Interaction of physical activity with *VTI1A* and *TCF7L2* polymorphisms on colon and breast cancer incidences in a Japanese general population

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Declaration of competing interest

The authors declare no conflicts of interest in association with the present study.

Background

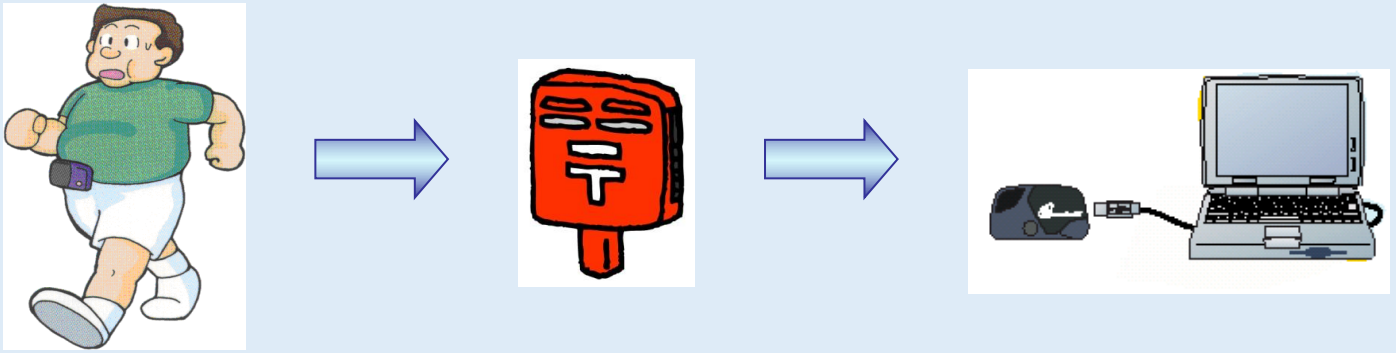
- Physical activity (PA) is inversely associated with the incidences of colon and breast cancers.
- Genome-wide association studies (GWAS) showed that gene polymorphisms of transcription factor 7-like 2 (*TCF7L2)* and vesicle transport through interaction with t-SNAREs 1A (*VTI1A)* were associated with colon and breast cancer risks.
- However, the potential interactions between PA and *VTI1A*/*TCF7L2* polymorphisms on the incidences of these two cancers have never been reported.

Purpose

- The purpose of the current study was to evaluate the interactions between PA and *VTI1A*/*TCF7L2* polymorphisms on the incident risks of colon and breast cancers in a Japanese general population.

Methods

- **Study design:** Prospective cohort study
- **Subjects:** Among the total participants of 12,068 middle-aged Japanese people (40–69 years) at the baseline survey (2005–2007) of the Saga JMICC Study, 10,859 participants remained for the main statistical analysis, after excluding those with several conditions, such as having current cancers at the baseline, missing PA data or gene polymorphism data.
- **Assessment of an independent variable:** Habitual total PA was measured by a single-axis accelerometer (Life-corder; Suzuken Co., Ltd., Nagoya, Japan).



- Subjects were instructed to wear accelerometer on the waist during all waking hours, except for when bathing, engaging in water activities for 10 days.
- After the accelerometer was worn for 10 continuous days, it was retrieved, and the recorded PA data were downloaded to a computer.

- Total PA was calculated as the sum of the mathematical products of the corresponding metabolic equivalents (METs) and the time spent at the corresponding intensity levels.
- *TCF7L2* (rs11196172, rs7903146, rs7904519) and *VTI1A* (rs12241008, rs10506868) polymorphisms were determined using a TaqMan method (Real-time PCR).

➢ **Assessment of dependent variables:** Incident colon and breast cancers confirmed by medical records (During follow-up [median 10.0 years], incidence rates of colon and breast cancers were 1.335 and 2.076 per 1,000 person-years).

➢ **Assessment of covariates:** All covariates, such as cigarette smoking and alcohol consumption, and disease history (described below in the Statistical analysis), except for body mass index (BMI), were assessed by a self-reported questionnaire. The BMI was determined by dividing measured body weight in kilograms by the square of measured in meters.

- **Model used for association analyses:** Cox proportional hazards model
- **Independent variable:** Total PA (MET·hours/day)
- **Dependent variables:** Incident colon and breast cancers
- **Covariates of the model for colon cancer:**

Sex, age, cigarette smoking, alcohol consumption, vegetables/fruit consumption, current cardiovascular disease, current stroke, current diabetes mellitus, education, family history of colon cancer, accelerometer wear time, and BMI

- **Covariates of the model for breast cancer:**

Age, cigarette smoking, alcohol consumption, vegetables/fruit consumption, current cardiovascular disease, current stroke, current diabetes mellitus, education, family history of breast cancer, accelerometer wear time, BMI, menopausal status, age at menopause, age at first birth, number of births, breastfeeding, and hormone therapy

- ☐ Interaction analyses were performed by adding an interaction term (total PA × gene polymorphisms) was added to the multiple linear regression model.
- ☐ Significance level (α) = 0.05
- ☐ SAS (version 9.4)

Table 1. Characteristics of subjects by quartiles (Q) of total PA at baseline

n = 11,307	Total PA (MET·hours/day) Q1 (lowest)	Q2	Q3	Q4 (highest)
Age (years)	57.7	55.5	55.1	55.2
Sex, men	1204 (42.6)	1071 (37.9)	1126 (39.8)	1243 (44.0)
BMI (kg/m^2)	23.4	22.8	22.7	22.6
Current smokers, yes	688 (24.4)	541 (19.1)	487 (17.2)	487 (17.2)
Current alcohol drinkers, +23g ethanol/day	556 (19.7)	566 (20.0)	563 (19.9)	641 (22.7)
Total PA (MET·hours/day)	2.02	3.13	4.13	6.19
Current cardiovascular disease, yes	58 (2.1)	37 (1.3)	48 (1.7)	32 (1.1)
Current stroke, yes	31 (1.1)	7 (0.3)	11 (0.4)	9 (0.3)
Current diabetes mellitus, yes	176 (6.2)	133 (4.7)	163 (5.8)	157 (5.6)
Accelerometer wear time (hours/day)	12.23	12.91	13.29	13.71
Family history of colon cancer, yes	218 (7.7)	170 (6.0)	177 (6.3)	194 (6.9)
Education, below high school	1646 (58.2)	1534 (54.3)	1492 (52.8)	1578 (55.8)
Vegetables/fruit consumption < 3 times/day	1150 (40.7)	1056 (37.4)	1020 (36.1)	1068 (37.8)
Women only (n = 6,663)				
Postmenopausal	1227 (75.7)	1170 (66.6)	1104 (64.9)	1020 (64.4)
Family history of breast cancer, yes	29 (1.8)	40 (2.3)	32 (1.9)	32 (2.0)
Age at menopause, lower than 12 years old	434 (26.8)	518 (29.5)	535 (31.5)	537 (33.9)
Age at first birth, higher than 30 years old	199 (12.3)	221 (12.6)	233 (13.7)	199 (12.6)
Experience of birth, no	228 (14.1)	202 (11.5)	172 (10.1)	156 (9.9)
Number of births, once or two times	894 (55.1)	960 (54.7)	892 (52.4)	825 (52.1)
Breastfeeding, yes	1276 (78.7)	1445 (82.3)	1425 (83.8)	1329 (83.9)
Hormone therapy, yes	215 (13.3)	180 (10.3)	190 (11.2)	161 (10.2)

Values are mean for continuous variables and n (%) for categorical variables.

Table 2. Association between total PA and risks of colon or breast cancer

Dependent variables	Hazard ratio (HR) (Total PA, MET·hours/day)	95% Confidence interval (CI)	*P*
Colon cancer (n = 10,888; colon cancer incidence: n = 137)	0.874	0.780—0.979	**0.020**
Breast cancer (n = 6,451; breast cancer incidence: n = 127)	0.942	0.833—1.066	0.343

Covariates of the model for colon cancer: sex, age, cigarette smoking, alcohol consumption, vegetables/fruit consumption, current cardiovascular disease, current stroke, current diabetes mellitus, education, family history of colon cancer, accelerometer wear time, and BMI

Covariates of the model for breast cancer: age, cigarette smoking, alcohol consumption, vegetables/fruit consumption, current cardiovascular disease, current stroke, current diabetes mellitus, education, family history of breast cancer, accelerometer wear time, BMI, menopausal status, age at menopause, age at first birth, number of births, breastfeeding, and hormone therapy

Table 3. Associations of *VTI1A* and *TNF7L2* polymorphisms with the risks of colon or breast cancer

Gene polymorphisms	Colon cancer Model adjusted for sex and age			Breast cancer Model adjusted for age		
	HR	95% CI	*P*	HR	95% CI	*P*
VTI1A						
rs12241008	0.963	0.736－1.261	0.786	1.036	0.778－1.381	0.808
rs10506868	0.964	0.734－1.265	0.790	0.902	0.675－1.205	0.484
TCF7L2						
rs11196172	1.001	0.778－1.288	0.995	1.017	0.785－1.317	0.898
rs7903146	0.948	0.503－1.784	0.868	0.927	0.491－1.750	0.816
rs7904519	0.911	0.662－1.252	0.564	1.017	0.754－1.372	0.912

Covariates of model for colon cancer: sex and age

Covariates of model for breast cancer: age

Table 4. Interaction between total PA and *VTI1A /TCF7L2* polymorphisms on the risks of colon or breast cancer

Gene polymorphisms	Colon cancer (n = 10,859)	Breast cancer (n = 6,435)
	$P_{interaction}$	$P_{interaction}$
VTI1A		
rs12241008	0.245	**0.0008**
rs10506868	0.590	**0.0218**
TCF7L2		
rs11196172	0.979	0.523
rs7903146	0.334	0.580
rs7904519	**0.0002**	0.858

Covariates of the model for colon cancer: sex, age, cigarette smoking, alcohol consumption, vegetables/fruit consumption, current cardiovascular disease, current stroke, current diabetes mellitus, education, family history of colon cancer, accelerometer wear time, and BMI

Covariates of the model for breast cancer: age, cigarette smoking, alcohol consumption, vegetables/fruit consumption, current cardiovascular disease, current stroke, current diabetes mellitus, education, family history of breast cancer, accelerometer wear time, BMI, menopausal status, age at menopause, age at first birth, number of births, breastfeeding, and hormone therapy

Table 5. Association between total PA and colon cancer risk, stratified by*TCF7L2* gene polymorphism

	Model of colon cancer (adjusted for sex, age, cigarette smoking, alcohol consumption, vegetables/fruit consumption, current cardiovascular disease, current stroke, current diabetes mellitus, education, family history of colon cancer, accelerometer wear time, and BMI)			
	HR	95% CI	*P*	$P_{interaction}$
TCF7L2 （rs7904519）				
AA (n = 9,463)	0.823	0.725—0.934	**0.0026**	
AG (n = 541)	1.104	0.642—1.897	0.720	**0.0002**
GG (n = 855)	1.475	1.031—2.111	**0.0333**	

Table 6. Association between total PA and breast cancer risk, stratified by *VTI1A* gene polymorphisms

	Model of breast cancer (adjusted for age, cigarette smoking, alcohol consumption, vegetables/fruit consumption, current cardiovascular disease, current stroke, current diabetes mellitus, education, family history of breast cancer, accelerometer wear time, BMI, menopausal status, age at menopause, age at first birth, number of births, breastfeeding, and hormone therapy ）			
	HR	95% CI	*P*	$P_{interaction}$
VTI1A (rs12241008)				
CC (n = 403)	3.354	0.945－11.900	0.061	
CT (n = 2,385)	1.046	0.859－1.274	0.653	**0.0008**
TT (n = 3,647)	0.808	0.675－0.968	**0.021**	
VTI1A (rs10506868）				
CC (n = 3,500)	0.831	0.698－0.990	**0.0383**	
CT (n = 2,514)	1.063	0.873－1.293	0.544	**0.0218**
TT (n = 417)	1.422	0.869－2.326	0.161	

Discussion

- The current results suggest that beneficial effect of habitual PA on the colon cancer risk may be greater in individuals with A allele of *TCF7L2* polymorphism (rs7904519) than those with G allele.
- The beneficial effect of PA on the breast cancer risk may be greater in individuals with T allele of *VTI1A* polymorphism (rs12241008) than those with C allele. Another *VTI1A* polymorphism (rs10506868) may also modify the association.
- Japanese individuals with major alleles of these polymorphisms in the *VTI1A* and *TCF7L2* to enjoy greater benefits from habitual PA in daily life.
- Strengths of the current study are prospective cohort design and objective assessment of PA by accelerometer.

Conclusion

- The current results suggest that the beneficial effects of habitual PA on the incident risks of colon and breast cancers are modified by *VTI1A/TCF7L2* gene polymorphisms in the Japanese general population.