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[Appendix]

List of Foods/Food Groups Included in a Short FFQ

1. Rice
2. Bread (including White Bread, Bun etc.)
3. Noodles (Japanese noodle; *Udon* [Wheat noodle], *Soba* [Buckwheat noodle], Chinese noodle; *Ramen)*
4. Margarine
5. Butter
6. Milk
7. Yogurt
8. *Miso* soup
9. *Tofu* (Soybean curd) for *Hiyayakko, Yu-dofu*
10. *Natto* (Fermented soybean), Soybean
11. Egg
12. Chicken
13. Beef, Pork
14. Liver
15. Ham, Sausage, Bacon, Salami-sausage
16. Fish
17. Bone-edible small fish (e.g. *Shirasuboshi* [Boiled and semi-dried whitebait], *Shishamo* [Smelt])
18. Canned tuna
19. Cuttlefish, Squid, Octopus, Shrimp, Crab
20. Shellfish (e.g. Short-necked clam, Corbicula, Oyster)
21. Fish egg (e.g. *Tarako* [Cod fish egg], *Ikura* [Salted salmon egg], etc.)
22. Fish paste products (e.g. *Kamaboko, Chikuwa*)
23. *Ganmodoki* (Fried *tofu* paste), *Nama-age* (Fried *tofu*)
24. Potatoes (e.g. Potato, Sweet-potato, Taro, Yam)
25. Pumpkin/squash
26. Carrot
27. Broccoli
28. Green leaves vegetables (e.g. Spinach, *Komatsuna, Shungiku,* etc.)
29. Other green-yellow vegetables (e.g. Green pepper, String beans, etc.)
30. Cabbage
31. *Daikon* (Japanese radish)
32. *Kiriboshi-daikon* (Dry strips of Japanese radish)
33. Burdock, Bamboo shoot
34. Other vegetables (e.g. Cucumber, Lettuce, Bean sprouts, Onion, Chinese cabbage etc.)
35. Mushrooms (e.g. *Shiitake, Shimeji, Enoki,* etc.)
36. Seaweeds (e.g. *Hijiki* [Brown algae], *Kombu* [Kelp], etc.)
37. Mayonnaise (including Salad dressed with mayonnaise [e.g. Potato-salad, etc.])
38. Deep fried food
39. Light fried food
40. Citrus fruits (e.g. Orange, Tangerine, Mandarin orange, etc.)
41. Other fruits
42. Peanut, Almond
43. Western style confectioneries (e.g. Short cake, Cream puff, etc.)
44. Japanese style confectioneries (*Manju,* etc.)
45. Green tea
46. Coffee
47. Alcohol

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Field Study

A Chronological Decrease in Type A Behavior Patterns among Japanese Male Workers in 1995–1999

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Abstract : A Chronological Decrease in Type A Behavior Patterns among Japanese Male Workers in 1995–1999: Masayo KOJIMA, *et al.* Department of Health Promotion and Preventive Medicine, Nagoya City University Graduate School of Medical Sciences—We examined the chronological change in Type A behavior pattern (TABP) among Japanese male workers for 5 yr. A brief questionnaire to measure TABP was administered to 21,711 male workers who underwent health check-ups at least once during the period from 1995 to 1999 and were born in 1936–1965. The mean TABP scores decreased year by year linearly. Then the repeated measurement analysis of variance was performed with the data of 5,689 subjects who completed the questionnaire successively through the study period. Both year and the age effects were highly significant ($p<0.001$, respectively), whereas the time trends were comparable by baseline age. In conclusion, TABP among Japanese male workers decreased in all generations during the period from 1995 to 1999.
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Key words: Type A, Psychosocial factor, Economy, Chronological change

"Type A man" was born of the clinical observations of two American Cardiologists in the mid-1950s. Friedman and Rosenman[1, 2] found that their cardiac patients presented an "overt behavior pattern", characterized by intense ambition, competitive drive, constant preoccupation with occupational deadlines, and a sense of time urgency. It was named "Type A behavior pattern (TABP)"[3, 4] and a series of studies were conducted to assess its association with coronary heart disease (CHD). After three large population studies showed a positive relationship between TABP and an increased risk of CHD[5, 6], the Review Panel on Coronary-prone Behavior and Coronary Heart Disease concluded in 1978 that TABP was an independent risk factor for developing CHD[7].

Nevertheless, a number of subsequent prospective epidemiological surveys failed to produce consistent results[8]. Moreover, psychological research, beginning in the mid-1960s, focused on emotions such as anger or hostility in isolation, thus fragmenting the concept of TABP into its component parts. Reviewing the articles concerning TABP from 1965 to 1998, Riska[9] described what happened to the "Type A man" as follows: "having the status of a distinct set of medical risk factors in the late 1960s and most of the 1970s, the Type A man has all but disappeared as a social and diagnostic category in the vocabulary of medicine." Has the "Type A man" disappeared from the world? He might have just become inconspicuous because we have less interest in him than before. Or has he just mellowed with time?

Up until October 2001, just one article could be found on the Medline database reporting the change in the prevalence of TABP over time in the general population. Smith and Sterndorff[10] administered the Jenkins Activity Survey Scale (JAS)[11] to four hundred Danish men and women, once in 1988 and again in 1992. The scores were lower in 1992 than in 1988, and they concluded that TABP had declined in the Danish population, but these were not consecutive reports from the same individuals. We believe this is the first study that demonstrates a chronological decline in TABP in a working male population over a period of 5 yr.

Subjects and Methods

Subjects

The study protocol was approved by the Ethics

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Table 1. Type A Behavior Pattern (TABP) scores in Japanese male workers from 1995 to 1999

Year	n	TABP Score			Age	
		Mean	SD	Chronbach's α	Mean	SD
1995	13,290	12.6	5.9	0.75	46.3	7.1
1996	13,090	12.5	5.9	0.80	47.9	7.1
1997	12,790	12.4	5.9	0.81	47.4	7.0
1998	12,361	12.2	5.8	0.81	47.9	7.1
1999	11,631	12.0	5.8	0.81	48.2	7.2

Committee of Nagoya City University, Graduate School of Medical Sciences. The samples of this study were male Japanese workers born in 1936–1965 who visited Gifu Prefectural Center for Health Check and Health Promotion ("the Center") during the period April 1995 to March 2000. The data on these subjects were taken from the medical records in the Center. Although individual written informed consent was not obtained from each subject, the investigators explained the aim of the study and confidentiality of the data to the Center administrators and got permission to access the data.

The Center is located in Gifu City, a middle-sized city in Central Japan with a population of 407,134 in 1995. According to the requirements of the law of Industrial Safety and Health, it is mandatory for workers to take an annual medical check-up. Therefore, the present sample can be regarded as a working male population of this Japanese semi-urban community.

Between April 1995 and March 2000, a total of 25,574 men underwent health examinations at least once. Those who were born before 1936 or after 1965, or those who reported having no stable job at any point during the study period, were excluded from the analysis. 21,711 subjects met all the criteria. Among the eligible subjects, 5,689 participants visited the center successively for 5 yr (mean age ± SD: 47 ± 6 yr, range from 29 to 60 yr at the baseline in 1995): that was 42.8% of the participants in 1995.

Methods

A self-report 12-item questionnaire developed by Maeda[12, 13] was administered to the participants as one of the routine questionnaires from the Center; inquiring about past and present illness, demographic background, dietary habits, sports, sleep, and so on as part of the health evaluation. Maeda's "Brief Questionnaire" was an original scale, designed to evaluate TABP tendencies in Japanese populations. Each item is rated on a three-point Likert scale ranging from "usually" (scored 2) to "hardly ever" (scored 0), with a double score given to the three items. The total score ranges from 0 to 30, and the author recommends a cut-point score of 17 or more for TABP screening. The correlation coefficient with JAS[11] was reported as 0.72, and the concordance of the Type A judgment by Maeda's scale and by JAS was 75%[12]. A recent cross-sectional study reported the discriminant validity of this scale between non-fatal myocardial infarction patients and healthy controls[14].

The participants were requested to complete the questionnaire in advance, and public health nurses checked all items during individual interviews carried out at the end of the health checkups. If there were missing items, the nurses asked the participants to complete them.

Analyses

Data were analyzed with SAS for Windows version 8.01 (SAS Institute, Cary, NC, USA). All statistical tests were two-sided. p-values ≤ 0.05 were considered statistically significant. In order to evaluate the internal reliability of Maeda's Brief Questionnaire, Cronbach's alpha coefficient was calculated for each year's data.

A repeated-measurement analysis of variance was then performed to examine the year effect and the generation difference on the chronological change in the TABP score. The subjects were divided into three groups by the baseline age (29 to 39 yr old, born in 1956–65; 40 to 49 yr old, born in 1946–55; 50 to 59 yr old, born in 1936–1945). The interaction between baseline age group and year, and the differences in the TABP scores by the baseline age group by year were examined.

Results

Table 1 shows the mean TABP scores ± standard deviation (SD), Chronbach's alpha coefficients, and mean ages ± SD of the each year sample from 1995 to 1999. Alpha coefficients were at an optimal level (above 0.70), indicating good internal consistency of the scale. The mean scores of the total samples by year decreased linearly from 1995 to 1999.

Then, to test the time and generation effect on the score change, a repeated measurement analysis of variance was performed with the data for subjects who took the annual health examination successively through the study period. A total of 5,689 subjects, 42.8% of the study participants in 1995 were included in the analysis. The chronological change in the mean TABP score by generation is shown

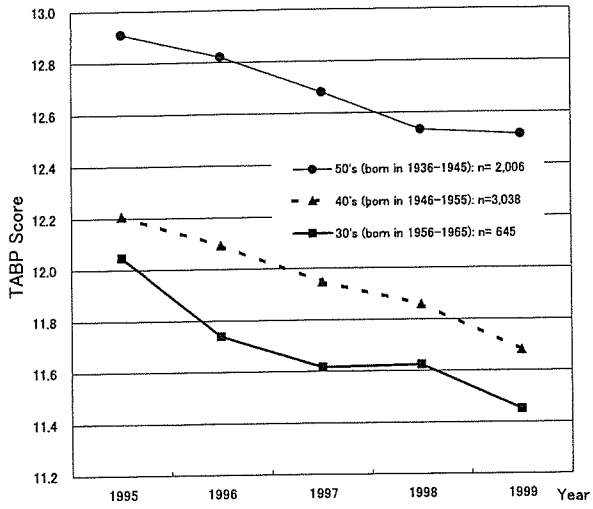

Fig. 1. Trends in Type A Behavior Pattern score of Japanese male workers from 1995 to 1999 by baseline age.

in Fig. 1. There was no significant interaction between year and generation ($F_{8, 1153}$=.43, p=.90): the time trends were comparable by baseline age groups and TABP scores decreased linearly in all generations by year. The year effect was highly significant ($F_{4, 5765}$=15.81, p< .001), and the difference by generation was also significant ($F_{2, 5768}$=16.56, p< .001).

Discussion

We have demonstrated a significant decrease in TABP scores across all generations of the male working population of a Japanese semi-urban community. No significant interaction between age and year was confirmed by repeated measurement analysis of variance; all generations showed similar tendencies to decrease the TABP score linearly by year. Although we cannot specify the reason for the chronological decline in the TABP scores from available data, it is speculated that there has been some factor affecting the psycho-behavioral pattern of our subjects to reduce the TABP score regardless of generations.

We observed a significant age difference in TABP scores through the study period; those who were born in between 1936 and 1945 had significantly higher TABP scores than younger generations. This generation difference in TABP score seems reasonable because male workers aged 50–59 are more likely to have more responsible and demanding position in the work place than the younger generations.

During the study period from 1995 to 1999, the unemployment rate increased across the age spectrum[16], and the rate of suicide kept increasing especially among the working male population in Japan[17]. Although we do not have financial information on the present subjects, social and economic environments are known to influence TABP[18]. The economic recession and other changes in modern society may help workers relieve their TABP tendency. On the other hand, recent social and economic decline might induce other maladies, such as depression. Actually, according to the Patient Survey Japan[19], conducted by the Ministry of Health, Labor, and Welfare, the estimated number of patients suffering from affective disorders, including depression in Japan increased from 48 per 100,000 populations in 1996 to 51 in 1999. Depression is known to suppress the manifestation of type A characteristics[7]. Moreover, it is well established that depression is a risk factor for a variety of illness and for delayed recovery[7, 20]. Recent epidemiological studies have reported a more consistent association of CHD with depression than with TABP[8]. Considering these trend, the scope of psychological support aimed at reducing CHD morbidity and improving the general health of the working population should be widened to focus on the detection and treatment of psychosocial factors such as depression, rather than confined to attempts to reduce perceived causes of TABP.

We should note several limitations to the interpretation of our results. First, all the participants received the results of health examinations including the TABP scores after health checkups, although further efforts to reduce the TABP scores were not provided by the public health specialists at the Center. Some effects of memory and response sets due to the repeated administration of the same questionnaire on the results cannot be excluded, but the mean TABP scores of the total subjects including new or single visitors to the Center also showed the same tendency (shown in Table 1). Therefore the influence of repeated administrations of the same questionnaire seems not to be strong. Next, the follow-up rate of our study was relatively low (42.8%). Those who take annual health checks for five successive years are supposed to be health conscious and financially stable. We should consider some selection bias; the subjects might be more likely to regulate their own lifestyle and behavior than subjects who were excluded from the analysis.

In conclusion, this study demonstrates a decline in the incidence of TABP among workers in Japan, complementing other recent research showing a reduced association of TABP with CHD. We need further investigation to confirm its association with social and economic change to achieve better health management and promotion in working populations.

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LETTER

Seaweed as a Beneficial Iodine Food Source

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Vitti and colleagues (2003) have discussed iodine deficiency in Europe and have launched programs to eradicate the malady. The problem still remains worldwide, however, as stressed by WHO (2001). A clue to how it may be overcome is provided by the finding by Koutras et al (2003) that iodine deficiency is no longer a problem in Greece due to improvement in socioeconomic and nutritional conditions, and increased use of produced foods. We here would like to propose the consumption of seaweeds not only as a good source of iodine but also from the overall nutritional perspective.

There are few people suffering from iodine deficiency in Japan because people often consume seaweeds (or kelp) in addition to fish, chicken eggs, milk, and dairy products (Health Promotion and Nutrition Division, 2003; Tokudome et al., 2002). Seaweeds are particularly rich in iodine, at 100-1,000 times the level in fish. For example, kombu, a typical and commonly consumed seaweed, contains more than 100,000μg of iodine/100g, while sardine and horse mackerel, as examples of fish with the highest iodine concentrations, feature only approximately 250μg of iodine/100g (Science and Technology Agency, Japan, 2001). Japanese chicken eggs are also rich in iodine because chickens receive bone meal and shells as a supplementation for minerals, including calcium, in particular.

Seaweeds also contain vitamins and dietary fiber (Science and Technology Agency, Japan, 2001). Important minerals in seaweeds other than iodine are calcium and iron. Vitamins include vitamin B complex, folic acid and carotenoids including α- and ß-carotenes, chlorophyll, and fucoxanthin, which act as anti-mutagens or anti-oxidants (Moore MA et al., 1998; World Cancer Research Fund/American Institute for Cancer Research, 1997). Water-soluble dietary fiber in seaweeds, in particular, may play roles in improving bacterial flora, ameliorating metabolism of carbohydrate, fat, cholesterol, and bile acids, and benefiting insulin resistance.

Fortified salt and other foods clearly can prevent iodine deficiency. However, we need to limit salt consumption because it is related to hypertension. Intake of seaweeds is advised not only for prevention of lifestyle-related diseases, including cancer, cardiovascular and cerebrovascular disease but also of iodine deficiency. Furthermore, seaweed is a very palatable food because it contains glutamic acid providing a pleasant taste. Eating seaweeds has thus far been largely limited to certain Asian-Pacific countries/areas, but people worldwide could enjoy those well-balanced healthy sea vegetables as ample natural food resource if we can maintain our surrounding seas free from pollution.

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A prospective study on the possible association between having children and colon cancer risk: Findings from the JACC Study

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If having children is regarded as an exposure in life, its effect on a host could be considered as being due to female sex hormones associated with pregnancy in women and some lifestyle factors associated with large families in both men and women. To explore the roles of having children in the etiology of colon cancer, we examined 36,629 women and 24,877 men aged 40–79 years who completed a questionnaire on the number of children and other lifestyle factors from 1988 to 1990 in the Japan Collaborative Cohort Study for Evaluation of Cancer Risk. During 291,080 and 200,648 person-years of follow-up, we documented 198 female and 202 male incident colon cancers, respectively. After adjusting for some factors known or suspected to modify the risk of colon cancer, compared with the women with no children, the multivariate-adjusted relative risks of colon cancer were 0.74 (95% confidence interval [CI]: 0.30–1.84) for one child, 1.00 (95% CI: 0.46–2.20) for two, 0.70 (95% CI: 0.31–1.55) for three, and 0.59 (95% CI: 0.26–1.33) for four or more. The risk of colon cancer showed a significantly monotonic decrease with increasing number of children (*P* value for trend=0.047). There was no association between the number of children and colon cancer risk among men. From these prospective data, having children may reduce risk of colon cancer among women, but not among men, suggesting that modifications of hormone profiles secondary to pregnancies may influence female colon cancer risk. (Cancer Sci 2004; 95: 243–247)

If having children is regarded as an exposure in life, its effect on a host might arise in two ways. One would be through the changes in female sex hormones associated with pregnancy among women. The other could be changes in some lifestyle factors associated with large families in both men and women.

Most of the hormone-dependent cancers such as breast, ovarian, endometrial, and prostatic cancers are sex-specific. Although colon cancer is frequent among both men and women, it has been suggested to share etiologic factors common to cancers of the breast and reproductive organs in women.[1,2] The hypothesis that parity may be important in the etiology of female colon cancer has been tested in a considerable number of epidemiological studies.[3–26] Several mechanisms have been suggested to explain a positive protective effect of pregnancy. These include modifications of hormone profile secondary to pregnancies and their effects on bile acid metabolism[27,28] and immunological influences of ABO-incompatible fetal antigens.[29] It has also been claimed that some lifestyle factors associated with large families, such as physical activity, may account for a substantial part of the protective effect.[3]

Despite reasonable biological mechanisms, as mentioned above, the results from epidemiological studies,[3–26] mainly those with case-control study design,[10–26] have been conflicting. The limitation of case-control studies in assessing lifestyle characteristics predating the disease may account for some of the observed inconsistencies.

Thus, we examined the influence of having children on colon cancer in both men and women by means of a prospective study design. Examining the effects of having children on colon cancer risk among men will be helpful in verifying the hypothesis that its protective effect may be due to some lifestyle factors associated with large families. Moreover, we examined the influence of children's gender on colon cancer from the viewpoint of the difference in hormonal factors associated with fetal gender.

Materials and Methods

The JACC study. The Japan Collaborative Cohort Study for Evaluation of Cancer Risk, the JACC Study (sponsored by the Ministry of Education, Culture, Sports, Science and Technology of Japan) is a nationwide multicenter collaborative study to prospectively evaluate the effects of various risks and/or protective factors on cancer mortality and incidence. Study methods and ethical issues have been described in detail elsewhere.[30] Briefly, our study was initiated in 1988, and enrollment continued until the end of 1990. We enrolled 127,477 apparently healthy inhabitants in these areas with completion of the questionnaire. Two strategies were applied to obtain informed consent for participation in the majority of study areas, i.e., by asking individuals to sign the cover page of the questionnaire, or at the group level by explaining the aim of the study and the confidentiality of the data to community leaders. Of 127,477 enrolled, 110,792 (46,465 men and 64,327 women), aged 40–79 years, were followed up.

Subjects for the present analysis were restricted to 65,184 individuals who lived in 24 study areas, where cancer registries are available. Of 65,184 participants, we excluded from analysis 26 subjects with a history of colon cancer at baseline, 619 subjects who had less than 1 year of follow-up time, and 3103 with an unknown number of children, leaving 61,506 eligible subjects (24,877 men and 36,629 women) for the analysis.

Data collection. A self-administered questionnaire was used to assess the baseline characteristics of participants. It covered

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medical history and included lifestyle-related items such as diet, physical activity, drinking, smoking, and family history of several medical conditions including cancer. Reproductive histories were asked only among women. It also included questions about the numbers of sons and daughters. The number of sons plus the number of daughters was defined as the total number of children. We divided the number of children into five categories: no child, one, two, three, and four or more children. As regards the children's gender, we also created three categories: only female, only male, and mixed. Due to missing values for certain variables, the total number of cases and person-years of follow-up varied somewhat between analyses.

Follow-up and identification of colon cancer cases. We used population registries in local municipalities to determine the vital and residential status of the subjects. Registration of death is required by the Family Registration Law in Japan and is enforced throughout the country. For logistical reasons, we discontinued the follow-up of subjects who moved out of their study areas.

We ascertained the incidence of cancer by consulting the records of population-based cancer registries, supplemented by a systematic review of death certificates. In some areas, medical records were also reviewed in local major hospitals. The follow-up was conducted from the time of the baseline survey through to the end of 1997, except for three areas where it ended in 1994, 1995, and 1996.

The incidence to death ratio for colon cancer was 2.57 in the cohort covered by cancer registries. This figure is comparable with those in acceptably accurate population-based cancer registries in Japan[31] (1.69 to 3.45) and indicates that a reasonably high proportion of colon cancer cases was identified.

Finally, the mean follow-up period was 7.6 years (7.7 years for men and 7.6 years for women). During 200,648 and 291,080 person-years of follow-up, 202 male and 198 female incident colon cancers were identified.

Statistical analysis. In the present study, variables of interest are the total number of children and the gender of children. For each participant, the person-years of follow-up were calculated from the date of filling out the baseline questionnaire to development of colon cancer, death from any cause, moving out of the study area, or the end of the follow-up period, whichever occurred first. Those who died from causes other than colon cancer or moved out of the study areas were treated as censored cases.

We used a Cox proportional hazards model to compute relative risks (RRs), adjusted for age at enrollment. In another multivariate analysis, smoking status (never, past, current), alcohol drinking habit (none, past, present), exercise: "How long do you take exercise or sports in a week?" (≥5, 3–4, 1–2 h per week, seldom), spinach and green leafy vegetable intake (3–7, 1–2 days per week, seldom), meat intake (3–7, 1–2 days per week, seldom), family history of colon cancer (yes, no), and body mass index (≤18.5, 18.5–<22.0, 22.0–<25.0, ≥25.0 kg/m^2) were further adjusted. Menopausal status (yes/no) and age at menarche were additionally adjusted among women. These variables were assessed by the baseline questionnaire and were selected as covariates because they were known or suspected to modify the risk of colon cancer. In the analysis, all variables were entered as dummy variables except for age at enrollment. Missing values for each covariate were treated as an additional category in the variable and were included in the model. A linear trend of association was assessed by means of a regression model assigning scores (0, 1, 2, ...) to the levels of the independent variable.

All data were analyzed using SAS software. The 95% confidence intervals (CIs) are presented for all RRs. All P values were based on 2-sided tests, and $P<0.05$ was considered statistically significant.

Results

Characteristics of the subjects according to the number of children among women. Table 1 summarizes background characteristics of the women. Those who have more children were likely to be older. The proportions of current smokers and alcohol drinkers decreased with increase of the number of children. The mean values of BMI and age at menarche increased with the number

Table 1. Characteristics of the subjects according to the number of children among women

Characteristics	Number of children					P for difference[2]	P for trend[3]
	0 (n=1,317)	1 (n=3,088)	2 (n=13,858)	3 (n=11,720)	≥4 (n=6,646)		
Age (years)[1]	59.9	58.3	54.7	57.2	66.4	<0.01	<0.01
Current smoker (%)	7.7	9.0	5.0	3.9	4.4	<0.01	<0.01
Current alcohol drinker (%)	22.4	24.4	25.8	23.0	19.5	<0.01	<0.01
Familial history of colon cancer (%)	0.8	1.1	1.0	1.1	0.9	0.73	0.65
Body mass index (kg/m^2)[1]	22.5	22.6	22.9	23.0	23.0	<0.01	<0.01
Age at menarche (years)[1]	15.1	14.9	14.7	14.9	15.4	<0.01	<0.01
Menopause (%)	60.4	68.6	62.4	67.2	80.8	<0.01	<0.01
Exercise (h/week) (%)							
≥5	4.3	3.8	3.2	4.1	6.9		
3–4	5.0	4.3	5.1	5.3	7.6	<0.01	<0.01
1–2	14.0	14.6	14.8	14.0	13.2		
Seldom	76.7	77.4	76.9	76.7	72.4		
Meat intake (day/week) (%)							
Seldom	31.2	26.7	21.2	21.4	29.7		
1–2	32.5	33.7	34.6	33.8	32.8	<0.01	<0.01
3–7	36.3	39.7	44.2	44.8	37.5		
Green leafy vegetables intake (day/week) (%)							
Seldom	7.8	7.6	7.8	7.3	8.2		
1–2	27.5	27.2	27.8	28.6	26.4	0.13	0.97
3–7	64.7	65.2	64.4	64.1	65.4		

1) Mean value.
2) Pearson χ^2 test or analysis of variance (ANOVA).
3) Mantel-Haenszel χ^2 test or trend analysis in a one-way ANOVA (PROC GLM with CONTRAST statement in SAS).

of children. The rate of menopause also became higher as the number of children increased. Those with more children tended to take more time to exercise and to consume more meat.

Characteristics of the subjects according to the number of children among men. Table 2 shows background characteristics of the men. The men who have more children were also likely to be older and the proportion of current smokers decreased with increase of the number of children. Those with more children tended to exercise and to consume meat more frequently. The men seemed to consume less green leafy vegetables than the women but those with more children were likely to consume more green leafy vegetables.

Association of having children with the risk of colon cancer. Table 3 presents the age-adjusted and multivariate RRs for colon cancer by the number of children. Compared with the women with no children, the multivariate-adjusted RRs of colon cancer were 0.74 (95% CI: 0.30–1.84) for one child, 1.00 (95% CI: 0.46–2.20) for two, 0.70 (95% CI: 0.31–1.55) for three, and 0.59 (95% CI: 0.26–1.33) for four and more. The risk of colon cancer showed a significant monotonic decrease with increasing number of children (P value for trend=0.047). However, there was no association between the number of children and colon cancer risk among men.

Association of children's gender with the risk of colon cancer. We also examined the risks for colon cancer by gender of children. The gender of children was not associated with risk of colon cancer among either women or men.

Discussion

In our prospective study, we observed a statistically significant protective effect of having children against development of colon cancer among women, and the effect was independent of lifestyle factors known to modify the risk of colon cancer. However, there was no association between having children and the risk of colon cancer among men.

It is thought that having children may be related to the development of colon cancer in females through two mechanisms. One mechanism is based on participation of female sex hormones and the other is based on the lifestyle factors related to

Table 2. Characteristics of the subjects according to the number of children among men

Characteristics	Number of children					P for difference[2]	P for trend[3]
	0 (n=871)	1 (n=1,891)	2 (n=10,089)	3 (n=8,414)	≥4 (n=3,612)		
Age (years)[1]	57.3	56.7	55.3	57.8	66.7	<0.01	<0.01
Current smoker (%)	53.7	53.5	52.5	51.8	50.6	0.18	<0.05
Current alcohol drinker (%)	67.8	72.7	76.4	77.6	68.4	<0.01	0.15
Familial history of colon cancer (%)	1.0	0.8	1.0	1.0	0.9	0.87	0.74
Body mass index (kg/m^2)[1]	22.5	22.6	22.7	22.7	22.2	<0.01	0.17
Exercise (h/week) (%)							
≥5	6.1	5.5	5.9	6.5	10.9		
3–4	6.7	6.4	7.3	7.7	10.0	<0.01	<0.01
1–2	17.9	17.2	18.6	18.0	16.4		
Seldom	69.4	71.0	68.2	67.8	62.7		
Meat intake (day/week) (%)							
Seldom	32.2	26.4	23.2	23.1	26.0		
1–2	32.4	36.8	36.9	35.6	35.4	<0.01	<0.01
3–7	35.4	36.8	39.9	41.3	38.7		
Green leafy vegetables intake (day/week) (%)							
Seldom	15.3	13.1	12.4	10.4	10.4		
1–2	30.9	30.6	32.1	30.8	28.5	<0.01	<0.01
3–7	53.8	56.3	55.5	58.8	61.2		

1) Mean value.
2) Pearson χ^2 test or analysis of variance (ANOVA).
3) Mantel-Haenszel χ^2 test or trend analysis in a one way ANOVA (PROC GLM with CONTRAST statement in SAS).

Table 3. Relative risk (RR) and 95% confidence interval of colon cancer according to the number of children

	Number of children					P for trend
	0	1	2	3	≥4	
Women						
Number of cases	10	16	69	53	50	
Person-years of follow up	10,250	22,560	105,471	90,520	49,821	
Age-adjusted RR	1.00	0.83 (0.38–1.83)	1.02 (0.52–2.00)	0.74 (0.38–1.46)	0.70 (0.35–1.38)	0.09
Multivariate RR[1]	1.00	0.74 (0.30–1.84)	1.00 (0.46–2.20)	0.70 (0.31–1.55)	0.59 (0.26–1.33)	<0.05
Men						
Number of cases	6	14	74	77	31	
Person-years of follow up	6885	14,245	78,181	65,783	26,515	
Age-adjusted RR	1.00	1.22 (0.47–3.18)	1.29 (0.56–2.96)	1.35 (0.59–3.10)	0.87 (0.36–2.09)	0.46
Multivariate RR[1]	1.00	1.03 (0.39–2.68)	1.07 (0.46–2.48)	1.12 (0.49–2.57)	0.72 (0.30–1.74)	0.30

1) Adjusted for age at baseline, smoking status (never, past, current), alcohol consumption (none, past, regular), exercise (≥5, 3–4, 1–2 days/week, seldom), meat intake (3–7, 1–2 days/week, seldom), green leafy vegetable intake (3–7, 1–2 days/week, seldom), family history of colon cancer (yes, no) and BMI at baseline (<18.5, 18.5–<22, 22–<25, 25–kg/m^2). Additionally adjusted for menopausal status and age at menarche among women.

large families. Many studies[3–26] have investigated the effect of parity on colon cancer risk. There has been evidence of a protective effect of parity in less than half[12, 14, 19, 20, 22, 23] of the 17 case-control studies[10–26] and only two[3, 6] of the seven published prospective studies[3–9] have shown non-significant inverse associations between parity and colon cancer.

Several mechanisms have been suggested to explain a protective effect of pregnancy on colon cancer. The bile acid hypothesis was suggested by McMichael and Potter.[27, 28] Female sex hormones influence the hepatic cholesterol metabolism and bile production. Progestins in pregnancy reduce hepatic clearance of plasma cholesterol and reduce bile production and thus may decrease the risk of colon cancer. The ABO-incompatible fetal antigen hypothesis was suggested based on the fact that the protective effect of multiple pregnancies was limited to women with blood group O in a case-control study.[29] However, we could not analyze that effect due to the lack of data on blood groups.

Alternatively, parity may be a surrogate for other exposures relevant to colon cancer risk. Physical activity associated with large families has been suggested as such an exposure.[3] In our study, the women with more children were likely to take more time to exercise at baseline. However, the protective effect of having children was unchanged after adjustment for physical activity besides smoking, alcohol intake, and diet. These findings suggest that having children may be associated with reduced risk for developing female colon cancer independently of lifestyle factors associated with large families.

To some extent, a high-parity lifestyle, whatever that may include, is shared by both parents. Therefore, it is interesting to elucidate the effect of having children on colon cancer in men when we study epidemiologically the mechanisms underlying the protective effect of having children on female colon cancer. In our study, the lifestyle characteristics according to the number of children showed a similar pattern in men and women. Previously, only four studies[3, 6, 14, 19] have analyzed the effects of having children in men. One[19] of them reported a significant and protective effect of having children and the others found no significant effect. There was also no association of having children with the risk of colon cancer among men in our study. The mother's use of time may be more strongly correlated with her familial obligations than that of the father. More research on gender-specific differentials of having children in important lifestyle factors is needed. The independent protective effect of having children on female colon cancer observed in our study may be due to some as-yet unidentified factors specific to the women, such as social, or psychological factors.

To our knowledge, this is the first study to examine whether gender difference of children affects colon cancer risk. A few studies[32–34] have examined whether the gender of the fetus influences subsequent maternal breast cancer risk, since gender differences in the maternal levels of serum hormone-binding globulin, α-fetoprotein, and chorionic gonadotrophin have been reported that might be related to maternal breast cancer. One study[31] found that deliveries of male offspring had a protective effect, but the others[32, 33] reported no modification. Thus, we tried to study whether gender difference of children affects colon cancer risk. Although the women with male offspring only had a statistically non-significant and low risk for colon cancer, the gender of children does not seem likely to influence colon cancer risk. However, this needs to be investigated further.

The strengths of the present study include its prospective design and large size. Data on exposure were collected before diagnosis and incidence of colon cancer, which should preclude recall bias. Moreover, since data on many kinds of exposure known or suspected to modify the risk of colon cancer were collected in the present study, we could elucidate the independent effects of reproductive factors by multivariate adjustment. The first limitation of this study is in the absence of information about specific subsites of origin in the large bowel, since it has been suggested that the influence of sex hormones should be greater on, or restricted to, the right side of the large bowel.[28] Second, our study showed an independent protective effect of having children on female colon cancer by multivariate-adjusted model. But, we did not have information on lifestyle during the child-rearing years.

In summary, the present prospective study showed a significant inverse association of having children with colon cancer risk among women, but not among men, independently of some lifestyle factors. These results suggest that modifications of hormone profiles secondary to pregnancies may influence female colon cancer risk. Our study also provides additional support for the earlier suggestions by McMichael and Potter *et al.* However, some as-yet identified factors which are related to large families and specific to the women may exist.

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PAPER

A prospective study of body size and colon cancer mortality in Japan: The JACC Study

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OBJECTIVE: To determine whether body size measurements are risk factors for colon cancer death among the Japanese.
DESIGN AND SUBJECTS: A nationwide prospective study, the Japan Collaborative Cohort (JACC) Study from 1988 to 1999. The present analysis included 43 171 men and 58 775 women aged 40–79 y who respond to a questionnaire on current weight and height, weight around 20 y of age, and other lifestyle factors. Body mass index (BMI) at baseline and 20 y of age (B-BMI and 20-BMI, respectively) were calculated.
RESULTS: We identified 127 deaths from colon cancer during the follow-up of 424 698 person-years among men and 122 deaths during the follow-up of 591 787 person-years among women. After adjustments for the lifestyle factors known to modify the risk of colon cancer, weight at baseline showed a significant positive association in women, while no such association was seen in men. There was also a significant trend of increasing risk with the increase in B-BMI among women. Women with B-BMI $\geq 28\,kg/m^2$ had a relative risk (RR) of 3.41 (95% confidence interval (CI): 1.44–8.06) compared with those with BMI of 20–$<22\,kg/m^2$. 20-BMI also presented the same trend of increasing risk as B-BMI. Women with 20-BMI of <22 and B-BMI of $>26\,kg/m^2$, that is, excessive BMI gain, had a high RR of 3.41 (95% CI 1.29–9.02) compared with those with 20-BMI of <22 and B-BMI of $<22\,kg/m^2$. There were no corresponding trends of colon cancer risk for B-BMI, 20-BMI, or BMI change among men.
CONCLUSIONS: These study data suggest that obesity and excessive weight gain are associated with the risk of colon cancer death in Japanese women but no such relationship was found in Japanese men.
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Keywords: body size; body mass index; weight change; colon cancer; cohort study

Introduction

Colon cancer is now the fourth leading cause of cancer death among men and the third among women in Japan. This malignancy has markedly increased since the end of World War II. The ratio of the age-adjusted rate (adjusted by the 1985 Japanese model population) in 1999 to that in 1960 was 4.1 (from 3.6 to 14.7 per 100 000 population) and 2.7 (from 3.6 to 9.8 per 100 000 population) among men and women, respectively.[1] International comparison studies[2] and observations[3] of increased rates in subjects who migrate from low- to high-risk regions indicate that westernization or industrialization may lead to an increase in the rates of colon cancer. Although the precise causes of colon cancer remain unclear, various dietary components such as high consumption of red meat or animal fat, physical

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inactivity, and obesity have been studied as possible risk factors.[4–27]

Despite the number of prospective[4–18] and case–control[19–27] studies that have examined the association between body size and colon cancer in greater or lesser detail, the evidence of obesity as a risk factor is inconclusive. Several studies[4–13,19,22–24] have found positive associations between body mass and risk of colon cancer in men, whereas most of the studies[4–7,9,14–16,20–26] in women suggested either no association or only weakly positive associations. A few studies[8,17] have shown that obesity is indeed related to colon cancer in women. Some studies[20,26] found no association in either men or women, and one study[18] reported that men who developed colon cancer weighed slightly less than those who did not. Height also appeared to be associated with an increased risk of colon cancer in some studies,[11] but not all.[25] Few studies, however, have been addressed the effect of body size on colon cancer risk among Asians, who are generally shorter and leaner than Occidentals among whom the incident and mortality rates of colon cancer are higher. Since the prevalence of obesity has gradually increased in Japan in recent years, it is important to characterize its role in colon cancer mortality.

To elucidate the effects of body size on the risk of colon cancer death among Japanese, we prospectively examined the associations of height, weight and body mass index (BMI) at baseline (B-BMI), BMI around age 20 (20-BMI), and BMI change with colon cancer among Japanese men and women, using nationally representative large-scale cohort data.

Subjects and methods

JACC study

The Japan Collaborative Cohort Study for Evaluation of Cancer Risk, the JACC Study (sponsored by the Ministry of Education, Culture, Sports, Science, and Technology of Japan), is a nationwide multicenter collaborative study to prospectively evaluate various risks or preventive factors as they relate to cancer mortality and incidence. Study methods and ethical issues have been described in detail elsewhere.[27] Briefly, our study was initiated in 1988, and enrollment was continued until the end of 1990. Subjects were followed until the end of 1999 unless they had moved out of the study areas. A total of 45 municipalities were involved in this prospective study, including six cities (35% of the cohort population) and 34 towns and five villages (65%). These municipalities were selected from seven out of eight districts in Japan, thus covering almost the entire country. Enrollment was based on the participants in general health checkups periodically provided by these municipalities. We enrolled 127 477 apparently healthy inhabitants of these areas who had completed the questionnaire. Two strategies were applied to obtain informed consent for participation: in the majority of study areas. In some areas consent was obtained by signing the cover page of the questionnaire. In others, it was obtained at the group level by explaining the aim and confidentiality of the data to leaders of the community. Of 127 477 participants enrolled, 110 792 (46 465 men and 64 327 women) aged 40–79 y were followed up for mortality to the end of 1999.

The Ethics Committee of Fujita Health University approved this investigation.

Present study subjects

Of 110 792 subjects enrolled, we excluded from analysis 1258 with a history of any cancers at baseline, 6070 of unknown height, and 4393 of unknown weight. We also excluded subjects with extreme height (<120 cm or ≥200 cm: 47 subjects), weight (<30 kg or ≥120 kg: 27 subjects), or calculated BMI (<15 kg/m^2 or ≥45 kg/m^2: 201 subjects). To minimize confounding the data by undiagnosed diseases, we further excluded 933 subjects who had less than 1 year of follow-up time. Therefore, 43 171 men and 58 775 women were finally enrolled in the present study. In another analysis of the effects of BMI around aged 20 y and BMI change on colon cancer risk, we further excluded 27 483 subjects of unknown weight around 20 y of age, 65 extremely under- or overweight subjects (<30 kg or ≥120 kg), and 143 subjects with extreme calculated 20-BMI (<15 kg/m^2 or ≥45 kg/m^2). This left 31 585 men and 42 735 women eligible for the second analysis.

Data collection

A self-administrated questionnaire was used to assess baseline characteristics of the participants. It covered medical history and included lifestyle-related items such as diet, physical activity, drinking and smoking, and family history of several medical conditions including cancer. In the questionnaire, weight in kilograms and height in centimeters were entered by participants after the words 'Current weight and height' and 'Weight around 20 y of age'. BMI at baseline was computed as current weight in kilograms divided by current height in square meters. 20-BMI was also computed as weight around 20 y of age in kilograms divided by current height in square meters.

Follow-up and identification of colon cancer cases

Our primary end points were death from any causes or 31 December 1999 (censored). Those who had moved away were also treated as censored. The mean follow-up period was 10.0 y (9.8 y for men and 10.1 y for women).

The vital status of subjects was checked annually in each study area by reviewing their population register sheets from the Ministry of Public Management, Home Affairs, Post and Telecommunications. For the deceased, causes of death were determined by death certificates available from the Ministry of Health, Labor and Welfare and coded according to the ninth revision of International Classification of Diseases (ICD-9) by the end of 1994 and according to ICD-10 from

1995. Colon cancer cases were defined by 153.0–153.9 (ICD-9) or C18.0–C18.9 (ICD-10). Certification of vital status was believed to be accurate because of the firmly established population registration system in Japan.

Statistical analysis

In the present study, variables of interest are current weight and height, B-BMI, 20-BMI, and BMI change. Tertiles of weight and height were defined separately for men and women from the distribution of total study subjects. BMI categories were defined as follows: <20.0, 20.0–<22.0, 22.0–<24.0, 24.0–<26.0, 26.0–<28.0, ≥28.0 kg/m^2 to enable a detailed examination of the association of BMI and colon cancer mortality. In the analysis of BMI change, these six categories were combined into three (<22.0, 22.0–<26.0, ≥26.0), and the subjects were divided into nine groups of B-BMI/20-BMI combinations.

For each participant, the person-years of follow-up were calculated from the date of filling out the baseline questionnaire to death, moving away from the community, or the end of 1999, whichever occurred first. We used Cox proportional hazards modeling to compute relative risks (RRs), adjusting for age at enrollment. In another multivariate analysis, further adjustments were made to smoking status (never, past, current), alcohol drinking habit (none, past, present), exercise (≥5, 3–4, 1–2 hours per week, seldom), green leafy vegetable intake (3–7, 1–2 days per week, seldom), meat intake (3–7, 1–2 days per week, seldom), and family history of colon cancer. These variables were assessed by the baseline questionnaire and were selected as covariates because they were known or suspected to modify the risk of colon cancer. In the analysis, all variables were entered as dummy variables except for age at enrollment. Tests for trends were performed by modeling the categories of variable of interest as equally spaced ordinal variable.

All data were analyzed using SAS (Statistical Analysis System) software. The 95% confidence intervals (CIs) were presented for all RRs. All *P*-values were based on two-sided tests, and $P<0.05$ was considered statistically significant.

Results

We identified 127 deaths from colon cancer during the follow-up of 424 698 person-years among men and 122 deaths during the follow-up of 591 787 person-years among women.

The associations of weight and height at baseline with colon cancer death risk by gender are presented in Tables 1 and 2. In multivariate analysis, weight at baseline showed a significant positive association in women, while no corresponding association was seen in men. We compared RRs among the nine categories of weight/height combinations to assess the effects of weight and height. Among men, the tallest were likely to show elevated RR at each stratum of weight, but no significant association was seen. RRs in light (<49.0 kg) and tall (≥153.1 cm) women were significantly higher (RR 3.48, 95% CI 1.27–9.50) than in women who were light and short (<149.0 cm). Women who were heavy (≥55.1 kg) and short, and those who were heavy and

Table 1 Adjusted relative risk (RR) for colon cancer death by weight and height at baseline among men, JACC study, 1988–1999

Baseline weight and height		*No. of deaths*	*Person-years*	*RR*[a]	*95% CI*	*RR*[b]	*95% CI*
Weight (kg)							
Lowest tertile (<56.0)		52	136 639	1.00		1.00	
Tertile 2 (56.0–<63.1)		37	145 847	0.95	0.62–1.46	0.90	0.52–1.55
Highest tertile (63.1–)		38	142 212	1.29	0.83–1.99	1.13	0.64–1.99
P-value for trend					0.30		0.72
Height (cm)							
Lowest tertile (<160.1)		55	153 418	1.00		1.00	
Tertile 2 (160.1–<165.1)		37	134 638	1.04	0.68–1.59	0.97	0.55–1.71
Highest tertile (165.1–)		35	136 642	1.34	0.87–2.08	1.58	0.91–2.73
P-value for trend					0.21		0.12
Weight (kg) and height (cm)							
Weight	Height						
<56.0	<160.1	33	84 550	1.00		1.00	
<56.0	160.1–<165.1	13	36 814	1.12	0.59–2.13	1.11	0.48–2.54
<56.0	165.1–	6	15 275	1.43	0.60–3.41	1.51	0.51–4.45
<56.0–<63.1	<160.1	13	49 754	0.87	0.46–1.65	0.77	0.32–1.84
<56.0–<63.1	160.1–<165.1	14	54 032	1.07	0.57–2.01	0.79	0.33–1.90
<56.0–<63.1	165.1–	10	42 062	1.22	0.59–2.50	1.58	0.70–3.57
63.1	<160.1	9	19 114	1.73	0.83–3.63	1.26	0.42–3.72
63.1	160.1–<165.1	10	43 792	1.04	0.51–2.13	0.92	0.36–2.34
63.1	165.1–	19	79 306	1.50	0.83–2.71	1.45	0.69–3.07

[a]Adjusted for age at baseline. [b]Adjusted for age at baseline, smoking status (never, past, current), alcohol consumption (none, past, regular), exercise (≥5, 3–4, 1–2 days/week, seldom), meat intake (3–7, 1–2 days/week, seldom), green leafy vegetable intake (3–7, 1–2 days/week, seldom) and family history of colon cancer.

Table 2 Adjusted RR for colon cancer death by weight and height at baseline among women, JACC study, 1988–1999

Baseline weight and height		*No. of deaths*	*Person-years*	*RR*[a]	*95% CI*	*RR*[b]	*95% CI*
Weight (kg)							
Lowest tertile (<49.0)		39	189 958	1.00		1.00	
Tertile 2 (49.0–<55.1)		46	214 488	1.49	0.97–2.29	1.87	1.06–3.29[e]
Highest tertile (55.1–)		37	187 341	1.65	1.04–2.62[e]	2.17	1.21–3.92[d]
P-value for trend					<0.05		<0.01
Height (cm)							
Lowest tertile (<149.0)		45	185 721	1.00		1.00	
Tertile 2 (149.0–<153.1)		43	208 873	1.26	0.83–1.92	1.30	0.77–2.19
Highest tertile (153.1–)		34	197 193	1.54	0.97–2.44	1.38	0.77–2.48
P-value for trend					0.07		0.26
Weight (kg) and height (cm)							
Weight	Height						
<49.0	<149.0	22	98 645	1.00		1.00	
<49.0	149.0–<153.1	9	61 920	0.93	0.43–2.02	0.62	0.17–2.23
<49.0	153.1–	8	29 393	2.24	0.99–5.05	3.48	1.27–9.50[e]
49.0–<55.1	<149.0	15	60 270	1.39	0.72–2.69	1.77	0.75–4.18
49.0–<55.1	149.0–<153.1	17	85 371	1.56	0.82–2.96	2.15	0.94–4.92
49.0–<55.1	153.1–	14	68 847	2.29	1.15–4.55[e]	2.71	1.10–6.71[e]
55.1–	<149.0	8	26 806	1.83	0.81–4.11	3.24	1.30–8.08[e]
55.1–	149.0–<153.1	17	61 582	2.30	1.21–4.38[e]	3.45	1.54–7.71[d]
55.1–	153.1–	12	98 953	1.45	0.70–2.98	1.27	0.46–3.53

[a]Adjusted for age at baseline. [b]Adjusted for age at baseline, smoking status (never, past, current), alcohol consumption (none, past, regular), exercise (≥5, 3–4, 1–2 days/week, seldom), meat intake (3–7, 1–2 days/week, seldom), green leafy vegetable intake (3–7, 1–2 days/week, seldom) and family history of colon cancer. [d]$P<0.01$. [e]$P<0.05$.

medium height (149.0–<153.1 cm) had multivariate-adjusted RRs of 3.24 (95% CI 1.30–8.08) and 3.45 (95% CI 1.54–7.71), respectively, compared with light and short women. However, the RR for tall and heavy women was 1.27 (95% CI 0.46–3.53).

The relations between B-BMI and BMI in young adults (20-BMI), and colon cancer death risk by gender are shown in Table 3. Among men, those with B-BMI of <20.0 had a significantly lower RR (0.44, 95% CI 0.21–0.93) than those with BMI of 20–<22. 20-BMI in men also showed no association with risk. In contrast, there was a significant trend of increasing risk with the increase in B-BMI among women. The strongest association was for the highest category (B-BMI ≥28) (RR 3.41, 95% CI 1.44–8.06). 20-BMI of women also presented the same trend of increasing risk as B-BMI. 20-BMI was significantly correlated with B-BMI among both men and women (Pearson $r=0.52$, $P<0.0001$, and $r=0.45$, $P<0.0001$, respectively).

We compared RRs among the nine categories of 20-BMI/B-BMI combinations to assess the effects of 20-BMI and B-BMI, and the effect of BMI change (Table 4). When the subjects with low 20-BMI (<22.0) and low B-BMI (<22.0) were referenced, no association was seen in men by multivariate analysis, whereas the RR of women with medium 20-BMI (22–<26) and B-BMI (22–<26) was 2.01 (95% CI 1.02–3.97), and those with high 20-BMI (≥26) and B-BMI (≥26) was 3.33 (95% CI 1.46–7.63). We also found that women with low 20-BMI and high B-BMI, that is, excessive BMI gain, had a high RR of 3.41 (95% CI 1.29–9.02).

Discussion

In Japan, the incidence and mortality rate of colon cancer are much lower than that in Western countries. This difference may be attributed in part to the fact that both Japanese men and women are generally shorter and lighter than Occidentals. Therefore, we examined whether BMI exhibited a positive association with colon cancer in such a low-risk population, as had been observed in some Western countries. Interestingly, in the Japanese population, BMI at entry into the study was strongly predictive of colon cancer over the almost 10-year follow-up period only among women but not among men.

Among prospective studies,[4–18] at least six[4–9] included both men and women and presented separate estimates of RR of obesity for colon cancer. All six studies showed positive associations in men, but only two[6,8] reported positive associations in women. As for the role of obesity in the etiology of colon cancer, Giovanucci[28] has proposed that obesity results in insulin resistance, and that the resulting prolonged elevated insulin levels may increase colon cancer risk by acting as a tumor growth promoter or mitogen. Mckeown-Eyssen[29] also suggested that the serum levels of glucose and triglycerides, which tend to be higher in obese people, may affect the fecal bile acids that have been implicated in the pathogenesis of colon cancer.

Although the reasons for the gender difference in previous studies,[4,5,7,9] that is, that the association between increased BMI and colon cancer risk is stronger in men than in women, are not completely understood, the male tendency toward

Table 3 Adjusted RR for colon cancer death by BMI at baseline and around age 20 by gender, JACC study, 1988–1999

BMI	*No. of deaths*	*Person-years*	*RR*[a]	*95% CI*	*RR*[b]	*95% CI*
Men						
BMI at baseline (kg/m^2)						
<20	16	66 030	0.52	0.29–0.92[e]	0.44	0.21–0.93[e]
20–<22	42	111 439	1.00		1.00	
22–<24	33	119 748	0.80	0.51–1.26	0.63	0.35–1.11
24–<26	22	80 532	0.86	0.51–1.43	0.65	0.33–1.27
26–<28	12	31 691	1.24	0.65–2.36	0.73	0.28–1.90
28–	2	15 259	0.44	0.11–1.81	0.64	0.15–2.69
P-value for trend				0.32		0.97
BMI at around age 20 (kg/m^2)						
<20	11	52 202	0.87	0.40–1.67	0.89	0.42–1.90
20–<22	23	90 432	1.00		1.00	
22–<24	30	89 552	1.20	0.70–2.06	1.03	0.56–1.89
24–<26	14	46 620	1.00	0.51–1.94	1.09	0.54–2.20
26–<28	7	15 891	1.51	0.65–3.51	1.05	0.36–3.07
28–	2	8028	0.83	0.20–3.51	1.02	0.24–4.37
P-value for trend				0.42		0.68
Women						
BMI at baseline (kg/m^2)						
<20	24	93 436	1.28	0.72–2.28	1.61	0.73–3.56
20–<22	23	140 635	1.00		1.00	
22–<24	23	157 409	0.95	0.54–1.70	1.28	0.59–2.79
24–<26	26	110 785	1.50	0.86–2.63	2.23	1.06–4.68[e]
26–<28	12	54 934	1.37	0.68–2.75	2.27	0.96–5.35
28–	14	34 689	2.54	1.31–4.94[d]	3.41	1.44–8.06[d]
P-value for trend				<0.05		0.01
BMI at around age 20 (kg/m^2)						
<20	16	93 069	1.15	0.58–2.25	0.84	0.36–1.94
20–<22	18	117 956	1.00		1.00	
22–<24	22	106 907	1.25	0.67–2.233	1.17	0.57–2.40
24–<26	20	62 675	1.73	0.91–3.27	1.96	0.97–3.99
26–<28	11	25 559	1.99	0.94–4.23	2.54	1.15–5.64[e]
28–	5	12 976	1.68	0.62–4.54	1.36	0.39–4.75
P-value for trend				0.05		<0.01

[a]Adjsuted for age at baseline. [b]Adjusted for age at baseline, smoking status (never, past, current), alcohol consumption (none, past, regular), exercise (≥5, 3–4, 1–2 days/week, seldom), meat intake (3–7, 1–2 days/week, seldom), green leafy vegetable intake (3–7, 1–2 days/week, seldom) and family history of colon cancer. [d]$P<0.01$. [e]$P<0.05$.

central adiposity and higher insulin levels may play a significant role. Another potential explanation for the weak or no association between BMI and colon cancer in women seen in previous studies[4,5,7,9,14,15,20–24,26] may be the possible protective effects of estrogen. Estrogen replacement therapy appears to reduce colon cancer mortality.[30] In postmenopausal women, the conversion of androgens to estrogens by adipose tissue is thought to be the primary source of extra-ovarian estrogen production, and circulating bio-available estrogen increases with age and excess body fat.[31,32] In contrast, elevated estrogen levels as a consequence of obesity in men seems to lead to increased insulin resistance and elevated insulin.[33]

Why did our Japanese population study show a positive association between BMI and colon cancer shown in women but not in men? Both Japanese men and women have lower BMI than Occidentals (mean BMI at baseline in our study; men: 22.7 kg/m^2, women: 22.9 kg/m^2), possibly explaining our results. Since the degree of central or abdominal adiposity is low in Japanese men, the carcinogenetic effects of insulin resistance and hyperinsulinemia on colon cancer is considered to be weaker among them than among Occidental men. It is also supposed that the protective effect of extra-ovarian estrogen by body fat is weaker in Japanese women than in Occidental women. Recently, it was reported that obesity was associated with an increased risk of colon cancer in premenopausal but not postmenopausal Occidental women.[17] One hypothesis to explain this observation is that obesity increases risk through hyperinsulinemia; however, high estrogen levels associated with obesity in postmenopausal women may have a countering influence. The opposing influences of insulin and estrogen appear to approximately cancel each other out. In our study, however, a positive association of obesity with colon cancer risk was observed even among women aged 55 y or older, suggesting that the adverse influence of obesity on hyperinsulinemia may predominate.

Table 4 Adjusted RR for colon cancer death in nine groups according to BMI at baseline and around age 20 by gender, JACC study, 1988–1999

		BMI at baseline (kg/m²)					
		<22		*22–<26*		*26–*	
BMI around age 20 (kg/m²)							
Men							
<22	No. of deaths	24		9		1	
	Person-years	91 158		43 822		7653	
	RR[a] 95% CI	1.00		1.00	0.46–2.15	0.67	0.09–4.96
	RR[b] 95% CI	1.00		0.62	0.25–1.54	0.62	0.08–4.61
22–<26	No. of deaths	17		21		6	
	Person-years	31 958		92 988		11 227	
	RR[a] 95% CI	1.51	0.81–2.81	0.9	0.50–1.62	2.49	1.01–6.11[e]
	RR[b] 95% CI	1.37	0.71–2.64	0.7	0.37–1.33	1.59	0.55–4.64
26–	No. of deaths	0		4		5	
	Person-years	2125		7054		14 740	
	RR[a] 95% CI	—		1.71	0.59–4.93	1.48	0.56–3.89
	RR[b] 95% CI	—		1.73	0.60–5.03	0.65	0.15–2.77
Women							
<22	No. of deaths	23		5		6	
	Person-years	119877		72 788		18 359	
	RR[a] 95% CI	1.00		0.44	0.17–1.16	1.99	0.81–4.89
	RR[b] 95% CI	1.00		0.61	0.20–1.88	3.41	1.29–9.02[e]
22–<26	No. of deaths	9		28		5	
	Person-years	39 693		106235		23 654	
	RR[a] 95% CI	0.94	0.43–2.03	1.37	0.79–2.38	1.21	0.46–3.18
	RR[b] 95% CI	1.11	0.42–2.92	2.01	1.02–3.97[e]	1.64	0.53–5.05
26–	No. of deaths	0		5		11	
	Person-years	4045		11 630		22 860	
	RR[a] 95% CI	—		1.54	0.58–4.06	2.07	1.01–4.26[e]
	RR[b] 95% CI	—		2.15	0.70–6.63	3.33	1.46–7.63[d]

[a]Adjusted for age at baseline. [b]Adjusted for age at baseline, smoking status (never, past, current), alcohol consumption (none, past, regular), exercise (≥5, 3–4, 1–2 days/week, seldom), meat intake (3–7, 1–2 days/week, seldom), green leafy vegetable intake (3–7, 1–2 days/week, seldom) and family history of colon cancer. [d]$P<0.01$. [e]$P<0.05$.

In our study, in agreement with others,[34] the positive association of colon cancer risk with high BMI around age 20 seemed impressive in women but it may have been affected by inaccuracy in recalling weight. It may be also explained in part by the effect of B-BMI because 20-BMI is correlated with B-BMI. However, in fact, obesity has been shown to be associated with the risk of colorectal polyps.[11] Therefore, our data support the possibility that high BMI and/or factors related to positive energy balance in early life may act on the later as well as earlier stages of colon carcinogenesis.

We also found that women with low 20-BMI and high B-BMI had a high RR of 3.41 (95% CI 1.29–9.02) compared to those with low 20-BMI and low B-BMI. This result suggests that excessive BMI change, that is, high adult weight gain, is associated with a significant increase in the risk of colon cancer among women. For most women, weight gains occur during pregnancy and menopause, which are the very periods when women experience the major biological effects of hormonal changes. Possibly the time and/or age of weight gain may be critical in elucidating the association between weight change and colon cancer risk. The various effects of the time and/or age of weight change needs further investigation.

It was suggested that tall people among both men and women seemed to be at elevated risk of colon cancer even in the Japanese population which is shorter, although this association was not significant, and the underlying mechanism is unknown. Adult height may be a proxy of positive energy balance during childhood, and inadequate nutritional intake in early life will stunt overall growth and organ cellularity in particular.[35] Height also correlated closely with the total length of the human colon,[36] and the greater number of stem cells in tall people could increase their exposure to potential carcinogens.

The strengths of our study include its prospective design and large size. We could analyze both men and women by similar methods and were able to control for a large number of other potential risk factors. Limitations of the present study also warrant discussion. First, since our results were based on mortality data, they reflect the potential effects of body size not only on colon cancer incidence but also on survival or both. A second limitation is the reliance on

self-reported measurements of weight and height. It is well known that self-reported current weight and height, and past weight are influenced by factors such as gender and obesity. However, many studies[37–39] have reported that they were accurate enough to use in an epidemiologic study. Third, we have no information on colon cancer screening. If lean individuals are more likely to get colon cancer screening, they would be expected to have more diagnosed polyps and fewer invasive cancers. This potential bias could not be verified since we did not collect any information during follow-up about the subjects' screening participation. Fourth, we could not analyze by subsite of colon cancer because subsite data were not available.

In conclusion, there was a significant and positive association between BMI and colon cancer death in Japanese women but not in men. This association in women could be extended to lower BMI levels than that in Western populations. We also found that both obesity in early life and gains in adult body mass are predictors of colon cancer risk. The increased prevalence of obesity in Japan in recent years may bode ill for future trends in colon cancer incidence and mortality. The results of our study also suggested that the avoidance of excessive weight gain during adult life, that is, weight control may reduce colon cancer risk.

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CORRESPONDENCE

n-6 Polyunsaturated Fatty Acids and Breast Cancer

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Rissanen et al. (1) reported that the risk of breast cancer, the postmenopausal type in particular, might be decreased with elevated proportions (wt% of the total fatty acid, FA) of n-6 polyunsaturated fatty acids (PUFAs) and linoleic acid in the serum. It seems, however, incompatible with recent scientific findings (2–9): that is, n-6 PUFAs, possibly along with a high concentration of all FAs, are tumor promoters, as discussed by the authors, whereas n-3 PUFAs are anti–mutagenic/carcinogenic nutrients.

The authors should supply information on whether they collected blood under morning fasting conditions or on a spot sampling basis. If the latter, the data should be carefully assessed because the authors mention that they analyzed FAs using whole serum, not the cholesterol fraction. They might also provide values for triglycerides, which are affected by the immediate diet.

The authors showed no significant differences in the proportions of n-6 PUFAs between breast cancer cases and controls based on the *t*-test. However, they exhibited decreased odds ratios in proportion to the percentages of n-6 PUFAs. They could not detect any associations between concentrations of long-chain PUFAs and risk of breast cancer due to the degradation of relevant FAs in serum frozen for 25 yr at –20°C. Are there any plausible reasons that they noted contradictory results only in the comparisons for the first 10 yr? In other words, they may have found an opposite relationship using the remaining subjects because there were no differences in the whole series.

Finally, the authors should also provide the relevant data based on the absolute concentrations of FAs (mg/dl or mol/l), rather than percentages, to precisely clarify the effects of n-6 PUFAs, including arachidonic acid, an ultimate bioactive chemical of the eicosanoid cascade; competitive n-3 PUFAs, including α-linolenic acid, eicosapentaenoic acid, and docosahexaenoic acid; and the ratio of n-6 PUFAs to n-3 PUFAs on mammary carcinogenesis.

Acknowledgments and Notes

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