REVIEW

What Do Cancer Registry and Household Expenditure Data in Japan Tell Us About Variation in Tumour Burden ?

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Abstract

Data from the total of six Japanese Cancer Registries presently reporting to Cancer Incidence in Five Continents demonstrate marked variation in relative prevalence of cancers at particular sites, despite the genetic homogeneity of the Japanese population. Thus either major differences in registry procedures or local environment must be playing an important role and since the variation is clearly changing with time, the former must be considered likely. Over the last 25 year period, incidence rates for the esophagus have been generally increasing in Japan, except in Miyagi where they have been persistently high. Stomach cancer rates are on the decrease, although the trend is not so clear in Yamagata and Hiroshima, while colon and rectal cancers have both demonstrated consistent increment throughout the period surveyed, with a remarkable correlation between the two sites evident on cross-registry comparisons. Continued increases have also been apparent in lung, kidney, urinary bladder and prostate cancers in males and in breast, endometrium and thyroid neoplasms in females. Cervical cancer, in contrast, is decreasing, although a plateau may now have been reached in Miyagi. In the hepatopancreatic axis, patterns have generally showed elevation followed by a recent reduction, although without correlations among liver, gallbladder and pancreas rates at the cross-registry level. Common lifestyle factors may to some extent underly the increases seen in colon, breast, urinary bladder and thyroid incidence rates, given the significant relations apparent for these in the latest data across registries. Whether analysis of variation in dietary intake and exposure to other risk factors, for example using data for household expenditure, may provide clues to explaining the variation apparent across Japan is a question warranting further consideration. If so an expanded role for the cancer registry could well be envisaged.

Introduction

The basis for all cancer preventive efforts must be an accurate awareness of the depth and nature of the problem and for this we need effective population-based cancer registration. In Japan there are now six registries reporting to the International Agency for Cancer Research publication Cancer Incidence in Five Continents and in the present review we concentrate attention on change in the incidences of major cancers documented in the last five volumes IV-VIII (Waterhouse et al., 1982; Muir et al., 1987; Parkin et al., 1992;1997;2002). While questions of completeness of registration have been raised (Ajiki et al., 1998), this does not appear to vary between registries so that a comparative approach appears warranted, without forgetting possible variation in precise diagnostic criteria applied. Hitherto there have only been limited comparisons of available data for different regions of Japan in the English language and variation in trends in particular body sites (Tsukuma et al., 2004).

It is clear from migration studies that the environment exerts a greater impact than the genetic background regarding neoplastic development. Among the five most common cancers, the migrant effect has been strongest for colon and stomach cancers, with prostate and breast cancers affected to a lesser degree, and lung cancer risk differing little between Japanese in Japan and Hawaii (Maskarinec and Noh, 2004) The large variation in time for migrants to adopt the host population's cancer risk, furthermore, suggests that risk factors have organ-specific effects, or operate at different times in life. In Japan itself there has also been major alteration in lifestyle in the last few decades. and even over the five years food intake was found to be considerably changed in the Japan Collaborative Cohort Study for Evaluation of Cancer Risk (JACC Study) (Suzuki et al., 2005).

Across the country there is a remarkable uniformity of incidence of insulin-dependent diabetes mellitus (Anonymous, 1993), indicative of genetic homogeneity. This contrasts with geographical variation in lifestyle related

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diseases like cancer, where the importance of societal characteristics is evidenced by spatial disease clusters (Fukuda et al., 2005). The question thus arises of what a comparison of actual incidence rates over time in the various cancer registries can tell us, viewed in the light of regional data for risk factors, to the limited extent that they exist at present. The data presented here are all age-standardised rates adjusted for the world population.

Organs

Oesophagus

As shown in Figure 1a, rates for oesphageal cancer have demonstrated a consistent recent increase, with the exception of Miyagi having clearly elevated values as compared to the other registries. This can not be explained by differentials among Japanese registries for squamous cell carcinomas (SCCs) and adenocarcinomas (ACs), notable in the Western world, since over 90% of oesphageal lesions in Japan appear to be of SCC type, independent of the registry (see Table 1). Whether the differences in incidence data can be explained by regional variation over time in the established risk factors, like thermal effects of hot tea, alcohol drinking, smoking and low consumption of green-yellow vegetables (Kinjo et al., 1998), remains to be clarified.

Stomach

Stomach cancer remains number one in incidence in males throughout Japan, and is number one or two (after breast) in females. Rates are decreasing rapidly in some registries but this does not appear to extend to the same extent to Hiroshima or Yamagata (see Figure 1b). It has been reported that the marked decline in gastric cancer incidence observed in the young population is due to a drop in the prevalence of Helicobacter pylori infection (Kobayashi et al., 2004). However, variation in gastric cancer mortality in Japan may be partly accounted for by regional differences in consumption of rice, bean paste soup, pickled vegetables, green vegetables, and yellow vegetables, along with the included sodium, carotene, and possibly ascorbic acid (Tsubono et al., 1997a;1997b). Plasma levels of beta-carotene and alpha-tocopherol, and possibly alpha-carotene, lycopene, and ascorbic acid are also known to be important (Tsubono et al., 1997).

Colorectum

In both the colon and the rectum there has been a

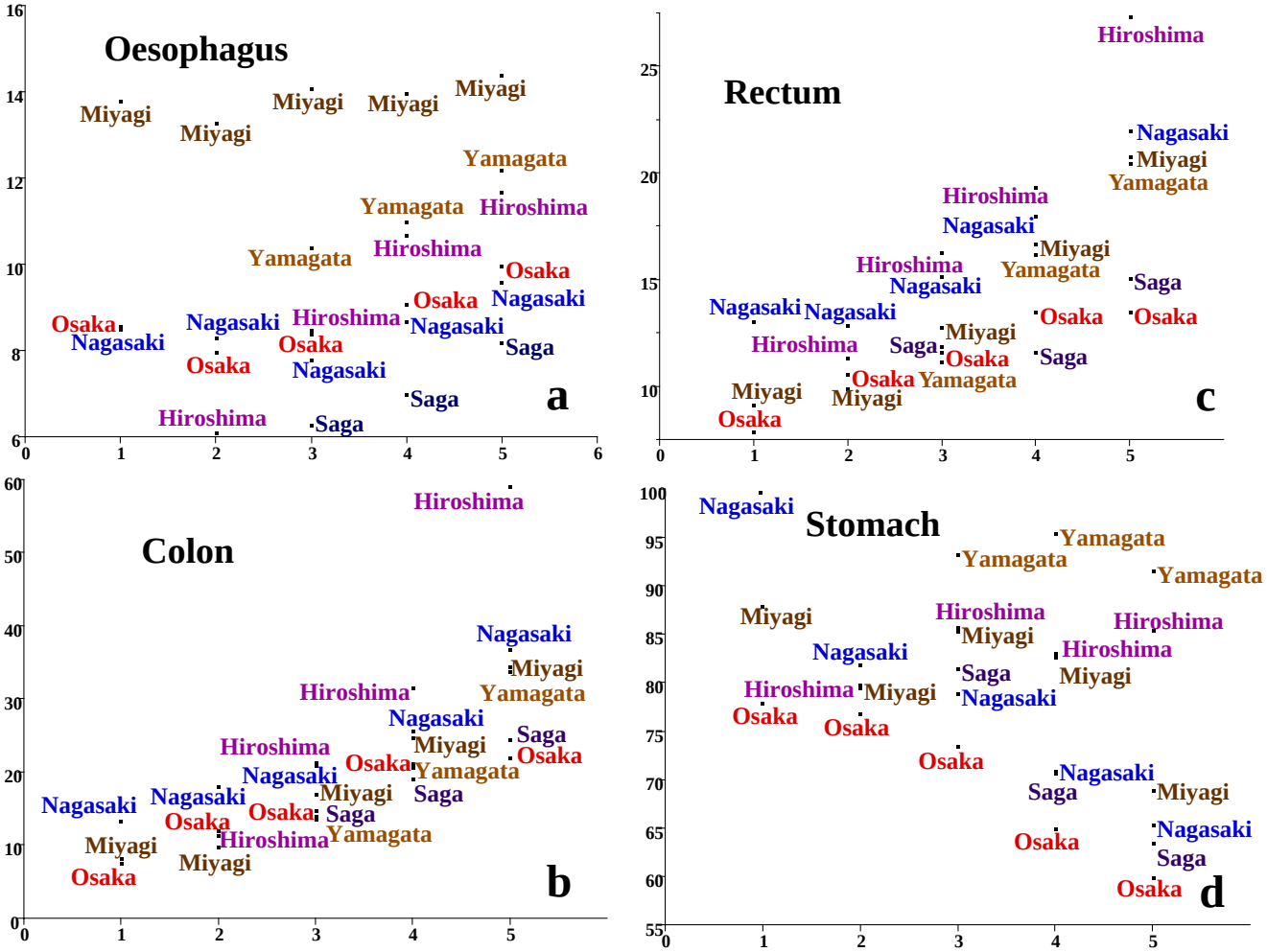

Figure 1. Change in Incidence Rates for Alimentary Tract Cancers Over Time (Data from Cancer Incidence in Five Continents IV-VIII, 1982-2002)

Table 1. Ratios for Histopathological Diagnoses (% Data) in Males

Registry	Oesophagus			Lung			Kidney			Urinary Bladder		
	SCC	AC	Ratio	SCC	AC	Ratio	Renal	TCC	Ratio	TCC	SCC	Ratio
Hiroshima	95.3	2.7	35.3:1	37.2	41.4	0.9:1	53.9	41.1	1.3:1	95.1	1.7	55.9:1
Miyagi	92.2	3.2	28.8:1	38.5	29.2	1.3:1	61.9	28.1	2.2:1	92.3	2.9	31.8:1
Nagasaki	92.7	3.3	28.1:1	34.3	38.7	0.9:1	63.6	32.4	2.0:1	93.7	3.0	31.2:1
Osaka	90.3	3.8	23.8:1	34.3	33.7	1.0:1	60.3	27.4	2.2:1	90.3	1.8	50.2:1

Data from Cancer Incidence in Five Continents, 1997

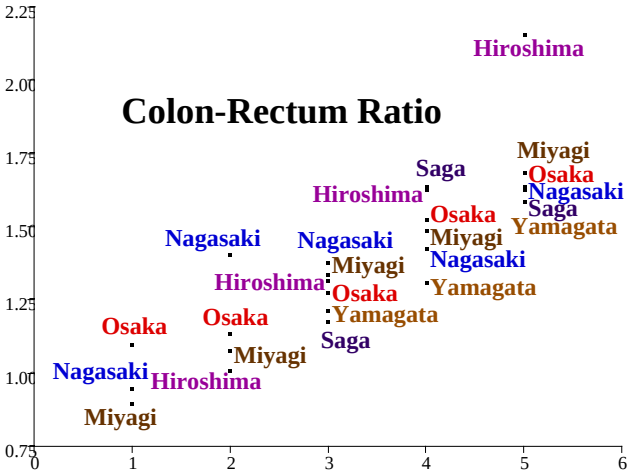

Figure 2. Change in Colon Rectum Cancer Ratios Over Time (Data from Cancer Incidence in Five Continents IV-VIII, 1982-2002)

continuous increase in incidence rates, with the highest burden in Hiroshima, Nagasaki and Miyagi (see Figure 1c and 1d). A shift in the subsite distribution has also been observed in Japan over time, with a decreasing proportion of rectal cancers (Takada et al., 2002) (see Figure 2). Colon cancer appears more closely associated than rectal cancer with environmental factors leading to obesity, and this association is more pronounced in men than in women (Nakaji et al., 2003). Rectal lesions in contrast appear linked to alcohol consumption and tobacco smoking (World Cancer Research Fund, 1997). Both alcohol consumption and smoking have been found to be clearly associated with colorectal cancer in men (Otani et al., 2003).

Regarding possible explanations for the inter-registry data, dietary variation with the region may offer clues. Clear effects of diet have been reported for colorectal cancer and particularly fat intake (Tokudome et al., 2000) and a recent ecological study showed positively associations with fat and oil intake, of both plant and animal types (Yang et al., 2002). It has been argued that drastic reduction in cereals is one of the most important dietary factor determining the risk of colon cancer in Japan (Kono and Anh, 2000) along with temporal change in fat and meat intake (Kono, 2004). Kuriki et al (2004) have shown that colon cancer among Japanese might be closely associated with the increment in type II diabetes, reflecting the westernization of food intake.

Liver

Liver cancer rates, highest in Osaka and lowest in Yamagata, now appear to be on the decrease, after a rapid

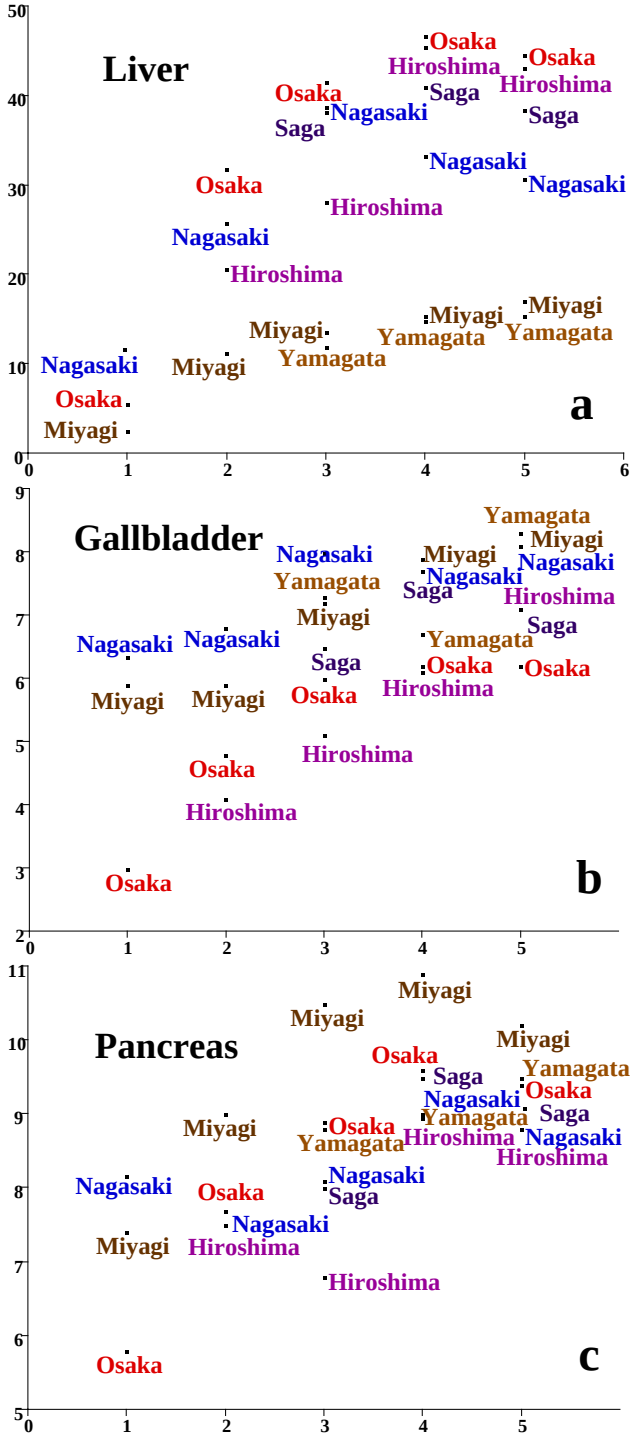

Figure 3. Change in Incidence Rates for Hepatopancreatic Axis Cancers Over Time (Data from Cancer Incidence in Five Continents IV-VIII, 1982-2002)

rise in the 1970s and 1980s (see Figure 3a). Time and registry-dependent changes in hepatocellular carcinoma development presumably reflect the geographic pattern of HCV infection as well as that of HBV, as earlier noted for residents of Osaka (Tanaka et al., 1994). Whether other factors, like consumption of alcohol of different types might also be playing a role remains to be determined. There does appear to be some variation in the relative incidences of cholangiocellular carcinoma of the liver, which also needs to be explained

Gallbladder

Gallbladder cancer appears to be increasing, exept in the Saga and Nagasaki registries, with the highest incidences in Yamagata (see Figure 3b). Major risk factors for gall bladder cancer are gallstones, obesity, a poorly balanced diet and low fresh fruit intake (Zatonski et al., 1997). In a prospective study in Japan, constipation and a history of hepatic disease were found to elevate the risk of gallbladder cancer death (Yagyu et al., 2004). Another factor may be carcinogen generation under inflammatory conditions, and in this context it should be noted that high risk areas in Japan, as well as Chile, have high rates of mutagenicity for bile (Mano et al., 1996).

Pancreas

Incidence data for pancreatic cancer show some similarity to those for liver, with recent decrease in all registries (see Figure 3c). However, in this case Miyagi has the highest prevalence. Conditions such as diabetes, chronic pancreatitis, as well as nutrition and lifestyle factors, like smoking are known to play important roles in the etiology. While the variation among registries in Japan was major for earlier periods, this now appears no longer to be the case.

Larynx

After a rise in the 1980s, laryngeal cancer appears have started to decrease in almost all registreis in Japan (see Figure 4a). Nagasaki and Hioshima have historically had the highest incidences and these have shown marked drops. What might underly the varaition across registreis is unclear, smoking and alcohol being the major rsik factors, along with exposure to dusts and enironmental pollutants.

Lung

Across all of the registries covered in the present paper, a steady increase in male lung cancer has been apparent over the last two decades (see Figure 4a). Highest rates in both males and females have been reported in Osaka and Nagasaki. An earlier comparative epidemiologic study on geographic distributions of cancers showing lung cancer to highly correlate with industrialization-related factors such as localization of manufacturing industries, automobile traffic and air pollution,is clearly interesting in this respect (Murata et al., 1988).

In Japan, where there has also been a shift to ACs (Sobue et al., 1999, Yoshimi et al., 2003), application of a Bayesian age-period-cohort (APC) model to the National Vital Statistics data from 1952 to 2001, suggesting that the number of deaths due to lung cancer will double for men and women during the next 3 decades due to the aging of the baby-boomer generation (Kaneko et al., 2003). It has been argued that male current smokers in Japan are at lower risk of lung cancer compared with those in the US (Marugame et al.,

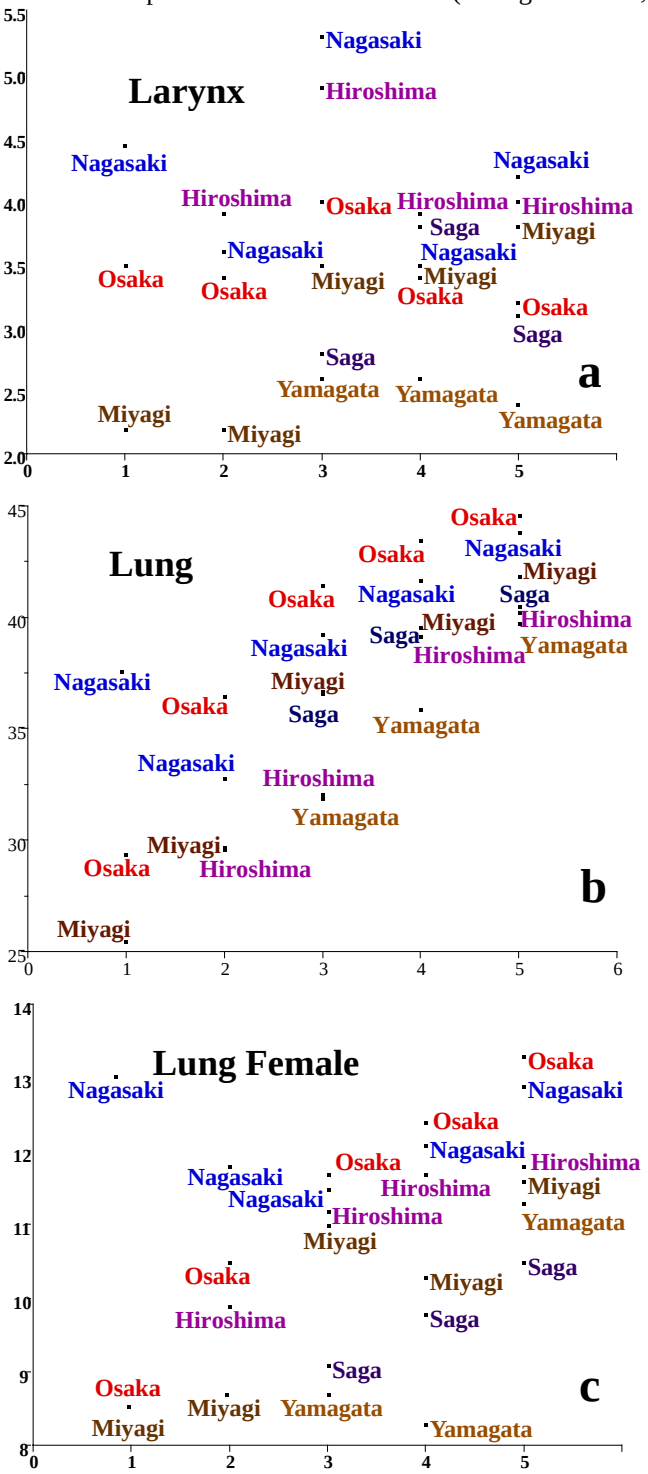

Figure 4. Change in Incidence Rates for Laryngeal and Lung Cancers Over Time (Data from Cancer Incidence in Five Continents IV-VIII, 1982-2002)

2004).The shift in histology from SCC to AC might be due to changes in cigarette type. However, among subjects aged 65 years or more, no differences in histological type appeared related to type of cigarette smoked, implying that other factors are also associated with increases in adenocarcinoma, at least among older Japanese (Marugame et al., 2004).

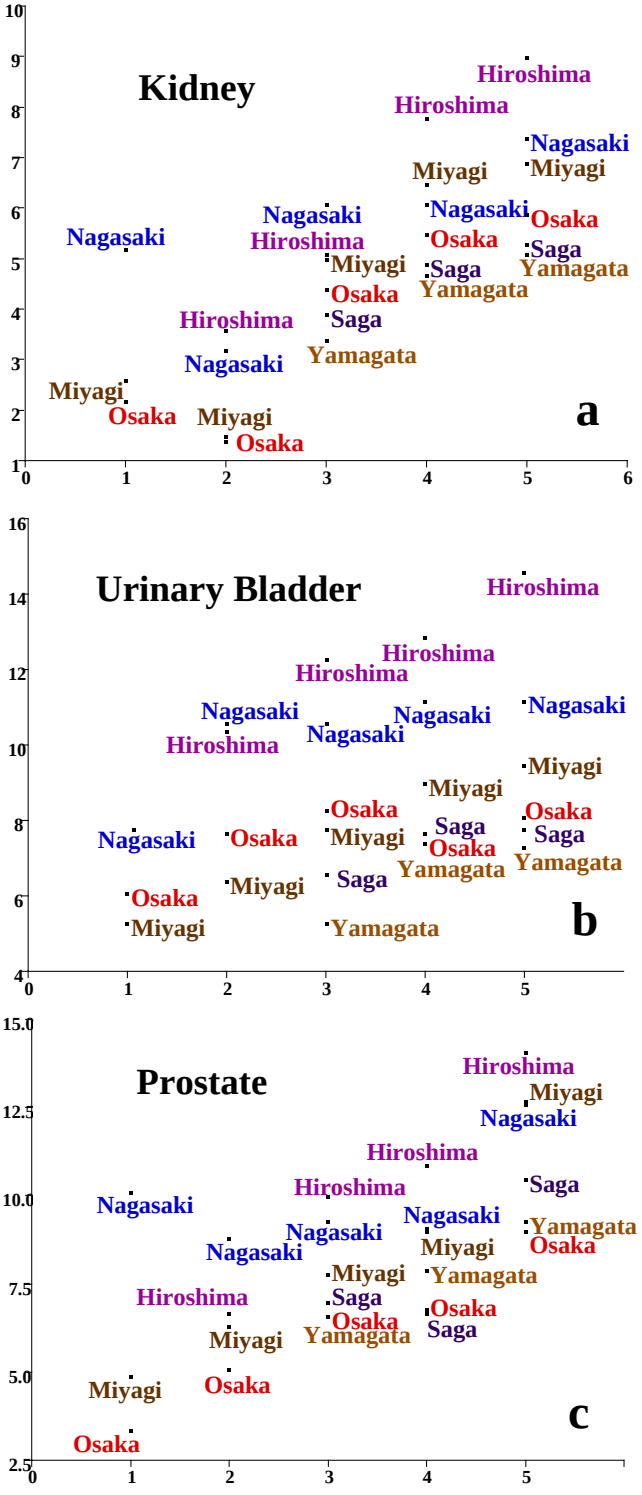

Figure 5. Change in Incidence Rates for Male Urinary Tract Cancers Over Time (Data from Cancer Incidence in Five Continents IV-VIII, 1982-2002)

Furthermore, after cessation of smoking, odds ratios are much higher for SCC than AC (Sobue et al., 2002) and the pattern of incidence of lung cancer by histologic type in Japan differs between high- and low- risk areas, especially in females, squamous cell carcinoma and small cell carcinoma being 2.5-3.3 times higher in Osaka and Okinawa compared to Nagano, while adenocarcinoma is almost equal in the 3 areas (Sobue et al., 2000).

Kidney

The fact that reported incidences of kidney cancers are increasing, independent of the registry (see Figure 5a) might point to a link with Westernization of the lifestyle but there also could be a role for improved imaging techniques. Renal-cell cancer has been reported to be related to tobacco smoking, an elevated body mass index, specific medical conditions, use of beta-blockers, a family history, high intake of dairy products and low intake of fruit and vegetables and, in women, multiparity (Tavani and La Vecchia, 1997), so that variation in the velocity of adoption of a Western lifestyle could be significant in Japan.

Urinary Bladder

While urinary bladder transitional cell carcinomas may be becoming more prevalent in Japan, there appear to be exceptions like Nagasaki and Osaka, where rates have tended to remain constant. Cigarette smoking appears to be the most significant environmental risk factor (World Cancer Research Fund, 1997), and as expected in this context, fruit and green-yellow vegetable intake is negatively associated with risk, particularly in Japanese men (Nagano et al., 2000; Wakai et al., 2000).

Prostate

While absolute rates are still very low compared to those prevailing in the Western world, there has been a steady rise in prostate cancer over the last decades in Japan, with Hiroshima leading and Osaka having the lowest incidences (see Figure 5c). While screening is considered to be contributing largely to rising incidences in the West, this does not appear to be the case in the Japanese (Wakai, 2005). Since comparative geographic-pathologic autopsy studies have suggested that rates for asymptomatic precancerous lesions may not differ markedly between high incidence America and low incidence Japan, promoting factors for progression of prostate cancer may be of prime importance (Watanabe et al., 2000). High levels of testosterone and low levels of sex-hormone binding globulin (SHBG) are considered to be positively linked to prostate cancer development and the fact that soy products are protective (Lee et al., 2003), apparently exerting benefit because of effects on serum estrone levels (Nagata et al., 2001) suggests that the androgen/estrogen balance may be of importance. There is also evidence that insulin could be playing a role with the relatively long period of hyperinsulinemia prior to onset of diabetes exerting a promotive influence (Giovannucci et al.,1998).

Breast

As shown in Figure 6a, cancer of the breast is exhibiting the most rapid rate of increase of any of the lifestyle-related cancers, the incidences more than doubling over the 25 year period covered in most registries. There is very little likelihood that screening is making any contribution in Japan, and the considerable spread between Saga and Hiroshima is presumably due to dietary factors, including soy protein intake, which is generally considered protective (Hirose et al., 2002; Yamamoto et al., 2003), along with fish (Hirose et al., 2003). International ecological correlations indicate that younger age at menarche, older age at menopause, longer duration of reproductive life, and longer delay to first birth are of particular significance (Morabia et al., 2000), but it is unclear whether there is appreciable national variation in these parameters within Japan.

Endometrium

Similar to the breast case but to a much lower extent, endometrial cancer rates have been increasing, especially in Hiroshima, but here the variation among individual registries is less pronounced. The major risk factor for endometrial cancer is estrogen, with progesterone exerting protection (Hinkula et al., 2002) and it has been argued that increase in the incidence of endometrial cancer in Japan may be largely attributed to decrease in parity (Inoue et al., 1994). It should be noted in this context that phytoestrogenic compounds are also associated with reduced risk of endometrial cancer (Horn-Ross et al., 2003). In contrast, overweight and/or weight gain in adult life is a risk factor (Hirose et al., 1999), along with frequent intake of boiled or broiled fish (Hirose et al., 1996).

Cervix

With the success of Pap smear screening, squamous cell carcinoma rates have become drastically reduced, especially in the Hiroshima and Nagasaki registries (see Figure 6c). In the developed countries the predominant pattern shown by cancer registries is a reduction in the incidence of squamous cervical cancer but an increase in ACs of the cervix (Vizcaino et al., 1998; 2000). The data are limited for Japan in this respect but comparison of relative values in Cancer Incidences in Five Continents for Vols VII and VIII does show a tendency for increase of more ACs, but at around 12% of the total the proportion is much lower than in the US (approximately 20%). Since the major risk factor for both SCCs and ACs is persistent infection with a high-risk HPV, together with smoking (Moore and Tajima, 2004), the

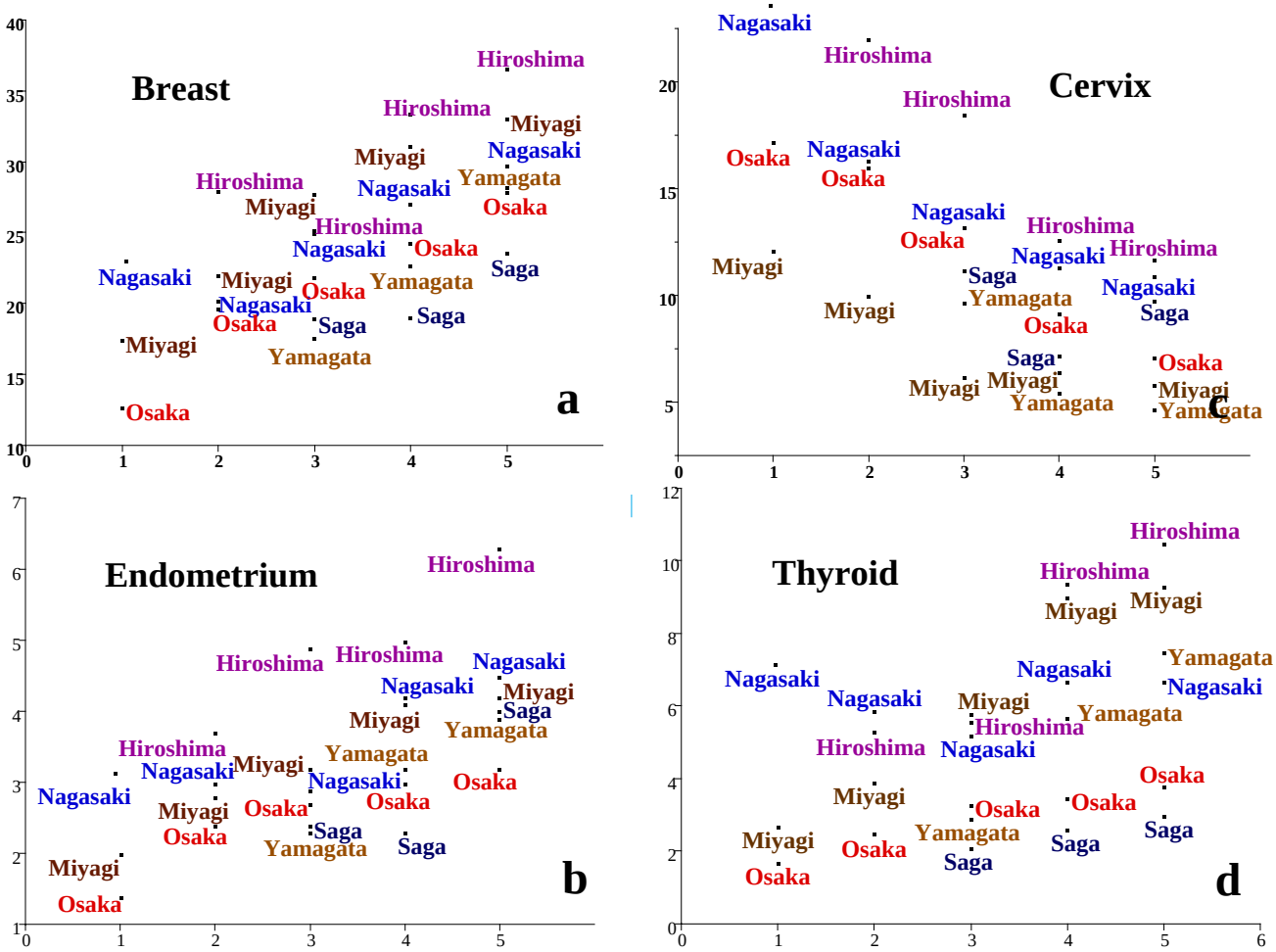

Figure 5. Change in Incidence Rates for Breast, Uterine and Thyroid Cancers in Females Over Time (Data from Cancer Incidence in Five Continents IV-VIII, 1982-2002)

observed inter-registry variation may point to differences in transmission and clearance rates for viruses within Japan.

Thyroid

Thyroid cancer, well established to be more prevalent in females than males, is decidedly increasing in Japan, with relatively high rates in Hiroshima and Miyagi, and low incidences in Osaka and Saga (see Figure 5d). Regarding risk factors in Japan, there is evidence of a link with HCV infection of the liver (Fujino et al.,2004), a past history of benign thyroid mass or goiter (Takezaki et al., and there could be a very weak promotive role of fish consumption (Bosetti et al., 2001). However, probably more important given the present findings is the association with BMI (Dal Maso et al., 2000).

Cross-Registry Correlations Between Sites

Many of the major risk factors for cancer development are shared between body sites and therefore it might be expected that correlations would exist across registries. This is particularly the case for the colon and rectum and within Japan there is indeed a clear and highly significant link between their incidences of cancers (see Figure 6a). However, significance was not noted for oesophageal and lung cancer (p=0.7), despite the fact that tobacco consumption is the most important risk factor in both cases. The fact of variation in the SCC/AC ratio in the lung but not the oeophagus might here be significant. Clearly there is no positive link between the liver and gallbladder (see Figure 6c), where in fact an inverse link appears more likely. Significant links in males, however, were also observed for urinary bladder with colon and rectum, and prostate cancer with kidney and bladder.

In the female cases, significance was only attained for colon and rectum (p<0.005), and thyroid and breast (p<0.05), colon (see Figure 6d) and rectum (p<0.01). This would suggest that there are indeed shared risk factors and that comparisons of dietary and other lifestyle factors in the regions covered by the registries included in this review might be illuminating.

Household Expenditure Findings

Data are available in Japan for regional consumption in the form of household expenditure tables, published every

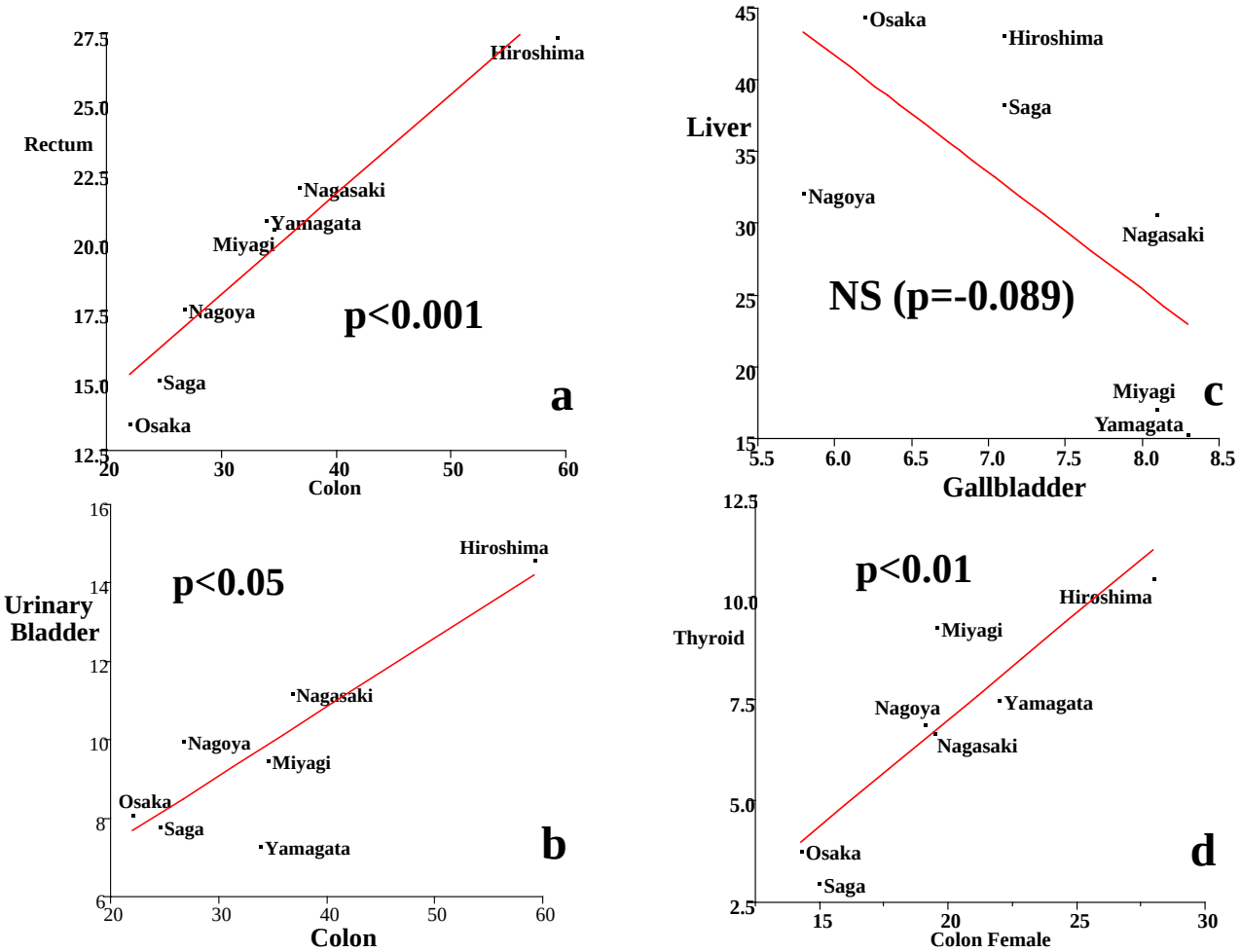

Figure 6. Cross-registry Correlations Between Cancer Incidences in Particular Organ Sites (Data from Cancer Incidence in Five Continents VIII, 2002)

Table 2. Expenditure/Consumption of Various Lifestyle-related Items (Relative to Sendai)

Location	Sendai	Yamagata	Nagoya	Osaka	Hiroshima	Saga	Nagasaki
Tobacco	9.8 (1)	13.9 (1.4)	10.9 (1.1)	15.1 (1.5)	12.7 (1.3)	14.5 (1.5)	7.9 (0.8)
Alcohol	38.5 (1)	51.6 (1.3)	38.1 (1.0)	49.8 (1.3)	55.2 (1.4)	38.2 (1.0)	37.5 (1.0)
Food							
Rice	83.0 (1)	114.5 (1.4)	97.4 (1.2)	90.4 (1.1)	77.1 (0.9)	82.8 (1.0)	103.5 (1.2)
Bread	39.0 (1)	34.1 (0.9)	49.3 (1.3)	51.5 (1.3)	47.8 (1.2)	41.0 (1.0)	44.6 (1.1)
Fish Fresh	41.9 (1)	42.5 (1.0)	36.7 (0.9)	38.7 (0.9)	40.8 (1.0)	37.2 (0.9)	49.1 (1.2)
Fish Salted	9.7 (1)	12.0 (1.2)	9.4 (1.0)	7.9 (0.8)	8.1 (0.8)	9.4 (1.0)	10.4 (1.1)
Meat Fresh	37.3 (1)	41.5 (1.1)	34.9 (0.9)	41.8 (1.1)	41.8 (1.1)	41.3 (1.1)	42.6 (1.1)
Milk	104.1 (1)	117.1 (1.1)	108.2 (1.0)	110.2 (1.1)	103.8 (1.0)	85.4 (0.8)	88.3 (0.8)
Butter/Cheese	29.7 (1)	32.6 (1.1)	27.4 (0.9)	23.6 (0.8)	28.8 (1.0)	23.5 (0.8)	22.3 (0.8)
Veg Fresh	182.8 (1)	217.7 (1.2)	188.8 (1.0)	178.2 (1.0)	173.2 (1.0)	168.7 (0.9)	164.5 (0.9)
Fruit Fresh	95.5 (1)	115.2 (1.2)	106.2 (1.1)	92.7 (1.0)	87.7 (0.9)	83.1 (0.9)	89.4 (0.9)
Bean Curd	75.5 (1)	87.2 (1.2)	75.0 (1.0)	67.9 (0.9)	83.2 (1.1)	76.1 (1.0)	75.8 (1.0)
Soy Sauce	95.2 (1)	149.2 (1.6)	76.5 (0.8)	84.6 (0.9)	75.6 (0.8)	88.1 (0.9)	108.6 (1.1)
'Miso'	101.0 (1)	111.5 (1.1)	79.3 (0.8)	50.3 (0.5)	56.8 (0.6)	71.3 (0.7)	95.2 (0.9)
'Wakame'	17.6 (1)	19.1 (1.1)	7.2 (0.4)	9.8 (0.5)	8.9 (0.5)	6.6 (0.4)	13.3 (0.8)
Salt	29.1 (1)	42.9 (1.5)	26.9 (0.9)	16.7 (0.6)	18.7 (0.6)	15.3 (0.5)	18.4 (0.6)

year. Comparisons for data for the same towns as house registries are given in Table 2 for tobacco and alcohol costs and amounts of foodstuffs consumed in 2003.

There are major differences in tobacco outlay, most remarkably between low smoking Nagasaki on the one hand and high smoking Osaka and Saga on the other, but this is in remarkable discordance with the incidence data for laryngeal cancer, where Nagasaki rates are much higher than those for the other two registries. There is also no obvious link to oesophageal as well as lung cancer, although here we should bear in mind the relative proportions of SCCs and ACs, the latter having a less direct link to tobacco consumption.

Regarding alcohol consumption it should be borne in mind that there is considerable variation in the type of alcoholic drink preferred. For example the sake and beer sales in Yamagata are nearly twice as high as in neighbouring Sendai, which has a far greater consumption of wine. Overall, the highest levels of intake are in Hiroshima, Osaka and Yamagata, but liver cancer is only high in the former two.

Looking at traditional items of the Japanese diet like soy, miso, and wakame, as well as salt, Hiroshima clearly has much lower consumption than Yamagata, presumably reflecting differences in penetration of Western dietary habits. While Yamagata does have the highest rates of stomach cancer, Hiroshima is however second on the list. There does not appear to be major variation in intake of bean curd or tofu, despite the major spreads apparent for breast and endometrial cancer.

Thus, there are no obvious correlates between population level household expenditure and population-based registry data, but of course it is necessary to look at the situation in the past if we wish to understand the present, so that consumption patterns 20-30 years ago may be more important than present data with regard to most cancer sites, as with diabetes and colorectal cancer risk (Kuriki et al., 2004). It will now be necessary to obtain detailed information for past trends in tobacco, alcohol and food consumption if the hypothesis that population level exposure determines population level disease. Furthermore, it will be necessary to assess whether profiles of sub-groups of individuals with shared tastes in dietary and social lifestyle can be generated at the local community level to assist in drawing conclusions as to the actual impact of proposed risk and beneficial factors. Very recently, results of a number of very large-scale cohorts have been published casting doubt on any importance of fruit and vegetable consumption for cancer development. In the Women's Health Study, no link was demonstrated with colorectal cancer risk (Lin et al., 2005), in the Netherlands cohort study an absence of any association was concluded for renal cell carcinoma risk (van Dyke et al., 2005), in two studies in the US there was no influence on pancreatic cancer in males or females and in the EPIC study in Europe, interim results suggest that total or specific vegetable and fruit intake is not associated with risk for breast cancer (van Gils et al., 2005). Furthermore, two pooled studies in Japan covering almost 90,000 individuals, again found no association between fruit and vegetable consumption and colorectal cancer (Tsubono et al., 2005). It must now be a high priority to determine whether these documented findings reflect a true lack of association, astounding though that would be given the massive evidence to the contrary (World Cancer Research Fund, 1997), or whether the cohort approach might require some re-evaluation.

Immense effort and expense is involved in setting up and following cohorts. Should we also be assessing other approaches to epidemiological assessment using the cancer registry as a basis for conducting research in the local community which might provide reliable clues (Moore, 2005). If the same rigorous methodology were applied to gathering information on lifestyle and other diseases as is now the case for cancer registration, detailed comparisons between registries, not only within but also between countries, would become feasible. This might herald a new age of epidemiological research located in and responsive

to regional communities, capable of providing comprehensive surveys which 20 years down the road would usefully complement continued cohorts.

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