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Cancer Incidence in Hiroshima and Nagasaki, Japan, 1958–1987

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The Hiroshima and Nagasaki tumour registries, which have been in operation since 1958, are among the few population-based cancer registries in Japan. This analysis evaluated cancer incidence in Hiroshima and Nagasaki between 1958 and 1987. The overall age-adjusted (World Population Standard) cancer incidence has increased from 217 to 301 per 100 000 among males, and from 176 to 197 per 100 000 among females during the first 30 years of cancer registration. The most recent rates are intermediate to rates in other countries. Despite a gradual decrease, gastric cancer remained the most common malignancy among males and females throughout the surveillance period, accounting for 24% of all cancers by the late 1980s. The rate of liver cancer has increased dramatically among males during the past 20 years, with a 2-fold increase in incidence in the past 10 years alone. The populations of Hiroshima and Nagasaki now have among the highest rates of liver cancer in the world. Breast cancer incidence in Hiroshima and Nagasaki, in contrast, is among the lowest in the world, although incidence rates have doubled since the 1960s. Other common malignancies include cancers of the lung, colon and rectum among males and cancers of the colon, cervix and lung among females.

Key words: breast cancer, cancer incidence, cervix cancer, colorectal cancer, Japan, liver cancer, lung cancer, stomach cancer, tumour registry

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INTRODUCTION

THE HIROSHIMA CITY tumour registry was established in 1957 by the Hiroshima City Medical Association in collaboration with the Atomic Bomb Casualty Commission. Shortly thereafter, a similar population-based registry was started by the Nagasaki City Medical Association with support from the Atomic Bomb Casualty Commission. These registries were among the first cancer programmes in Japan. Only two other large, population-based tumour registries are located in Japan, in Miyagi and Osaka, established in 1959 and 1962, respectively, underscoring the importance of the Hiroshima and Nagasaki registries as national resources. Another feature also distinguishes the Hiroshima and Nagasaki data. Many of the Japanese migrants to the U.S.A emigrated from Hiroshima prefecture and Fukuoka prefecture (the latter located on Kyushu, bordering Nagasaki), enabling the comparison of cancer rates among Japanese Americans and native Japanese.

This paper provides a brief description of cancer incidence patterns in Hiroshima and Nagasaki during the 30 years between 1958 and 1987. A more comprehensive review of cancer incidence in these two cities is in preparation. This descriptive study is timely because there are few long-standing population-based cancer registries in Japan and few documentations of cancer rates. Furthermore, epidemiological research and cancer control activities in Hiroshima and Nagasaki prefectures, and beyond, depend significantly on the data provided by the Hiroshima and Nagasaki tumour registries. Our cancer incidence data will be useful in monitoring trends, and evaluating cancer control investigations and patient management.

MATERIALS AND METHODS

A total of 56 842 cases of cancer were reported to the Hiroshima and Nagasaki tumour registries between 1958 and 1987. Cases of malignant neoplasm, neoplasm of uncertain nature, or one of several selected benign neoplasms were included in the data base. Most (80–85%) cases were ascertained through hospital visits, which included review of clinical and surgical records, radiology, cytology and pathology reports and autopsy records when available. The tumour registry abstract contains information on cancer site, diagnostic procedures and findings, histology, staging and treatment.

Several additional methods of passive surveillance of the population were used. Notification of the tumour registries by physicians, although not legally required, has been promoted by the local medical associations. Death certificates are obtained for all persons dying with cancer, and 7–9% of tumour registry cases

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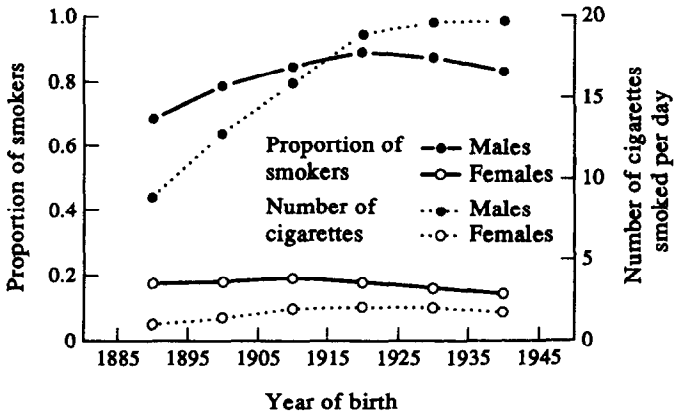

Figure 1. Proportion of lifetime smokers and average number of cigarettes smoked per day by birth cohort and sex among the life span study cohort [6].

are identified thereby. A recent analysis of the data showed that over 70% of cases are histologically verified [1].

The quality of the data is ensured through consistency in case ascertainment and data handling, regular in-house training of personnel, independent review of each case by at least two coders, and edit and logic checks built into the computer software to evaluate the consistency and validity of the responses. Special studies and ongoing monitoring programmes also improve data accuracy and completeness.

The data presented were classified according to the International Classification of Diseases for Oncology [2]. Disease groups were based on the same classification scheme used in the Cancer Incidence in Five Continents monograph series [3], so that the data were compatible. Age-, sex- and registry-specific incidence rates were calculated for each cancer site histology group. Data for both registries combined are presented because there was little variation between registries in the rates for common cancers. Detailed analyses of specific cancer sites will be conducted in the future. Age-adjusted incidence rates were computed by the direct method [4], using the World Standard Population by 5-year age groups, per 100 000 population. Census data were used for the denominators in the calculation of the rates [5]. Trends in cancer incidence are shown by grouping the data into six 5-year periods. Information from a cohort of 40 346 residents of Hiroshima and Nagasaki responding to a mail survey in 1980 [6] was used for Figures 1 and 2.

RESULTS

All cancer

The incidence rate for all cancer sites combined was 217 among males and 176 among females during the 5-year period 1958–1962. These rates had increased to 301 among males and 197 among females by 1983–1987 (Figure 3). Despite the increase, the overall cancer rates in Hiroshima and Nagasaki continued to be intermediate to the rates in other countries, and lower by and large than rates reported in North America and Europe, although similar to the cancer rates among Japanese Americans in Los Angeles and Hawaii [3]. Stomach cancer was the most common cancer among men, followed by cancers of the liver, lung, colon and rectum (Figure 4). Among females, the stomach, breast, colon, cervix and lung were the five most common cancer sites.

Digestive organs

The rate for stomach cancer in Hiroshima and Nagasaki, as in other parts of Japan, is among the highest in the world [3], and gastric malignancies now account for about 24% of the cancer incidence in these two cities. Among males in Hiroshima and Nagasaki, the incidence of stomach cancer is more than twice that for the next most common malignancy, cancer of the liver (Figure 4). Among women, stomach cancer incidence also exceeds that of other cancers, although it appears that breast cancer may soon overtake stomach cancer as the most frequent malignancy. Thus, stomach cancer remains a continuing public health problem in these populations.

Stomach cancer incidence in Hiroshima and Nagasaki has been decreasing gradually over the past 30 years among males and females, although the rate has stabilised among males during the past decade (Figure 5). This contrasts with the sharp decline in gastric cancer mortality rates during the past 15 years in these cities. This divergence in mortality and incidence has not been reported by the Osaka cancer registry [7], and may partially reflect increased survival through the use of more sophisticated diagnostic tools, such as screening endoscopies for the earlier detection of gastric cancer in Japan, as well as improved accuracy in death certificate diagnosis. The continued declining trend in stomach cancer incidence in Osaka may also reflect regional differences in exposure to gastric carcinogens.

Most gastric cancers in high-risk populations occur distal to the cardia, and they are especially common near the junction of the pyloric antrum with the corpus of the stomach. The regional

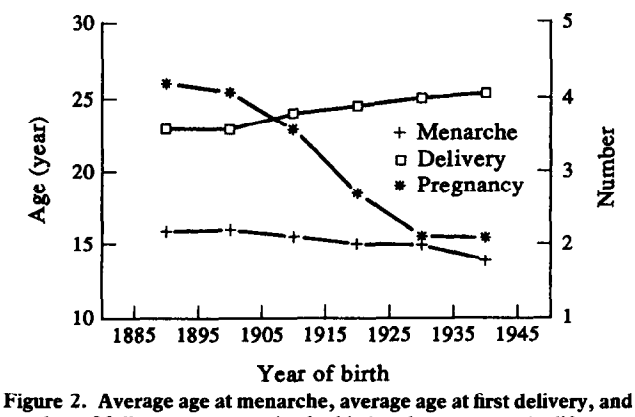

Figure 2. Average age at menarche, average age at first delivery, and number of full-term pregnancies by birth cohort among the life span study cohort [6].

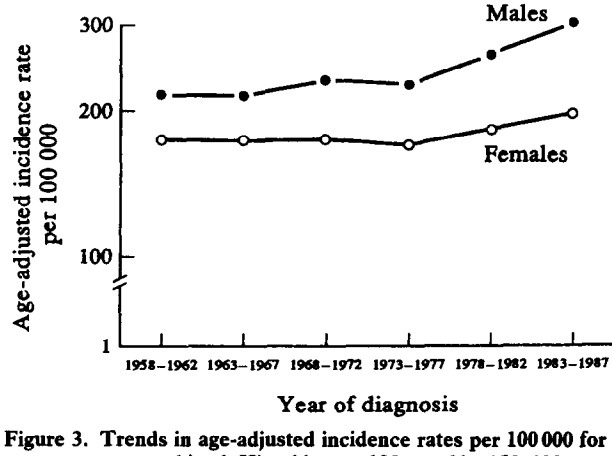

Figure 3. Trends in age-adjusted incidence rates per 100 000 for all cancers combined, Hiroshima and Nagasaki, 1958–1987.

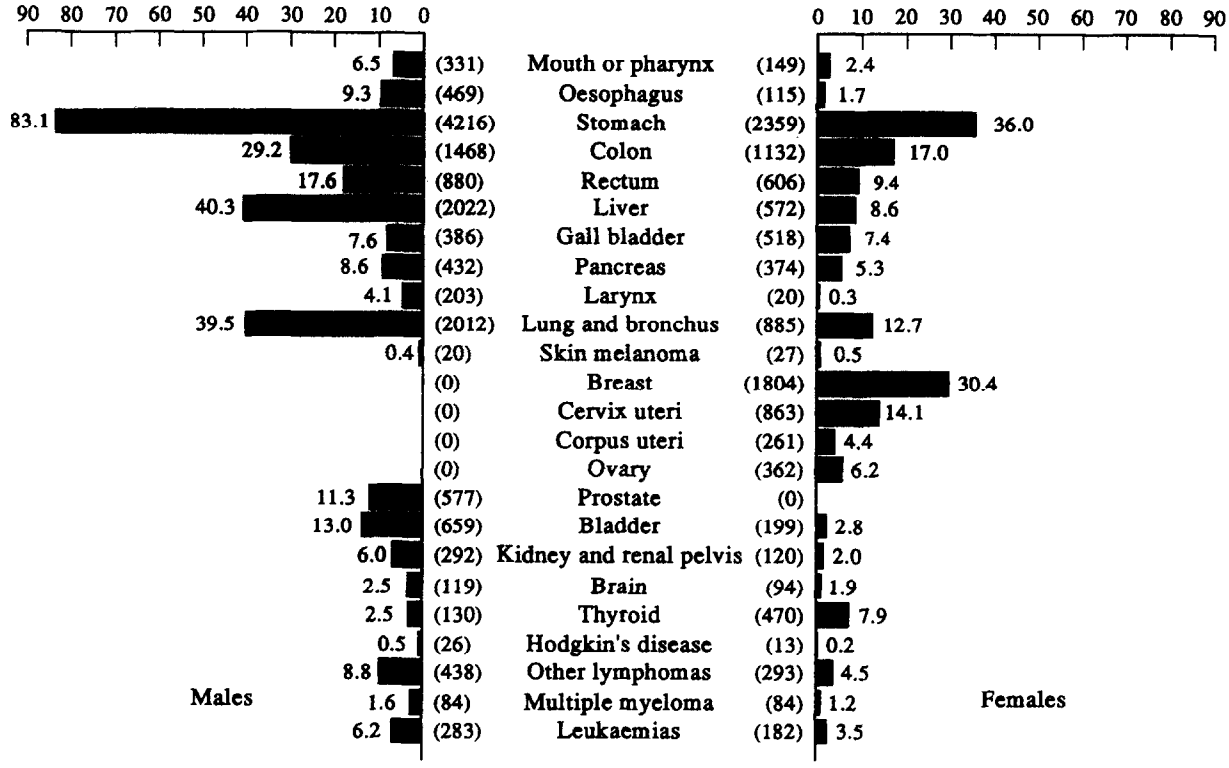

Figure 4. Age-adjusted incidence rates per 100 000 for major cancer types, Hiroshima and Nagasaki, 1958–1987. Number of registered cancer cases is given in parentheses.

distribution of stomach cancer in Hiroshima and Nagasaki was no exception: the pyloric antrum and corpus were the most common locations (68%) of cancer (data not shown). Rates for cancer of the cardia and pylorus declined during the observation period, whereas rates for corpus cancer increased considerably. A possible explanation for these site-specific trends is the easier detection of corpus cancer through gastric screening. These findings may be worthy of further investigation.

Rates for liver cancer among males in Hiroshima and Nagasaki have been increasing rapidly during the past 20 years, with a 2-fold increase in incidence during the past 10 years alone (Figure 5). This trend contrasts with much more gradual increases in the liver cancer rates in many other high-risk countries [3]. The liver cancer rate among all age groups has been rising (Figure 6), suggesting a change in the prevalence of some risk factor(s) with time. We should note, however, that the slight downward trend in liver cancer incidence among young males in the most recent 5-year time period may signal the end of the rapid growth of this malignancy.

There has been little secular change in liver cancer incidence among females. Thus, the rate ratio for men compared with females has risen from 2 in the 1960s to more than 4 in the late 1980s. Data from the Osaka cancer registry show a similar dramatic change in the sex ratio of liver cancer [7]. Among Osaka males, the incidence has increased 3-fold during the past

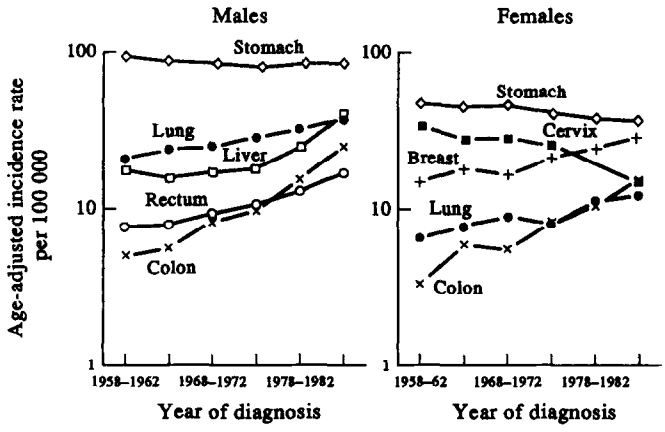

Figure 5. Trends in age-adjusted incidence rates per 100 000 for common cancers, Hiroshima and Nagasaki, 1958–1987.

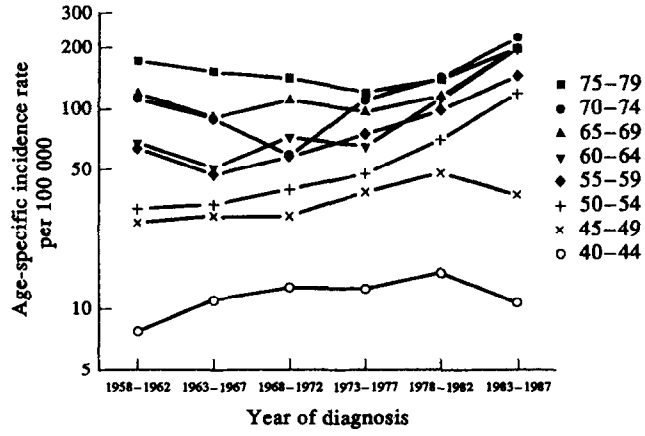

Figure 6. Age-specific (in years) incidence rates per 100 000 for liver cancer among men in Hiroshima and Nagasaki, 1958–1987.

25 years. This result deserves attention and should be considered in formulating aetiological hypotheses regarding liver cancer.

The sharp increase in the incidence of liver cancer, especially among males during the past 20 years, is cause for some concern. Liver cancer rates among males in Hiroshima and Nagasaki are surpassed only by rates among males in Khon Kaen, Thailand (90.0) and Qidong, China (89.9), which are mainly cholangiocarcinomas associated with liver flukes, and are equivalent to rates among Chinese males in Hong Kong (39.2), Shanghai (30.6, Tanjin (23.6) and Singapore (26.8) [3]. Thus, males in Hiroshima and Nagasaki are now at particularly high risk of this disease.

There has been a 5-fold increase in colon cancer in Hiroshima and Nagasaki during the past 30 years among males and females (Figure 5). The rising trend in the rate of rectal cancer among males has been more modest than the trend for colon cancer, although rates have more than doubled in the past three decades. The increase in large bowel cancer mainly results from an increased incidence of more distal cancers, including the sigmoid colon and rectosigmoid, in accordance with data among Japanese Americans [8]. The incidence of left-sided colon cancer in Hiroshima and Nagasaki has increased more than 7-fold during the past 30 years, in contrast to relatively stable rates in the U.S.A. and Europe. This is consistent with the observation that populations in which there is a high risk of colon cancer have a high ratio of sigmoid colon cancer to caecum-ascending colon cancer [9]. However, the possibility of an artifactual increase in the ratio of distal to proximal bowel cancers because of the easier accessibility of distal cancers through modern screening techniques cannot be precluded.

The incidence of large bowel cancer is lower in Japan, Singapore and other parts of Asia than in western Europe, North America, Australia and New Zealand [3], although this gap appears to be closing. Japanese American men in Hawaii have among the highest rates of colon cancer in the U.S.A and Japanese migrants to Hawaii experience a rapid increase in the incidence of colon cancer [10], suggesting that changes in exposure to certain environmental factors in adulthood may influence the development of this cancer. A gradual shift in Japan toward more fat and less carbohydrate in the diet [11] may be a partial explanation for the rapid increase of this cancer in Hiroshima and Nagasaki.

Gall bladder and biliary tract cancer are rare in most of the world [3]. The incidence of gall bladder cancers in Hiroshima, Nagasaki and other parts of Japan is surpassed only by the incidence among the indigenous people of North America [12] and South America [13] (Figure 4). Gall bladder and biliary tract cancer rates in Hiroshima and Nagasaki rose from 3 in 1960 to more than 6 in 1985 (Figure 1). As observed in other populations, gall bladder and biliary tract cancers are the only malignancies that are as common among females as among males, with the exception of thyroid cancer.

Oesophageal cancer incidence among males in Hiroshima and Nagasaki (Figure 2) is higher than in many European countries, and also exceeds the rate among Japanese Americans [3]. While part of the relatively high rate of oesophageal cancer can be attributed to the smoking and alcohol drinking patterns among Japanese men [11], misclassification of the primary sites of adenocarcinoma of the distal oesophagus and cancer of the gastric cardia could occur if the diagnosis is based solely upon a small endoscopic biopsy. We are unable to judge the quality of evidence used to identify the primary sites of tumours near the gastrooesophageal junction.

Respiratory system

Lung cancer incidence has risen substantially in Hiroshima and Nagasaki, with a 2-fold increase among males and a 50% increase among women during the past 30 years (Figure 5). Despite this increase, the lung cancer rate among males in Hiroshima and Nagasaki is about one half that among U.S whites and less than one third that among U.S blacks and New Zealand Maoris [3].

Tobacco-smoking patterns are generally acknowledged to be closely related to the risk of lung cancer. Accordingly, rising trends in lung cancer incidence among males are well correlated with the increase in smoking in Japan through the 1960s [11]. Tobacco-smoking prevalance and personal consumption of cigarettes appear to have peaked among males who were born between 1915 and 1925 (Figure 7), and these men are now at high risk of lung cancer.

It is interesting that, although the rate of lung cancer among males is considerably lower in Japan than in the U.S.A, the prevalance of cigarette smoking among males in Japan has been higher than that among males in the U.S.A since the 1950s [11]. Part of this difference may be explained by the low cigarette consumption in Japan before 1950 and the long promotional phase of smoking on lung cancer [14]. Although most people begin smoking as teenagers, lung cancer incidence does not peak until late adulthood.

Breast and female genital organs

Cancers of the breast, uterine corpus and ovary tend to covary internationally and probably have similar risk factors. The rates for these cancers in Japan are comparatively low, which is unusual because breast and female reproductive cancers are associated with affluence. Cancers of the breast, uterine corpus and ovary account for about 20% of the cancers in Hiroshima and Nagasaki, compared with approximately 40% of the cancers in the U.S.A and Europe [3].

Rates for breast cancer in Japan remain lower than in many other countries [3] (Figure 4), although the incidence in Hiroshima and Nagasaki has doubled in the past 30 years (Figure 5), and may represent an emerging public health problem. Breast cancer incidence curves have flattened or even declined among younger groups in most countries with high rates [15]. This has not been the experience in Hiroshima and Nagasaki, where the incidence has risen among all females after the age of 30 (Figure 2).

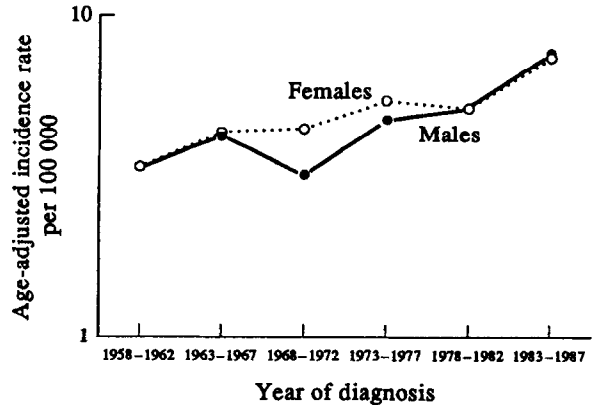

Figure 7. Trends in age-adjusted incidence rates per 100 000 for gall bladder and biliary tract cancers, Hiroshima and Nagasaki, 1958–1987.

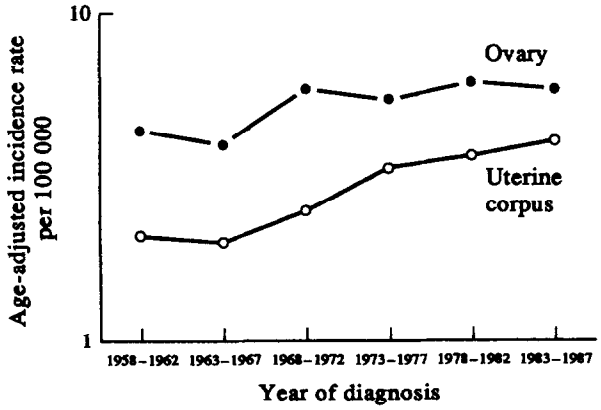

Figure 8. Trends in age-adjusted incidence rates per 100 000 for uterine corpus and ovarian cancers, Hiroshima and Nagasaki, 1958–1987.

Age-specific incidence curves for breast cancer in Japan markedly contrast to similar incidence curves for North American and European females. Breast cancer rates in Hiroshima and Nagasaki are either stable or they decline after the age of 50 years, suggesting that risk had been constant after the menopause [16]. In contrast, the age-specific incidence curves for breast cancer in countries with high rates display the characterstic Clemmensen's Hook at perimenopausal ages [17], with an increased incidence through age 65.

The risk for uterine corpus cancer in Japan is among the lowest in the world [3] (Figure 4), and the rate for this disease in Hiroshima and Nagasaki is only 10–15% of the rate in most North American and European countries, despite a small annual increase of 0.1%, from 2.1 in 1958–1962 to 4.1 in 1983–1987 (Figure 8).

Reproductive history is an important determinant of breast and uterine corpus cancers, with higher risk associated with later age at first full-term pregnancy and low parity [15,18]. Part of the increase in breast cancer risk in Japan may be associated with a decreased birth rate, delayed parenthood and earlier age at menarche (Figure 9). Comparison of data from the Life Span Study cohort [6] with information from the United States National Center for Health Statistics Health Examination Survey has shown that the proportion of nulliparous Japanese women is considerably lower than that among females in the U.S.A

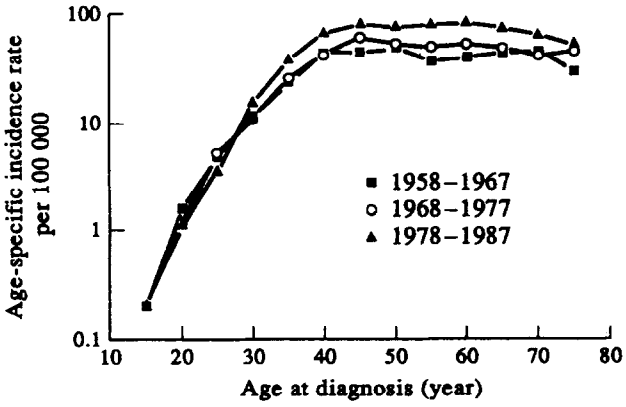

Figure 9. Age-specific incidence rates per 100 000 for breast cancer among women in Hiroshima and Nagasaki by period of diagnosis, 1958–1987.

[16]. However, differences in reproductive factors alone cannot account for the large dissimilarity between the breast cancer and uterine corpus cancer rates in Japan and the western world. Other characteristics of Japanese women, such as later menarche and earlier menopause [16], lower fat and higher soy intake [11,19], infrequent use of oral contraceptives and oestrogens [20], and low prevalance of obesity and alcohol use [16,21,22], may also contribute to the relatively low rates for these malignancies.

Ovarian cancer rates are comparatively low in Hiroshima and Nagasaki (Figure 4), with little temporal variation in incidence (Figure 8). As with breast and uterine cancers, ovarian cancer is more common in economically developed countries, with the notable exception of Japan [3]. The internation variation in ovarian cancer incidence does not correlate well with known risk factors, such as low parity or infertility, or with protective factors, such as multiple pregnancies and oral contraceptive use [23,24]. However, the substantial dietary differences between populations may provide other clues about the differences between Japanese and Western rates for ovarian cancer. Ecological data have suggested a strong, positive correlation between per capita fat consumption, particularly animal fat, and suggested a negative correlation between vegetable and cereal intake and ovarian cancer incidence and mortality [25,26]. A recent international correlation study found a positive association of milk consumption and lactase persistence with the incidence of ovarian cancer [27]. Aside from differences in eating patterns, lactase deficiency is much lower among northern Europeans and Caucasians in the U.S.A than among Japanese and other Asian populations [28].

The incidence of cervical cancer has declined in Hiroshima and Nagasaki from 34 in 1958–1962 to 14 by 1983–1987 (Figure 5), but cervical cancer rates in Hiroshima and Nagasaki are still higher than in many parts of the world [3]. The relatively high rate for cervical cancer is surprising because the low rate of sexually transmitted diseases in Japan suggests that promiscuity is uncommon, although data on sexual activity among Japanese females are lacking. In North Amercia and western Europe, cervical cancer rates have been decreasing at a faster pace [3], presumably because of the widespread use of Pap smears to screen for cancer. Pap smear screening has not been popularised in Japan, which may explain the more gradual decline of cervical disease in Hiroshima and Nagasaki.

Other sites

The incidence of other malignancies, such as cancer of the prostate, kidney and bladder, melanoma of the skin, lymphoma, multiple myeloma and leukaemia tend to be lower in Hiroshima and Nagasaki than elsewhere (Figure 4). The prostate cancer rate in Hiroshima and Nagasaki is about one third of that among Japanese in Los Angeles and less than one eighth of the rate among United States blacks [3]. Recent evidence suggests that the ethnic variation in prostate cancer incidence is associated with ethnic differences in levels of androgen [29], a hormone possibly linked to cellular proliferation. Tobacco smoking is positively related to the risk of kidney and bladder cancers [30], and the low rates for these malignancies accord with the relatively low rate for other tobacco-associated cancers in Hiroshima and Nagasaki. The virtual absence of melanoma among Japanese, in both Japan and the U.S.A, is likely associated with phenotypic distinctions among populations, such as complexion, and the avoidance of sunlight by many Asians [31]. Chronic lymphocytic leukaemia is almost non-existent among the populations in

Hiroshima and Nagasaki (data not shown), and represents less than 5% of leukaemia in other Asian countries [32]. It has not been established whether or not Asians living in western countries are at higher risk of this disease. The risk of adult T-cell leukaemia/lymphoma is particularly high in Nagasaki (data not shown) where human T-cell leukaemia/lymphoma virus–1 is endemic [33].

DISCUSSION

Comparative studies of cancer incidence between registries are influenced by variations in cancer ascertainment and reporting, disease classification, and coding practices. The low percentage of cases identified through death certificate only (<9%) and the high percentage of histological confirmation (>70%) suggest that the quality of the cancer registry data in Hiroshima and Nagasaki is comparable to other established registries worldwide [1]. The Hiroshima and Nagasaki cancer registries conform to the same standards of data collection and coding as the Surveillance, Epidemiology and End-results (SEER) programme in the U.S.A. [34].

As in any cancer registry, there may be differences in the completeness of the data over time resulting from changes or improvements in registration. This is an important concern in studies of cancer trends, such as ours, because it is difficult to separate real from artifactual changes in disease incidence. Although intensive efforts have been made to identify reportable cases retroactively, and revise earlier data when problems with data quality were discovered, the completeness of case ascertainment may still vary with time. We have recently [1] used two quantitative measures to evaluate the completeness of case finding in our populations: change in death certificate only rates and changes in the mortality/incidence ratio. Both of these gauges were stable during the three decades surveyed for this report, suggesting little or no change in death certificate only rates or mortality/incidence ratios over time.

The accuracy of cancer diagnosis is also an important consideration in evaluating tumour registry data. The Hiroshima and Nagasaki registries have histological verification rates of 67–84% [1], which are among the best in Japan, and comparable to those from established registries in other countries. The primary site is known for >98% of all cases included in this report, and demographic characteristics, such as age, are known for nearly 100% of the tumour registry population.

The Hiroshima and Nagasaki tumour registries were initially established to monitor cancer incidence in two populations exposed to atomic bomb radiation. Much research conducted at the Radiation Effects Research Foundation depends upon information furnished by the tumour registries [1]. For example, risk estimates of the association of cancer incidence with radiation exposure are based on these data [35,36]. However, the majority of the population currently in these two cities received little or no atomic bomb radiation exposure. We estimate that about 500 of the cancer cases including in this report (<1%) can be attributed to radiation exposure, and thus do not contribute substantially to any of the observed cancer trends.

Although cancer incidence has increased in Hiroshima and Nagasaki between 1958 and 1987, recent rates are intermediate to rates in other countries. Gastric cancer incidence in Hiroshima and Nagasaki is among the highest in the world, and remained the most common malignancy among males and females throughout the surveillance period. Knowledge is lacking regarding the cause of stomach cancer and, hence, the reason for its decline [37]. Perhaps multi-centred, international studies in high-risk and low-risk areas will help unravel the actiology of this disease. However, until more is known about risk factors for stomach cancer, it is likely to continue to be an important health problem in Hiroshima and Nagasaki.

With the exception of cervical cancer, the incidence for the other common malignancies, notably liver, lung, breast, colon and rectum, have risen substantially during the past three decades. Liver cancer incidence especially has been rising at an alarming rate, although there is evidence of a recent decline among the younger age groups. The reduction in cervical cancer incidence follows that in other populations, although the rate remains higher than in many industrialised countries with similar health care. Increased use of cervical cancer screening through Pap smears might lower the rate of cervical cancer even further.

Healthy lifestyle characteristics are probably associated with the moderate cancer incidence in Hiroshima and Nagasaki. The Japanese diet has been traditionally low in animal fat and protein, and rich in carbohydrate, with vegetables included in many Japanese dishes. Obesity, a major contributor to morbidity and mortality in the West, is uncommon among the Japanese.

Unfortunately, the prevalence of tobacco smoking among males is high (Figure 7), and the rise in tobacco-related cancers is anticipated to continue through the end of this decade. In Japan, males have not given up smoking to the same degree as males in other industrialised countries, and tobacco advertising is common in both broadcast and print media.

Apart from differences in lifestyle, another reason for the comparatively low rates of cancer and other diseases in Japan is the universal access to health care. The Japanese National Health Plan insures over 99% of the population. Physician visits and hospital stays cost modest amounts that probably do not deter care. The Japanese have pioneered mass screening for stomach cancer, and have made much progress in the prevention and early detection of this malignancy. Although a vaccine against hepatitis C is not available for general use, a nationwide hepatitis B vaccination programme might help to reduce the rapid increase in the rate of liver cancer.

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