痛に対する問診を行うか、又は質問票を用いて胸痛の有無を確かめない限り、当然症例を見落とすことになる。狭心症の年次推移が最初にピークを迎えた1963-64年には、胸痛に関する質問票調査が行われ、そのため多くの狭心症の症例が発見された。この中には、更に医師による詳しい問診を受け、又は運動負荷心電図検査で狭心症の診断が確定された者が多い。

本研究実施時に、広島放影研臨床部には3名の米国人医師が所属しており、そのいずれも心臓専門医であった。更に、同部に赴任してきた3名の日本人医師もこの分野を専門とし、当然、通常の臨床診察の一項目として胸痛の有無を問診した。また、他の臨床部医師にもおのずとその影響があり、全体として心臓疾患に対する注意が高まり、より多くの狭心症の症例が発見されるようになった可能性が非常に強い。

The incidence of AP is remarkably low compared with that of MI, except in 1963-64, but an American report³⁹ shows that incidence rates for MI and AP are approximately the same, so that, although it is difficult to apply the American data directly to the study in Japan, there is a strong possibility of a number of AP cases having been missed in the present medical records review. In this sense, it is highly likely that the trend shown in Figure 5 does not represent the actual trend.

Despite the tendency for cholesterol levels to increase with time, the fact that no overt increase has been observed in MI may be attributable to the tendency for blood pressure levels to decline. However, the trend (mentioned earlier) for blood pressure levels among those under age 50 to increase, gives rise to concern about the possibility that this disease may increase in the future. As is evident from the NI-HON-SAN study,^{38,40,41} the incidence of CHD varies with life-style, even among people of the same race. The more Westernized a Japanese becomes, the higher the risk is. Although recent death statistics indicate that CHD mortality in Japan has shown a slight decrease,¹⁰ it is possible that it will increase if the life-style of the Japanese continues to become Westernized. Therefore, it is essential that relevant observation be continued, and as soon as possible, studies must be made of possible preventative measures.

1963-64年を除き、狭心症の発生率は心筋梗塞と比較して著しく低い、米国の報告³⁹では両者はほぼ半々である。米国の資料を直接日本の調査へ応用しにくいものの、今回の医学記録検討では、恐らく狭心症の症例を若干見逃していることであろう。この意味でも、図5の傾向は真のものでない可能性が大である。

コレステロールの経時的増加傾向にもかかわらず、心筋梗塞の増加がさほど明らかでないのは、血圧が下降傾向にあったためと考えられる。しかし、50歳未満の血圧値上昇傾向(前述)は、本疾患が将来増加していく可能性を憂慮せしめるものである。これまでNI-HON-SAN Study^{38,40,41}で明らかにされたように、同一人種でも生活習慣の相違により、虚血性心疾患の発生率には差があり、欧米化した日本人ほど危険度は高くなる。最近の死亡統計では、日本の虚血性心疾患の死亡率はやや減少してきているものの、¹⁰ 今後日本人の生活習慣の欧米化が継続すれば、本疾患の増加が考えられる。したがって、引き続き適切な観察を行うことが必須であるが、同時に予防の方策を早急に検討すべきである。

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