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	66030	0.52	0.29–0.92[e]	0.44	0.21–0.93[e]
20–<22	42	111439	1.00		1.00	
22–<24	33	119748	0.80	0.51–1.26	0.63	0.35–1.11
24–<26	22	80532	0.86	0.51–1.43	0.65	0.33–1.27
26–<28	12	31691	1.24	0.65–2.36	0.73	0.28–1.90
28–	2	15259	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	52202	0.87	0.40–1.67	0.89	0.42–1.90
20–<22	23	90432	1.00		1.00	
22–<24	30	89552	1.20	0.70–2.06	1.03	0.56–1.89
24–<26	14	46620	1.00	0.51–1.94	1.09	0.54–2.20
26–<28	7	15891	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	93436	1.28	0.72–2.28	1.61	0.73–3.56
20–<22	23	140635	1.00		1.00	
22–<24	23	157409	0.95	0.54–1.70	1.28	0.59–2.79
24–<26	26	110785	1.50	0.86–2.63	2.23	1.06–4.68[e]
26–<28	12	54934	1.37	0.68–2.75	2.27	0.96–5.35
28–	14	34689	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	93069	1.15	0.58–2.25	0.84	0.36–1.94
20–<22	18	117956	1.00		1.00	
22–<24	22	106907	1.25	0.67–2.233	1.17	0.57–2.40
24–<26	20	62675	1.73	0.91–3.27	1.96	0.97–3.99
26–<28	11	25559	1.99	0.94–4.23	2.54	1.15–5.64[e]
28–	5	12976	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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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/m²)[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/m²). 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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ORIGINAL ARTICLE

Reduction in gastric cancer mortality by screening based on serum pepsinogen concentration: A case-control study

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Abstract

Objective. Pepsinogen testing is widely used in Japan as a method of screening for gastric cancer. To evaluate the efficacy of this method, a case-control study was conducted in a rural town in Hiroshima prefecture, Japan, where no previous pepsinogen testing had been performed. ***Material and methods.*** Three age-and gender-matched control subjects were randomly selected for each of 41 individuals who had died of gastric cancer. The three control subjects were selected from individuals who were living in the same area as the patient when gastric cancer was diagnosed. ***Results.*** The odds ratios for death from gastric cancer among control subjects screened within 1 and 2 years before the individuals were diagnosed versus those not screened were 0.238 (95% confidence interval (CI): 0.061–0.929), and 0.375 (95% CI: 0.155–0.905), respectively. ***Conclusions.*** The study results suggest that gastric cancer screening using the pepsinogen method may reduce mortality from gastric cancer.

Key Words: *Gastric cancer, mortality, pepsinogen, screening*

Introduction

Gastric cancer is a major cause of cancer death in many countries, including Japan. However, the mortality rate for gastric cancer has been decreasing in Japan, partly because of the introduction of mass screening programs [1]. The validity of indirect photofluorography, which is the conventional screening method used in Japan, has been recognized [1–5], but indirect photofluorography is associated with certain drawbacks, such as exposure to radiation and the need for specially trained technicians and special equipment, which limit its use. Therefore, simpler and more effective screening strategies for gastric cancer are needed.

Helicobacter pylori (*H. pylori*) infection can cause gastric inflammation, and glandular atrophy [6,7], which affects serum concentration of pepsinogen (PG), is the major risk factor for atrophic gastritis [8–10]. Many gastric cancers develop in areas of severe and extensive atrophic gastritis [11–14]. We have reported a high prevalence of gastric neoplasms in populations with atrophic gastritis diagnosed on the basis of the serum PG concentration [15]. Thus, serum PG measurement can be applied as a gastric cancer screening method [16–20]. The accuracy of PG testing in comparison with photofluorography or endoscopy or with follow-up study has been reported [15–20]; however, there have been no reports on the effectiveness of such screening in reducing the number of deaths from gastric cancer. In the present case-control study, we evaluated the relation between testing and mortality due to gastric cancer.

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Material and methods

Study area

The study was conducted in a town located in a rural area of Hiroshima Prefecture, Japan, with a total population of approximately 4500 (male/female ratio: 0.91), 39.3% of the population being over 65 years of age. The town was chosen for this study because gastric cancer screening by serum PG concentration testing had been conducted there since 1989. Data pertaining to diagnosis of gastric cancer were obtained from the death certificate records and the Hiroshima Prefectural Cancer Registry. Individuals residing in the town during the relevant time period were selected at the town office. The study was approved by the ethics committee of Hiroshima University School of Medicine and by the Ministry of Public Management, Home Affairs, Posts and Telecommunications of Japan.

Screening by serum pepsinogen testing

Fasting blood samples were obtained from the participants, and serum samples were stored at −20°C until use. Serum PG I and II were measured by radioimmunoassay (Dainabot, Tokyo, Japan) [18,19]. Screening results were determined according to established cut-off values: individuals with a value less than the cut-off value were considered to be at high-risk for gastric cancer and were advised to undergo a more specific examination. The cut-off levels during the study period were as follows: a PGI/PGII ratio of less than 2 in 1989; a PG I concentration of less than 30 ng/ml or a PGI/PGII ratio of less than 2 in 1990–92; a PG I concentration of less than 50 ng/ml and a PGI/PGII ratio of less than 3 after 1993, as reported previously [15,18,19]. The screening was offered annually in the town through the local government. The target population comprised all residents aged 40 years or older. In 2002, there were 1596 residents in the town aged 40 years or older and 663 (41.5%) individuals participated in the gastric cancer screening. During 13 years, 873 residents had positive screening tests by serum pepsinogen and 585 (67.0%) underwent more specific examinations (gastointestinal endoscopy; 539 (92.1%), photofluorography; 46 (7.9%)). Some of the results were reported previously [15,18,19].

Identification of individuals who died from gastric cancer

The case series consisted of residents of the town, who, according to the death certificate records and the Hiroshima Prefectural Cancer Registry, died from gastric cancer during the period April 1989 to March 2002. Forty-nine individuals died from gastric cancer during the period. Gastric cancer death was confirmed in 46 (93.9%) of these individuals (28 M, 18 F). Of the 46 deaths, 5 were prior to the initiation of serum PG testing; thus, 41 cases were finally selected for the study.

Identification of control subjects

For each of the 41 individuals who died of gastric cancer, 3 gender-matched control subjects with the same birth year were selected randomly from the residents that were alive on the date that the individual died. When there were fewer than three other residents with a matching birth year, the matching was done with residents whose birth year was within ±3 years. For the 41 individuals who died from gastric cancer, a total of 123 control subjects were selected.

Identification of screening history

Records of the gastric screening program were reviewed to obtain screening histories for the 41 individuals who died and the 123 control subjects during the 2 years before each diagnosis of gastric cancer.

Data analysis

The Mantel-Haenszel procedure was used to estimate odds ratios (ORs) and 95% confidence intervals (CIs). ORs were calculated for control subjects who participated in the screening once during the 1 or 2 years before case diagnoses, in comparison with those who did not participate in the screening during this period. The relation between participants' age and reduction in deaths from gastric cancer was examined. In the analysis, age was categorized as less than 65 years, less than 70 years, less than 75 years, less than 80 years, and less than 85 years.

Results

Age and gender of the individuals who died from gastric cancer and the control subjects are reported in Table I. The male-to-female ratio of the individuals who died was 25/16, and the mean age of these individuals was 71.9 years (range, 44–92 years).

The ORs for death from gastric cancer among control subjects who participated in the screening once during the 1 year and once during the 2 years before the diagnosis of cases, as opposed to death from gastric cancer among those who did not participate in the screening during these periods,

Table I. Age and sex of individuals who died from gastric cancer and control subjects.

	Case (n=41)	Control (n=123)
Age (years) at diagnosis		
40–59	3	10
60–69	15	31
70–79	9	52
80–	14	30
Male/female ratio	25/16	75/48

Table II. Mantel-Haenszel odds ratios for death from gastric cancer in PG testing performed during 1 year before gastric cancer diagnosis.

	Number of screening participants (out of 3 matched controls) during the year before gastric cancer diagnosis			
	0	1	2	3
Gastric cancer deaths				
Screening history	1	1	0	0
No screening history	22	14	2	1

were 0.238 (95% CI: 0.061–0.929) and 0.375 (95% CI: 0.156–0.905), respectively (Tables II and III). Thus, the number of gastric cancer deaths was reduced by 76% among subjects participating in PG screening within 1 year and 62% among subjects participating in PG screening within 2 years of the time of gastric cancer diagnosis in the corresponding individuals who died from gastric cancer. The OR for death from gastric cancer among subjects participating in screening once during the 1 year before the diagnosis of cases was lower than that of subjects who participated once during the 2 years before diagnosis.

The reduction in the number of deaths from gastric cancer did not correlate with age of subjects who underwent screening once during the 1 year before diagnosis of the cases (Table IV). The reduction was not related to age in any subjects with the exception of those less than 85 years of age who underwent screening once during the 2 years before diagnosis of the cases (OR: 0.321; 95% CI: 0.120–0.862; p=0.027).

Discussion

This is the first case-control study evaluating the relation between mass screening on the basis of PG concentration and gastric cancer mortality. In Japan, mass photofluorography screening programs for gastric cancer were initiated around 1960 [1]. The usefulness of such screening has been reported. A

Table III. Mantel-Haenszel odds ratios for death from gastric cancer in PG testing performed during 2 years before gastric cancer diagnosis.

	Number of screening participants (out of 3 matched controls) during 2 years before gastric cancer diagnosis			
	0	1	2	3
Gastric cancer deaths				
Screening history	3	1	1	0
No screening history	15	13	5	3

Abbreviation: PG =pepsinogen.

population-based, case-control study of screening based on photofluorography showed a 55% reduction in gastric cancer deaths for individuals who participated in the screening at least once during a 2-year period [1–4]. Lee et al. reported a 2-fold decrease in gastric cancer mortality in subjects who participated in photofluorography screening during the preceding 1 year versus control subjects [5]. At present, about 5 million people in Japan are screened annually by photofluorography.

The sensitivity of photofluorography is by no means high when endoscopy is used as a yardstick. Thus, measurement of serum PG concentrations has recently gained attention as a new screening method for gastric cancer. The results of studies of PG concentration testing show that this method has a superior cancer detection rate and is less expensive than the conventional photofluorography-based mass screening [21,22]. Furthermore, the percentage of early gastric cancers detected by PG testing is higher than that of conventional screening, and a considerable number of individuals with gastric cancer identified by PG testing have been treated by endoscopic surgery. Miki et al. reported the incidence of gastric cancer to be 0.05% by X-ray detection and 0.18% by PG testing in populations who underwent X-ray and PG screening simultaneously, and that 90% of gastric cancers detected by the PG method were in the early stages [21]. It has been reported that screening by serum PG testing may be useful in detecting small asymptomatic cancer of non-ulcerated morphology, and well-differentiated histology [1]. Small asymptomatic cancers of this type are relatively difficult to detect by photofluorography, whereas such conventional screening is effective in detecting cancers of ulcerated morphology and poorly differentiated histology as well as advanced cancers, which are frequently symptomatic. In addition, the PG method has many advantages over the X-ray method. For example, PG testing is easy to perform, and patients do not feel much discomfort. There is no radiation exposure,

Table IV. Reduction in gastric cancer mortality and age.

Age (years)	*n*	Participation in screening during 1 year before gastric cancer diagnosis in 3 matched controls			Participation in screening during 2 years before gastric cancer diagnosis in 3 matched controls		
		OR	95% CI	*p*-value	OR	95% CI	*p*-value
<65	11	–	–	0.562	0.600	0.081–4.444	>0.999
<70	18	–	–	0.188	0.385	0.094–1.567	0.166
<75	25	0.429	0.056–3.726	0.444	0.333	0.096–1.156	0.146
<80	30	0.500	0.100–2.495	0.514	0.500	0.163–1.532	0.306
<85	36	0.294	0.072–1.209	0.161	0.321	0.120–0.862	0.027
All	41	0.238	0.061–0.929	0.043	0.375	0.155–0.905	0.036

Abbreviations: OR = odds ratio; CI = confidence interval.

and there is no barium ingestion, with its related side effects. The PG method is fast, and many serum samples can be analyzed simultaneously. If man-power, costs, and efficiency were not issues, the highest sensitivity could be reached in all individuals by using a combination of PG and photofluorograhy screening. However, since man-power and cost are limiting factors, and photofluorography produces some harmful effects, the more efficient screening method should be determined on the basis of scientific and epidemiologic evidence.

There have been no studies directly examining whether screening on the basis of the serum PG concentration is associated with reduced gastric cancer mortality. A randomized, controlled trial is the most suitable method for evaluating the effectiveness of a cancer screening program; however, mass screening programs for gastric cancer have been so widely implemented in Japan that it is impossible to undertake such a trial. As an alternative, we undertook this case-control study.

Because the screening histories of the individuals who died from gastric cancer and the control subjects in the present study were obtained from the same data source, recall bias and inter-observer bias were thought to be eliminated. Measurement bias was also eliminated because the record linkage on the computer was performed similarly for cases and control subjects. However, our study had two weaknesses. First, the self-selection bias could not be controlled because some information could not be obtained. If a family history of cancer increased the risk of death from gastric cancer, the effectiveness of the screening might have been underestimated if this factor was not taken into account. Similarly, if habitual smoking increased the risk, the effectiveness might have been overestimated. In fact, in several studies it is suggested that the risk of gastric cancer may be associated with a family history of cancer and with habitual smoking [23,24]. These factors and other factors, such as socio-economic status, dietary habits, and health practices, should be controlled in order to evaluate the screening method more precisely. Another consideration is the effect of mass X-ray screening. The effect was not evaluated in the present study because we could not sufficiently investigate the subjects' histories of X-ray screening.

The present study indicated that the effect of screening based on the serum PG concentration lasts for at least 2 years. Fukao et al. reported that the effect of screening by photofluorography remains for at least 5 years [3]. We previously reported that, in more than 90% of cases, the PG concentration was similar to that obtained 5 years previously [25]. We investigated the natural course of the PG concentration in a prospective study over a period of 9 years. Of 207 PG-negative subjects, 182 (87.9%) were still PG negative after 9 years [26]. Therefore, repeated examination of the PG concentration might not be required. However, the optimal interval between PG tests should be decided by the effectiveness of the screening method. Further study is necessary to confirm the optimal interval.

In conclusion, the results of the present case-control study suggest reductions of 76% and 62% in gastric cancer mortality among individuals who participate in screening for gastric cancer on the basis of the PG concentration once a year or once every 2 years, respectively. A large-scale study including factors related to self-selection bias is needed not only to evaluate the effectiveness of screening based on PG testing more precisely but also to determine the optimal frequency and interval of screening by this method.

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【原 著】

足立区におけるペプシノゲン法による胃検診の5年間の追跡調査による有効性の検討

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Five years follow up study of gastric cancer screening using the pepsinogen test method in Adachi city

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要 旨

足立区では特定年齢(40・50・60歳)を対象とした区民健診としてペプシノゲン法(PG法)による胃がんのマススクリーニングを1996年4月から開始した。今回1996年度に行ったPG法による胃がん検診受診者5449人(40歳1464人、50歳1829人、60歳2156人)を対象に、胃がん検診受診から5年間の生存、死亡、転出につき追跡調査を行った。調査にあたっては足立区個人情報保護条例に基づき必要な情報を収集した。血中ペプシノゲンⅠ値が70ng/mL以下かつペプシノゲンⅠ/Ⅱ比が3.0以下をカットオフ値として、陽性者に対しては内視鏡による二次精密検査の受診勧奨を行った結果、精検受診者1009人(61.2％)中、検診受診後2年間で早期胃がん5人、進行がん3人が発見された。5年間の観察期間中、胃がんによる死亡者3人、胃がん以外の死亡者47人、観察中止者654人であった。対象者の5年後の標準化死亡比(95％信頼区間)は、対象年齢における全国での胃がん死亡率を基準として0.34(0.07-0.98)であった。観察期間中に胃がんで死亡した3名中2名がPG法陰性がんであった。今回の検討ではX線などの他検査やPG法複数回受診の影響を極力排除した上で、PG法を受診した集団における胃がんによる実死亡者数が受診から5年後に約1/3に抑制されていたが、これはPG法単独単回施行後の胃がん死亡抑制の最大評価と考えられた。

キーワード：ペプシノゲン法、スクリーニング、胃がん

Purpose: We started a new screening method for gastric cancer in 1996 by measuring the serum concentration of pepsinogen (PG) I and II. This PG test method can identify individuals with atrophic gastritis. We have conducted a follow up study to reveal the reduction of gastric cancer mortality among participants in the PG test method in the five years observation period after the screening.

Methods: A total of 5,449 residents in Adachi city aged 40, 50 and 60 years old in 1996 were measured serum PGI and PGII levels. Individuals with PGI level ≦ 70 ng/ml and PGI/PGII ≦ 3.0 were advised to have an upper gastro-intestinal (GI) endoscopy to detect the gastric cancer. The participants who moved out of the city, had second screening by the PG test

を日本全体として胃癌死亡の標準化死亡比(SMR)を算出した．胃癌のSMRは0.3を若干超える値であり，SMRの95%信頼区間は，1を含まないで1未満に分布しており，全国の胃癌死亡状況と比較して統計学的に有意に胃癌死亡率が低下していた．自己選択バイアス（self-selection bias）の影響は否定できないが，PG法による胃癌検診の胃癌死亡率減少効果を示唆する結果であった[12]．

しかしながら，この検討のみでPG法の有効性を判断することはできない．厚生労働省三木班においては，症例対照研究の手法で調査を続けている．

おわりに

萎縮性胃炎のマーカーである血清PGは，胃癌のマーカーとしてスクリーニングに応用され，従来の間接X線検診を補う方法として実施する施設が増えてきている．

陰性胃癌の問題や，要精検率が高すぎるなど，単独の胃癌スクリーニングマーカーとしては問題点が多く，また有効性評価も確立していない．しかしながら，間接X線検査だけではなく，Hp検査との組み合わせや，内視鏡検査を前提としたハイリスク群の絞り込みなど，他の検査との併用を工夫していくことで，胃癌検診システム全体を向上させることが期待される．

なお，PG法についての情報は，厚生労働省三木班提供『ペプシノゲン・ホームページ(http://www.pepsinogen.org)』をご参照ください．

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method, or died from other causes than gastric cancer were defined as censored cases during the 5 years follow up period. Standardized mortality ratios (SMR) of gastric cancer among participants were calculated based on the sex, age and year specific gastric cancer mortality using Japan as a standard population.

Results: Five early gastric cancer cases and 1 advanced gastric cancer case were diagnosed within a year after screening. Two advanced gastric cancer cases were found by further examinations during the follow up period of 2 - 5 years. There were 701 censored cases and 3 gastric cancer death cases including 2 cases with negative result at the screening. SMR (95% confidence interval) of gastric cancer in the 5 year observation period were 0.34 (0.07 ? 0.98).

Conclusions: Participants for screening by the PG test method showed a reduction in gastric cancer mortality in comparison with the general population in Japan.

Key words: pepsinogen test method, screening, stomach neoplasms

【はじめに】

足立区では集団胃検診としてペプシノゲン法(PG法)導入以前の平成4年から7年度まで4年間、バリウムを用いた間接X線法による検診を行っていたが、検診受診率の低減化とX線検診受診者の再検診固定化により硬直化していた胃検診から更に一般区民への普及をはかるために、平成8年4月から特定年齢(40・50・60歳)を対象とした区民健診(節目健康診査)に本法による集団胃検診を開始した。PG法による胃がん検診についてはこれまでの報告で有用性につき一定の評価が得られている[1]。足立区におけるPG法導入後のこれまでの4年間の検討では、採血検査のため簡便に実施可能であり、受診者における身体的負担が少なく一次検診受診率の改善が認められたこと、要精検者あたりの胃がん発見率は、PG法導入前の間接X線法と比較して共に0.40％と同等で、費用対効果が改善したことがあげられた。更にPG法検査では早期胃がんの発見率が高いことも特徴とされているが、PG法導入前の4年間のX線検診では発見胃がんにおける早期胃がんの割合は56％であったのに対してPG法導入後は68.7％に増加していた[2,3]。今回の検討では、胃がん検診の有用性評価として同法を受診することによる胃がん死亡率の改善効果につき、足立区でのPG法導入初年度である平成8年度に施行したPG法の受診から5年間の経過を観察した。

【対　象】

1996年(平成8年)度に足立区の節目健診時に行ったPG法による胃がん検診受診者を対象とした。PG法による胃がん検診を行うに当たっては、事前に問診を行い、上部消化器症状がある人、胃手術後の人、

表1 対象群の観察期間中の経過

年齢	経過		開始時	1年後	2年後	3年後	4年後	5年後
40	生存	男性	620	593	584	574	558	540
		女性	844	824	806	788	747	710
	死亡（胃がん以外）	男性		1	2	0	0	0
		女性		0	1	1	1	1
	胃がん死亡	男性		1	0	0	0	0
		女性		0	0	0	0	0
	転出	男性		25	7	10	16	18
		女性		20	17	17	40	36
50	生存	男性	627	620	616	602	581	558
		女性	1202	1192	1176	1158	1104	1048
	死亡（胃がん以外）	男性		1	2	0	2	2
		女性		0	0	0	1	2
	胃がん死亡	男性		0	0	0	0	0
		女性		0	0	0	0	0
	転出	男性		6	2	14	19	21
		女性		10	16	18	53	54
60	生存	男性	793	781	773	759	737	709
		女性	1363	1352	1340	1317	1243	1180
	死亡（胃がん以外）	男性		4	4	3	3	4
		女性		2	1	2	4	3
	胃がん死亡	男性		0	1	0	0	0
		女性		0	0	0	0	1
	転出	男性		8	3	11	19	24
		女性		9	11	21	70	59

プロトンポンプ阻害剤内服中の人、腎不全のある人については同検査に不適当として除いた。またPG法による検査は胃がんの有無を測定するのではなく、胃がんの高危険群である萎縮性胃炎の検出を行なう方法であることにつき同意を得てから行なった。表1に対象者における年齢・性別に観察期間中の経過を示す。対象者は5449人で、40歳1464人(男性 620人、女性 844人)、50歳1829人(男性 627人、女性 1202人)、60歳2156人(男性 793人、女性 1363人)であった。同年度中に検診対象となった年齢層全体のうち、PG法を受診した区民の割合は、22.0％(男性 15.9％、女性 28.4％)であった。

表2に対象者の年齢・性別のPG法の結果を示す。PG法による陽性者(要精検者)は、1650人(30.3％)で、そのうち二次精検を受診した人は1009人(61.2％)であった。

表2 対象群におけるPG法の結果

年齢	性別	対象者数	要精検者数 (PG法陽性者数)	要精検率 (PG法陽性率)	二次精検 受診者数	二次精検 受診率	発見胃がん者数	発見胃がん率
40	男性	620	96	15.5%	47	49.0%	0	0%
	女性	844	117	13.9%	78	66.7%	0	0%
50	男性	627	180	28.7%	82	45.6%	0	0%
	女性	1202	318	26.5%	204	64.2%	0	0%
60	男性	793	349	44.0%	201	57.6%	5	2.49%
	女性	1363	590	43.3%	397	67.3%	3	0.76%

【方 法】

上記対象者の検診受診日を確認し、受診日から6年目に足立保健所の保健衛生情報システム(区民の検診受診歴データベース)をもとに住民基本台帳の登録の有無と検診受診歴を確認した。登録者は「生存」(観察期間5年)に区分した。登録抹消者は「死亡または転居」に分類し、登録抹消時点で観察を打ち切った。「死亡または転居」に分類されたものは要精検者台帳から検診発見胃がん者を、死亡小票から胃がん死亡者の匿名化リストを作成し、それ以外のものは「区外転出」とした。以上の情報については各々足立区個人情報保護条例第57条に基づき足立保健所が閲覧し、必要な情報を収集した。また、足立区では節目健診の他に35歳以上を対象とした自由申し込みによる「PG法消化器がん検診」を平成11年度から施行している。対象者のうち観察期間中に節目検査外のPG法を受診した者については、2回目の検査受診時に観察打ち切りとした。

その他考察資料として、胃がん検診要精検者台帳を参照し、対象者のうち胃がん検診で胃がんを発見された者及び対象者の内で観察期間中に間接X線による胃がん検診を受診し、かつ胃がんを発見された者についても、各々匿名化されたリストを作成した。これらのリストは、連結不可能な匿名リストとし、個人情報保護の観点から最大限の配慮を行った。

以上のリストを参照し、追跡開始から1年ごとに5年間の観察を、性別・各年齢階層別に行った。平成8年から各年度5年間、全国・東京都・足立区それぞれの対象年齢層の人口及び実胃がん死亡者数を用いて、対象群での、性・年齢構成の影響を除去した期待胃がん死亡数(対象群の胃がん死亡予測数)を算出し、統計処理による期待胃がん死亡者数誤差範囲を確認した。また同期間に観察された対象者中の胃がん死亡数から各々の標準化死亡比(SMR)と95％信頼区間(95％CI)を求めた。血清ペプシノゲン値の測定はPG Ⅰ値が70ng/mL以下かつPG Ⅰ/Ⅱ比が3.0以下をカットオフとし、該当者は要精検者として医療機関への受診勧奨を行った。さらに一次検診直後の二次精検受診率の改善をはかる目的で、PG法の初回受診時陽性者のうち、2年間精検受診を行っていない人に対して個別に勧奨通知を発送し、精検結果の把握につとめた。

【結 果】

対象者中の胃がん死亡者を表3に示す。5年間の観察期間中、胃がんによる死亡者は3人(40歳1人、60歳2人)、胃がん以外の死亡者数は47人(40歳7人、50歳10人、60歳30人)、転出者は299人(40歳136人、50歳88人、60歳75人)、節目健診外でPG法検査を受診したことによる観察途中打ち切り者355人(40歳70人、50歳125人、60歳160人)。観察期間中の総観察人年は25914.9人年で、5年間の追跡率は87.1％であった。

PG法受診後の二次精検で発見された胃がん者につき表4に示す。今回の対象者のうち、検診直後の初回精検による胃がん発見者は6人で、早期胃がん5人、進行がん1人。2年後の受診勧奨で、更に進行がんが2人追加発見された。検診で発見された胃がん者の観察期間中における死亡者は認めなかった。基準人口別に5年間観察後の期待死亡者数、

SMR、95％CIを表5に示す。観察期間を通じての胃がんによる期待死亡者数は、全国を基準人口とした場合、8.91人。東京都を基準人口とした場合、8.98人。足立区全体を基準人口とした場合、9.57人であった。PG法による胃がん検診受診者の5年後のSMR(95％CI)は、各々0.34(0.07-0.98)、0.33(0.07-0.98)、0.31(0.06-0.92)であった。全国を基準人口とした場合の観察期間中のSMRの推移を図1に示す。1年ごとのSMRの推移では、受診後より次第にSMRは低下しており、検査後4年で最小となっていた。

また足立区においては、節目健診時に行う胃がん検診のほかに間接X線検査による「消化器がん検診」も引き続き行っている。表6に間接X線法受診により発見された胃がん者の内訳を示す。1996年度に節目健診を受診した対象者のうち、1997年以降に間接X線検査を受けた人は324人で、その内4人にがんが発見され、全例早期がんであった。

表3　対象者中の胃がん死亡者

年齢	性別	死亡日	PG法受診日	PG法結果	二次精検受診日	精検結果
40	男性	1997.2	1996.6	陰性		受診勧奨無
60	男性	1998.2	1996.10	陰性		受診勧奨無
60	女性	2001.12	1997.2	陽性	1997.11	ポリープ

表4　PG法受診後の二次精検による胃がん発見者

年齢	性別	PG法受診日	精検結果(直後)	精検受診日(2年後受診勧奨後)	精検結果(2年後受診勧奨後)
60	男性	1996.4	早期がん		
60	女性	1996.4	未受診	1999.4	進行がん
60	男性	1996.4	胃炎	2000.1	進行がん
60	男性	1996.7	早期がん		
60	女性	1996.8	進行がん		
60	男性	1996.10	早期がん		
60	女性	1996.10	早期がん		
60	男性	1997.1	早期がん		

表5　基準人口別のPG法受診5年後のSMR

基準人口	全国	東京都	足立区
期待死亡者数	8.91	8.98	9.57
SMR	0.34※	0.33※	0.31※※
95%CI	0.07-0.98	0.07-0.98	0.06-0.92

※:p=0.07 ※※:p=0.05

表6　PG法受診後、間接X線法受診により発見された胃がん者

年齢	性別	PG法受診日	PG法結果	PG法後精検結果	間接X線法受診日	間接X線法後精検結果
60	女性	1996.6	陰性	受診勧奨無	1998.7	早期がん
60	男性	1997.1	陰性	受診勧奨無	1999.11	早期がん
60	女性	1996.12	陰性	受診勧奨無	1999.1	早期がん
60	女性	1996.6	陽性	異常なし	1998.3	早期がん

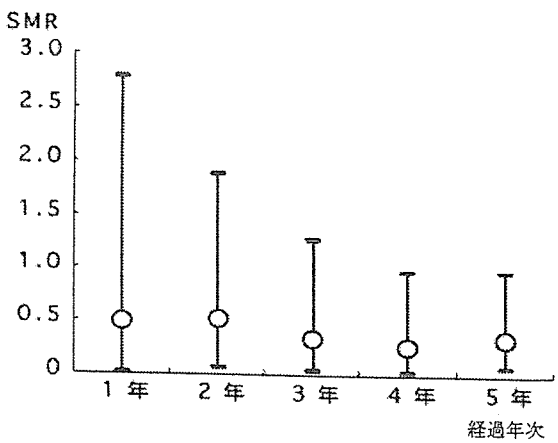

図1　全国を基準人口とした時のSMRと95%CIの年次推移

【考　察】

対象者群全体における要精検率（PG法陽性率）は年齢と共に上昇することが知られているが、年齢階級別の陽性率および胃がんの発見率は諸家の報告と類似していた[4,5]。これまでの報告では、間接X線法による胃がん検診の死亡率減少効果について過去に一度でも検診を受診した場合のオッズ比は0.3～0.6程度に見積もられている[6,7]。しかし単独単回施行されたPG法検査が胃がん死亡率の減少に対してどの程度寄与しているかについては一定の見解は得られていない。

今回の観察期間中のSMRは、単独でPG法による検査を施行した場合の胃がん死亡抑制効果の最大評価と考えられた。また間接X線法により発見された4人の胃がん者をPG法による見のがし例とみなし、全例胃がんにより観察期間中に死亡したと仮定した場合、全国を基準人口としたSMR(95％CI)は0.79(0.32-1.62)となり、これはPG法施行による胃がん死亡抑制の最小評価と考えられた。したがって今回の観察ではPG法単独単回による胃がん死亡率の抑制効果はSMRで0.34から0.79の間にあると推定される。しかし間接X線法による胃がん発見者は全例早期がんで進行がんが存在しなかったことと、早期がんの5年生存率は90％以上[8]であることを考慮すると、今回の検討における5年間の観察期間中の妥当なSMRは、胃がん死亡率抑制の最大評価に近いものと考えられた。

【まとめ】

PG法検査単独単回施行において検診5年後のSMR(95％CI)は、0.34(0.07-0.98)～0.79(0.32-1.62)と推定され、胃がん死亡率減少効果のある可能性が示唆された。

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