

## The decade of the seventies in the *Journal*

The article by George G. Rhoads, Gary A. Globber and Grant N. Stemmermann: *A Review of Some Tumors of Interest for Demographic Study in Hawaii*, published in the *Hawaii Medical Journal* of Vol 33, No 8 August 1974, exemplifies the importance and advances made in the field of medicine in the seventies.

The origin and etiology of cancer still remain an enigma. However, this carefully detailed article sheds additional light and understanding into the subject of cancer.

By statistical demographic analysis of the incidence of various cancers in various ethnic groups in Hawaii, clues were found in various cancer sites as compared with the rates in the respective countries of origin and with respect to Westernizing environmental influences. It appears that significant environmental factors must account for some of the extensive cancer rate differences among the various countries around the Pacific.

This kind of epidemiological study advances a better understanding of and insight into cancer. This can lead to a reduction in cancer morbidity and mortality. Research of this nature is highly commendable and continued study along these lines is to be encouraged.

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... types of cancer related to ethnic groups and culture

## A review of some tumors of interest for demographic study in Hawaii\*

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*Because of its multiracial character, Hawaii presents a unique opportunity to carry out demographic investigations of the etiology of certain common cancers. Tumors with substantially different incidence rates among the major ethnic groups in the Islands, or between a given immigrant group and its country of origin, are of particular interest for such studies. Among the cancer sites meeting these criteria, nasopharynx, stomach, prostate, large bowel, liver, female breast, uterine corpus, ovary, bladder, and thyroid are particularly prominent.*

With the development of cancer centers at various sites around the United States, it is to be hoped that such centers may become important national resources for cancer research.<sup>1</sup>

Planning and development of such a center in Hawaii has begun. An acting core group representing multidisciplinary interests would implement the center program, their activity supervised by a policy task force representing various community groups.

Several factors make Hawaii a good place to look for clues to carcinogenic factors for some common cancers. Three sizable Asian groups, as well as persons of European and Hawaiian ancestry insure a diversity of ethnic groups available for study. On islands it is relatively easy to define populations and to follow cases. With the total population of Hawaii less than a million, only relatively common tumors are of sufficient number for study.

A differential in incidence rates of various ethnic groups aids in carrying out etiologic studies among them. The Asian people in Hawaii having immigrated in the last 2 or 3 generations, they are presumably genetically similar to populations in their respective countries of origin, but they have been exposed to strong Westernizing environmental influences and have developed different patterns of disease.

Advantage can be gained from this spontaneous socio-medical experiment by making 2 kinds of comparisons. First, tumor incidence rates in a given ethnic group in Hawaii can be

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compared to the respective rates in the country of origin. Clues to possible carcinogenic factors can be derived from known differences in the environments and tested with case-control or cohort studies in the respective Hawaiian and indigenous Oriental populations. This approach has to date been most successfully employed in comparisons between people in Japan and Japanese Americans now living in Hawaii and California. Similar comparisons might be possible for Filipinos and Chinese.

A second type of comparison can be made among the several racial groups now living in Hawaii. They have different disease experiences, different environments arising from socio-economic and cultural factors, and different genetic and physiologic characteristics. Since the various groups are in

geographic proximity, it is feasible to compare these parameters, minimizing methodologic differences in interviewing and laboratory techniques which threaten any cross-cultural study. Thus the following hypotheses may be constructed: environmental differences → physiologic differences → disease (tumor) differences.

Within this general background, some cancers which invite demographic study in Hawaii may be listed. They are tumors which occur frequently enough to study in the relatively small populations, and which: (1) have incidence substantially different from those in the 3 oriental countries of origin and in the United States; or (2) have substantially different incidence among ethnic groups in Hawaii.

This review is based on standard references giving interna-

TABLE 1: Age-adjusted death rates for selected cancers in Japan, China, and the United States (Caucasians) by sex (1964-65)\*

	MALE RATES PER 100,000				FEMALE RATES PER 100,000			
	U.S. Caucasians	Japan	Taiwan	China Hong Kong	U.S. Caucasians	Japan	Taiwan	China Hong Kong
All sites	143.9	140.2	96.4	159.9	104.5	94.7	73.6	94.5
Esophagus	3.3	7.1	8.3	12.4	0.8	2.2	2.1	2.5
Stomach	9.4	68.6	22.5	21.3	4.7	35.3	12.8	12.3
Intestine (except rectum)	13.7	3.3	4.5	6.5	12.8	3.2	4.3	5.0
Rectum	5.4	4.7	2.4	4.7	3.4	3.5	2.4	2.9
Liver and biliary passages (includes secondaries)	4.5	14.6			4.2	9.2		
Lung bronchus and trachea	36.9	12.6	8.9	29.8	5.8	4.5	6.0	14.6
Breast					21.8	3.8	4.0	9.6
Uterus (all parts)					10.3	13.5	15.6	12.1
Ovary, fallopian tube and broad ligament					7.3	1.7		
Prostate	12.7	1.9	1.0	2.8				
Bladder and other urinary organs	5.0	2.2			1.7	1.0		
Thyroid	0.3	0.3			0.5	0.5		

\*Summarized from Segi M, Kurihara M, and Matsuyama T. *Cancer Mortality for Selected Sites in 24 Countries, No. 5 (1964-1965)* Department of Public Health, Tohoku University School of Medicine, Sendai, Japan. 1969, pp. 106, 118, 122, 126, 159.

TABLE 2: Age-adjusted incidence rates per 100,000 for selected cancers in men in Japan, Singapore, Hawaii, and the Mainland U.S.<sup>1</sup>

	U.S. Mainland		Hawaii (1960-64)					Japan		Singapore
	Alameda County Whites (1960-64)	Connecticut (1963-65)	Hawaiian	Caucasian	Chinese	Filipino	Japanese	Miyagi (1962-64)	Okayama (1966)	Chinese
Nasopharynx	0.5	0.5	7.8	1.1	10.4	3.1	0.9	0.1	0.4	16.1
Stomach	15.3	14.7	45.9	16.9	9.5	9.7	47.6	95.3	93.9	12.9
Colon	24.0	26.7	20.2	19.3	35.9	12.6	20.7	4.1	4.6	2.6
Rectum	15.5	16.3	6.8	12.6	15.8	12.4	11.7	4.8	6.7	5.0
Liver (primary)	2.4	—	15.2	4.3	7.3	6.1	6.7	1.3	0.3	8.6
Bronchus, Trachea <sup>2</sup>	47.8	44.0	70.3	43.8	27.2	17.1	26.3	15.6	15.3	12.9
Prostate	38.0	33.0	30.0	43.4	9.8	17.6	13.9	3.2	4.3	0.9
Bladder <sup>2</sup>	17.9	19.9	9.9	19.3	9.4	1.5	9.0	4.7	—	2.1
Thyroid	2.8	0.8	5.7	4.4	3.5	5.0	1.7	0.8	1.1	0.5

<sup>1</sup>These data for all locations except Singapore are taken from Doll R, Muir C, and Waterhouse J, *Cancer Incidence in Five Continents, Volume II*. Springer-Verlag: New York, 1970. The Singapore data are from Volume I (1966) of the same reference. Age standardized to World population.

<sup>2</sup>"Benign" Papilloma is included in Mainland U.S. and excluded in Japan. It is not known how it was handled in Hawaii or Singapore.

<sup>3</sup>Includes primary and secondary.

(Continued) ►

TABLE 3: Age-adjusted incidence rates per 100,000 for selected cancers in women in Japan, Singapore, Hawaii, and the Mainland U.S.<sup>1</sup>

	U.S. Mainland		Hawaii (1960-64)					Japan		Singapore
	Alameda County Whites (1960-64)	Connecticut (1963-65)	Hawaiian	Caucasian	Chinese	Filipino	Japanese	Miyagi (1962-64)	Okayama (1966)	Chinese
Nasopharynx	0.2	0.1	0.7	0.9	4.6	0.0	0.3	0.1	0.0	5.8
Stomach	7.4	6.8	24.5	8.8	14.2	1.5	26.9	44.7	45.7	3.7
Colon	22.9	26.7	12.1	27.5	23.5	14.8	15.3	4.0	4.6	2.2
Rectum	10.1	10.7	6.9	9.8	9.4	13.4	9.3	5.0	4.5	2.6
Liver (primary)	0.9	—	4.0	1.9	0.0	5.3	1.1	0.8	0.4	1.2
Bronchus, Trachea <sup>4</sup>	7.4	7.8	22.3	10.2	16.7	17.4	7.6	6.0	5.2	3.2
Breast	62.4	62.3	52.3	62.9	44.3	19.5	23.0	11.0	12.4	8.0
Cervix Uteri	17.9	10.3	26.4	15.4	19.6	22.0	14.6	20.6 <sup>2</sup>	22.4 <sup>2</sup>	21.4
Corpus Uteri	16.8	15.3	23.9	17.5	19.5	16.2	10.8	1.3	2.2	4.2
Ovary	12.6	11.3	16.6	14.8	13.1	4.8	9.4	1.9	2.8	3.2
Bladder <sup>2</sup>	5.6	5.9	5.0	5.9	0.0	4.0	2.1	1.6	—	0.5
Thyroid	7.4	3.0	10.1	5.4	20.7	14.3	6.5	2.0	3.3	1.0

<sup>1</sup>These data for all locations except Singapore are taken from Doll R, Muir C, and Waterhouse J, *Cancer Incidence in Five Continents*, Volume II. Springer-Verlag: New York, 1970. The Singapore data are from Volume I (1966) of the same reference. Age standardized to World population.

<sup>2</sup>Includes case of carcinoma-in-situ.

<sup>3</sup>"Benign" Papilloma is included in Mainland U.S. and excluded in Japan. It is not known how it was handled in Hawaii or Singapore.

<sup>4</sup>Includes primary and secondary.

tional comparisons of cancer incidence<sup>2,3</sup> and mortality.<sup>4</sup> Age-standardized summaries are presented for the mortality data in Table 1, and for the incidence data in Tables 2 and 3. The age-standardized rates may conceal important age variability which is evident in age-specific rates, and readers are urged to investigate points of interest to them in more detail in the original sources. Extensive reference is also made to the Hawaii Tumor Registry data,<sup>5</sup> and to Haenszel and Kurihara's previous work on mortality from cancer and other diseases among Japanese in the United States.<sup>6</sup>

#### Sites of common cancers

##### NASOPHARYNX

This cancer is frequent among Chinese, particularly those from South China. Frequency remains high in Chinese emigrants, but is lower among the children and grandchildren of emigrants in California,<sup>7</sup> Hawaii,<sup>8,9</sup> and Australia.<sup>10</sup> In Singapore, where the Chinese population is presumably less Westernized, the descendants of emigrants do not enjoy a lower risk.<sup>11</sup> Thus, the impact of Westernization appears to protect against this cancer. Careful case-control studies might be productive in implicating one or more aspects of the Chinese environment in the carcinogenesis of this tumor. Demonstrated relationships between nasopharyngeal carcinoma and EB virus<sup>12</sup> could be studied among cases from various ethnic groups in the Islands. Such a study would have to extend over several years in order to accumulate sufficient cases of this relatively infrequent tumor.

##### STOMACH

Stomach cancer is more than 5 times as frequent among Japanese as among the U.S. white population. People of Japanese ancestry living in Hawaii have less stomach cancer than have people living in Japan, but substantially more than is found on the U.S. Mainland. Comparisons of the frequency

of stomach cancer among racial groups in the Islands have been previously reviewed.<sup>13</sup> It is most common in Japanese and part-Hawaiians. High rates in the latter group have been largely ignored by investigators interested in this tumor.

On a histologic basis, gastric cancer has been divided into 2 major types: intestinal and diffuse.<sup>14</sup> Evidence suggests that excess occurrence of the disease in Japan is predominantly of the intestinal type, which may be more apt to be induced by environmental carcinogens than is the diffuse type. There is also evidence that sex-tumor type interactions may result in better survival of women with diffuse cancer than of men. A larger percentage of women are without node development, and this may be a racial effect seen oftenest [sic] in Orientals.<sup>15</sup>

Among Japanese-Americans, rates among Issei have remained high, while the Nisei may have a slightly lower susceptibility.<sup>6</sup> This suggests that stomach cancer has an extremely long induction period, perhaps as long as 30 to 40 years. Recent case-control studies in this community by Haenszel et al, suggest that dried and salted fish and pickled vegetables have been more commonly eaten by persons with gastric cancer than by controls.<sup>16</sup> In an earlier Hawaii study, Quisenberry also reported excess consumption of pickled food items in persons with gastric cancer.<sup>13</sup> Stomach cancer is one of the focuses of the Japan-Hawaii Cancer Study, which is examining and following more than 7,500 older Japanese men on Oahu. Plans are to extend these observations to younger persons and to include women. Persons of European ancestry living in Hawaii and Japanese still living in Japan will also be studied. Assays of pepsinogen and gastrin levels are being carried out in subsamples of these groups, in hope of uncovering physiologic differences which may underlie the high incidence of gastric carcinoma among the Japanese.

##### PROSTATE

Age-adjusted death rates for carcinoma of the prostate are

6 times as high in the United States as they are in Japan. Low rates are also reported for Taiwan, Hong Kong, and the Philippines. Cancer registry data suggest that, in Hawaii, Caucasians (whites) are 3 times more likely to get prostatic cancer than are Japanese. Low age-adjusted rates are also reported by the Hawaii Tumor Registry for the Chinese and Filipinos here, with an intermediate rate reported for the Hawaiians/part-Hawaiian group.

Incidence of clinical carcinoma of the prostate increases rapidly with age, and small asymptomatic carcinomas are a frequent incidental finding at autopsy in older men. Karube has found latent carcinomas of the prostate in Japanese autopsy specimens with a frequency comparable to that in U.S. whites.<sup>17</sup> This suggests that prostatic cancer may arise in the 2 populations with equal frequency, but that some environmental factor nurtures and makes them more clinically manifest in the U.S. An alternative explanation is that some inhibitory mechanism, perhaps of an immunologic nature, operates more effectively in Japan than in the U.S.

Akazaki and Stemmermann have compared the frequency and histologic appearance of these latent carcinomas between Japanese living in Japan and living in Hawaii. Using strictly comparable methodology, they found little difference in the overall frequency of carcinomatous foci, but those in Hawaii were larger and more anaplastic than were those in Japan.<sup>18</sup>

Epidemiologic studies have suggested possible relationships of prostatic cancer to particulate air pollution<sup>19</sup> and to cadmium exposure,<sup>20</sup> but these factors do not appear to explain the large difference in incidence between the U.S. and Japan. Further studies are indicated, perhaps in Hawaii.

#### *LARGE BOWEL*

Cancers of the colon and rectum might be regarded as closely related clinically, but there is reason to separate them epidemiologically. While deaths from carcinoma of the colon are about 4 times as common among U.S. white men as among men in Japan, there is little difference in the rates for rectum cancers. Somewhat different patterns emerge among Chinese and Filipinos, but the predominant implication of Table 1 is that cancer arising above the rectosigmoid junction is epidemic in the United States. Cancer registry data confirm that the gradient between the U.S. and the Orient is greater for the colon than for the rectum, and they suggest that Japanese and Chinese men in Hawaii are already experiencing rates of colon cancer comparable to those found among whites. Oriental women may still be enjoying a somewhat lower rate, a point of some interest for future investigations of this cancer.

Detailed necropsy studies of the colon were undertaken by Stemmermann among Hawaii Japanese.<sup>21</sup> He found that asymptomatic carcinomas were frequently missed clinically in the older patients. This results in an understatement of the true incidence of the disease in Japanese but may not greatly affect interracial comparisons, since similar findings have been reported in whites and blacks from Los Angeles.<sup>22</sup> More recent studies include an effort by Stemmermann and Yatani to evaluate the possible relationship of carcinoma of the colon to diverticulosis and polypoid disease.<sup>23</sup> Haenszel and his group have been investigating demographic and dietary histories of Hawaii Japanese with colon cancer. The Japan-Hawaii Cancer Study is planning to relate large bowel cancer to antecedent

risk factors and are carrying out sophisticated analyses of stools of patients in an effort to find possible carcinogenic mechanisms:

#### *LUNG*

The highest rate for lung cancer in the Islands is among the Hawaiians and part-Hawaiians. Men of European ancestry have slightly lower rates, but they are still twice as likely to develop the disease as the local Japanese men. Rates for Chinese and Filipino men are comparable to those for the Japanese. In most of the racial groups, women have about one-third the rate of lung cancer that men have.

The epidemic of carcinoma of the lung now occurring in the United States has been clearly linked to cigarette smoking. Other factors, such as air pollution, may well play a role, however, and the disparate backgrounds of Hawaii's people might contribute to the evaluation of other factors. Quantitative study of past and present differences in smoking habits to see if they are sufficient to explain the varying rates of lung cancer in the several racial groups would be needed. Comparisons of each racial group to its population of origin would also be pertinent. The Japanese community is under study in a case-control format by Haenszel and Lee.

#### *LIVER*

According to registry data, primary cancer of the liver is more common in Hawaii than on the U.S. Mainland or in Japan. The rates for Caucasians (whites) are 50% higher in the Islands than in Alameda County, and among men, all of the other major ethnic groups in Hawaii have still higher rates. Among women, Japanese and Chinese appear to enjoy low rates, though the population numbers are small. High rates of primary liver cancer have been reported from the Philippines<sup>24</sup> and in Chinese populations in San Francisco<sup>25</sup> and in Singapore.<sup>26</sup> In the latter city, these rates were lower in second generation persons.

Stemmermann found hepatomas in 61% of Japanese patients with cirrhosis at autopsy and noted that similar findings have been made in Japan.<sup>27</sup> Only 3 to 8% of cirrhotics are found to have hepatoma in white populations,<sup>28</sup> suggesting that some difference in the process leading to or associated with cirrhosis in various racial groups may account for excess hepatomas in the Orient.

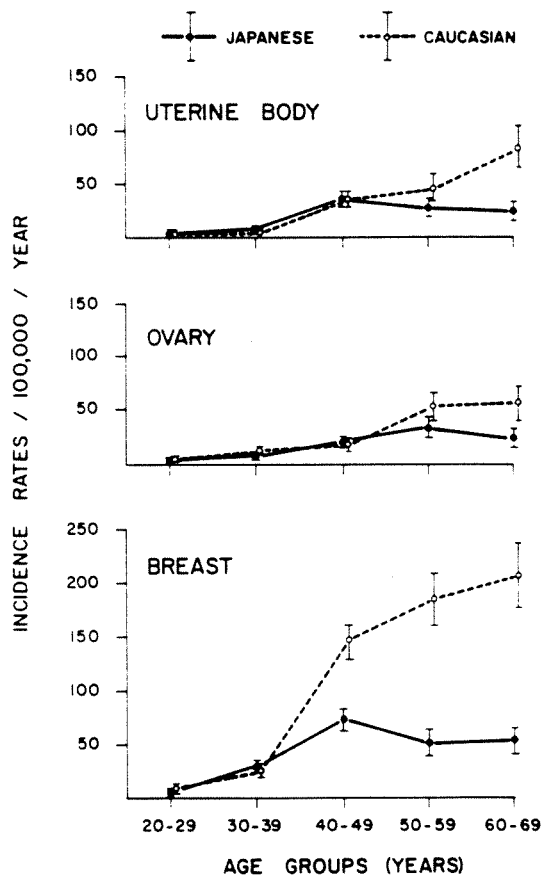
Increased rates of liver cancer among Asian groups are by no means as high as the rates reported from certain sections of Africa, where liver cancer accounts for as many as 50% of cancers coming to autopsy.<sup>28</sup> Africans are most commonly affected between the ages of 25 and 45, whereas only 5 of 120 cases recorded by the Hawaii Tumor Registry occurred in persons under the age of 40.<sup>5</sup> A large number of substances have been found to be carcinogenic for the liver in animals; different mechanisms may account for human hepatic cancer in separate parts of the world. The relationship of the hepatitis-associated antigen (Australia antigen, hepatitis type B antigen) with the induction of cirrhosis and hepatoma might be a worthwhile area of investigation.

#### *BREAST*

Large international differences in the incidence of breast cancer among women have long been known. While the hypo-

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FIGURE 1 — Incidence rates, Japanese women and Caucasian by age groups.



thetic protective effect of prolonged lactation has never been clearly substantiated, recent evidence indicates early child-bearing is associated with a lower risk of breast cancer in later life. However, this accounts for only a small fraction of the international rate differences.<sup>29</sup>

Doll reported incidence rates in Japan and Singapore at less than one-quarter the rate in Connecticut. The Hawaii Tumor Registry data suggest that Filipino women have a rate akin to that in the Orient; that Japanese women have an intermediate rate, and that the incidence among the Chinese is approaching that of whites. The Japanese and white rates appear similar below the age of 40, but differ widely in the older age groups (Figure 1). Japanese women in Hawaii have tended to have smaller cancers, with fewer metastases than have Mainland white women, and 5-year survival has been somewhat better.<sup>30</sup> Possibly this better experience could be explained by either earlier diagnosis in the smaller Japanese breast, or slower growth as a result of genetically related factor, resulting in a more effective host response.

Cole and MacMahon have hypothesized that estriol protects against breast cancer, and they have been coordinating an international study of urinary estrogen fractions in young women as an indirect test of this hypothesis.<sup>31</sup> Hawaii has participated in this study under the local direction of Dr Louis Dickinson. Kumaoka and Bulbrook have found different patterns of progesterone and androgen metabolism in Japanese

and white populations.<sup>32</sup> Further studies of hormonal fractions in breast cancer are being planned by the Japan-Hawaii Cancer Study in conjunction with Dr Greenwood.

#### UTERINE CORPUS

Carcinoma of the endometrium accounts for most cancer of the uterine corpus in this country, but in Japan choriocarcinoma comprises 40% of cases.<sup>6</sup> Thus, the substantial increase in cancer at this site in the U.S. reflects an even greater relative excess of endometrial carcinoma. Because of classification problems, quantitation of rate differences is difficult, but a conservative guess puts the Japanese rate for endometrial carcinoma at less than a third of the U.S. rate. Japanese women in Hawaii appear to have rates comparable to whites below the age of 50, but the older Japanese are relatively protected. Age-adjusted rates for Hawaiians, Filipinos, and Chinese were reported a little higher than for whites, but the numbers are small and the age-specific rates erratic. Cancer of the uterine corpus is rare among Chinese in Singapore.

Epidemiology of the carcinoma of the endometrium parallels that for breast cancer.<sup>6</sup> Both are more common in nulliparous patients, and in international comparisons, rates for the 2 sites are highly correlated.<sup>2,3</sup> Haenszel has pointed out that in migrant studies, rates for breast cancer adjust more slowly to a Westernized environment than do rates for uterine corpus. Data on Japanese women in Hawaii suggest it takes 10 years longer for breast rates to equalize than for corpus rates (Fig. 1). This could be due to a longer delay in the adoption of those aspects of Western culture which are responsible for the high rates of breast cancer than for those aspects associated with endometrial carcinomas whatever they might be; or it could simply reflect different induction periods between exposure to a common carcinogen and the development of the 2 diseases.

#### OVARY

Hawaii Tumor Registry reported 144 cases of ovarian carcinoma between 1960 and 1964. Age-adjusted mortality rates indicate a gradient of about 1 to 4 going from Japan to the U.S. Mainland. A large gradient from both Japan and Singapore to the U.S. is indicated by the international incidence comparisons.

Epidemiologically, ovarian cancer is similar to breast cancer and endometrial carcinoma in that it is more common in single women and tends to be a disease of more developed countries.<sup>2,33</sup> Ovarian cancer tends to rise in a migrant population in concordance with cancer of the uterine body;<sup>6</sup> it does not show the delayed rise associated with breast cancer (Fig. 1).

#### UTERINE CERVIX

Incidence gradients for cancer of the cervix between the U.S. and Japan are somewhat confused by 2 problems. First, *in situ* carcinoma of the cervix is included in the data from the Miyagi and Okayama cancer registries. Since the number of *in situ* cancers will depend on the extent of Pap smears, measures limited to invasive carcinoma are probably more comparable. However, the number of invasive carcinomas is reduced by an effective cervical cytology screening program,<sup>34</sup> so there is no available method to get truly comparable data. Second, both morbidity and mortality data from Japan include a sub-

stantial number of uterine cancers of unspecified site. There is reason to believe that these are mostly cervical cancers.<sup>6</sup>

Haenszel and Kurihara estimated that age-adjusted mortality for American-Japanese women for cervical cancer was about one-half the rate in Japan and slightly, but not significantly, lower than the rate for U.S. whites.<sup>6</sup> Data from Hawaii Tumor Registry show age-adjusted rates for invasive cases which are quite similar for Japanese, Caucasians, Chinese, and Filipinos, with a somewhat higher rate for part-Hawaiian. There is a suggestion that Japanese women over 60 have more cervical cancer than those of European ancestry of like age. Cancer registry data from Singapore show rates for cervical cancer which are similar to those found in Japan. In general, the reported gradients across the Pacific or among ethnic groups in Hawaii do not exceed twofold. Investigations of genital herpes virus or other possible etiologies of cervical cancer remain to be carried out.

#### URINARY BLADDER

Carcinoma of the urinary bladder is about 4 times as common in Connecticut as in Japan. The Singapore rate is also very low. Hawaii Tumor Registry reported about half as much bladder cancer among Japanese as in whites, suggesting that the Japanese-Americans have rising rates. Chinese and Hawaiian men have rates similar to Japanese, while Filipino men seem particularly protected. In all races except Filipinos, the disease is more than twice as common in men as in women; in Japanese, this discrepancy is 5 times.

Smokers risk developing bladder cancer more than twice as often as non-smokers;<sup>35</sup> this may explain some international and sex differences. Rising mortality from bladder cancer in Japan<sup>36</sup> would be consistent with some effect from tobacco, though it could also reflect changing certification practices. In the U.S., there has been no rise in bladder cancer concomitant with rise in lung cancer.<sup>37</sup>

Certain aromatic amines are carcinogenic for urinary bladder and have been associated with an excess of cases in dye industry workers. The average time lapse between exposure and tumor is 16 years,<sup>38</sup> giving some clue to the delay that may explain international cancer differences. No evidence available suggests that exposure to industrial carcinogens explains the international differences in this cancer.

#### THYROID

Data from Hawaii Tumor Registry (1960-1964) suggested carcinoma of the thyroid is more common in Hawaii than anywhere else in the world.<sup>2</sup> This high rate was confirmed by Haber and Lipkovic in a review of cases from 5 major Oahu hospitals during 1962-1966.<sup>39</sup> Presumably there was considerable overlap of cases for 1962-1964. The number of cases in any group is small after classification by sex and race; women are affected more than twice as often as men. Age-adjusted rates among men do not vary greatly among the ethnic groups in Hawaii, except Japanese men seem relatively protected. Among women, whites and Japanese have lowest rates, Hawaiians and Filipinos come next, and Chinese are highest. The gradient between Japanese and Chinese is more than threefold.

Rates for thyroid cancer reported from Japan do not differ greatly from those in Connecticut. However, Alameda County

reported a rate twice as high as either of them, so that there is some variability within the U.S. Mainland. Chinese women appear to have 20-fold more thyroid cancer in Hawaii than in Singapore, a phenomenon for which no ready explanation is available. Several benign diseases of the thyroid are also particularly frequent among Chinese women in Hawaii.<sup>40</sup>

Fukunaga and Lockett have shown that careful study of the thyroid gland from routine autopsies among Japanese reveals a high prevalence rate of occult papillary carcinoma in Hawaii (24%)<sup>41</sup> and similar findings have been reported from Japan (18%).<sup>42</sup> These studies also indicate that occult tumors do not increase in frequency with age; some of these lesions appear to be partially necrotic, suggesting that new tumors may not evolve into disseminated tumors but may be contained by some host factor. These prevalences of occult thyroid carcinomas among Japanese are many times higher than those found by comparable studies among whites.<sup>43</sup>

Only 2 of the 158 cases in the review by Haber and Lipkovic were incidental findings at autopsy. Of the 159 cases in Hawaii Tumor Registry, 149 had received treatment. In a survey of general population in Japan, persons whose thyroids were abnormal to palpation were referred for work-up and possible surgery; a prevalence rate of papillary carcinoma of at least 1 per 1000 was demonstrated from the surgical pathology.<sup>44</sup> Therefore, though Japanese have a high prevalence rate of occult papillary carcinoma, it apparently seldom causes the affected individuals any inconvenience. By contrast, in whites the prevalence of occult disease is less, but more often becomes clinically manifest.

In races where the prevalence of occult thyroid carcinoma is high, the frequency of surgery might have a large impact on the reported incidence of clinical disease. An evaluation of the frequency of occult thyroid carcinoma at autopsy among Chinese, part-Hawaiians, and Filipinos would lead to understanding the high rates reported for those groups. The influence of dietary iodine upon the genesis and progression of those tumors needs to be investigated.

#### SKIN

As skin cancer is not uniformly reported among cancer registries, reliable international rate comparisons are few in number. Since most cases are non-lethal, mortality comparisons have limited usefulness. The more invasive cancers are sufficiently rare to be difficult to study in Hawaii. Only 13 cases were recorded by Hawaii Tumor Registry from 1960-1964.<sup>5</sup>

The effects of sun exposure and race on the incidence of squamous cell and basal cell carcinoma have been the subject of considerable epidemiologic investigation. Both these entities are most common in areas of low latitude and in persons of European extraction. Allison and Wong reported a study of skin cancer which was carried out in Honolulu in 1955 and 1956.<sup>45</sup> They found that among Caucasians rates were higher in Hawaii than on the Mainland. In Table 4, their data are compared to more detailed breakdowns from 4 northern and 4 southern U.S. cities reviewed by Haenszel.<sup>46</sup> A clear excess of cases of both basal cell and squamous cell carcinoma is seen as one progresses from north to south.

Allison and Wong reported an overall skin cancer rate of 138 per 100,000 among whites and only 3.1 per 100,000 among non-whites in Honolulu. They found no significant dif-

(Continued) ►

TABLE 4: Incidence of basal cell and squamous cell carcinoma among Caucasians in Honolulu and the U.S. Mainland

	Four Northern Mainland Cities* (1947)		Four Southern Mainland Cities* (1947)		Honolulu** (1955-56) Both Sexes
	Men	Women	Men	Women	
Basal cell	15.7†	12.4†	61.2†	40.6†	67.5
Squamous cell	8.9	5.3	32.3	14.3	62.0

\*From Haenszel W. Variations in skin cancer incidence within the United States in U.S. *National Cancer Insti. Monograph No. 10*, 1963, pp 225-243. The figures are age-adjusted to the 1950 US population.

\*\*Crude rates from Allison SD and Wong KL. Skin cancer: some ethnic differences. *Arch Derm* 76:737-739, 1957.

†Includes baso-squamous cell carcinomas.

ference among the various non-white races, though there was a tendency for those racial groups coming from tropical areas to have lower rates than did the more northerly groups. Thus, the crude combined rate ( $\pm 1$  standard deviation) for Hawaiians, part-Hawaiians, and Filipinos was  $1.5 \pm 0.9$  per 100,000, while the overall rate for Japanese, Koreans, and Chinese was  $4.3 \pm 1.1$  per 100,000.

Questions to be answered include those of timing and duration of exposure, and the length of latent period between exposure and development of squamous cell and basal cell carcinomas. The history of immigration of whites to Hawaii provides a spectrum of age and of duration of residence in the tropics which might be fertile ground in which to seek some of these answers. The Islands would also be a favorable location for controlled trials of para-aminobenzoic acid or other agents intended to protect the skin from ultra-violet radiation.

#### OTHER CANCERS

With the exception of nasopharyngeal carcinoma and skin cancers (which are mostly not reported), more than 100 cases of each of the tumors discussed above were enumerated by Hawaii Tumor Registry from 1960 to 1964.<sup>5</sup>

A variety of other cancers have rate gradients across the Pacific and are potentially of interest for study in Hawaii, though they may not be quite as common. Prominent among these are the specific leukemias, Hodgkin's disease, choriocarcinoma, renal cell carcinoma, and cancers of the pancreas, esophagus, and gall bladder and extra-hepatic ducts. Investigation of these problems might require decades to accumulate sufficient cases.

#### Discussion

Important environmental determinants of common cancers must account for some of the extensive rate differentials among the various countries around the Pacific. The combination of ethnic and cultural diversity in the presence of sophisticated medical diagnosis and care makes Hawaii a favorable location to identify these determinants.

A number of difficult problems arise in trying to identify specific cultural or dietary practices which are associated with chronic diseases. Most prominent among these is the untangling of a single identifiable cause from the mass of variables which change in the process of acculturation. Many of these variables tend to change simultaneously in a given ethnic community, and even in a given individual. An individual who grows up in Hawaii and goes to college will differ from his

immigrant parents in many ways, including diet, social and cultural practices, and type of job. These changes may induce physiologic and anatomic changes, including greater stature, obesity, and higher serum cholesterol. If such a person gets a "Western" type of disease, ascertaining which environmental or physiologic changes are responsible may be difficult.

The first approach to the problem lies in characterizing a number of cases, comparing them to appropriate controls, and subjecting the results to univariate and multivariate statistical analyses. A second approach would be to add a dimension to the variability by looking at more than one racial group. Up to the present time, comparisons between Japanese and whites have attracted the most attention because of population size, and because there is a fair amount of reliable health data available from Japan to which comparisons can be made. Studies of the Filipino community would be of advantage, as has been suggested by Bennett.<sup>47</sup> Available information suggests that Filipinos are less Westernized and have lower rates of cardiovascular disease and cancer than do Japanese. They now constitute a substantial group in Hawaii. Their pattern of acculturation to life here is likely to differ somewhat from the Japanese pattern and might provide added insight into environmental determinants of certain cancers and other chronic diseases. The administrative feasibility of cohort and case-control studies in the Filipino community needs to be investigated.

A second major problem that will be encountered in studying cancer in Hawaii is the time lag between environmental influences which may produce disease and the actual appearance of the disease. Studies of radiation and of industrial carcinogens indicate that this delay is often measured in decades. Interracial differences in disease rates now may have been partly determined by cultural differences that existed before World War II. To quantitate past diets, habits, and sociocultural factors on an individual basis is difficult. To obtain data now on individuals to be followed for disease which may not occur for 20 or 30 years is expensive; furthermore, its practicality would be strained because of long-term follow-up problems and because of the short half-life of investigators.

On the other hand, some insight might be gained into the comparative extent of these time lags for different cancers by looking at age-specific secular trends among the 5 major ethnic groupings in Hawaii, and relating them to what is known of the social history of these populations. Such an analysis should be possible using death certificate information. If the methodologic problems were not too severe, the information



gained would provide a useful background for future demographic investigations in the Islands and elsewhere.

Another way of dealing with the time-lag problem is to identify "marker lesions," which carry an increased risk of the later development of a particular cancer but which appear at an earlier age. Some possible examples might be cirrhosis in liver cancer, or polyposis in colon cancer. Possible risk factors should be evaluated both in patients with benign lesions and in cancer cases. That such "marker lesions" are often more common than the actual cancers is an added advantage.

The problems of disentangling multiple variables and of allowing for time lags between casual factors and the appearance of disease are not, of course, peculiar to Hawaii. They are obstacles to any epidemiologic approach to chronic disease. That they can be overcome is demonstrated by past successes in linking radiation and cigarette smoking to cancer. Basic and clinical research may eventually lead to more effective ways of preventing and treating cancer. But at the present time, international differences in incidence of various cancers are among the best indicators that a reduction in cancer morbidity and mortality should be possible. Few settings in the world are more favorable to the investigation of these differences than Hawaii.

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NOTE: In this article, the terms Caucasian, white and European are interchangeable.

#### REFERENCES

- Saunders JP: Role of the National Cancer Institute in the development of cancer centers I. National Cancer Institute Center Programs. *Cancer* 29:882-887, 1972.
- Doll R, Payne P. and Waterhouse J: *Cancer Incidence in Five Continents*. A technical report. Distributed for the International Union Against Cancer by Springer-Verlag New York, 1966.
- Doll R, Muir C, and Waterhouse J: *Cancer Incidence in Five Continents, Volume II*. Distributed for the International Union Against Cancer by Springer-Verlag: New York, 1970.
- Segi M, Kurihara M, and Matsuyama T: *Cancer Mortality for Selected Sites in 24 Countries, No. 5 (1964-1965)*. Department of Public Health, Tohoku University School of Medicine: Sendai, Japan, 1969.
- Hawaii Tumor Registry: Cancer in Hawaii, Morbidity and Treatment: Five Years 1960-1964. *Hawaii Med J* 27:409-456, 1968.
- Haenszel W, Kurihara M: Studies of Japanese Migrants. I. Mortality from cancer and other diseases among Japanese in the United States. *J Nat Cancer Inst* 40:43-68, 1968.
- Zippin C, Tekawa IS, Brugg KV, Watson DA, Linden G: Studies on heredity and environment in cancer of the nasopharynx. *J Nat Cancer Inst* 29:483-490, 1962.
- Pang LQ: Cancer of the nasopharynx. *Hawaii Med J* 19: 529-532, 1960.
- Quisenberry WB, Reimann-Jasinski D: Ethnic differences in nasopharyngeal cancer in Hawaii. *International Union Against Cancer, Monograph Series* 1:77-81, 1967.
- Worth RM, Valentine R: Nasopharyngeal carcinoma in New South Wales, Australia. *International Union Against Cancer, Monograph Series* 1:73-76, 197.
- Shanmugaratnam K, Tye CY: A study of nasopharyngeal cancer among Singapore Chinese with special reference to migrant status and specific community (dialect group). *J Chron Dis* 23:433-441, 1970.
- Goldman JM, Goodman ML, Miller D: Antibody to EBV in American patients with carcinoma of the nasopharynx. *JAMA* 216:1618-1622, 1971.
- Quisenberry WB: Stomach cancer among Japanese in Hawaii and the United States Mainland. *Acta Un Int Cancer* 17:858-866, 1961.
- Lauren P: The two histological main types of gastric carcinoma: diffuse and so-called intestinal-type carcinoma. *Acta Path et Microbiol Scandinav* 64:31-49, 1965.
- Stemmermann GN, unpublished data.
- Haenszel W, Kurihara M, Segi M, Lee RKC: Stomach cancer among Japanese in Hawaii. *J Nat Cancer Inst* 49:969-987, 1972.
- Karube K: Study of latent carcinoma of the prostate in Japanese based on necropsy material. *Tohoku J Exper Med* 74: 265-285, 1961.
- Akazaki K, Stemmermann GN: A comparative study of latent carcinoma of the prostate among Japanese in Japan and Hawaii. *J Nat Cancer Inst*, in press.
- Winkelstein W Jr, Kanlor S: Prostatic cancer: relationship to suspended particulate air pollution. *Amer J Pub Health* 59: 1134-1138, 1969.
- Kipling MD, Waterhouse JAH: Cadmium and prostatic cancer letter. *Lancet* 1:730-732, 1967.
- Stemmermann GN: Cancer of the colon and rectum discovered at autopsy in Hawaiian Japanese. *Cancer* 19:1567-1572, 1966.
- Berg JW, Downing A, and Lukes RJ: The prevalence of undiagnosed cancer of the large bowel found at autopsy in different races. *Cancer* 25:1076-1080, 1970.
- Stemmermann GN, Yatani R: Diverticulosis and polyps of the large intestine: a necropsy study of Hawaii Japanese. *Cancer*, in press.
- Barrera B, Carlas BD Jr, Gyegkeng J: An analysis of malignant tumors among Filipinos seen in the UP-PGH Medical Center during the 10 year period (1947-1956). *Philipp J Cancer* 2:189-215, 1958.
- Wilbur DL, Wood DA, Willet FM: Primary carcinoma of the liver. *Ann Intern Med* 20:453-485, 1944.
- Shanmugaratnam K, Tye CY: Liver cancer differentials in immigrant and local born Chinese in Singapore. *J Chron D-Dis* 23:443-448, 1970.
- Stemmermann GN: Patterns of disease among Japanese living in Hawaii. *Arch Environ Health* 20:266-273, 1970.
- Alpert ME, Hutt MSR, Davidson CS: Primum hepatoma in Uganda. *Amer J Med* 46:794-802, 1969.
- MacMahon B, Cole P: Endocrinology and epidemiology of breast cancer. *Cancer* 24:1146-1150, 1969.
- Stemmermann GN, Lipkovic P: Carcinoma of the breast in Japanese women living in Hawaii. *GANN* 60:181-186, 1969.
- Cole P, MacMahon B: Oestrogen fractions during early reproductive life in the aetiology of breast cancer. *Lancet* 1:604-606, 1969.
- Kumaoka S, Bulbrook RD: Personal communication.
- Wynder EL: Epidemiology of cancer of the ovary. *Cancer* 352:-370, 1969.
- Dickinson L, Mussey ME, Soule EH, et al: Evaluation of the effectiveness of cytologic screening for cervical cancer I. Incidence and mortality trends in relation to screening. *Mayo Clin Proc* 47:534-544, 1972.
- Cole P, Monson RR, Haning H, Friedell MD: Smoking and cancer of the lower urinary tract. *New Engl J Med* 284:129-134, 1971.
- Segi M, Kurihara M: *Cancer Mortality for Selected Sites in 24 Countries No. 4 (1962-1963)*. Department of Public Health, Tohoku University School of Medicine, Sendai, Japan, 1966.
- Burbank F: *Patterns in Cancer Mortality in the United States: 1950-1967*. National Cancer Institute Monograph No. 33. U.S. Government Printing Office. Washington, DC. 1971.
- Ferber KH: Industrial bladder cancer: a progress report and some unanswered questions. *J Nat Cancer Inst* 43:245-248, 1969.
- Haber MH, Lipkovic P: Thyroid cancer in Hawaii. *Cancer* 25:1224-1227, 1970.
- Gilbert F: Personal communication.
- Fukunaga FH, Lockett LJ: Thyroid carcinoma in the Japanese in Hawaii. *Arch Path* 92:6-13, 1971.
- Sampson RJ, Key CR, Buncher CR, Iijima S: Thyroid carcinoma in Hiroshima and Nagasaki. *JAMA* 209:65-70, 1979.
- Farooki MA: Epidemiology and pathology of cancer of the thyroid I. Material, methods, and results. *Int Surg* 51:232-243, 1969.
- Maruchi N, Furihata R, Makiuchi M: Population surveys on the prevalence of thyroid cancer in a non-endemic region, Nagano Japan. *Int J Cancer* 7:575-583, 1971.
- Allison SD, Wong KL: Skin cancer. Some ethnic differences. *Arch Derm* 76:737-739-1957.
- Haenszel W: Variations in skin cancer incidence within the United States. *National Cancer Institute Monograph No. 10*, 1963, 225-243.
- Bennett B: Personal communication.