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An Inverse Association between Serum Gamma Glutamyl Transpeptidase Activity and Breslow's Lifestyle Index; Its Practical Application for Screening of Subjects with Unhealthy Lifestyles

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Abstract: An Inverse Association between Serum Gamma Glutamyl Transpeptidase Activity and Breslow's Lifestyle Index; Its Practical Application for Screening of Subjects with Unhealthy Lifestyles: Hirokazu YOKOYAMA, *et al.* Health Center, School of Medicine, Keio University—We examined whether serum γGTP activity (γGTP) is associated with Breslow's lifestyle index and whether it could be used as a tool to detect subjects with unhealthy lifestyles. To that effect, 724 male Japanese workers excluding patients suffering from hepatitis virus infection, autoimmune liver diseases and apparently active bile duct diseases were cross-sectionally examined. γGTP was inversely associated with the total score of Breslow's index for all subjects (λ=30.643) and in subjects aged 40 or more (λ=37.073). The association was consistent even after adjustments of subjects' ages and levels of triglycerides, total cholesterol and uric acid (p=0.0001). Among the seven lifestyle factors comprising Breslow's index, improper habits of drinking (p<0.0001), smoking (p=0.0204), exercise (p=0.0189) and body weight control (p<0.0001), were associated with increased γGTP. Even in a survey in which subjects who had proper habits of drinking and body weight control were selectively examined, improper habits of smoking and exercise still tended to be associated with increased γGTP. Receiver operating characteristic curves indicated that γGTP was beneficial for detecting subjects who scored two or less on Breslow's index, at least in subjects aged 40 or more. γGTP was associated with insulin resistance level estimated by the homeostasis model assessment (p<0.0001), which was inversely associated with Breslow's index (p=0.0040). γGTP could be used as an objective substitute of Breslow's index, allowing us to identify subjects with low scores on Breslow's index, at least after sorting subjects properly. Such screening would enable interventions to correct subjects' unhealthy lifestyles, helping to solve lifestyle-related disease issues.
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Key words: γGTP, Breslow's index, Lifestyle-related diseases, Insulin resistance, Ethanol

The issue of the ever-increasing incidence of lifestyle-related diseases, which is now threatening to national health and medical economics, has become critical, especially in developed countries. Most Japanese enterprises cannot bypass this issue because the associated morbid conditions lead to a shortage of workers and increase the medical expenses of employees that are partially charged to employers under the Japanese medical insurance system. "Japanese Industrial Safety and Health Law" obligates Japanese enterprises to engage at least one industrial physician in each workplace who is expected to tackle problems of safety and health, including lifestyle-related disease issue.

Although the concept of lifestyle-related diseases is still obscure, its definition should be "multiple morbid conditions that develop in subjects with unhealthy lifestyles". Its essence may be suitably explained by the views of Breslow and his co-workers[1)]. Namely, a healthy life in a modern society can be achieved by properly keeping seven habits regulating drinking, smoking, exercise, sleeping, body weight control, breakfast, and snacking between meals. Subjects who cannot keep these habits fall into various morbid conditions, i.e. lifestyle-related diseases. Indeed, subjects who could properly follow only three or less of the seven habits were shown to live shorter lives than those who followed six or more[2)].

In this context, the ultimate solution for the lifestyle-related disease issue should be to evaluate subjects'

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lifestyle statuses, identify subjects with unhealthy lifestyles, and advise them on how to properly correct their lifestyles. Using seven simple questionnaires regarding the seven lifestyles, Breslow established a scale known as Breslow's index, allowing us to easily estimate a subject's lifestyle status[1]. However, an examination based on self-administered questionnaires may be prone to false representations, especially when carried out in a work environment. Since employees usually want to avoid being labeled 'unhealthy', which would disadvantage their employment position, it is doubtful whether they always answer faithfully to self-administered questionnaires on their health condition. Thus, it would be worthwhile to establish simple and objective tools reflecting Breslow's index to evaluate lifestyle status.

Serum gamma glutamyl transpeptidase (γGTP) activity has been classically used as a sensitive marker of liver disease[3–5] or excessive ethanol consumption[6–9] in clinical cases. It is also one of the items in annual health checkups that are regulated by the "Ordinance on Industrial Safety and Health" in "Japanese Industrial Safety and Health Law". Interestingly, the recently prevailing view is that increased serum γGTP activity is also associated with obesity[10–15], excessive smoking[11, 15–17], and an improper exercise habit[11, 13, 18, 19]. Namely, improprieties of four of the seven lifestyle factors comprising Breslow's index are implicated in increasing serum γGTP activity. It is, therefore, conceivable that serum γGTP activity is associated with Breslow's index and could be used as a substitute. The aim of this study was to verify these views, namely to ascertain whether serum γGTP activity could be used as an objective tool to identify subjects with unhealthy lifestyles. We believe that our results enable an objective measurement of lifestyle-related disease, and also give a more thorough interpretation of serum γGTP activity in clinical cases.

Methods

All studies in this report were approved by the ethics committee of the Health Center, Keio University, based on the ethical guidelines of the 1975 and 1983 Declaration of Helsinki. All subjects were informed and consented to the use of their data in this study. All were teaching or clerical staff of a branch of our university and on its active list, and subjects who were absent from duties for any reason including drinking problems or severe sickness were not included. All subjects fully understood the meaning of this study and that they were expected to answer accurately and faithfully to the self-administered questionnaires in this study. Medical staff of our department assisted them in completing the questionnaires upon request. Subjects who did not complete the questionnaires for any reason were excluded. Since gender difference in serum γGTP activity has been reported[20], only male subjects were enrolled in the present study. Subjects who were judged to be suffering from liver diseases due to HBV or HCV infections or autoimmune liver diseases were excluded. The population did not include subjects who were suffering from apparently active bile duct diseases or those who were advised to stop taking any medications because of their adverse effects. Subjects who received insulin, thiazolidinediones, sulfonyl ureas, phenyl-alanine derivatives, or alpha-glucosidase inhibitors which may affect insulin resistance levels were also excluded. Ultimately, 724 males aged 30 to 65 (median 45) yr were enrolled. Body mass indexes (BMI) were calculated from the height and weight measurements for each subject. Their lifestyle statuses were assessed by Breslow's index, comprising seven self-administered questionnaires on their habits of breakfast, exercise, sleeping, drinking, eating between meals, smoking, and body weight control[1], with some modifications as described in detail previously (Table 1)[21]. Blood samples were collected from each subject after fasting for at least 10 h. Serum levels of γGTP activity, total cholesterol (TC), triglycerides (TG), uric acid (UA), and glucose were routinely measured in each subject. The upper limit of

Table 1. Questionnaires for estimation of subjects' lifestyle status based on Breslow's lifestyle index

1) Do you sleep for 7–8 h almost every day?
2) Do you avoid smoking?
3) Do you avoid eating between meals (snacks)?
4) Do you take breakfast almost everyday?
5) Do you participate in active sports at least three times in a week?
6) Do you keep your body mass index (BMI) at 26.1 kg/m^2 or less?
7) Do you limit ethanol intake to less than 200 g in a week?

Table 2. Characteristics of subjects

	Median (range)	
Age (yr)	45	(30–65)
Body Mass Index (Kg/m^2)	22.8	(15.9–37.6)
Breslow's index	5	(1–7)
γGTP (IU/l)	32	(9–1551)
Total Cholesterol (mg/dl)	196	(97–339)
Triglyceride (mg/dl)	95	(18–1088)
HOMA-IR (Unit)	1.07	(0.19–18.30)
Uric acid	6.1	(2.5–9.8)

(n=724)

HOMA-IR; the homeostasis model assessment-insulin resistance.

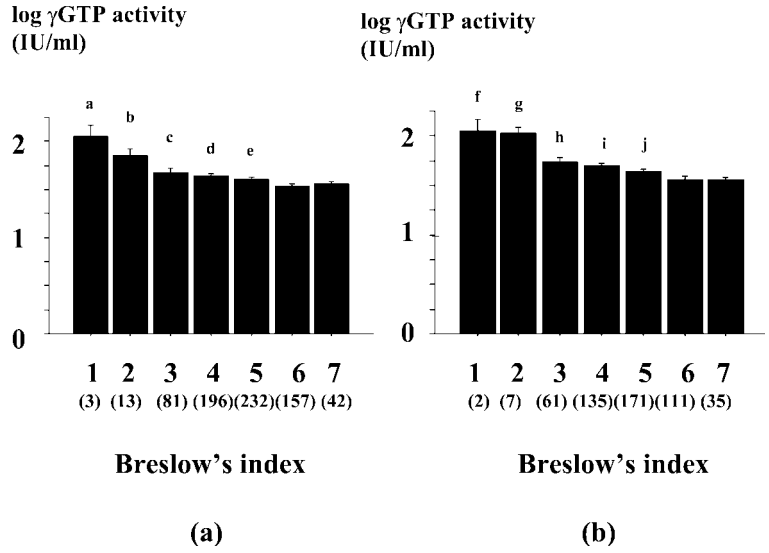

Fig. 1. Association between the total scores on Breslow's lifestyle index and the logarithmic serum γGTP activity. Subjects with lower scores on the lifestyle index showed higher levels of serum γGTP activity (λ=30.643, p<0.0001, a). The association became stronger when 522 subjects aged 40 or more were selectively studied (λ=37.073, p<0.0001, b). Each box and bar indicate the mean and standard deviation of logarithmic serum γGTP activity in each group. Differences among groups were assessed by one-way ANOVA followed by Fisher's PSLD test as a *post hoc* test. a: p<0.05 compared to groups 5,6,7; b: p<0.005 compared to group 5,6,7 and p<0.05 compared to group 4; c: p<0.005 compared to group 6 and p<0.05 compared to groups 7; d: p<0.001 compared to groups 6; e: p<0.05 compared to group 6 in Fig 1-a. f: p<0.05 compared to groups 6,7; g: p<0.05 compared to group 3, p<0.005 compared to groups 4, 5, p<0.001 compared to group 5 and p<0.0001 compared to group 6; h: p<0.05 compared to group 5 and p<0.005 compared to group 7 and p<0.0005 compared to group 6; i: p<0.05 compared to group 7 and p<0.001 compared to groups 6; j: p<0.05 compared to group 6 in Fig 1-b.

the normal range of serum γGTP activity for male subjects was 78 IU/l in our laboratory. The serum insulin level was also measured by radioactive immune assay. The insulin resistance level in each subject was determined by homeostasis model assessment (HOMA-IR[22]). Values of TG, γGTP, and HOMA-IR were transformed into logarithms to obtain their normal distributions which were judged by the shapes of histograms and the coincidence of means and medians. Values were expressed by medians and their ranges or means and standard deviations (SD). Differences among multiple groups were examined using one-way ANOVA followed by Fisher's PSLD test as a *post hoc* test. Associations between factors were evaluated by single regression analysis, Spearman's rank correlation analysis, multiple regression analysis, or multiple logistic regression analysis. Before the construction of multiple regression models, significant positive or inverse associations between the dependent variables and selected independent variables were confirmed by single regression analyses. Specificity and sensitivity of γGTP for subjects with unhealthy lifestyles were evaluated at various γGTP levels and receiver operating characteristic (ROC) curves of γGTP to Breslow's index were drawn. All statistical analyses were performed by StatView® (ver 5.0, SAS Institute Inc. NC, USA) using a Macintosh PowerBook G3 (Apple Japan, Inc. Tokyo, Japan). P-values less than 0.05 and 0.1 were considered to indicate significance and statistical trend, respectively. ROC curves were draw by StatFlex® using a Sony notebook computer (PCG8E2N, Sony Inc. Tokyo, Japan).

Results

The profiles of subjects in the present study are shown in Table 2. In this population, a one-way ANOVA was performed to examine whether serum γGTP activity was associated with the total score of Breslow's index. Since this population did not include subjects who scored 0 points by the total scores of Breslow's index, the subjects were divided into 7 groups according to the scores and the level of logarithmic serum γGTP activity was examined in each group. As shown in Fig. 1-a, as the total score of Breslow's index became lower, logarithmic serum γGTP activity became higher, indicating that an inverse association exists between the two factors (λ=30.643, p<0.0001). The inverse association became more significant when 522 subjects aged 40 or more were selectively examined (λ=37.073, p<0.0001, Fig 1-b).

Table 3. Regression between the total score of Breslow's index and various examination items in health checkups (Multiple regression analysis for the total score of Breslow's index n=724)

total score of Breslow's index VS	Regression coefficient (standard error)	Standardized regression coefficient	p-value
log γGTP activity	–0.603 (0.158)	–0.158	0.0001
log Triglycerides	–0.725 (0.198)	–0.155	0.0003
Total cholesterol	0.001 (0.002)	0.023	0.5519
Uric acid	0.035 (0.038)	0.035	0.3613
Age	0.015 (0.004)	0.129	0.0006

Multiple coefficient of determination (R^2): 0.068
Adjusted multiple coefficient of determination: 0.061

Table 4. Ratio of subjects with γGTP activity of more than 78 mIU/ml

Breslow's index	1	2	3	4	5	6	7
Subjects with increased γGTP	100.0	61.5	45.0	12.0	11.0	10.8	4.2
	n=3	n=13	n=81	n=196	n=232	n=157	n=42
Subjects with increased γGTP	100.0	85.7	32.7	22.0	20.5	12.6	2.9
(aged 40 or more)	n=2	n=7	n=61	n=135	n=171	n=111	n=35

The associations between the total score of Breslow's index and the logarithmic serum γGTP activity was further studied using a multiple regression analysis in which various factors that might have affected serum γGTP activity, namely the subjects' age and the levels of TC, UA, logarithmic TG[23], were adjusted. Even after adjusting for these factors, logarithmic serum γGTP activity was significantly associated with Breslow's index. The standardized regression coefficient between Breslow's index and logarithmic serum γGTP activity was –0.158 (p=0.0001, Table 3).

As shown in Table 4, the incidences of increasing serum γGTP activity, namely that of more than 78 IU/l, were 100% and 61.5% in subjects who scored 1 and 2 points on Breslow's index, respectively. When subjects aged 40 or more were selectively studied, the incidences were 100% and 85.7%, respectively. On the other hand, the incidences were 10.8 % and 4.2% in subjects who scored 6 and 7 points in Breslow's index, respectively, and were 12.6% and 2.9% even in subjects aged 40 or more.

The power of the serum γGTP activity to detect subjects with unhealthy lifestyles was examined in subjects aged 40 or more using ROC curves based on the sensitivity and specificity of γGTP for Breslow's index. When subjects with unhealthy lifestyles were designated as those who scored two or less on Breslow's index, its area under the curve (AUC) was 0.863 +/– 0.028 (mean +/– SD, Fig 2-a). However, the AUC became smaller (0.618 +/– 0.038) when subjects with unhealthy lifestyles were designated as those who scored three or less on Breslow's index (Fig. 2-b).

Among the seven lifestyle factors comprising Breslow's index, particular lifestyles accounting for increasing γGTP activity, i.e. more than 78 IU/l, were specified by multiple logistic regression analyses in which subjects' ages were adjusted. As shown in Table 5, a BMI of 26.1 kg/m^2 or less (p<0.0001), ethanol consumption less than 200 g per week (p<0.0001), avoiding smoking (p=0.0204), and participating in active sports more than 3 times per week (p=0.0189) were shown to be significant factors keeping serum γGTP activity normal.

To study interactions between factors which were strongly associated with serum γGTP and those which were weak in the above-mentioned association, another model of multiple logistic regression analysis was constructed in which the associations between serum γGTP activity and the statuses of five lifestyle factors in Breslow's index (excluding the habits of drinking and body weight control) were examined. The associations were examined in four different groups that were divided by subjects' statuses of body weight control and drinking. As shown in Table 6, when 531 subjects who had proper drinking habits and proper body weight were selectively studied, avoiding smoking (p=0.0622) and participating actively in sports more than three times per week (p=0.0539) showed trends toward normal γGTP activity. Among 74 subjects who had proper drinking habits but were overweight, avoiding smoking was a significant factor accounting for normal γGTP activity (p=0.0122;

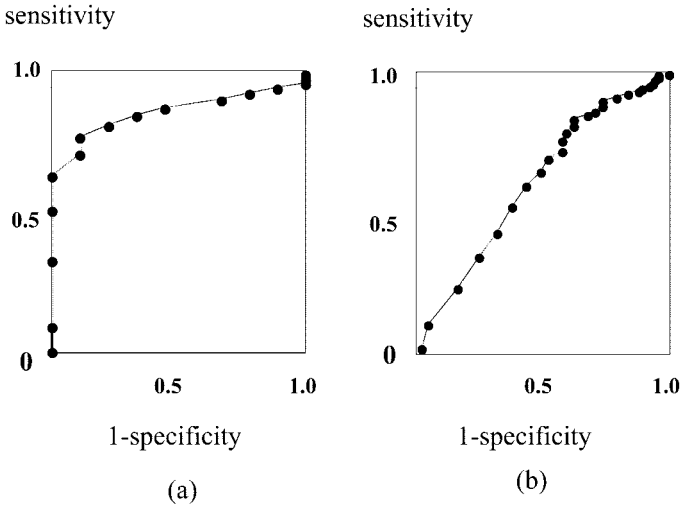

Fig. 2. Specificity and sensitivity of γGTP in detecting subjects with unhealthy lifestyles. Receiver operating characteristic (ROC) curves based on specificity and sensitivity of γGTP for subjects with unhealthy lifestyles were drawn. When subjects with unhealthy lifestyles were designated as those who scored two or less on Breslow's index, γGTP was a considerably effective tool for detecting such subjects: area under curve (AUC), 0.863 +/– 0.028 (a). However, when subjects with unhealthy lifestyles were designated as those who scored three or less, it was a less effective tool: AUC, 0.618 +/– 0.038 (b).

Table 5. Association between the seven lifestyle items in Breslow's index and serum γGTP activity

	γGTP ≤78 IU/l (n=595) vs γGTP>78 IU/l (n=129)		
	Partial correlation coefficient	Odds ratio (95%CI)	p value
Age	0.053	0.97 (0.96–1.0)	0.0472
Sleeping 7–8 h almost every day (n=385) or not (n=339)	<0.001	0.87 (0.58–1.31)	0.4922
Avoiding smoking (n=583) or not (n=141)	0.071	1.75 (1.11–2.81)	0.0204
Avoiding eating between meals (n=346) or not (n=378)	<0.001	1.22 (0.80–1.86)	0.3608
Taking breakfast almost every day (n=602) or not (n=122)	<0.001	1.44 (0.85–2.44)	0.1762
Participating in active sports ≥3 times/week (n=301) or not (n=423)	0.072	1.68 (1.09–2.58)	0.0189
Limiting ethanol consumption < 200 /week (n=605) or not (n=119)	0.198	3.65 (2.27–5.86)	<0.0001
Maintaining BMI ≤26.1 kg/m^2 (n=630) or not (n=94)	0.154	2.97 (1.80–4.91)	<0.0001

CI: Confidence interval, BMI: Body mass index, (n=724)

Table 6. Association between five lifestyle items in Breslow's index excepting statuses of drinking and body weight control and serum γGTP activity in subjects with proper habits of drinking and body weight control

		γGTP ≤78 IU/l (n=471) vs γGTP>78 IU/l (n=60)	
	Partial correlation coefficient	Odds ratio (95%CI)	p value
Age	0.084	0.97 (0.95–1.00)	0.0820
Sleeping 7–8 h almost every day (n=288) or not (n=243)	<0.001	0.89 (0.46–1.44)	0.4743
Avoiding smoking (n=444) or not (n=87)	0.080	1.54 (0.92–2.14)	0.0622
Avoiding eating between meals (n=237) or not (n=294)	<0.001	1.17 (0.66–2.10)	0.5878
Taking breakfast almost every day (n=451) or not (n=80)	0.050	1.73 (0.84–3.59)	0.1402
Participating in active sports ≤3 times/week (n=216) or not (n=315)	0.055	1.85 (0.99–3.46)	0.0539

CI : Confidence interval, BMI: Body mass index, (n=531)

odds ratio, 5.769, confidence interval, 1.465–22.717) whereas proper exercise habit was not a factor accounting for normal γGTP activity. In other groups comprising subjects with improper drinking habits and overweight (n=20) or those with improper drinking habits but normal body weight (n=99), neither proper smoking habit nor proper exercise habit were associated with serum γGTP activity.

Spearman's rank correlation analyses demonstrated that the HOMA-IR level was significantly associated with serum γGTP activity (ρ=0.266, p<0.0001) and inversely associated with Breslow's index (ρ=–0.108, p=0.0040). The associations between the total score of Breslow's index and the logarithmic serum γGTP activity was re-examined using multiple regression analysis with the same conditions mentioned above but with the logarithmic HOMA-IR level added to the adjusting factors. Even in this condition, the inverse association between Breslow's index and the logarithmic serum γGTP activity was consistent, however, the standardized regression coefficient became smaller (–0.146, p=0.0005) compared to the condition in which the HOMA-IR was not taken into account.

Discussion

If lifestyle-related diseases are indeed attributable to unhealthy lifestyles, the best solution for lifestyle-related diseases would be to identify subjects with unhealthy lifestyles and guide them away from their unhealthy lifestyles. To that effect, Breslow's index[1] is highly recommended because of its simplicity and economic efficiency. The index should precisely reflect subjects' lifestyle statuses to a certain extent when they are cooperative like the present subjects. However, such an examination based on self-administered questionnaires may sometimes be unreliable, especially in the work environment where employees want to avoid being thought of as unhealthy by employers. Thus, it is necessary to establish an objective substitute for Breslow's index. Here, since we displayed an inverse association between serum γGTP activity and the total score of Breslow's index in Japanese male workers, we propose that measuring serum γGTP activity could allow the objective screening of subjects with unhealthy lifestyles and serve as a substitute for Breslow's index.

Serum γGTP is one of the enzymes expressed in hepatocytes, and an increase in its activity sometimes indicates the destruction of hepatocytes; namely, exacerbation of various liver diseases due to hepatitis viral infection, autoimmune disorders, administration of medicines, or bile duct disorders[3–5]. However, the current consensus is that some lifestyle habits such as ethanol consumption[6–9], body weight control[10–15], smoking[11, 15–17] and exercise[11, 13, 18, 19] are also factors affecting serum γGTP activity regardless of liver damage. In addition to these views, the present ANOVAs and multiple regression analysis demonstrated that serum γGTP activity is also associated with Breslow's index, a comprehensive indicator of multiple lifestyle statuses.

Ethanol consumption, body weight control, smoking, and exercise are four of the seven lifestyles assessed in Breslow's index and excessive ethanol consumption, excessive smoking, under exercise and being overweight are known to contribute to decreasing Breslow's index

and also increase serum γGTP activity[6–19]. Consistently, the present multiple logistic regression analysis (Table 5) indicates that improprieties of the aforesaid four lifestyles, among the seven lifestyles assessed in Breslow's index, significantly contributed to an increase in serum γGTP activity. Thus, an inverse association between the serum γGTP activity and Breslow's index was fully understandable, especially when subjects suffering from the liver diseases mentioned above were excluded.

The multiple logistic regression analysis also indicated that excessive ethanol consumption and improper body weight control had strong associations toward an increase in γGTP activity among all the seven lifestyles assessed in Breslow's index. To rule out possibilities that the associations between serum γGTP activity and factors other than the two strong factors were just secondary to the strong associations, another model of multiple logistic regression analysis was constructed. Namely, the associations between lifestyles in Breslow's index (excluding habits of drinking and body weight control) and serum γGTP activity were studied in the population excluding subjects who scored 0 point on drinking habits and on body weight control in Breslow's index, i.e. excluding those who drank 200 g ethanol or more per week and had BMIs more than 26.1 kg/m^2. Since excessive smoking and under exercise tended to be associated with an increase in serum γGTP activity even under these conditions, they were also considered as independent factors accounting for increases in serum γGTP activity. Although an exception was found, associations between excessive smoking or under exercise and serum γGTP activity were not significant in the other three different groups in which subjects had impropriety in drinking habit or body weight control or both. This may support the view that the association between excessive smoking or under exercise and serum γGTP activity is not a secondary effect of excessive drinking or over weight.

Because subjects who score three or less on Breslow's index have a shorter life expectancy than those who score six or more[2], it is critical to identify subjects with 0–3 points on Breslow's index. Since the incidences of increasing serum γGTP activity were 61.5% and 100% in subjects who scored 2 and 1 points on Breslow's index, respectively, and the incidences were further increased when subjects aged 40 or more were selectively studied, serum γGTP activity may be useful for identifying such subjects. Indeed, the present ROC curves support the view that γGTP exerts considerably significant power to identify subjects who score two or less on Breslow's index, at least among subjects aged 40 or more, whereas its power is insufficient when subjects who scored three on Breslow's index became the target of the identification.

We must take care, because the present findings were valid only after various exclusions, indicating that serum γGTP activity may not be a useful marker of unhealthy lifestyles in the general population. Furthermore, 10.8% and 4.2% of subjects (12.6% and 2.6% in subjects aged 40 and more) who scored 6 and 7 on Breslow's index showed increased serum γGTP activities, respectively, even after the present selection. However, we believe that such a shortcoming can be overcome by its practical application, schematized as follows. A subject with increased serum γGTP activities is simply advised to visit the office of a physician, for example, an industrial physician. First, the physician rules out various disorders which would cause an increase in serum γGTP activity. When the patient is diagnosed with such disorders, he or she should be introduced to the respective specialist. If such disorders are not found, the physician should examine the patient's lifestyle status in detail and give advice on how to improve it. Since lifestyle-related diseases should be caused by unhealthy lifestyles, we believe that such lifestyle intervention should contribute to a decrease in the incidences of lifestyle-related diseases.

Recently, a relation between insulin resistance and serum γGTP activity has been highlighted. Multiple lines of evidence including our own suggest that serum γGTP activity is associated with the statuses of various morbid conditions of insulin resistance syndrome[23, 25, 26], especially with those of type 2 diabetes mellitus[27, 28], hypertension[29, 30], hyperlipidemia[31], fatty liver[32] and the insulin resistance level per se[33, 34]. Meanwhile, we also found an inverse association between Breslow's index and the insulin resistance level in Japanese male subjects[11]. The present Spearman's rank correlation analyses indicated an association between serum γGTP activity and the insulin resistance level assessed by the HOMA-IR and an inverse association between the insulin resistance level and Breslow's index. Thus, it is fully conceivable that insulin resistance status mediated the inverse association between Breslow's index and the serum γGTP activity, at least in part. Indeed, the present multiple regression analyses showed that the inverse association between the two factors became weaker when HOMA-IR was added to the adjusting factors. However, the inverse association was still significant after adjusting HOMA-IR, indicating that HOMA-IR could not thoroughly account for the inverse association.

An inverse association between serum γGTP activity and lifestyle status, suitably agrees with the facts that increasing mortality is associated with both increased serum γGTP activity[18, 25] and decreased Breslow's indexes[2]. It is easily conceivable that excessive drinking, excessive smoking and the insulin resistance state etc. are linked to the increasing mortality. At any rate, these statistical facts could be an extrinsic motivation for patients with increased γGTP due to unhealthy lifestyles to improve their lifestyles.

Since the cost of measuring serum γGTP is much higher than that of performing questionnaires for Breslow's index, the question of economy could arise. However, the "Ordinance on Industrial Safety and Health" in "Japanese Industrial Safety and Health Law" obligates Japanese employers to have their employees undergo annual health checkups in which serum γGTP activity is also examined; therefore, serum γGTP activity is automatically checked for all employees every year in Japan. Thus, the economical issue can be disregarded at least in occupational fields in Japan.

Although this study was conducted on a limited cross-sectional basis, serum γGTP activity was shown to be inversely associated with Breslow's index. Although we must wait outcomes of prospective studies to be certain, we here propose that serum γGTP activity is considerably useful for identifying subjects with unhealthy lifestyles who score two or less on Breslow's index and who are expected to have short lives, at least when subjects are properly sorted. γGTP screening would enable us to intervene with lifestyle corrections that would contribute to solving the lifestyle-related disease issue, which has become increasingly serious, especially in developed countries. Moreover, we believe that the classical interpretation of serum γGTP activity, that its increase indicates progression of liver diseases and excessive ethanol consumption, should be modified to show that various unhealthy lifestyles also affect it, particularly in this era of lifestyle-related diseases in which unhealthy lifestyles are serious public health problems.

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