SERUM COMPONENTS AND LIFESTYLE FACTORS - II

Time Spent Walking or Exercising and Blood Levels of Insulin-Like Growth Factor-I (IGF-I) and IGF-Binding Protein-3 (IGFBP-3): A Large-Scale Cross-Sectional Study in the Japan Collaborative Cohort Study

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Abstract

The preventive effects of physical activity against cancer may partly be ascribable to a possible decrease in insulin-like growth factor-I (IGF-I) induced by the activity. To examine the association of physical activity with IGF-I and IGF-binding protein-3 (IGFBP-3), we analyzed the data for control participants in a case-control study nested in the Japan Collaborative Cohort Study. A total of 3,598 men and 3,359 women throughout Japan, aged 40 to 79 years, were administered a lifestyle questionnaire and provided serum samples. The age- and body mass index (BMI)- adjusted serum levels of IGF-I and IGFBP-3 were lower among those who walked for longer times with a significant trend in both sexes (trend *P* < 0.01). Among participants who walked one hour or more per day, the mean levels of serum IGF-I and IGFBP-3 were 138.7 ng/ml and 2.87 μg/ml in men and 125.7 ng/ml and 3.14 μg/ml in women, respectively. The corresponding figures among those rarely walked were 147.4 ng/ml and 2.99 μg/ml in men and 132.3 ng/ml and 3.21 μg/ml in women. For IGF-I, adjustment for serum IGFBP-3 did not essentially alter such associations although the trend in women did not reach statistical significance. A decreased level of serum IGF-I was associated with longer exercise time in men even after adjustment for serum IGFBP-3 (trend *P* = 0.033 after adjustment for age, BMI, and serum IGFBP-3), whereas the time was positively correlated with serum IGF-I in women (trend *P* = 0.048). Our findings may partly explain the protective effects of physical activity against several sites of cancer.

Keywords: IGF-I – IGFBP-3 - physical activity - cancer risk

Asian Pacific J Cancer Prev, **10**, JACC Supplement, 23-27

Introduction

Many cohort and case-control studies have related physical activity to a decreased risk of many sites of cancer. They include cancer of the colon, breast, and endometrium (World Cancer Research Fund and American Institute for Cancer Research, 2007). The preventive effects of physical activity have been attributed to several mechanisms: beneficial effects on body fatness, a reduction in insulin resistance, effects on endogeneous steroid/sex hormone metabolism, a decreased gut transit time, possible strengthening of the immune system, and induction of the enzymes that protect against oxidative stress (World Cancer Research Fund and American Institute for Cancer Research, 2007).

Insulin-like growth factor-I (IGF-I) may be involved in one of such mechanisms (Grimberg, 2003) if physical activity lowers its blood and/or tissue levels. By increasing IGF signaling, a cell can enhance survival and proliferation while avoiding apoptosis. IGF-I induces an angiogenesis agent, vascular endothelial growth factor (VEGF). IGF-I may also promote cancer indirectly, through interactions with oncogenes and tumor suppressors, and interactions with other hormones, especially sex steroids. In addition, circulating IGF-I may facilitate cancer development even if it unlikely causes cancer to form. Several epidemiological studies reported that the higher blood level of IGF-I was associated with an elevated risk of prostate cancer, colorectal cancer, and premenopausal breast cancer (Yu and Rohan, 2000; Renehan et al., 2004; Roddam et al., 2008).

Whether daily physical activity decreases the level of

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circulatory IGF-I, however, remains controversial (Goodman-Gruen and Barrett-Connor, 1997; Yu and Rohan, 2000; Voskuil et al., 2001; Allen et al., 2003). Although some studies have provided support for the hypothesis, others did not corroborate it. To further address this issue, we examined the association of physical activity in daily life with serum IGF-I in a large-scale cross-sectional study using the data derived from the Japan Collaborative Cohort Study (JACC Study) (Ohno and Tamakoshi, 2001; Tamakoshi et al., 2005). The IGF-binding protein-3 (IGFBP-3), which is a principal binding protein of blood IGF-I and may have IGF-independent effects on cell growth and apoptosis (Grimberg, 2003), was simultaneously considered.

Materials and Methods

We analyzed the data of control participants in a case-control study nested in the Japan Collaborative Cohort (JACC) Study. In the case-control study, the JACC Study Group measured serum levels of several molecules including IGF-I and IGFBP-3 to elucidate associations of these substances with various sites of cancer and other diseases. The details of the study (Tamakoshi et al., 2009) and the biochemical assays (Ito et al., 2005) have been described elsewhere. The serum levels of IGF-I and IGFBP-3 were determined by the immuno-radiometric assay (IRMA).

In brief, 39,242 participants aged 40 to 79 years, administered a questionnaire on lifestyle factors and donated serum samples at baseline survey from 1988 to 1990. The sera were stored in deep freezers at –80 ºC until analyzed in 1999 and 2000. Those who had died through 1997 or suffered from cancer through 1994 were regarded as cases of the nested case-control study. For each case, we randomly selected 3 to 4 controls, matching for sex, age, and participating institution. Eventually, 2,867 cases and 10,350 controls were chosen, and the respondents for the present analysis were selected from the control group. The Ethical Board at the Nagoya University School of Medicine approved the study design and use of serum samples.

Of the 10,350 control participants, we excluded four for whom adequate serum samples were not left for the measurement of IGF-I and IGFBP-3, 89 with a previous history of cancer at baseline, and 927 who were recruited in a study area where information on walking time was not available. In addition, 2,373 controls were omitted due to lack of data on walking and exercise time or those on body mass index (BMI) as a covariate (Voskuil et al., 2001; Allen et al., 2003), resulting in 3,598 men and 3,359 women from 17 study areas throughout Japan for our analysis. The mean ages ± SD were 63.6 ± 7.1 years in men and 62.3 ± 9.3 years in women.

With regard to physical activity, the study participants reported walking and exercise time in four possible responses in the baseline questionnaire, namely, almost none, about 30 min., 30 min. to 1 hour, and 1 hour or more per day for time spent walking, and almost none, 1 to 2 hours, 3 to 4 hours, and 5 hours or more per week for time spent exercising. These questions about physical activity have been proved to be reasonably reproducible and valid (Iwai et al., 2001).

Statistical analysis

BMI at baseline was calculated based on the height and weight reported in the questionnaire survey. The differences in serum IGF-I and IGFBP-3 levels between sexes were statistically tested by *t* test. The inter-relationships among age, BMI, and serum IGF-I and IGFBP-3 were examined using the Pearson correlation coefficient.

To assess the associations of walking or exercise with serum levels of IGF-I and IGFBP-3, we computed the means of their serum levels by time spent walking or exercising and sex. They were adjusted for age and BMI by using analysis of covariance. In addition, the means of

Table 1. Pearson Correlation Coefficients among Age, BMI, IGF-I and IGFBP-3 by Sex

Men (n = 3,598)				Women (n = 3,359)			
	Age	BMI	IGF-I		Age	BMI	IGF-I
BMI	-0.11			BMI	-0.09		
IGF-I	-0.16	0.15		IGF-I	-0.32	0.10	
IGFBP-3	-0.19	0.16	0.55	IGFBP-3	-0.19	0.12	0.53

P < 0.001 for all the coefficients

Table 2. Adjusted Means for Serum IGF-I and IGFBP-3 Levels by Daily Walking Time and Sex

Walking time per day	n	IGF-I (ng/ml) Age- and BMI-adjusted[1] Mean (95% CI)		IGF-I (ng/ml) Age-, BMI- and IGFBP-3-adjusted[2] Mean (95% CI)		IGFBP-3 (µg/ml) Age- and BMI-adjusted[1] Mean (95% CI)	
Men (n = 3,528)							
Almost none	460	147.4	(142.9 - 152.0)	146.4	(142.5 - 150.2)	2.99	(2.92 - 3.06)
About 30 min.	517	149.8	(145.5 - 154.0)	145.2	(141.6 - 148.9)	3.09	(3.02 - 3.16)
30 min. to 1 hour	675	144.6	(140.8 - 148.3)	140.9	(137.7 - 144.1)	3.06	(3.00 - 3.12)
1 hour or more	1,876	138.7	(136.5 - 141.0)	141.5	(139.6 - 143.4)	2.87	(2.84 - 2.91)
		Trend *P* < 0.001		Trend P = 0.013		Trend *P* < 0.001	
Women (n = 3,245)							
Almost none	341	132.3	(127.0 - 137.6)	131.9	(127.3 - 136.4)	3.21	(3.13 - 3.29)
About 30 min.	537	132.8	(128.6 - 137.0)	129.0	(125.3 - 132.6)	3.32	(3.25 - 3.38)
30 min. to 1 hour	663	129.1	(125.3 - 132.9)	127.3	(124.0 - 130.6)	3.25	(3.19 - 3.31)
1 hour or more	1,704	125.7	(123.3 - 128.0)	127.7	(125.6 - 129.7)	3.14	(3.10 - 3.17)
		Trend *P* = 0.001		Trend *P* = 0.14		Trend *P* < 0.001	

[1]Adjusted for age and BMI by analysis of covariance; [2]Adjusted for age, BMI, and serum IGFBP-3 by analysis of covariance

Table 3. Adjusted Means for Serum IGF-I and IGFBP-3 Levels by Exercise Time and Sex

Exercise time per week	n	IGF-I (ng/ml) Age- and BMI-adjusted[1] Mean (95% CI)	IGF-I (ng/ml) Age-, BMI- and IGFBP-3-adjusted[2] Mean (95% CI)	IGFBP-3 (µg/ml) Age- and BMI-adjusted[1] Mean (95% CI)
Men (n = 3,481)				
Almost none	2,257	143.3 (141.3–145.4)	143.9 (142.1–145.6)	2.94 (2.91–2.98)
1 to 2 hours	496	146.7 (142.4–151.1)	142.5 (138.7–146.2)	3.09 (3.02–3.16)
3 to 4 hours	292	144.7 (139.0–150.4)	142.6 (137.7–147.5)	3.02 (2.94–3.11)
5 hours or more	436	135.3 (130.6–140.0)	138.8 (134.8–142.8)	2.85 (2.78–2.93)
		Trend *P* = 0.026	Trend *P* = 0.033	Trend *P* = 0.44
Women (n = 3,204)				
Almost none	2,265	127.7 (125.6–129.7)	127.8 (126.0–129.6)	3.19 (3.16–3.22)
1 to 2 hours	474	130.0 (125.5–134.5)	128.4 (124.5–132.3)	3.25 (3.18–3.31)
3 to 4 hours	227	129.5 (122.9–136.0)	129.7 (124.0–135.3)	3.19 (3.09–3.29)
5 hours or more	238	132.5 (126.1–138.9)	134.1 (128.6–139.7)	3.15 (3.05–3.25)
		Trend *P* = 0.12	Trend *P* = 0.048	Trend *P* = 0.73

[1]Adjusted for age and BMI by analysis of covariance; [2]Adjusted for age, BMI, and serum IGFBP-3 by analysis of covariance

serum IGF-I level were also adjusted for IGFBP-3 because IGFBP-3 regulates the action of IGFs. Age, BMI, and serum IGFBP-3 were incorporated as continuous variables in the linear models. The 95% confidence intervals (CI) of the adjusted means were estimated based on the standard errors derived from the models. To test for trends in the means over categories of walking or exercise time, we assigned scores of 1, 2, 3, and 4 to almost none, about 30 min., 30 min. to 1 hour, and 1 hour or more per day for walking, and almost none, 1 to 2 hours, 3 to 4 hours, and 5 hours or more per week for exercise, respectively, and then included the score into the model for analysis of covariance. All *P* values are two-sided and all the statistical analyses were performed using the Statistical Analysis System version 9.1.

Results

The serum level of IGF-I tended to be higher in men than in women (Figure 1; mean ± SD, 142.6 ± 50.8 ng/ml in men and 128.3 ± 52.8 ng/ml in women; $P < 0.001$ for difference between sexes). On the contrary, the serum level of IGFBP-3 was slightly increased in women than in men (Figure 2; mean ± SD, 2.96 ± 0.80 µg/ml in men and 3.20 ± 0.78 µg/ml in women; $P < 0.001$ for difference between sexes). In both men and women, age was negatively correlated with serum levels of IGF-I and IGFBP-3 while BMI was positively associated with the levels (Table 1; $P < 0.001$ for all correlations). The correlations, however, were weak except for that between age and IGF-I in women (correlation coefficient, -0.32). Serum IGF-I and IGFBP-3 were strongly correlated with each other.

More than half of men (53.2%) and women (52.5%) reported that they walked one hour or more per day at baseline. The age- and BMI-adjusted serum levels of IGF-I and IGFBP-3 were lower among those who walked longer time with a statistically significant trend in both sexes (Table 2; trend $P < 0.01$). Among participants who walked one hour or more per day, the mean levels of IGF-I and IGFBP-3 were 138.7 ng/ml and 2.87 µg/ml in men and 125.7 ng/ml and 3.14 µg/ml in women, respectively. The corresponding figures among those rarely walked were 147.4 ng/ml and 2.99 µg/ml in men and 132.3 ng/ml and 3.21 µg/ml in women. For IGF-I, adjustment for serum IGFBP-3 did not essentially alter such associations although the trend in women did not reach statistical significance.

About two thirds of participants seldom exercised (64.8% in men and 70.7% in women). A decreased level

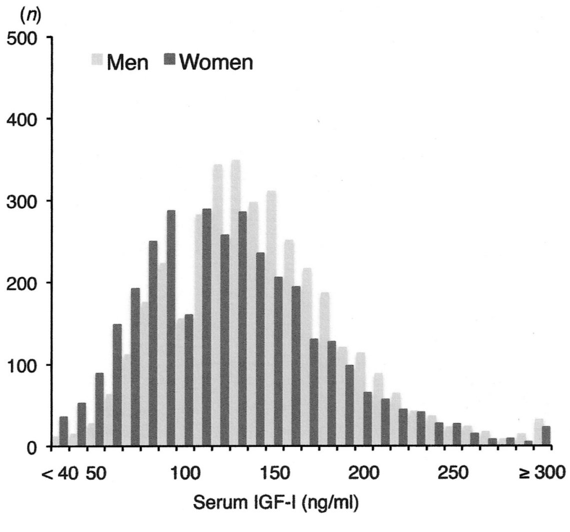

Figure 1. Distribution of Study Participants by Serum Level of IGF-I and Sex (3,598 men and 3,359 women)

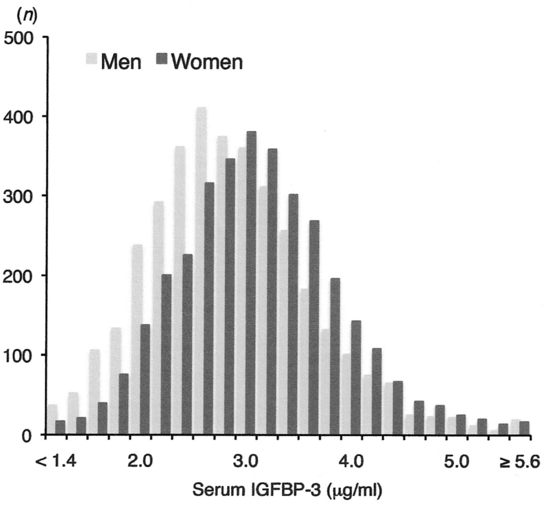

Figure 2. Distribution of Study Participants by Serum Level of IGFBP-3 and Sex (3,598 men and 3,359 women)

of serum IGF-I was associated with longer exercise time in men even after adjustment for serum IGFBP-3 (Table 3; trend P = 0.033). This association, however, was in contrast to that in women; exercise time was positively correlated with the serum level of IGF-I after adjustment for age, BMI, and serum IGFBP-3 (trend $P = 0.048$). The serum level of IGFBP-3 was scarcely correlated with exercise time.

Discussion

In this cross-sectional analysis, the mean levels of serum IGF-I and IGFBP-3 were lower among men and women who walked longer time. Adjustment for serum IGFBP-3 did not essentially change the association of IGF-I. On the other hand, the association of serum IGF-I levels with time spent exercising varied between sexes; an inverse correlation was found in men while a positive one was detected in women.

Walking appeared to account for a large part of physical activity in the study population. The inverse correlation of time spent walking with circulatory IGF-I level, therefore, may partly explain the protective effects of physical activity against several sites of cancer. However, the increase in IGFBP-3 may decrease free and biologically active IGF-I because IGFBP-3 is a major binding protein of blood IGF-I (Grimberg, 2003). We found a decreasing trend in serum IGFBP-3 with an increasing walking time, which may, in turn, increase bioactive IGF-I level. The net impact of walking would depend on the balance between the effects of IGF-I and IGFBP-3.

In women, time spent exercising was positively associated with the level of circulating IGF-I, which was in contrast to the inverse association in men. This discrepancy may not be due to the different validity of self-reported exercise time between sexes because the validity was reportedly somewhat higher in women than in men (Iwai et al., 2001). Instead, the contents of exercise may vary between men and women. Because exercise of 5 hours or more per week was relatively uncommon among women in our population (7.4% in women versus 12.5% in men), women in the longer exercise group may have characteristics different from men in the same group. Vigorous physical activity, at least in a short period, may increase circulating IGF-I (Yu and Rohan, 2000). If women who worked out longer time were engaged in more vigorous activity, their blood IGF-I level could be elevated.

Physical activity may be associated with the IGF system through its effects on circulating insulin levels and the insulin resistance; insulin enhances growth hormone-stimulated IGF-I synthesis (Kaaks and Lukanova, 2001). Further investigations, however, are required because previous findings on the associations have been inconsistent; some studies reported no significant correlations between physical activity and blood IGF-I and IGFBP-3 levels (Goodman-Gruen and Barrett-Connor, 1997; Yu and Rohan, 2000; Voskuil et al., 2001; Allen et al., 2003).

In the present study, we took advantage of a large-scale nested case-control study, which enabled us to examine the associations of physical activity with serum levels of IGF-I and IGFBP-3 with a large sample size. Some methodological issues, however, deserve discussion.

First, serum IGF-I and IGFBP-3 were assayed after more than ten years after blood draw. Nevertheless, we previously confirmed the stability of the substances in a long preservation of sera at -80 ºC (Ito et al., 2005). Second, the serum samples were collected in 17 study areas and the sample handling procedure somewhat varied among the sites. Although we found no study area with an extremely high or low mean level of serum IGF-I and IGFBP-3, the sample handling should be more strictly standardized in further studies.

Another issue may be that the subjects for the present analysis were selected from those who survived at least seven years and may be healthier than general population. This potential selection bias should be kept in mind when interpreting our findings. Finally, we only roughly measured physical activity among study participants using self-reported time spent walking or exercising as an indicator. The metabolic equivalent intensity could not be estimated due to the limitation of baseline questionnaire. However, the errors in assessment of physical activity are unlikely to depend on serum level of IGF-I or IGFBP-3. The measurement errors, therefore, would be undifferential, which may have resulted in attenuated associations between physical activity and serum IGF-I or IGFBP-3.

In conclusion, our findings on IGF-I may partly explain the protective effects of physical activity against several sites of cancer.

Member List of the JACC Study Group

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Medicine Graduate School of Medical Science; Dr. Kotaro Ozasa, Radiation Effects Research Foundation; Dr. Tsuneharu Miki, Kyoto Prefectural University of Medicine Graduate School of Medical Science; Dr. Chigusa Date, Faculty of Human Environmental Sciences, Nara Women's University; Dr. Kiyomi Sakata, Iwate Medical University; Dr. Yoichi Kurozawa, Tottori University Faculty of Medicine; Dr. Takesumi Yoshimura, Fukuoka Institute of Health and Environmental Sciences; Dr. Yoshihisa Fujino, University of Occupational and Environmental Health; Dr. Akira Shibata, Kurume University School of Medicine; Dr. Naoyuki Okamoto, Kanagawa Cancer Center; and Dr. Hideo Shio, Moriyama Municipal Hospital.

Acknowledgements

The JACC Study has been supported by Grants-in-Aid for Scientific Research (Nos. 61010076, 62010074, 63010074, 1010068, 2151065, 3151064, 4151063, 5151069, 6279102, 11181101, 17015022, 18014011, 20014026) from MEXT, Japan.

The authors express their sincere appreciation to Drs. Kunio Aoki and Yoshiyuki Ohno, Professors Emeritus, Nagoya University Graduate School of Medicine and former chairpersons of the JACC Study, to Dr. Haruo Sugano, the former Director of the Cancer Institute, Tokyo, who greatly contributed to the initiation and conduct of the JACC Study. The authors also wish to thank Dr. Tomoyuki Kitagawa, Director Emeritus of the Cancer Institute of the Japanese Foundation for Cancer Research and a former chairperson of a Grant-in-Aid for Scientific Research on Priority Area 'Cancer', for his valuable support of this study.

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