A Statistical Study on Human Cancer Induced by Medical Irradiation[1,2]

By

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in collaboration with

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抄　録

昭和36年及び37年の2ヶ年間，本邦の Intern 指定病院を主体に，癌患者及び非癌患者の既往の放射線照射の有無の調査を行つた。得られた結果は次の通りである。

1. 有効な調査数は癌患者 8,923，対照 11,556名である．
2. 調査全体でみると，癌患者における既往の放射線照射の割合（治療と X 線上腹部透視を含む）は対照のそれと略同率である．照射を治療のみに限定すると，腫瘍群では0.94%，対照群では0.61%で，これは統計学的に有意の差がある．しかし現在これは放射線生物学的観点よりは説明は困難なので，因果関係があるとはいいきれない．
3. 胃癌患者の照射率は非癌患者と略々同率である．
4. 線束内発癌を問題にすれば
   A 皮膚癌患者は対照に比べて，明らかに既往の放射線治療の割合が多く，統計学的に大きく有意の差がある．
   B 甲状腺等の頸部癌では対照に比べて，既往に頸部に治療照射を受けた割合が高く，統計学的に大きく有意の差がある．
5. 皮膚癌及び頸部癌の有照射例について発癌部の線量を推定し，線量と Relative Risk の関係を求めたところ両者は略直線的関係となり，2000～4000r の線量で Risk が略5倍となる結果が示された．
6. 本研究は Retrospective Survey で行つたので，線量効果関係の推定はできなかった．

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Introduction

The late effects of irradiation, especially carcinogenesis have been proved to occur by experiments in animals, but in humans, although there have been numerous case reports of similar occurrence, the actual relationship between radiation and carcinogenesis and evaluation of the risks involved remain to be clarified (1–5). With the recent trend to increased utilization of atomic energy, the need has arisen to study these problems thoroughly, and the present investigations were undertaken with this in mind. Studies were limited to medical radiation only, as this type of radiation has been most widely employed in the past, follow-up of the irradiated undertaken with relative ease, and the employed dose can be estimated fairly accurately.

The purpose of this paper is to describe whether or not cancer patients have more medical radiation histories than that controls have. For this study radiologists undertook the main responsibility in teams that included statisticians, pathologists, physicists and radiation biologists.

Methods

In undertaking such a type of survey, the need arises to select subjects with histories of radiation therapy for non-malignant diseases in the past, and to determine medically if malignant tumors have since developed or not; namely, a prospective survey becomes desirable. But, as has been pointed out by previous investigators, the possibility of successful follow-up is in general poor, while this prospective survey has the weak point of being expensive (6, 7). Further, in Japan the population migration during and after the War

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has been so active that this method of survey becomes very difficult (8, 9).

It was decided, therefore, to conduct a retrospective survey; namely of ascertaining by direct inquiry, whether patients bearing malignant tumors received irradiations in the past for benign diseases or not. For this, all cancer patients visiting hospitals during a definite period were surveyed and their radiation histories were investigated.

The hospitals that cooperated in this survey were Intern Hospitals selected from the Japanese Hospitals Directory in 1961 (10). Besides the above, well-known cancer hospitals were also included in this survey.

In this procedure the authors did not take an exact random sampling of all cancer patients and was practically impossible to survey irradiation histories in all cancer patients. However, since in Japan most cancer patients ultimately visit these hospitals with better staff and equipment, and since the survey was performed by excellent radiologists without any subjective intention for selection of patients, the authors' sampling method may be reliably appreciated. The members of our radiologists questioned from the radiological standpoint the radiation persistently until fully satisfied.

Persons with no cancer, without distinction of healthy or diseased individuals other than malignant tumor, visited the same hospitals during the same survey period, were questioned as control group. Therefore, in controls the similar statistical characters may be present as in cancer group described as above.

In case of the tumor group, the items to be checked in the survey were names of hospital and patient, sex, age, clinical diagnosis, method of diagnosis (by clinical features, X-ray examination, biological test of cancer, biopsy or surgery, etc.), date of onset (presumed) and date of diagnosis. Positive radiation history was specified by histories of irradiation 3 years or more before the presumed date of onset of the present cancer. The radiation history was pursued as regards period of irradiation, age at that time, body part irradiated, name of disease, number of irradiation received, name of the hospital where radiation therapy was received, etc. The control group was questioned for name of hospital, and present state of health. Those with histories of past irradiation were questioned for items similar to the tumor group. Besides the above, two additional items were also checked, for histories of professional exposure and exposure to the atomic bomb.

Two surveys were made, the primary extending from September 1 to October 31 of 1961 and included ambulatory and in-patients of the hospitals selected, while the secondary survey was made during August 15 to October 14, 1962, for only skin cancer and cancer of the neck including thyroid cancer for reasons mentioned later.

Results

A. Scrutiny of the survey cards.

In the primary survey conducted in 1961 a total of 21,923 cards were collected.

Some of the cards were found to be unsatisfactory, such as the case of the same patient attending 2 or more hospitals during the same period, and resulting in duplication of records. In such a case the card with more detailed description was adopted and the other was

discarded. Foreigners were excluded, as also cases of professional exposure and atomic bomb survivors, as our survey was limited to only Japanese exposed to medical radiation. Cards with age, sex and diagnosis unknown, as well as those suggesting the presence of benign tumors such as brain tumors were excluded. Again, carcinoma in situ was excluded from the cancer group, based on the advice of pathologists, while so-called "metastasierende Struma" or "goitre associated with metastatic foci" were included in the thyroid cancer group. As the site of the cancer was an important item in this survey, those with the primary focus unknown were excluded.

By the above procedure a total of 1,444 cards, namely 6.5% of the total, were discarded, and the cards available for study were 8,923 of the cancer group, which corresponds to about 6.5% of all Japanese cancer patients seen in one year, and 11,556 of the control group.

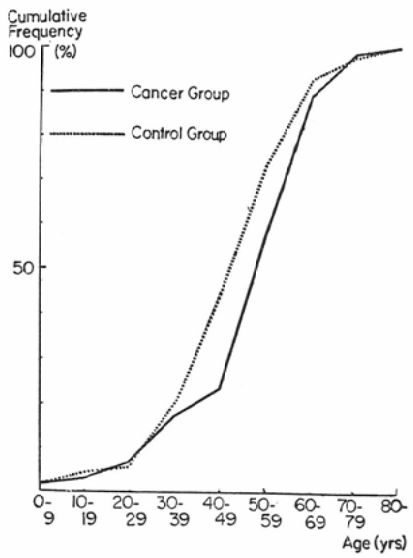
The cards were sorted according to the 8 main districts of Japan, each of the districts being comparable as regards population and number of hospitals. In all districts, females outnumbered males in the cancer group, there being 5,263 females to 3,660 males, or a ratio of 1 : 1.4. In the control group both sexes were almost equally represented, the ratio being 1 : 1.16 (text-fig. 1).

Text-figure 1. Valid survey cards collected according to district

The age distributions according to sex of the two groups are shown in text-figure 2. For simplicity the ages were divided into 10 year intervals. The age compositions of the 2 groups were very similar when shown by curves of age distribution, but in order to determine if this is really so statistically, the percentages of the age compositions of both groups were computed, and the respective cumulative frequency curves prepared are shown in text-figure 2. Based on these a test of comparability of the two distribution curves was made (11). The maximum difference of 18% seen in the class of 40–49 years was markedly

larger than the conformity of frequency functions, $1.36\frac{N_1+N_2}{N_1 N_2}$ $(=0.2)$, where N_1 being total males and N_2 total females (11). In other words the age distributions of the 2 groups were found to be not comparable statistically, and hence in comparisons of the two statistical manipulation becomes necessary.

Text-figure 2. -Age distribution of cancer and control groups (1961 survey)



Classification of malignant tumors according to primary site of the cancer group is shown in table 1. The % distribution almost corresponds with those of Mortality Statistics of Malignant Tumor of the Welfare Ministry (1958) (12) and of Segi's report (13).

The methods of diagnosis and accuracy become extremely important in a survey of this nature. Of the total cases 56.8% were diagnosed as cancer histopathologically, a method that can be considered to be 100% accurate. Of the remaining 43.2%, 9.2% were diagnosed by the clinical features, 12.7% by radiology, 19% by surgery and the remaining 2.3% by other methods. The reliability of these latter methods, has been studied by various investigators and is said to be 85% by radiology, 80% by cytology, 95% by surgery (14). Collectively, the mean accuracy of cancer diagnosis is estimated to be 92%. If we consider these grades of accuracy to hold true in our present survey, the reliability of diagnosis can be considered to be sufficiently high for a conclusion to be drawn.

Next, cards with records of radiation less than 3 years ago from the onset of malignant disease, not from the date of survey, were discarded as the fear exists of the present cancer having already been present.

In case of the non-cancer controls the need arose to decide how far back their radiation histories should be traced from the dates of survey, in order to make the conditions approximate those of the cancer cases. For this, the mean of the period extending back to the presumed date of onset of the cancer was computed from 200 survey cards selected at random from the cancer group.

Table 1. - Cancer classified by site

	Male	Female	Total
1 Malignant Brain Tumor	13	6	19
2 Paranasal Sinuses	239	165	404
3 Tongue	95	64	159
4 Pharynx or Larynx	266	60	326
5 Oral or Nasal Cavity	49	48	97
6 Thyroid	53	143	196
7 Parotid or Orbit	30	18	48
8 Breast	11	1,254	1,265
9 Lung	305	108	413
10 Esophagus	214	82	296
11 Stomach	1,314	669	1,983
12 Intestine or Rectum	277	246	523
13 Liver, Gall-bladder, Pancreas	112	72	184
14 Kidney or Bladder	120	55	175
15 Adrenals		2	2
16 Prostate or Testis	105		105
17 Uterus or Vagina		1,879	1,879
18 Ovary		96	96
19 Skin	117	90	207
20 Sarcoma (except lymphoma)	84	65	149
21 Malignant Lymphoma	193	96	289
22 Leukemia	63	45	108
Total	3,660	5,263	8,923

In 85 this interval was under 6 months, in 56 under 1 year, in 36 under 2 years, in 17 under 3 years and in 6 under 7 years, the mean being 11.08 months.

In other words the mean period of onset of the present cancer in the cancer group was 3 years plus this mean of 11 months. Such being the case, radiation histories of more than 3 years and 11 months, namely irradiations received previous to November 1957 were subjected to study in the control group.

In this survey irradiation consisted of therapeutic irradiation, and fluoroscopy of the upper abdomen. The reason why fluoroscopy of this area was included is that an exposure dose of about 50 r is still used today, while in the past a dose of more than 100 r was usual (15), and it was believed that such an exposure should not be excluded in our present investigations.

Next, in this study the presence of radiation histories in both cancer and control groups was ascertained only by the statement of patients based on their memory. Therefore some biases may be brought such as cancer patients are more likely than other persons to remember and report prior radiation exposure. This weak point could not be avoided in such a type of retrospective study under the situation of the post-war Japan, because the credit of patients' memory on prior radiation exposure could not be identified, as the long-time was made to loss prior exposure record and even the hospitals themselves. To avoid the memory bias of the retrospective study we organized the team of survey by the

radiologists. This investigation was carried out with a co-operation of excellent radiologists, who questioned radiation histories to all patients and persons equally from their specialists standpoints with an objective and thorough manner until fully satisfaction. Therefore the authors believe that there is no gross bias in this problem.

In cases with radiation histories the need arose to determine the radiation dosage, but, as information was obtained by direct inquiry from the patients, this was not possible from the records on the cards. Under the circumstances it was decided to obtain pertinent data of all cases with radiation history, by inquiries from hospitals where such irradiation has been conducted. But due to the time that has elapsed since irradiation, as well as to loss of such radiation records due to the war in most hospitals mentioned as above, accurate information of the exact dosage for each case could not be obtained.

As an alternative, indirect estimation of the dosage was attempted. Radiology Departments of the Intern Hospitals surveyed were first questioned for the type of radiation equipment and radiation conditions for therapy of benign tumors in the 4th and 5th decades of this century. The 305 replies collected were analysed in detail and the results are published in a separate report (15). From the data it was found that in radiation therapy of tuberculosis of the cervical glands the radiation conditions were, 120–150 kVp, 3 mm Al – 0.3 mm Cu filter (half value layer 0.2–0.7 mm Cu), radiation field 50–100 cm^2, period of therapy about 10 weeks, a single dose 60–120 r (in air) and total dose 1,000–3,000 r, with a dose of 1,800–2,500 r most commonly employed. Based on the above it was estimated that in tuberculosis of the cervical glands, the thyroid received about 580–2,800 r, and about 2,000 r in most cases.

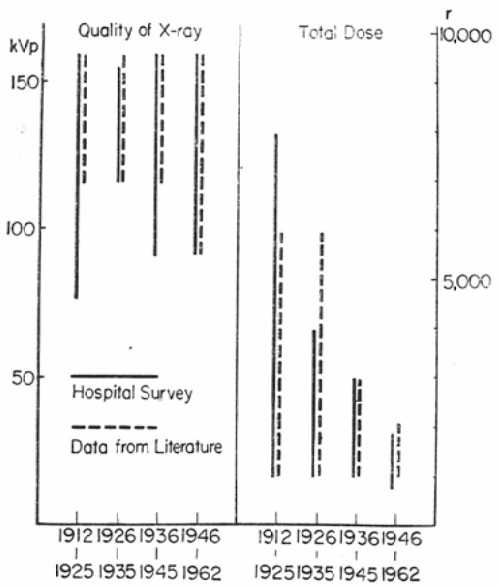
These investigations were based on the memories of physicians and radiologists still working in these hospitals, and in order to ascertain further the reliability of these figures, a study was made of 101 reports on radiation therapy for benign conditions in this country since 1905, and the radiation conditions for different periods were compared with the above data. As is shown in text-figure 3, the two were found to be closely alike. Details were described by the authors elsewhere (15). In this paper, therefore, the numbers of radiation received for each case with radiation history were multiplied by the basic doses and the total dose for each cancer site was computed.

As in the survey cards there are also recorded the changes and reactions of the skin after irradiation, these were used as reference for making certain corrections of the computed radiation dosage. By taking the above precautions the estimates of the radiation dose were made as reliable as possible.

B. Study of the control group.

Essentially, the attributes of both the control and cancer groups should be identical excepting for the difference of cancer or non-cancer. However, the two groups differed somewhat regarding age distribution of the subjects. Corrections have, therefore, to be made statistically to equalize the attributes. In addition there can exist the very important matter of bias in the control group regarding irradiation and when such exists the control group loses statistical significance. The need, therefore, arose to ascertain statistically if the

Text-fisure 3. – Quality of X-ray and total dosage for tuberculosis of cervical gland. Estimated from existing literature and hospital survey. Length of lines shows ranges of kVp and total dose reported.



irradiation ratio of the control is representative of the general population in Japan. As determination of the irradiation ratio of the entire nation is impossible, our Aichi prefecture with a population of 4,500,000 (about 1/20 of the entire nation) was selected for this study (16).

From the inhabitants registration card or voting list a total of 1,000 persons corresponding in sex and age distribution to the control group were selected at random from various cities, towns and villages in Aichi prefecture. By the mail survey method questionnaires were sent to these 1,000 persons and inquiries made of the history of medical radiation, its period and numbers. To those who did not reply the survey was repeated 4 times in rapid succession, but even then a total of 131 or 13.1% failed to respond. Next, 20 of these 131 persons were selected at random and interviewed. The reason for the non-response was found to be not intentional such as an attempt to hide a history of irradiation, and indicated that there was no special or characteristic bias in the non-response cases. The ultimate available response was therefore 869 or 86.9%.

Of these those that had received X-ray treatment including fluoroscopy of the upper abdomen were 57 (6.56%). On one hand, 730 (6.32%) out of the 11,556 controls of the main survey had also received similar types of irradiation. The rate of prior radiation exposure is nearly the same in both cases ($x^2=0.08$).

Next, in the survey for Aichi prefecture those that had received X-ray treatment numbered 10 (1.15%), but in the controls of the main survey (11,556) the number was 71 (0.61%) with a x^2 value of 2.80, and a significant difference was also not found.

A conclusion was therefore reached that the irradiation ratio of the controls did not differ significantly from that of the general population in Aichi prefecture, and if the results of the latter are supposed to be representative of the entire nation, the irradiation ratio of the control group can be considered to be representative also of the entire population, and bias could be ruled out.

C. Cancers developed within as well as outside the radiation beam.

As described before the sex and age distributions of the cancer and control groups differed, it was not possible to compare the two as they are regarding their radiation histories (17). The groups were therefore, examined for the irradiation ratios according to sex and age, and comparisons were made according to each age group (table 2), namely by the sign test method (18). It will be seen that of the 16 age groups in 7 the irradiation ratio was higher in the control, and a reverse tendency seen in the remaining seven. According to the sign test this is accidental and the irradiation ratios of the two groups were believed to be alike. Similar comparisons were made with only radiotherapy as criterion, shown in table 3. Of the 13 age classes 10 showed higher irradiation ratios in the cancer group, and by the sign test this distribution was found to be not accidental, and a significant difference to exist at the 5% level. In other words therapeutic histories were more frequent in cancer patients than in the controls.

From the above findings, it can be concluded that cancer patients receive X-ray treatment, including fluoroscopy, in a proportion similar to the controls but individually tend to receive relatively more numerous therapeutic radiation.

However, in cancer cases with radiation history past irradiation was not limited to only the site of the present cancer but covered other parts of the body. It is difficult at present to explain the biological significance of such irradiation in cancer development. Since the immediate purpose of this survey was determining whether cancer develops directly in the tissues within the radiation beam or not, special study was made mainly of such cancers. as described in the following chapters.

In this investigation, only the three-way correlation between age and sex, cancer incidence, and prior radiation exposure were studied. However, some factors or attributes other than these three, such as economic status, occupation, and urban versus rural, may not be disregarded. One may say that well-to-do patients may be more likely to have skin cancer treated in hospitals, and to have radiotherapy for benign diseases, than other persons. However, since in recent Japan the health insurance benifit is relatively widely prevailed, there may not be very few patients with malignant disease who do not visit hospital. Also the radiation histories were nearly equally detected in urban and rural from the Aichi-prefecture survey mentioned before.

Next, according to Japan Mortality Statistics indeed there are some occupational differences of cancer mortality. However it is generally very difficult to ascertain whether cancer mortality is parallel or not to cancer incidence. On the other words, we cannot know the all factors of influence to cancerogenesis even in the present days. Therefore the authors did not give considerations for this problem.

Table 2. – Irradiation ratios of cancer and control groups (1961 survey)
(Irradiation includes fluoroscopy for upper abdomen)

			0—9	10—19	20—29	30—39	40—49	50—59	60—69	70—79	80—	Total
Male	Irradiation Ratio	Cancer group	0/28	0/54	7/130 (5.38)	18/285 (6.32)	40/519 (7.71)	79/1072 (7.37)	71/1129 (6.29)	24/413 (5.81)	2/30 (6.67)	241/3660 (6.58)
		Control group	0/56	1/122 (0.82)	18/427 (4.22)	69/783 (8.81)	90/1235 (7.29)	131/1626 (8.06)	81/1173 (6.91)	19/355 (5.35)	0/26	409/5803 (7.05)
	Comparison			Ca<Co	Ca>Co	Ca<Co	Ca>Co	Ca<Co	Ca<Co	Ca>Co	Ca>Co	
Female	Irradiation Ratio	Cancer group	0/17	0/53	2/150 (1.33)	42/764 (5.50)	65/1380 (4.71)	100/1527 (6.55)	65/1032 (6.30)	22/309 (7.12)	1/31 (3.23)	297/5263 (5.64)
		Control group	0/38	1/202 (0.50)	23/549 (4.19)	50/829 (6.03)	90/1385 (6.50)	89/1534 (5.80)	60/908 (6.61)	8/267 (3.00)	0/41	321/5753 (5.58)
	Comparison			Ca<Co	Ca<Co	Ca<Co	Ca<Co	Ca>Co	Ca<Co	Ca>Co	Ca>Co	

Ca : Cancer Co : Control group

Table 3. – Therapeutic irradiation ratios of cancer and control groups (1961 survey)

			0—9	10—19	20—29	30—39	40—49	50—59	60—69	70—79	80—	Total
Male	Irradiation Ratio	Cancer group	0/28	0/54	6/129 (4.65)	3/270 (1.11)	4/483 (0.83)	5/993 (0.50)	6/1064 (0.56)	4/393 (1.02)	1/29 (3.45)	29/3448 (0.84)
		Control group	0/56	0/121	4/413 (0.97)	5/719 (0.70)	15/1160 (1.29)	4/1499 (0.27)	4/1096 (0.36)	1/337 (0.33)	0/26	33/5427 (0.61)
	Comparison				Ca>Co	Ca>Co	Ca<Co	Ca>Co	Ca>Co	Ca>Co	Ca>Co	
Female	Irradiation Ratio	Cancer group	0/17	0/53	0/148	11/733 (1.50)	14/1329 (1.05)	19/1446 (1.31)	8/975 (0.82)	3/290 (1.03)	0/30	55/5021 (1.10)
		Control group	0/38	0/202	4/529 (0.76)	12/791 (1.52)	10/1305 (0.77)	12/1457 (0.82)	0/848	0/259	0/41	38/5470 (0.69)
	Comparison				Ca<Co	Ca<Co	Ca>Co	Ca>Co	Ca>Co	Ca>Co		

Table 4. - Irradiation ratios of stomach cancer and control groups
(Irradiation includes fluoroscopy)

			0—9	10—19	20—29	30—39	40—49	50—59	60—69	70—79	80—	Total
Male	Irradiation Ratio	Stomach Cancer	0/0	0/1	0/23	8/67 (11.94)	15/241 (6.22)	29/440 (6.59)	28/411 (6.81)	10/126 (7.94)	0/5	90/1314 (6.85)
		Control	0/0	0/2	2/46 (4.35)	10/134 (7.46)	21/482 (4.36)	72/880 (8.18)	49/822 (5.96)	13/252 (5.16)	0/10	167/2628 (6.35)
	Comparison				Ca<Co	Ca>Co	Ca>Co	Ca<Co	Ca>Co	Ca>Co		
Female	Irradiation Radio	Stomach Cancer	0/0	0/0	0/17	4/81 (4.94)	7/154 (4.55)	12/184 (6.52)	14/182 (7.69)	6/47 (12.77)	0/4	43/669 (6.43)
		Control	0/0	0/0	3/34 (8.82)	11/162 (6.79)	20/308 (6.49)	19/368 (5.16)	25/364 (6.87)	4/94 (4.26)	0/8	82/1338 (6.13)
	Comparison				Ca<Co	Ca<Co	Ca<Co	Ca>Co	Ca>Co	Ca>Co		

D. Stomach cancer developed within the radiation beam.

Gastric cancers are the most frequent of malignant tumors in Japan, and our initial survey of 1961 also revealed gastric cancers to be most numerous. Of the total of 8,923 cancers there were 1,983 (22.2%) gastric cancers. This incidence however, is somewhat lower than the actual frequency of stomach cancers in Japan.

The 1983 cases of gastric cancer were classified according to sex and age, and to histories of irradiation (table 4). When the irradiation ratio of this group was compared with that of the control group, there was seen no significant difference between the two, when the sign test was applied (7 positive out of 12).

Next, a comparison of irradiation ratio was made of this stomach cancer group with a newly sampled control group (new controls) of similar age distribution (selected by random sampling according to sex and age from the 11,556 controls). The results showed 133 out of 1983 in the stomach cancer group (6.71%) and 249 out of 3966 in the new controls (6.28%), with an apparently slightly higher irradiation ratio in the cancer group, but the difference was not significant. Next, when therapeutic radiation of the upper abdomen was compared, the cases were 1 out of 1983 (0.05%) in the cancer group and 5 out of 3966 (0.13%) in the controls, with a higher ratio in the latter, but by the x^2-test there was seen no significant difference.

From the above it can be concluded that stomach cancer patients did not necessarily receive more irradiation in the past than non-cancer patients.

E. Other cancers developed within the radiation field.

Despite the fact that in the primary survey of 1961 a total of 8,923 cancer patients were

Table 5. – Skin cancer and controls classified according to sex, age and prior radiation exposure (1961 and 1962)

		Age	0—9	10—19	20—29	30—39	40—49	50—59	60—69	70—79	80—	Total
Skin Cancer	Male	Non-irradiated	4	2	3	11	19	36	49	37	9	170
		Irradiated (A)				1		4	3	4		12
		Irradiated (B)					2			1		3
		Total irradiated				1	2	4	3	5		15
		Total number	4	2	3	12	21	40	52	42	9	185
		Irradiation Ratio				8.33		10.00	5.77	9.52		6.49
	Female	Non-irradiated	2	1		12	10	24	34	26	11	120
		Irradiated (A)				2						2
		Irradiated (B)									1	1
		Total irradiated				2					1	3
		Total number	2	1		14	10	24	34	26	12	123
		Irradiaton Ratio				14.29						1.63
	Total	Total number	6	3	3	26	31	64	86	68	21	308
		Irradiation Ratio				11.54		6.25	3.49	5.88		4.55
Control	Male	Non-irradiated	10	5	8	29	49	100	127	102	23	453
		Irradiated				1	1		1			3
		Total number	10	5	8	30	50	100	128	102	23	456
		Ratio				3.33	2.00		0.78			0.66
	Female	Non-irradiated	5	3		35	25	57	83	65	30	303
		Irradiated						3				3
		Total number	5	3		35	25	60	83	65	30	306
		Ratio						5.00				0.98
	Total	Total cases	15	8	8	65	75	160	211	167	53	762
		Ratio				1.54	1.33	1.88	0.47			0.79

Irradiated (A) – Over area of cancer development

Irradiated (B) – Outside area of cancer development

Ratio – Irradiated Ratio over area of cancer development

questioned, there only 40 cases of cancer development within the radiation beam. Of these 7 were skin cancers and 14 of the neck (including cancer of the thyroid), and despite the relatively large number of other types of cancer investigated there were very few with records of previous irradiation. A discussion of the effects of irradiation history on the development of cancer was therefore rendered difficult, and the second survey of 1962 was hence undertaken with the object of studying more cases of cancer developing within the radiation beam, namely surface cancers, such as cancers of the skin, thyroid and neck.

The cases described below of these cancers are the totals from the surveys made in 1961 and 1962.

The cases of each type of cancer were first classified according to sex and age groups, and the controls were selected at random from the control group of the 1961 survey based on the above sex and age distributions, in order to make the composition of the control group coincide with that of the cancer group. Cancers that developed outside the radiation beam were discarded as being unrelated to the irradiation, and only the radiation history of the cancerous site was studied.

1. *Skin cancer*

A total of 308 cases of skin cancers were examined (table 5). Of these 14 (4.55%) had received radiotherapy of the present primary cancerous site, while in the control group the rate was 6 out of 762 (0.79%). The irradiation ratio of the cancer group was so extremely high that x^2 value was 14.86, and a significant difference was seen at the level of 1%. Of the 14 cancers with irradiation history a histological diagnosis was not made in one (table 6), while in another case the latent period was only 4 years (table 7), the disease for

Table 6. – Age of onset and histological diagnosis of radiation skin cancer

Histology \ Age (yrs)	30—39	40—49	50—59	60—69	70—79	Total
Squamous cell cancer	3		4	1	4	12
Basal cell cancer				1		1
Unknown				1		1
Total	3	0	4	3	4	14

Table 7. – Latent period and disease irradiated for in radiation skin cancer

Disease irradiated for \ Latent period (years)	3—5	6—10	11—15	16—20	21—25	26—30	31—35	36—40	41—	Total
Haemangioma			1							1
Tuberculosis of Bone and Joint						1	1	1		3
Eczema				1	1					2
Favus			2	1		1		1	1	6
Lupus vulgaris							1			1
Unknown	1									1
Total	1		3	2	1	2	2	2	1	14

Table 8. – Thyroid cancer and controls classified according to irradiation, sex and age

	Age (yrs)		0—9	10—19	20—29	30—39	40—49	50—59	60—69	70—79	Over80	Total
Thyroid Cancer	Male	Non-irradiated		6	16	21	22	32	30	15	1	143
		Irrad. of neck			4	3	1	1	1			10
		Irrad. of other area							2			2
		Total number		6	20	24	23	33	33	15	1	155
		Ratio			20.0	12,5	4,35	3.03	3.03			6.45
	Female	Non-irradiated		21	57	94	94	107	60	29	4	466
		Irrad. of neck			4	5	3	5	1	1		19
		Irrad. of other area								1		1
		Total number		21	61	99	97	112	61	31		486
		Ratio			6.55	5.05	3.09	4.46	1.64	3.23		3.91
	Total	Non-irradiated		27	73	115	116	139	90	44	5	609
		Irrad. of neck			8	8	4	6	2	1		29
		Irrad. of other area							2	1		3
		Total number		27	81	123	120	145	94	46	5	638
		Ratio			9.88	6.50	3.33	4.14	2.13	2.17		4.55
Control Group	Male	Non-irradiated		13	50	58	54	77	78	38	3	371
		Irrad. of neck					1					1
		Irrad. of other area				2		1				3
		Total number		13	50	60	55	78	78	38	3	375
		Ratio					1.82					0.27
	Female	Non-irradiated		49	150	228	229	261	143	75	8	1,143
		Irrad. of neck		1		3	3	1				8
		Irrad. of other area			3	2	1	3				9
		Total number		50	153	233	233	265	143	75	8	1,160
		Ratio		2.00		1.29	1.29	0.38				0,69
	Total	Non-irradiated		62	200	286	283	338	221	113	11	1,514
		Irrad. of neck		1		3	4	1				9
		Irrad. of other area			3	4	1	4				12
		Total number		63	203	293	288	343	221	113	11	1,535
		Ratio		1.59		1.02	1.39	0.29				0.59

Ratio indicates irradiation ratio of the cervical region.

which irradiation was conducted was unknown, and there was the possibility that cancer had already developed at the time of irradiation. When these 2 doubtful cases are excluded, $x^2=11.01$ and there was seen a significance at the level of 1%.

2. *Thyroid cancer.*

There were 638 cases of thyroid cancer. Of these 29 (4.55%) had histories of therapeutic irradiation of the thyroid within the radiation beam. The age distributions of the cases are shown in table 8. In the control group of similar age distribution irradiation ratio to the neck was 9 out of 1535 or 0.59%. The irradiation ratio of cancer patients was therefore found to be high, and x^2 was 38.84 so that a significant difference was seen at the level of 1%. Of these 29 cases of thyroid cancer there were, however, questionable ones, such as 6 with no histological diagnosis (table 9), 4 with latent periods of less than 5 years and with suspected cancer at time of irradiation, as well as 3 irradiated for nodular goitre which later became thyroid cancer (table 10). Actually there were 8 cases of nodular

Table 9. – Age of onset and histological diagnosis of radiation thyroid cancer

Histology \ Age (yrs)	20—29	30—39	40—49	50—59	60—69	70—79	Total
Papillary Adenocarcinoma	3	2	1	3	1		10
Follicular Adenocarcinoma	3	6	1		1		11
Undifferentiated Adenocarcinoma	1						1
Metastasierende Struma				1			1
Unknown	1		2	2		1	6
Total	8	8	4	6	2	1	29

Table 10. – Latent period and disease irradiated for in radiation induced thyroid cancer

Disease irradiated for \ Latent period (years)	3—5	6—10	11—15	16—20	21—25	26—30	31—35	36—40	Over41	Total
Tuberculosis of Cervical Nodes	1	2	2	4(1)	1	2	2	1(1)		15
Eczema	1									1
Parathyroidism			1							1
Toxic Thyroidism		1	1			1				3
Nodular Goitre	1(1)	5(2)		1					1(1)	8
Tonsillar Sarcoma	1									1
Total	4	8	4	5	1	3	2	1	1	29

Values in parenthesis indicate number of cases with unknown histological diagnosis.

goitre, but the remaining 5 belonged to one or the other of the former 2 categories and were duplicated. Among nodular goitres it has been reported that there are a fair number with cancer complications, and as there also exists the possibility of nodular goitre to change into cancer even when left alone, these cases perhaps should not be treated the same as others. As there were in all 13 such doubtful cases, these were excluded, and with the remaining 16 the x^2 test was conducted, resulting in $x^2=12.99$ and a significant difference was proved to exist at the level of 1%.

Table 11. – Cancer of neck (excl. thyroid cancer) and control group classified according to irradiation, sex and age

Age (yrs)			0—9	10—19	20—29	30—39	40—49	50—59	60—69	70—79	80—	Total
Cancer of Neck	Male	Non-irradiated	1	4	15	43	76	195	230	69	12	645
		Irrad. of neck				1	1	1		1		4
		Irrad. of other area										0
		Total number	1	4	15	44	77	196	230	70	12	649
		Irradiation Ratio				2.27	1.30	0.51		1.43		0.62
	Female	Non-irradiated	1	1	9	19	42	81	48	41	8	250
		Irrad. of neck				2		2	2	1		7
		Irrad. of other area										0
		Total number	1	1	9	21	42	83	50	42	8	257
		Irradiation Ratio				9.52		2.41	4.00	2.38		2.72
	Total	Total cases	2	5	24	65	119	279	280	112	20	906
		Irradiation Ratio				4.61	0.84	1.08	0.71	1.78		1.21
Control Group	Male	Non-irradiated	2	8	27	82	145	379	444	139	24	1,250
		Irrad. of neck				1	1		1			3
		Irrad. of other area			1	1	2	3	3	1		11
		Total number	2	8	28	84	148	382	448	140	24	1,264
		Irradiation Ratio				1.19	0.68		0.22			0.24
	Female	Non-irradiated	2	1	18	39	79	162	100	82	16	499
		Irrad. of neck		1		1	1	2				5
		Irrad. of other area						2				2
		Total number	2	2	18	40	80	166	100	82	16	506
		Irradiation Ratio		5.00		2.50	1.25	1.20				0.99
	Total	Total cases	4	10	46	124	228	548	548	222	40	1,770
		Irradiation Ratio		10.0		1.61	0.88	0.37	0.18			0.45

3. *Cancer of the neck excluding thyroid cancer.*

There were 906 cases of cancer of the neck excluding thyroid cancer; namely cancer of the pharynx, larynx, root of tongue, cervical esophagus, parotid, etc. Of these 11(1.21%) had histories of therapeutic irradiation of the neck. The details are shown in table 11. In the control group the figures were 8 out of 1,770, or 0.45%, indicating higher irradiation ratio of the neck in cancer patients, x^2 being 3.92, with a difference significant at the level of 5%.

Table 12. – Classification of cancers of neck

Age		30—39	40—49	50—59	60—69	70—79	Total	
Clinical diagnosis	Histological diagnosis							
Palate cancer	Squamous cell carcinoma		1				1	
Tonsillar cancer	Squamous cell carcinoma	1					1	2
	Cancroid	1					1	
Laryngeal cancer	Basal cell carcinoma			1			1	2
	Squamous cell carcinoma					1	1	
Pharyngeal cancer	Squamous cell carcinoma			1		1	2	
Parotid cancer	Malignant mixed tumor			1			1	
Esophageal cancer	Squamous cell carcinoma				1		1	3
	Spinocellular carcinoma	1					1	
	Unknown				1		1	
Total		3	1	3	2	2	11	

Table 13. – Latent period and disease irradiated for in cancer of the neck, excluding thyroid cancer

Latent period (years) / Disease irradiated for	3—5	6—10	11—15	16—20	21—25	26—30	31—35	36—40	41—	Total
Tuberculosis of cervical nodes		1	2	2	2			2	1	10
Breast cancer					1					1
Total		1	2	2	3			2	1	11

4. *Estimation of relative risk.*

In these three types of cancer, namely skin, neck and thyroid cancers, the irradiation ratio of cancer patients was in all cases higher than of the controls, and the differences were significant. In view of the above an estimation was made of the tissue dose, and the results for both cancer and control groups classified according to the dose level are shown in table 14. Since our survey method was not "matched sampling," it is not possible to make a direct comparison by merely the number of cases. Therefore the percentage of cases for each dose level were computed and these were compared. If a correlation does not exist

Table 14. – Relative risk according to dose level in radiation-induced cancer

Dose (r)		Not irradiat.	500— 2000	2000— 4000	4000— 6000	6000— 8000	8000— 10000	Over 10000	Total
Control	No. of cases	4044	10	10	2	1			4067
	Percentage	99.434	0.246	0.246	0.049	0.025			100.000
Cancer	No. of skin cancer	294	3	3	2	2	3	1	308
	No. of neck cancer	895	3	6	1	1			906
	No. of Thyroid cancer	609	6	13	5	3	1	1	638
	Total	1798	12	22	8	6	4	2	1852
	Percentage	97.084	0.648	1.188	0.432	0.324	0.216	0.108	100.000
	Expected percentage		0.240	0.240	0.048	0.024	(0.024)		
Relative risk		1.00	2.64	4.83	8.79	13.18	(21.97)		

Note: Relative risk was obtained by dividing actual percentage of the cancer group by expected percentage multiplied by ratio of percentage of cancer group to percentage of control of the not irradiated. For example, in case of the 500 to 2000 r range, relative risk will be: $\frac{97.084}{99.434} \times \frac{0.648}{0.240} = 2.64$

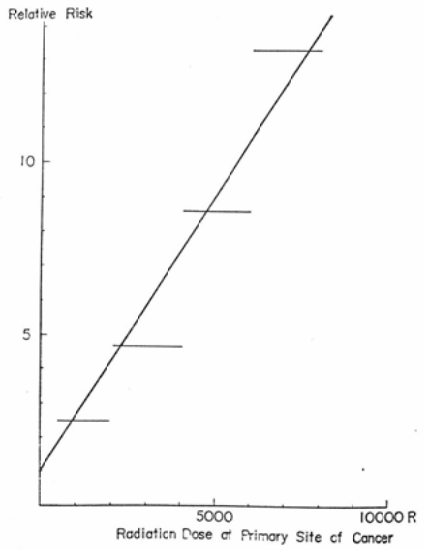
between cancer development and irradiation, the percentages of the two groups for each level should be approximately equal. And if the percentages of the cancer group for each dose correspond to those of the control group, they should also be approximately equal to the expected percentages of table 14. The expected percentages were obtained by the irradiation ratios of the controls of each dosage group multiplied by $\frac{\text{non-irradiated ratio of cancer group}}{\text{non-irradiated ratio of control group}}$. Actually, the irradiation ratio in the cancer group of each dose level shows a fairly large discrepancy from the expected percentage (table 14). Hence, when the ratio between actual value and expected percentage is taken into consideration this discrepancy may be said to present the relative risk (7, 19).

For each dose level this relative risk was computed and the results are shown in text-figure 4. In the control there were no cases of irradiation exceeding 8,000 r, and the expected percentage becomes 0 and the relative risk infinite, but this hypothesis becomes unqualified due to the small number of cases. Hence, when cases of more than 6,000 r are tentatively taken to form one group, with an average dose of 10,000 r, the relative risk becomes 21.97.

Compared with non-irradiated persons the carcinogenic risk thus becomes about 5 times with doses of 2,000–4,000 r, and about 10 times with doses of more than 5,000 r.

Similarly, an estimation was made of the relative risk according to length of the latent period of each of the cases and the results are indicated in table 15 and text-figure 5. There was seen a tendency for the risk to rise with lengthening of period after irradiation, with a saturation level tending to occur at about 40 years. This may be due to rise in rates of people dying from other diseases, when such an age is reached.

Text-figure 4. – Relative risk according to radiation dose. Showing nearly linear relationship. Horizontal lines represent ranges of radiation dose.



Text-figure 5. – Relative risk according to length of latent period. Horizontal lines represent ranges of latent period.

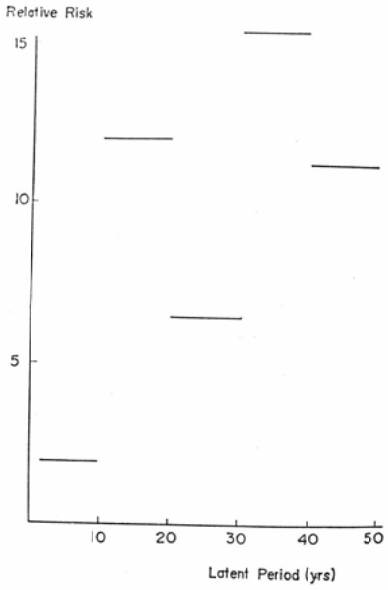


Table 15. – Relative risk according to length of latent period in radiation-induced cancer

Latent period		Not irradiated	Under 5 years	6—10 yrs	11—20 yrs	21—30 yrs	31—40 yrs	Over 41 yrs	Total
Control	No. of cases	4044	5	9	3	4	1	1	4067
	Percentage	99.434	0.123	0.221	0.074	0.098	0.025	0.025	100.000
Cancer	No. of cases	1798	5	9	16	12	7	5	1852
	Percentage	97.084	0.270	0.486	0.864	0.648	0.378	0.270	100.000
	Expected percentage		0.120	0.216	0.072	0.096	0.024	0.024	
Relative risk		1.00	2.20	2.20	11.72	6.59	15.38	10.98	

Summary

Survey cards were distributed to Intern Hospitals in Japan, and a retrospective survey was made to find if cancer patients had received therapeutic irradiation for non-malignant diseases more than 3 years previous to development of the cancer. At the same time similar studies were made of non-cancer patients, as controls.

A total of 8,923 cancer and 11,556 control cards were subjected to study.

When the cards of the cancer and control groups were sorted and cancers developing within and without the radiation beam were totalled and compared, cancer group has more prior radiation exposure than controls.

When only cancers developing within the radiation beam were subjected for study, the irradiation ratio, that is the rate of persons having a history of prior radiation exposure.

of skin cancer was greater than of the controls, and the difference was significant at the level of 1% risk.

The irradiation ratio was also greater in thyroid and other neck cancers such as cancer of the esophagus, pharynx, larynx etc.

Skin, thyroid and neck cancers were tentatively taken to compose one group and in place of the dose effect relationship the dose-relative risk relationship was studied.

If we can be allowed to substitute relative risk for radiation effect, the dose relative risk relationship was seen to rise linearly with increase of dose.

References

(1) Report of the United Nations Committee on the Effects of Atomic Radiation. United Nations, New York, 1962.
(2) Glucksmann, A. et al: Carcinogenic effects of radiation. Cancer edited by R. W. Raven, Vol. 1: 497–539, Butterworth Co., London, 1957.
(3) Furth, J.: Carcinogenesis by ionizing radiations. Radiation Biology edited by A. Hollaender, I, Part 2: 1145–1201, McGraw-Hill, New York, 1954.
(4) Tullis, J. L.: Delayed effects of ionizing radiations in man. Arch. Pathology 66: 403–417, 1958.
(5) Lindell, B.: Present-day assessments of radiation hazards. Physics in Med. Biol. 6: 173–198, 1961.
(6) Dorn, H. F.: Some problems arising in prospective and retrospective studies of the etiology of disease. New England J. Med. 261: 571–579, 1959.
(7) Doll, R.: Retrospective and prospective studies. Medical surveys and clinical trials edited by L. J. Witts, 64–90, Oxford Univ. Press, London, 1959.
(8) Kitabatake, T.: Some problems on epidemiology of radiation-induced cancer. Nippon Acta radiol. in press. (Japanese)
(9) Koga, S.: Present status of persons irradiated to various benign diseases in the past. A prospective survey. Nippon Acta radiol. 23: in press. (Japanese)
(10) Japanese Hospital Directory (1961). Medical Affairs Bureau of Ministry of Health and Welfare, 1961
(11) Quenouille, M. H.: Rapid statistical calculations. A collection of distribution-free and easy methods of estimation and testing. Charles Griffin Co., London, 1959.
(12) Mortality Statistics of Malignant Tumors. Welfare Minister's Secretariat, 1961.
(13) Segi, M.: Cancer mortality for selected sites in 24 countries. No. 2 (1958–1959), Department of Public Health, Tohoku University School of Medicine, Sendai, Japan, 1962.
(14) Kitabatake, T.: Reliability and accuracy of cancer diagnosis in Japan. Nippon Acta radiol. 23: in press. (Japanese)
(15) ——: Estimation of radiation dose for treatment of benign diseases in old Japan, Nippon Acta radiol. 23: in press. (Japanese)
(16) —— et al: Irradiation ratio in general population. Nippon Acta radiol. 23: in press. (Japanese)
(17) Masuyama, M.: Statistical analysis of retrospective survey on radiation cancer. Nippon Acta radiol. 23: in press. (Japanese)
(18) Mainland, D.: Statistics in medical research. Methods in medical research. Vol. 6, The year Book Publ., Chicago, 1954.
(19) Berkson, J.: The statistical study of association between smoking and lung cancer. Proc. Staff Meet. Mayo Clin. 30: 319–347, 1955.
(20) Harada, T. and Ishida, M.: Neoplasms among atomic bomb survivors in Hiroshima. ABCC Technical Report 10–59, 1959.
(21) Palmer, J. P. and Spratt, D. W.: Pelvic carcinoma following irradiation for benign gynecological diseases. Am. J. Obst. & Gynec. 72: 497–505, 1956.
(22) Simpson, C. L. and Hempelmann, L. H.: Association of tumors and roentgen-ray treatment of thorax in infancy. Cancer 10: 42–56, 1957.
(23) Saenger, E. L. et al: Neoplasia following therapeutic irradiation for benign conditions in childhood. Radiology 74: 889–904, 1960.

(24) Conti, E. A. et al: Present health of children given X-ray treatment to anterior mediastinum in infancy. Radiology 74: 386–391, 1960.
(25) Stewart, A. et al: A survey of childhood malignancies. Brit. Med. J. 5086: 1495–1508, 1958.
(26) Latourette, H. B. and Hodges, F. J.: Incidence of neoplasia after irradiation of thymic region. Am. J. Roentgenol. 82: 667–677, 1959.
(27) Garland, L. H.: Cancer of the thyroid and previous irradiation. Surg., Gynec. & Obst. 112: 564–566, 1961.
(28) Rubin, P. et al: Incidence of pelvic malignancies following irradiation for benign gynecologic conditions. Am. J. Roentgenol. 85; 503–514, 1961.

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