COMMENTARY

Comparison of Japanese, American-Whites and African-Americans - Pointers to Risk Factors to Underlying Distribution of Tumours in the Colorectum

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Abstract

Relative incidence rates for colon and rectal cancer vary greatly between populations in the world. While Japanese have historically had low prevalence, immigration to the United States has now resulted in equal if not higher rates than in Caucasian- or African-Americans. Furthermore, recent data from some population-based registries in Japan itself are also pointing to particularly high susceptibility. Of particular interest is the fact that Japanese in both the home country and the US in fact have far higher rates for rectal cancer than the other two ethnic groups. An intriguing question is whether they might also demonstrate variation from Caucasian- and African-Americans in the raltive incidence rates for proximal and distal colon cancers, given the clear differences in risk factors like diabetes, physical exercise, smoking, alcohol consumption, meat and fish intake and calcium exposure which have been shown to operate in these two sites. A comprehensive epidemiological research exercise is here proposed to elucidate ethnic variation in colorectal cancer development, based on cross-cancer registry descriptive and case control approaches. It is envisaged that additional emphasis on screened populations should further provide important insights into causal factors and how primary and secondary prevention efforts can be optimized.

Key Words: Colon cancer - proximal - distal - rectal cancer - registry data - case-control - endoscopy screening

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Introduction

While colon and rectal cancer rates in Caucasian-American, African-American and to some extent, Japanese-American populations appear to be now decreasing, in Japan itself they continue to increase, albeit at remarkably different rates in different registries (see Figure 1). In fact Japanese in some registries, both in the US and in Japan itself, now demonstrate higher rates than either their White or Black counterparts. There is also considerable variation in the relative incidences of colon as opposed to rectal cancer, and a trend has been evident for the ratios of colon to rectal cancers to increase over the last 25 years (see Table 1), as already documented in Japan (Takada et al., 2002).

Risk Factors

There are clear differences in risk and beneficial factors for the two body sites (Table 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, appearmore linked to alcohol consumption and tobacco smoking (World Cancer Research Fund, 1997; Toyomura et al., 2004), although both alcohol consumption and smoking have been found to be clearly associated with colorectal cancer overall in men (Otani et al., 2003). In one study, age, gender, family history of colon or rectal cancer, height, body mass index, physical activity, folate, intake of beef, pork or lamb as a main dish, intake of processed meat and alcohol were all found to be significantly associated with colon cancer risk, while only age and sex were associated with rectal cancer (Wei et al., 2004)

Division is not only necessary for colon and rectal cancers, but also for subsites within the colon. For all age groups in the US, a proximal migration of colon tumors over time was identified by Mostafa and coworkers (2004), although this might partly be attributable to decrease in the

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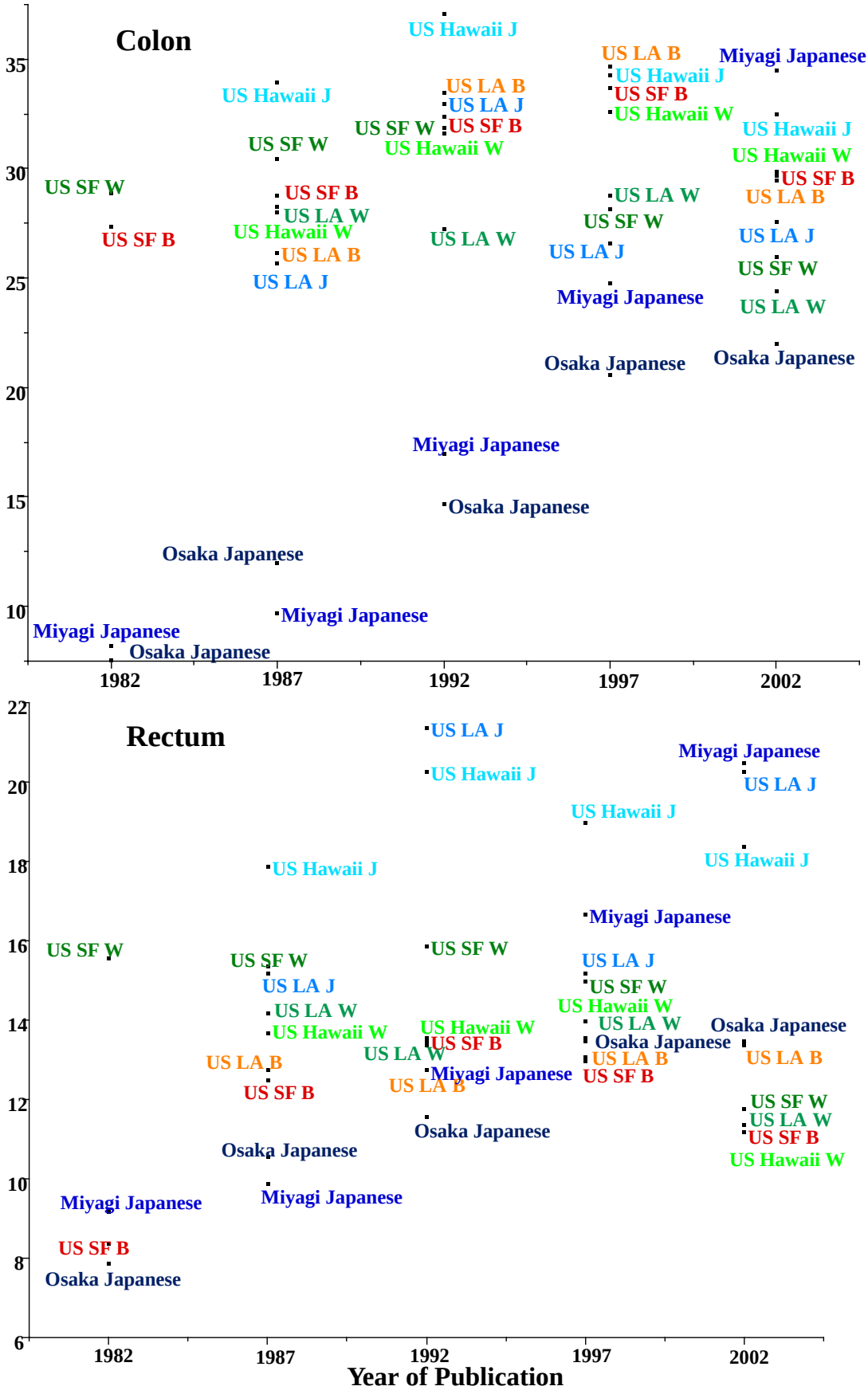


Text-Figure 1. Trends in Colon and Rectal Cancer Incidence Rates for Japanese, Blacks and Whites (Data from Cancer Incidence in Five Continents (Vols IV-VIII)

Table 1. Colon/Rectal Cancer Incidence Ratios for Selected Cancer Registries*

Asian Registry	1982	2002	Change	Western Registry	1982	2002	Change
China Hong Kong	1.3:1	1.6:1	++	Australia, NSW	1.7:1	1.6:1	-
China, Shanghai	0.7:1	1.3:1	+++	Colombia, Cali	1.3:1	1.6:1	++
Hawaii, Hawaiians	1.2:1	1.5:1	++	Slovakia	0.7:1	1.1:1	++
India, Bombay	0.8:1	1.2:1	++	Spain Zaragoza	1.1:1	1.4:1	++
Singapore, Chinese	1.0:1	1.3:1	++	Sweden	1.5:1	1.5:1	+/-
Singapore Indian	1.3:1	1.2:1	-	UK S Thames	1.3:1	1.5:1	+
Singapore, Malay	0.7:1	0.9:1	+	UK Scotland	1.6:1	1.7:1	+
Japan, Miyagi	0.9:1	1.7:1	++++	US SF White	1.9:1	2.2:1	++
Japan, Osaka	1.0:1	1.6:1	+++	US SF Black	3.3:1	2.7:1	---

*Values calculated from data in Cancer Incidences in Five Continents 1982 and 2002

incidence of distal cancers coupled with aging of the population (Rabeneck et al., 2003). Among non-Hispanic whites a decline in all sites and stages has been documented, but the decrease was most pronounced for rates of *in situ* and regional/distant tumors in the rectum and sigmoid (Cress et al., 2000). However, in African-Americans proximal cancer rates do appear to be increasing (Troisi et al., 1999). Asians and Pacific Islanders in the US, contrasting with their white and black counterparts, have approximately equal numbers of proximal and distal cancers (Wu et al., 2004). Division of the colorectum anatomically at the junction of the descending and sigmoid colon, and including the rectum above the anal canal with "distal" colorectal cancers demonstrated a predominance of African Americans among those at risk of proximal and a predominance of white males among those at risk of distal lesions (Nelson et al., 1997). In Canada, decreasing rates for colorectal cancer appear limited to tumours located in the distal colon and rectum; the incidence of cancers of the proximal colon has not changed over time (Gibbons et al., 2001). French results also confirm the existence of different trends in colorectal cancer incidence between subsites and sexes (Mitry et al., 2002). In Korea changes in the colon-to-rectal ratio appear mainly be due to an increase in left-sided colon cancer (Kim et al., 2002). It remains to be determined which site is now predominating in different Japanese populations but an earlier study suggested that distal cancer might be most affected by the change in diet in Japan (Tajima et al., 1985)..

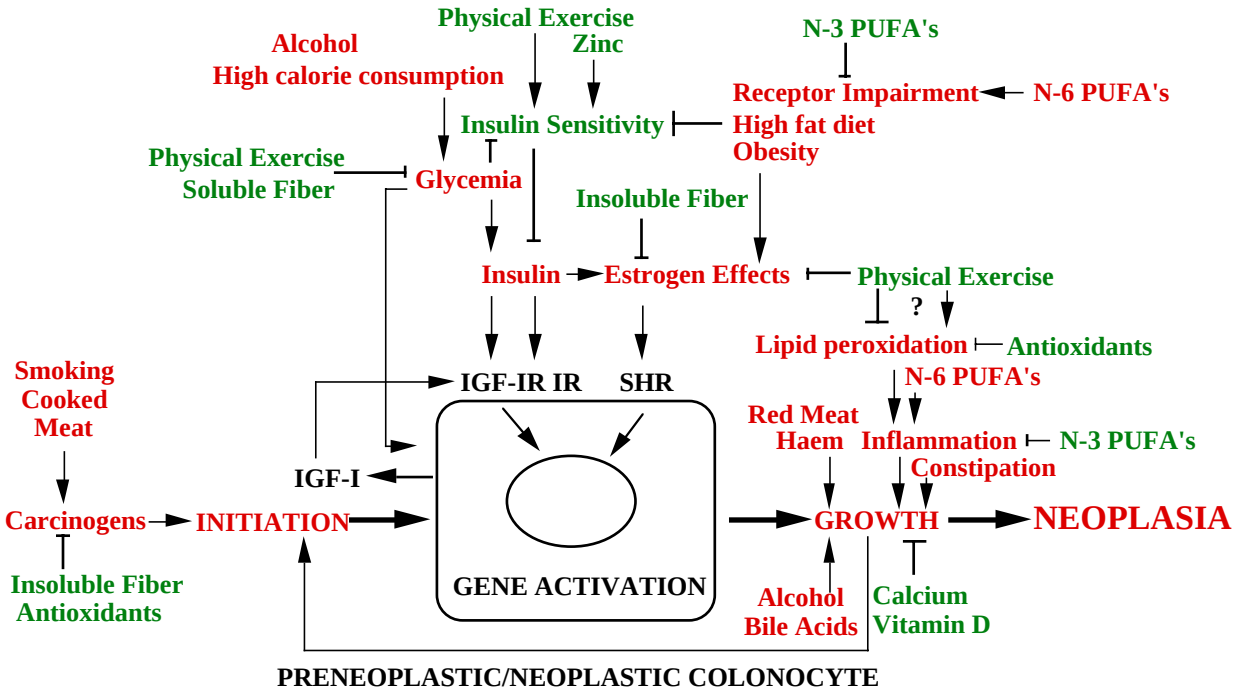
Table 2. Possible Risk and Protective Factors for Cancer of the Proximal and Distal Colon and Rectum

Factor	Proximal	Distal	Rectum
Risk			
Smoking	?	+	++
Alcohol	?	+	+
Western Diet	+	++	?
Asian Diet	+?	--	?
Red Meat	?	+	+
NIDDM	++	+	+
Constipation	+	++	?
Cholecystectomy	++	?	?
Protective			
Physical Activity	-	-	-?
Fibre Intake	-	-	?
Calcium	?	--	--
Vitamin D	?	--	--
Fish	-	-	-

+, ++ promotion -,-- inhibition +?/-? possible effect, ? unclear

A summary of data regarding separation of the different sites within the colorectum for risk factors is also provided in Table 2 and possible modes of action are illustrated in Figure 2. Cigarette smoking may be significantly associated with an increased risk of adenomas, regardless of the location, but most pronouncedly for rectal lesions in one study (Toyomura et al., 2004). In another in China, increasing tertiles of smoking duration in ever smokers was also associated with increased rectal cancer risk (Ho et al., 2004). 'Irritable bowel' (soft or loose feces) might be associated with distal subsites of colorectal cancer, independently or combined with habitual smoking (Inoue et al., 1995). Regarding the impact of alcohol, an increased risk of colorectal cancer was found in current drinkers (Ho et al., 2004), and daily consumption of any type was associated with increased risks of cancer of the distal colon and the rectum but not the proximal colon (Sharpe et al., 2002). Similar findings have been documented for adenomas in Japan (Toyomura et al., 2004). However, in 8 cohort studies a positive alcohol association was evident for cancer of the proximal colon, distal colon and rectum (Cho et al., 2004).

Clearly there must be effects of nutrition and in Korea, a Western dietary pattern was found to be associated with colon cancer risk, especially in females with distal colon cancer, while a traditional diet appeared linked to proximal lesions (Kim et al., 2005). Similarly, Japanese-style foods may decrease the risk of distal colon cancer, but increase the likelihood of proximal tumour development (Inoue et al., 1995). A moderately positive association between higher western pattern scores and risk of colon or distal colon adenomas has also been documented (Wu et al., 2004). One important component of the Western diet is red meat intake and there is evidence that this is an important determinant of colon cancer risk (Kono, 2004; Norat et al., 2005). In one study, highest versus lowest tertile meat consumption appeared significantly linked with both colon and rectal



Influences of major risk and beneficial factors on preneoplastic and neoplastic cells. PUFAs, polyunsaturated fatty acids; IGF-IR, insulin like growth factor I receptor; IR, insulin receptor; SHR, steroid hormone receptor; NSAIDs, non-steroid anti-inflammatory drugs; ⟶, enhancing stimulus; ⊣, inhibitory effect.

Figure 2. Mechanisms Whereby Risk and Protective Factors Could Impact on Colon and Rectal Cancer Development

cancer, independent of the sex (Ye et al., 2003), but in another substantial increase was only apparent for distal colon cancer (Chao et al., 2005; Larsson et al., 2005). Increased risk may be related to the cooking temperature and close contact of the food to the heating source, higher risks being observed for heavily browned surfaces when meats were barbecued or iron-pan cooked (Navarro et al., 2004). Dietary haem iron that is present in red meat is associated with an increased risk of proximal colon cancer, especially among women who drink alcohol (Lee et al., 2004), and it has been argued that the association between consumption of red meat and the risk of colon cancer is mainly due to its haem content, and is largely independent of any included dietary fat (Sesink et al., 2000).

Given the conclusion of protective effects of fruit and vegetables in the World Cancer Research Fund publication of 1997, recent cohort data offering little support for associations between intakes and colorectal cancer risk are surprising, although legume fiber did appear to have benefit (Lin et al., 2005). One problem is the considerable confounding by other dietary and lifestyle factors (Michels et al., 2005). With high intake of nuts and seeds a significant inverse association was observed in subgroup analyses for colon cancer in women (Jenab et al., 2004). In an earlier survey of 13 colon and rectum case-control studies (Howe et al.,1992), twelve demonstrated an inverse association with fiber, similar for both left and right sides of the colon. An international comparison of starch consumption similarly revealed a strong inverse link with colorectal cancer incidence (Cassidy et al., 1986). The drop in consumption of fiber by Japanese in the post-war period has in fact been found to be followed after a time-lag by increase in colon cancer (Tsuji et al., 1996).

Another protective factor may be consumption of raw or cooked fish, primarily in the colon but also to some extent in the female rectum (Yang et al., 2003). This was recently extended to total omega-3 polyunsaturated fatty acids (Kojima et al., 2005). A focus on distal adenomas, however, did not provide support for the hypothesis that a higher intake of marine n-3 fatty acids or a higher n-3/n-6 ratio reduces the risk (Oh et al., 2005).

Although one major study did not generate evidence in favour of an association of calcium and vitamin D intake and colorectal cancer risk (Lin et al., 2005), 800 mg of calcium per day confered an approximately 25% reduction in another (Flood et al., 2005). High levels of calcium intake were found to reduce risk of rectal cancer in women but not men (Slattery et al., 2004). In the same study, similar reduction in rectal cancer risk among women was observed for vitamin D, low-fat dairy products and sunshine exposure. An inverse association for milk has also been documented, but limited to cancers of the distal colon and rectum (Cho et al., 2004a). Furthermore, benefit from higher 25-hydroxyvitamin D 25(OH)D concentrations was observed for cancers of the distal colon and rectum, but not the proximal colon (Feskanich et al., 2004). Regarding mechanisms of action, reports of increased apoptosis (Miller et al., 2005) and reduced proliferation (Kallay et al., 2005) are of obvious relevance.

There have been a number of reports of increased risk

of proximal colonic cancer after cholecystectomy (Vernick et al., 1980; Alley and lee, 1983; Paul et al., 1993) and recently a decrease linked to a CYP7A1 polymorphism rendering less activity of the enzyme converting cholesterol to bile acids has provided compelling evidence (Hagiwara et al., 2005), in line with the proposed promoting role of bile acids and metabolic activity of colonic bacteria (Zuccato et al., 1993). Some data have been documented supporting the hypothesis that cholecystectomy may be a risk factor for right-sided colon cancer, but indicating that it may exert a protective influence against rectal cancer (Caprilli et al., 1989).

A great deal of interest has been concentrated on possible links between type II diabetes and associated obesity on the one hand and colorectal cancer on the other (see Moore et al., 1998 for review) and in Japan the time trends for the two diseases are in line with an important contribution (Kuriki et al., 2004).Waist circumference has been found to be a stronger predictor of colon cancer risk than BMI, central obesity being linked to an increased risk of cancer of both the proximal and distal colon (Moore et al., 2004). While NIDDM was associated with modestly increased risk of sigmoid colon adenomas in Japan (Kono et al., 1998), statistically significant elevation in relative risk was limited to the proximal colon in the US (Limburg et al., 2005). Of interest in this context is the finding that dietary zinc, protective against diabetes, is linked with a decreased risk in both proximal and distal colon sites (Lee et al., 2004). Diet with a high dietary glycemic load may increase the risk of colorectal cancer in women (Higginbotham et al., 2004) but this could not be confirmed for distal adenomas (Oh et al., 2004).

There may be a role for estrogen and reproductive factors like age at menarche, particularly in distal colon cancer (Yoo et al., 1999). An inverse association was detected between the number of full-term pregnancies and the risk of colon cancer in female subjects, as well as the age at menarche (Ghadirian et al., 1998). In this context, the possibility of protective effects of phytoestrogens, possibly due to competitive binding to estrogen receptors needs to be taken into account (Lechner et al., 2005).

There is considerable evidence in the literature that physical activity is associated with reduced risk of colon but not rectal cancer in both males and females (for review see Moore et al., 1998). The same conclusion was drawn from a major meta-analysis (Samad et al., 2005). However, a significant inverse association has been reported for moderate/heavy occupational activity in the distal colon and rectum but not in the proximal colon (Colbert et al., 2001). One possible mechanism whereby physical exercise might be protective is through effects on insulin actions (Moore et al., 1998a; 1998b). Another is on constipation, which has been shown to have a positive association with risk of colon cancer (Ghadirian et al., 1998), especially in the distal region in black women (Roberts et al., 2003). However, a meta-analysis (Sonnenberg and Muller, 1993), as well as a case control study focused on middle-aged adults (Jacobs and White, 1998), suggested the colon rather than the rectum to be the site of greatest impact of this factor.

Pointers for Future Research

Clearly there are a number of different factors which are active in different sites within the colorectum and presumably these reflect physiological variation. The major difference between the proximal and distal colon is that the former is far more active in absorbing water from the feces, while the latter has a greater role for storage before defecation through the rectum. Why should there be the observed variation in sub-site dependence of cancer development? Can we find plausible explanations as to the underlying mechanisms? One approach might be to take advantage in racial and geographical variation in incidence rates. For example the available data for colon and rectal cancers in Japan and the different racial groups in the US suggest that cancer registries are in a good position to clarify the situation regarding sub-site distributions of colorectal cancers in Japanese in Japan, Hawaii and the West Coast, as well as both Caucasian- and African-Americans. There is considerable variation between incidence rates among the racial groupings (see Figure 3), with striking separation on a racial basis, Japanese in the US continuing to group together with their counterparts in Japan itself. Elucidation of what might be the responsible factors is necessary for generation of effective programs for primary and secondary prevention and for this purpose cross-registry collaboration is essential. A number of concrete approaches can be envisaged marrying descriptive with analytical epidemiology.

1) Determination of Change in Sub-Site and Stage Distribution, as well as Age at Diagnosis and Size, of Colon and Rectal Cancers Over Time.

Access data from Japanese and American (Hawaii, California) Registries for the period 1976 to the present and make comparisons, taking into minor variation in diagnostic criteria.

2) Determination of the Sub-Site and Stage Distribution, as well as Age of Diagnosis and Size, of Lesions Detected by Colonoscopy Following a Positive ImmunoFOBT Test or Other Screening Result.

Access data from screening centers in Japan and where possible in the US to ascertain the influence of different screening modalities and diagnostic procedures.

3) Develop Consistent Food Frequency/Lifestyle Questionnaires for Use in Japan and the United States to Determine Risk and Beneficial Factors.

In order to allow full comparability of case-control studies between registries and countries, questionnaires need to be collated for consistency, as for example with the South-East Asia-Japan Project being conducted by Tokudome et al (2004).

4) Using Physician-Diagnosed or Screened Cases, Conduct Case-Control Studies of Risk Factors for Separate Colorectal Subsites as well as ChemopreventionTrials, feo example with NSAIDs.

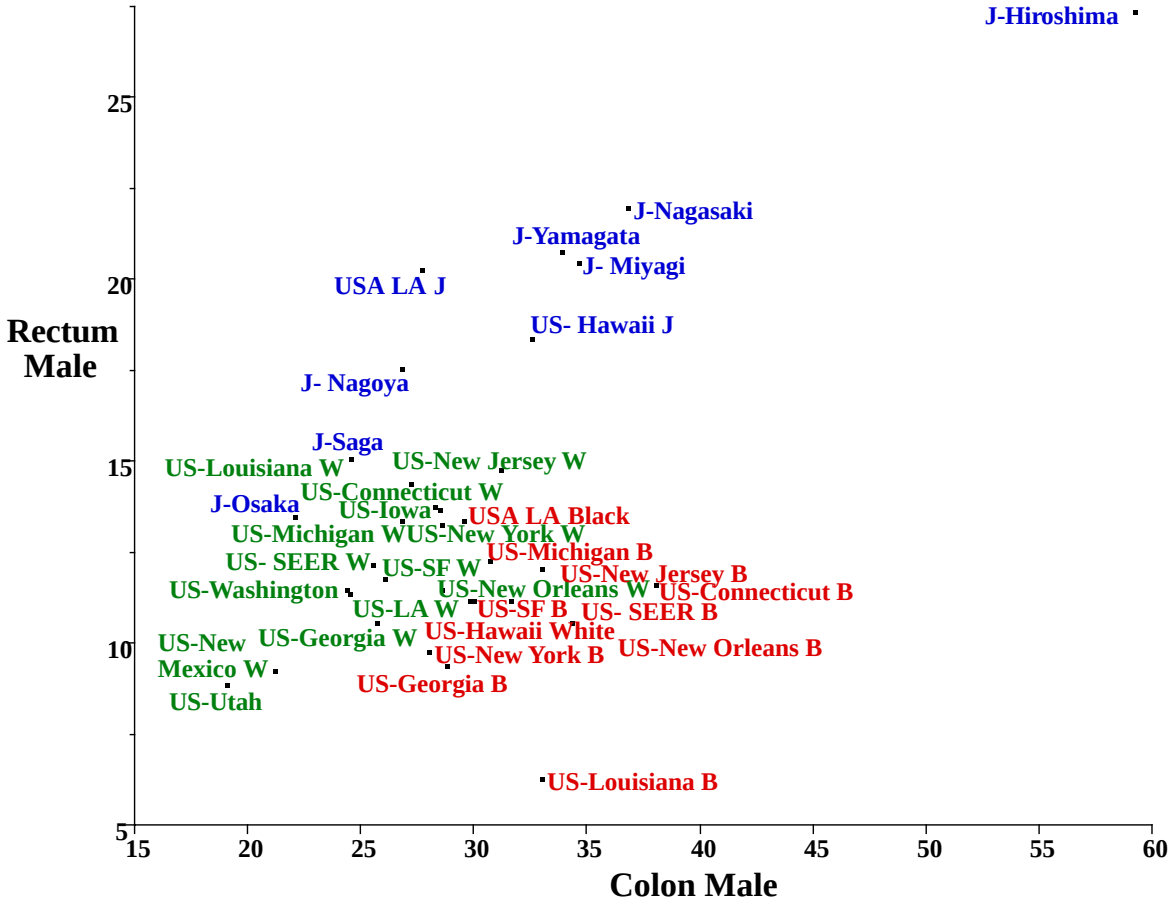


Figure 3. Colon-Rectal Cancer Ratios for Male Japanese, Blacks and Whites (Data from Parkin et al., 2002).

As collaborative efforts, comprehensive case-control studies focusing on colorectal physiology, diet, fecal characteristics, anthropomorphic parameters, diabetes, physical exercise, smoking and alcohol consumption as risk factor for separate subsites within the colon and rectum might be conducted in tandem by scientists in the US and Japan. On the Japanese side the HERPACC program of Aichi Cancer Center (Tajima, 2000) and the Fukuoka Colorectal Cancer Study (Kono et al., 2004) are concrete examples of research projects already underway which might be persuaded to participate in collaborative exercises.

While organization of cross-registry and cross-country research presents ergonomic problems because of distant locations, these are no more unsurmountable that the difficulties involved in setting up major cohort-based projects. Benefits might include the ability to effectively focus on ethnic variation in gene polymorphisms which could be participating in genetic-environmental interactions. Elucidation of what determines risk is essential to provide the basis for mechanism-based cancer prevention - international cooperation among scientists is a core tool for this purpose.

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