Table 1 Selected baseline characteristics according to educational background

Educational background (age)	Total			Women aged 18 years or above in 1949			Women aged under 18 years in 1949		
	<16	16–18	>18	<16	16–18	>18	<16	16–18	>18
n	11,622	17,573	3,451	6,995	8,045	1,393	4,627	9,528	2,058
Mean age (SD)	60.5 (10.0)	56.6 (10.8)	55.4 (10.2)	67.2 (5.8)	65.4 (5.5)	65.7 (5.6)	50.4 (5.3)	49.2 (5.5)	48.4 (5.5)
Mean body mass index (SD)	23.0 (3.6)	22.7 (3.2)	22.5 (3.7)	22.8 (3.8)	22.7 (3.6)	22.3 (3.2)	23.3 (3.1)	22.8 (2.9)	22.6 (3.9)
History of hypertension (%)	25.3	19.1	16.1	32.0	28.1	24.7	15.1	11.5	13.3
History of diabetes (%)	4.6	3.6	3.5	6.0	5.6	5.8	2.5	1.9	1.9
Attendance at a breast cancer screening program	17.2	25.0	27.2	13.9	20.0	21.8	22.2	29.2	30.7
Breast self-examination	22.9	37.0	41.7	16.1	29.4	34.5	33.2	43.4	46.6
Current smoker (%)	5.5	4.3	4.1	4.9	3.2	3.6	6.6	5.2	4.4
Habitual drinker (%)	20.4	24.5	25.4	16.8	21.1	21.5	25.8	27.4	28.0
Hours of walking per day (%)									
≥1.0	51.1	49.6	48.2	50.7	49.2	47.6	51.7	49.9	48.6
0.6–0.9	20.6	22.0	22.8	21.1	22.3	23.4	19.8	21.8	22.4
0.5	17.8	18.9	20.5	18.7	20.5	21.6	16.5	17.6	19.7
<0.5	10.5	9.5	8.6	9.4	8.1	7.4	12.0	10.7	9.3
Hours of exercise per week (%)									
≥5	5.3	4.1	4.3	7.4	6.0	6.2	2.4	2.7	3.1
3–4	5.2	5.3	6.6	6.7	6.2	7.1	3.2	4.5	6.3
1–2	11.4	16.0	19.3	12.0	16.5	19.9	10.6	15.5	18.9
<1	78.1	74.7	69.8	74.0	71.3	66.9	83.8	77.2	71.7
Perceived mental stress (%)									
Frequent	8.9	9.9	11.6	6.2	7.1	7.8	12.9	12.3	14.2
Occasional	8.2	11.2	15.0	6.5	8.6	10.7	10.7	13.3	17.8
Very occasional	62.1	60.0	55.2	63.2	62.2	59.9	60.6	58.2	52.0
Never	14.6	16.1	16.7	15.7	18.7	19.0	12.9	14.0	15.1
Nulliparous (%)	4.2	4.0	5.6	4.9	4.4	6.3	3.1	3.6	5.2
Average number of pregnancies (SD)	3.5 (1.7)	3.3 (1.6)	3.1 (1.6)	3.7 (1.9)	3.5 (1.7)	3.3 (1.7)	3.2 (1.5)	3.1 (1.4)	3.0 (1.4)
Average number of deliveries (SD)	2.9 (1.5)	2.5 (1.1)	2.4 (1.1)	3.3 (1.7)	2.8 (1.4)	2.6 (1.4)	2.4 (0.9)	2.3 (0.9)	2.3 (0.9)
Mean age at first delivery (SD)[a]	24.8 (3.3)	25.0 (3.2)	25.8 (3.3)	24.9 (3.4)	24.8 (3.4)	25.7 (3.2)	24.7 (3.1)	25.2 (2.9)	25.9 (3.3)
Mean age at menarche (SD)	15.2 (1.9)	14.8 (1.7)	14.6 (1.8)	15.6 (1.8)	15.2 (1.7)	15.2 (1.9)	14.5 (1.8)	14.4 (1.7)	14.1 (1.6)
In menopause (%)	73.1	65.6	60.9	86.9	91.3	92.8	52.2	44.0	39.3
Mean age at menopause (SD)[b]	48.5 (4.6)	48.8 (4.7)	49.0 (4.5)	48.7 (4.5)	49.1 (4.6)	49.3 (4.6)	48.0 (4.8)	48.1 (4.9)	48.5 (4.5)

[a] Among women who experienced delivery

[b] Among women in menopause

Table 2 Hazard ratios of educational background for breast cancer incidence by age-subgroup

Educational level	Person-years	Cases	Model 1		Model 2		Model 3	
			HR (95% CI)	p (p for trend)	HR (95% CI)	p (p for trend)	HR (95% CI)	p (p for trend)
Total subjects								
<16	116,854	40	reference		reference		reference	
16–18	176,965	100	1.32 (0.91–1.94)	0.147	1.37 (0.93–2.03)	0.114	1.33 (0.90–1.97)	0.152
>18	35,163	29	1.93 (1.18–3.16)	0.009	2.05 (1.24–3.39)	0.005	1.97 (1.19–3.26)	0.009
				(0.010)		(0.006)		(0.010)
Women aged 18 years or above in 1949								
<16	66,908	25	reference		reference		reference	
16–18	72,246	32	0.90 (0.52–1.55)	0.706	0.92 (0.53–1.62)	0.784	0.86 (0.49–1.53)	0.615
>18	13,242	11	1.67 (0.81–3.43)	0.164	1.86 (0.89–3.91)	0.100	1.60 (0.76–3.38)	0.215
				(0.356)		(0.243)		(0.419)
Women aged under 18 years in 1949								
<16	49,945	15	reference		reference		reference	
16–18	104,719	68	1.92 (1.08–3.39)	0.026	1.91 (1.07–3.39)	0.028	1.90 (1.07–3.38)	0.030
>18	21,921	18	2.44 (1.21–4.92)	0.013	2.44 (1.20–4.95)	0.013	2.51 (1.23–5.12)	0.012
				(0.010)		(0.011)		(0.009)

Model 1 adjusted for age

Model 2 adjusted for age, BMI, alcohol, smoking, stress, hours of walking, hours of exercise, attendance at a breast cancer screening program, and breast self-examination

Model 3 additionally adjusted for number of pregnancies, number of deliveries, age at first delivery, age at menarche, and age at menopause

In the multivariate model, compared with women with BMI <22, HR was 1.45 (95%CI: 0.90, 2.42; $p = 0.123$) for those with BMI of 22–23.9, 2.08 (95% CI: 1.30, 3.32; $p = 0.002$) for those with BMI of 24–25.9, and 1.72 (95% CI: 1.05, 2.80; $p = 0.030$) for those with BMI ≥26). In contrast, smoking and alcohol were not associated with the risk of breast cancer. Further, the multivariate HR of breast cancer was significantly lower for parous than nulliparous women (HR = 0.79, 95% CI: 0.68, 0.91; $p = 0.001$). Among parous women, moreover, the multivariate HR by number of births compared to those with one delivery were 0.71 (95% CI: 0.42, 1.19) for two deliveries, 0.63 (955 CI: 0.36, 1.08) for three, and 0.36 (95% CI: 0.17, 0.77) for four and more, showing a significant declining trend for the association between number of deliveries and risk (p-value for trend = 0.01). Further, among parous women, a borderline significant increase in risk of breast cancer was seen with increasing age at first delivery (p value for trend = 0.05), with the highest risk occurring in women who had their first delivery at age 35 or older (HR = 2.66, 95% CI: 1.00, 1.60; $p = 0.054$), compared with those who had their first delivery at age 25 or younger.

Discussion

Our investigation of 32,646 Japanese women over 328,931 person-years of follow-up showed that women with a higher educational level had a higher risk of breast cancer than those with a lower educational level. Unlike most other diseases and sites of cancer, breast cancer has been demonstrated to have a positive association with educational level. Most reports of this atypical association have come from studies in Europe [1, 3–5, 7, 8, 11, 12] and the United States [2, 6, 9, 10]. To our knowledge, the present study is the first to add support for this association in a non-white population in an Asian country.

The present study found an approximately 2-fold higher HR in the highest than in the lowest educational group. Although the size of this effect varies among studies, the present difference is substantially larger than those reported previously. One possible explanation for this is that the incidence of breast cancer in Japanese women is about one-third that in Caucasian women [14]. Higher absolute rates are more likely to lead to smaller relative risk than lower absolute rates, even if the absolute difference between the high and low educational groups is similar. Interpretation of this is further complicated by the different outcome measures used: some studies examined the incidence of breast cancer [1–3, 6, 10, 23] whereas others examined mortality [3, 7, 8, 11, 12, 24, 25]. A second cause of the difference between the present and previous results may be differences in educational grouping.

One possible explanation for this association may owe to the social distribution of breast cancer risk factors associated with education, such as reproductive factors,

diet, alcohol consumption, excess weight, and physical activity. In particular, reproductive factors may play an important role [1, 6, 10, 11]. Age at first birth and parity significantly reduced the association between educational level and breast cancer risk [1, 11]. In the present study, however, adjustment for reproductive factors did not substantially change the association between educational level and breast cancer. Further, we also found that multiparity was associated with a decreased risk and late age at first delivery with an increased risk. This has been comprehensively reported elsewhere [19]. This finding is supported by previous studies in which adjustment for reproductive factors attenuated but did not abolish the association between educational level and breast cancer [2, 4, 6]. We speculate that this might be partly explained by degree of disparity in reproductive behaviors across socioeconomic groups among countries. For example, in the present study, mean age at first delivery did not particularly differ, at 24.8 years in the lowest versus 25.8 years in the highest education group. Respective values in another study were 22 versus 27 years [11], while another reported similar results [6]. These results may suggest that this association is not only due to reproductive factors but also due to other mechanisms. As noted previously [26, 27], however, the association between socioeconomic status and health might be generally the result of a mixture of biological, lifestyle behavioral, environmental, and social factors rather than having one single cause.

The time trend of this association is also of interest. Several studies that conducted time trend analyses have suggested that the traditionally excessive rates of breast cancer among women with a high socioeconomic status are declining [7, 8, 15]. A study in Finland showed that this is mainly due to an increase in breast cancer mortality among less-educated women and a stable or decrease in mortality among better-educated women [7]. These authors suggested that this declining trend might have been due in part to a narrowing of the differences in reproductive behavior among younger generations, and a spread in the risk pattern of well-educated women to other social groups. For example, a decrease in the disparity of educational level according to the average number of children owed mainly to a decline in the number of children among less educated women [28]. In contrast, other studies investigating time trends in social inequalities have reported that the positive association between socio-economic status and breast cancer mortality remained stable between 1959–1972 and 1982–1996 in the United States [9], or appeared between 1981 and 1991 in Scotland [29]. Strand and colleagues recently reported a positive association between education and breast cancer in England, Wales, and Norway, and small and narrowing inequalities in Finland and France [12]. In the present study, the interaction term was not statistically significant ($p = 0.993$) when the analysis included an interaction term which multiplied educational level and generation. This suggests that there is no clear difference in time trend. However, it has been suggested that these tests are not very powerful, and that visual inspection of the size and pattern of the effect estimates across the strata is usually more informative than tests for interaction [30]. Although confidence intervals between the older and younger subgroups largely overlapped, the educational difference in breast cancer incidence was more evident among the younger than older subgroup. The gradient of educational level in breast cancer risk remains among the younger subgroup at least. Further investigation of the time trend for the association between educational level and breast cancer is warranted.

Some important limitations of our study warrant mention. First, the study failed to obtain information on several important possible confounding factors, such as the final term of pregnancy, breast feeding, and use of exogenous sex hormones. Although the model included attendance at breast cancer screening, this was baseline data. Thus, we assume that the model adjusted for the individual's attitude and health consciousness rather than the opportunity for finding breast cancer. Second, the validity of self-reported reproductive histories is uncertain. Some reproductive exposures occurred long before enrolment or any disease diagnosis. However, previous studies have shown good agreement between responses regarding reproductive events and medical records [31, 32]. Third, we could not fully control the cohort effect [33], although the present analyses were stratified by age subgroup. The meaning of education may have changed over time and older people tend to have a lower average level of education. The mixture of age cohorts may have attenuated the magnitude of the socioeconomic effect on breast cancer, and this is more likely to have affected the older subgroup.

Conclusion

The present study has identified a positive association between education level and breast cancer incidence among Japanese women. By age subgroup, the association was evident among younger women. Breast cancer is the most frequent cancer in Japanese women and the incidence has increased over time [34]. Against the background of social advancement for women following increases in educational level, cancer prevention strategies should recognize women with higher educational levels as a high risk group for breast cancer, in addition to those in a lower socioeconomic status, who are generally regarded as a high risk group for most cancers.

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Original articles

Independent associations of alexithymia and social support with depression in hemodialysis patients☆

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Abstract

Objective: The influences of alexithymia and social support on depression among chronically ill patients were examined prospectively. **Methods:** The study population was 230 outpatients receiving chronic hemodialysis (HD) therapy. The Beck Depression Inventory-II (BDI-II), the 20-item Toronto Alexithymia Scale (TAS-20), and two subscales of the Social Support Questionnaire were given to the subjects. The BDI-II was readministered after a 6-month interval, and subjects who showed deterioration in their depression score above the level predicted from their baseline score were identified. Multivariate logistic analysis adjusted for age, gender, cause of dialysis, and psychosocial variables were performed. **Results:** Baseline depression was significantly and independently associated with alexithymia and low satisfaction with available support. Deterioration of depression after 6 months was predicted by alexithymia and poor available support. **Conclusions:** Alexithymia and reduced social support might have independent associations with the presence and the prognosis of depression among HD patients.
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Keywords: Alexithymia; Depression; Hemodialysis; Prospective design; Prognosis; Social support

Introduction

Patients suffering from chronic diseases are at a greater risk of experiencing emotional disturbances [1]. These can interfere with behavior, cognitive processes, and social functioning, inducing specific and nonspecific biological responses and influencing the prognosis of physical disorders.

Depressive symptoms have consistently shown to be negatively correlated with measures of social support in various settings [2,3]. Furthermore, some prospective studies have suggested that depressed patients with high levels of social support experience more rapid improvement in their symptoms [4–8]. Social support should therefore be considered when exploring the influence of depression on the long-term prognosis of physical disorders.

Alexithymia, a personality construct that reflects difficulties in affective self-regulation [9], was noted by psychotherapists as a common characteristic among classic psychosomatic patients for whom therapy was unsuccessful

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[10,11]. Researches have revealed a broader linkage of alexithymia with various mental and physical health problems [12–15], including mortality in general population and treatment outcomes at clinical settings [16,17]. A significant positive association has been consistently reported between depression and alexithymia [18–25]. Moreover, lower levels of social support have been repeatedly documented among alexithymic than among nonalexithymic individuals [22,26].

The purpose of the current study was to examine the interrelationships between depression, alexithymia, and social support in hemodialysis (HD) patients with end-stage renal disease (ESRD). Depression has been identified as a possible independent risk factor associated with increased mortality among ESRD patients [27], and therefore, in order to improve their long-term prognosis, it is important to understand how depressive symptoms are associated with other health-related factors within this population.

In the present study, we aimed to examine the effects of alexithymia and social support on concurrent depressive symptoms, including their interaction within this clinical population. We also wanted to explore the influence of baseline alexithymia and social support on the 6-month prognosis of depressive symptoms as well.

So far, alexithymia has rarely been investigated prospectively in relation to depression. Few evidence has suggested its adverse effect on the prognosis of depression [28,29]. The prospective design of this study will allow us to detect any beneficial effect of social support or any adverse effect of alexithymia on the depressive symptoms of patients suffering from chronic diseases more clearly.

Recently, we examined the relationship between depression, social support, and alexithymia among Japanese workers and found a significant interaction between alexithymia and social support in terms of their effects on depression [30]. Among nonalexithymic individuals, those with low levels of perceived social support had significantly higher depression scores than those with high levels of support: by contrast, alexithymics showed no variation in their depression score according to the level of perceived support. Based on these previous findings, we speculated that alexithymic individuals might be unable to benefit from social support because of their cognitive emotional deficits.

According to the extensive review by Cohen and Wills [31], social support could have a beneficial effect on well being in two different ways: an overall beneficial effect (the direct-effect model) and protection from the potentially pathologic influence of stressful events (the buffering model). Cumulative evidences suggest that a buffering effect can be expected when the individuals perceive the available support as adequate [31,32]. To detect the effect of social support on depression properly, we evaluated the perceived amount of available support and the degree of satisfaction with it separately. As far as we know, the association between depression, alexithymia, and social support has never been discussed with this framework.

Methods

Subjects

The subjects were recruited from a group of patients who had been screened for the Nagoya Kidney Center (NKC) study. The prospective NKC study was designed to explore the influence of psychosocial factors on the long-term prognosis of ESRD patients who were receiving chronic HD therapy. The Research Ethics Committee of Nagoya City University Graduate School of Medical Sciences, Japan, approved the research protocol. Between May 2001 and May 2002, the ESRD patients who were receiving regular HD therapy (that is, one 4-h HD session three times per week) at any of three clinics in Japan (the Nagoya Central Clinic, the Anjoh Central Clinic, and the Hekikai Central Clinic) and who met the study selection requirements were recruited by research assistants. The selection criteria were as follows: less than 70 years old and can read and complete the self-administered questionnaire unaided. To avoid the transitional influences of suffering from life-threatening states on psychological factors, we excluded those who had experienced episodes of acute myocardial infarction (AMI) or stroke, major surgical procedure within the past 2 months, or malignant neoplasm or any psychiatric diagnosis within the past 5 years. Trained research assistants interviewed the candidates and confirmed if the candidates met the selection criteria and showed no cognitive impairments. Of the 538 patients registered, 207 were excluded for the following reasons: 132 patients were aged 70 years or above; seven patients had been diagnosed with cancer; 22 patients had experienced episodes of AMI, stroke, or major surgical procedures; 32 patients had visual or cognitive difficulties that would prevent them from completing the questionnaire unaided; eight patients died before they were interviewed; and six patients moved out of the study area before interview. Of the 331 remaining eligible patients, 21 moved out of the study area before completing the questionnaire, eight did not complete the questionnaire due to illness, and 72 refused to complete the questionnaire. Thus, a total of 230 patients provided written informed consent for participation in the study and completed the questionnaires.

Procedures

At the time of enrollment, trained research assistants conducted baseline interviews, and assessed the participants' demographic characteristics and medical histories. The medical data obtained from hospital charts included the serum albumin concentration, protein catabolic rate (PCR), and Kt/V, a marker of dialysis adequacy [33]. These nutritional and dialytic parameters are established indices associated with survival in HD patients [34–37]. All of the participants completed a battery of well-validated self-

reporting inventories described below for psychological evaluation. These were translated into Japanese using the back-translation method.

Psychological measures

Beck Depression Inventory-II. The second edition of the Beck Depression Inventory-II (BDI-II) [38,39] was used to assess the level of depressive symptoms. The BDI is the most popular self-reporting tool for measuring depressive symptoms and has often been used to evaluate mental health among ESRD patients [40,41]. It was revised to correspond to the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (*DSM-IV*) criteria and was published as the BDI-II in 1996. The BDI-II scores range from 0 to 63, and the cutoff score of 14 is considered to indicate at least a mild-to-moderate level of depression. The depressive symptoms were reassessed using the BDI-II after a 6-month interval.

Twenty-item Toronto Alexithymia Scale. The 20-item Toronto Alexithymia Scale (TAS-20) was used to evaluate alexithymia [42–44]. The total TAS-20 scores range from 20 to 100, and a score of 61 or higher was suggested for use in alexithymia screening by the original authors [45].

Social Support Questionnaire. The six-item version of the Social Support Questionnaire (SSQ) was used to assess social support [46,47]. The SSQ consists of two subscales to quantify the two basic elements of social support. The first subscale measures the number of available persons whom the subject feels that s/he can turn to when s/he needs to (the number score or SSQ-N). The second subscale assesses the degree of satisfaction with the available support (the satisfaction score or SSQ-S). Both scores range from 0 to 36. The lower quartile was used as the cutoff point in order to dichotomize the subscale scores.

Statistical analysis

Data were analyzed using SPSS for Windows (version 12.0; SPSS Inc., Chicago, IL, USA). All statistical tests were two-sided, and a probability (P) value of $<.05$ was considered statistically significant. All values are reported as the mean±standard deviation (S.D.) unless otherwise stated.

The baseline characteristics were compared between the depressed and nondepressed patients using the chi-square (χ^2) statistic for categorical variables, and analysis of covariance (ANCOVA) for continuous variables, with adjustments for age and gender. Spearman's correlation coefficients were calculated in order to examine the interrelationships between age, duration of HD (years), and psychological variables. The interaction between alexithymia and social support, in terms of depression severity, was evaluated based on the BDI-II scores by two-way ANCOVA using the general linear model with adjustment for age and gender.

The impact of alexithymia and reduced social support on baseline depression was examined by using logistic regression analysis. Models adjusted for age, gender, marital status, and cause of ESRD were initially performed, and then multivariate adjusted models including all variables were subsequently calculated. Multivariate logistic regression analysis was also used to assess the prognostic value of the measured baseline variables on depressive symptoms during the 6-month period.

Finally, we examined the impact of alexithymia and reduced social support on the deterioration of depressive symptoms during the 6-month period. In order to identify those subjects whose depressive symptoms had worsened over the expected from the baseline, we computed the residualized gain score for each patient based on the BDI-II scores at the baseline and after a 6-month follow-up using linear regression analyses [6,48]. The residualized gain score is the difference between the actual posttest score and the predicted score from the regression equation—what enabled us to measure how did the patients change as compared to the baseline score. We used the upper quartile of the standardized residual score as the cutoff point to define a worsening of depression. Multiple logistic regression analysis was performed to assess the impacts of baseline factors associated with the deterioration of depressive symptoms.

Results

Background characteristics

The mean age of the 230 participants was 56.0±9.6 years (min–max=23–71 years), the duration of HD ranged from 0.3 to 27.7 years (mean±S.D.=7.3±6.4 years), and 43.9% of the patients were women. As one participant failed to answer any of the items on the SSQ-S, this analysis was limited to 229 subjects. The Cronbach alpha (α) scores of the baseline BDI-II, TAS-20, SSQ-N, and SSQ-S were 0.90, 0.78, 0.94, and 0.93, respectively. In total, 43% of the subjects were depressed according to the BDI-II cutoff score of ≥14.

Comparisons of the demographic, laboratory, and psychosocial variables for the depressed and nondepressed patients are shown in Table 1. There were no statistically significant differences in age, gender, smoking habits, or clinical characteristics according to the presence of depressive symptoms. However, the depressed patients were less likely to be married (P=.01) and scored higher in the TAS-20 (P<.001) and lower in the SSQ-N and the SSQ-S (P<.001 in both cases) than the nondepressed patients.

Interrelationships between the baseline variables

The Spearman's correlation coefficients between the baseline variables are shown in Table 2. Age and duration of HD were not associated with any variables, while the psychosocial variables correlated significantly with one another.

There was no significant interaction between alexithymia and the level of social support measured by either subscale of the SSQ: for alexithymia SSQ-N, $F_{1,223}$=.01

Table 1
Comparisons of demographic, clinical, and psychosocial characteristics between depressed and nondepressed patients with ESRD

		Nondepressed BDI-II<14 (n=131)	Depressed BDI-II≧14 (n=99)	P value
Sociodemographic characteristics				
Age (years)*	Mean±S.D.	55.9±9.7	56.2±9.4	.77
Female	%	46.6	40.4	.35
Unmarried	%	17.6	31.6	.01
Current smoker	%	26.0	31.6	.35
Clinical characteristics				
Duration of HD (years)	Mean±S.D.	7.2±6.3	7.4±6.5	.84
Cause of ESRD				
Nephritis	%	51.9	45.5	.08
Diabetes	%	21.4	34.3	
Others	%	26.7	20.2	
Laboratory measurements				
PCR (g/kg per day)	Mean±S.D.	0.97±0.16	0.97±0.17	.84
Kt/V	Mean±S.D.	1.43±0.22	1.42±0.21	.83
Mental health and physical function measurements				
Alexithymia (TAS-20)	Mean±S.D.	46.0±8.7	55.2±8.2	<.001
Perceived social support				
Available number (SSQ-N)	Mean±S.D.	20.3±9.6	14.9±8.8	<.001
Satisfaction (SSQ-S)	Mean±S.D.	30.1±4.7	27.2±5.6	<.001

and P=.92; for alexithymia SSQ-S, $F(1,224)$=.69, and P=.41. Fig. 1 demonstrates the age- and gender-adjusted mean scores with 95% confidence intervals (CIs) for the BDI-II according to the dichotomized level of alexithymia and SSQ-S. A significant mean difference in the BDI-II scores was observed according to the level of alexithymia [$F(1,224)$=28.1, P<.001] and SSQ-S [$F(1,224)$=6.3, P=.01]. Regardless of the degree of alexithymia, patients who reported low SSQ-S had significantly higher BDI-II scores than the other subjects. Similar results were obtained for the relationship between alexithymia and the SSQ-N. A significant mean difference in the BDI-II scores was observed according to the level of alexithymia [$F(1,225)$=29.4, P<.001], and a marginally significant difference was observed according to the level of SSQ-N [$F(1,225)$=2.80, P=.096].

Impacts of Alexithymia, Social Support on Concurrent Depression at Baseline

Alexithymia, low SSQ-N, and low SSQ-S all showed significantly increased odds ratios (ORs) associated with the presence of baseline depression in the initial models (Table 3). Even after adjustment for each other, alexithymia and low SSQ-S showed independent associations with baseline depression. Alexithymics were 3.8 times more likely to be depressed than nonalexithymics, while those who had low SSQ-S were 2.3 times more likely to be depressed than the other subjects. Low SSQ-N lost statistical significance in the association with baseline depression after adjustment for the other variables.

Depression at the follow-up after 6 months and baseline variables

Follow-up data for the BDI-II after a 6-month interval was obtained from 207 subjects (83.8% of all participants). There were no significant differences in baseline variables between those who failed to provide follow-up data and the remaining subjects. At the time of the follow-up survey, a total of 81 patients (39.1%) was depressed. Of these, 62 patients had been depressed throughout the study period, while 19 patients had recently developed depressive symptoms. Almost half of the subjects (n=103) had remained without depression, and 23 patients had recovered from depression during the 6-month period. The Spearman's correlation coefficients for the follow-up BDI-II compared with the baseline BDI-II, TAS-20, SSQ-N, and SSQ-S scores were 0.70, 0.45, 0.23, and 0.86, respectively (P<.001 in all cases).

Table 2
Spearman's correlation coefficients between psychosocial variables in 230 patients with ESRD

		Age	Duration	TAS-20	SSQ-N	SSQ-S
Duration of HD (years)		0.07				
Alexithymia	(TAS-20)	0.06	0.004			
Perceived social support						
Available number	(SSQ-N)	0.01	0.11	0.34*		
Satisfaction	(SSQ-S)	0.10	0.0004	0.35*	0.40*	
Depression	(BDI-II)	0.09	0.05	0.57	0.28	0.29

* P<.001.

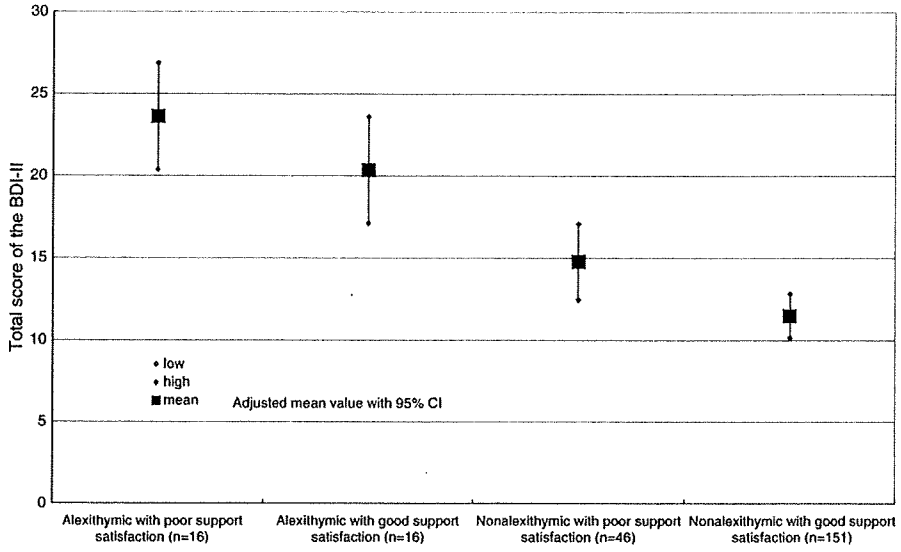

Fig. 1. Relationships between mean BDI-II score, alexithymia, and social support, adjusted for age and gender, with 95% CIs, among patients with ESRD. Alexithymia was defined as a score of ≥61 on the TAS-20. Social support was measured by the satisfaction subscale of the SSQ, and a score under 25 (lowest quartile) was defined as "poor support."

The impacts of alexithymia, SSQ-N, SSQ-S, and baseline depression on depressive symptoms at the 6-month follow-up survey were evaluated by logistic regression analysis (data not shown in tables). In the initial models, all of the variables showed significant or marginally significant associations with depressive symptoms at the 6-month follow-up: for baseline depression, OR=19.0, 95% CI=8.8–41.2, Wald value=55.6, $P<.001$; for alexithymia, OR=8.1, 95% CI=3.1–21.1, Wald value=18.3, $P<.001$; for low SSQ-N, OR=2.0, 95% CI=1.0–4.0, Wald value=4.0, $P=.04$; and for low SSQ-S, OR=2.3, 95% CI=1.2–4.4, Wald value=6.6, $P=.010$. However, after adjustment for the other variables, the social support variables lost their statistical significance, while baseline depression and alexithymia retained significant associations with depression at the 6-month follow-up. Patients who were depressed at baseline were 17.7 times (95% CI=7.7–40.4, Wald value=46.4, $P<.001$), and alexithymics were 5.3 times (95% CI=1.7–16.1, Wald value=8.5, $P=.004$) more likely to be depressed at the 6-month follow-up.

Alexithymia, support, and the deterioration of depressive symptoms over the expected from baseline status

Finally, the prognostic values of alexithymia and social support on the deterioration of depressive symptoms during the 6-month period over the expected from baseline depression status were assessed using logistic regression analysis (Table 4). Alexithymia and low SSQ-N showed independent associations with increased risks of deterioration of depression, while low SSQ-S failed to show a significant association. The results remained unchanged even after adjustment for all variables.

Discussion

In the current study, we observed significant associations between baseline depression, alexithymia, and unsatisfactory social support. We also confirmed that alexithymia and poor available support predicted the deterioration of

Table 3
Multivariate logistic regression: ORs for baseline depression according to the level of the baseline variables

		OR_1	95% CI	Wald value	*P* value	OR_2	95% CI	Wald value	*P* value
Alexithymia									
Alexithymics	TAS-20≧61	4.82	2.02–11.46	12.62	<.001	3.76	1.54–9.21	8.43	.004
Nonalexithymics	TAS-20<61	1.00				1.00			
Perceived social support									
Available number	SSQ-N≦10	2.30	1.23–4.30	6.77	.009	1.58	0.80–3.15	1.71	.191
	SSQ-N>10	1.00				1.00			
Satisfaction	SSQ-S≦25	3.02	1.62–5.60	12.24	<.001	2.31	1.19–4.48	6.17	.013
	SSQ-S>25	1.00				1.00			

OR_1, adjusted for age, sex, marital status, and cause of ESRD; OR_2, adjusted for age, sex, marital status, cause of ESRD, and psychosocial variables with each other.
Depression is defined by a total score of ≧14 on the BDI-II.

Table 4
Multivariate logistic regression: ORs for the deterioration of depression at 6-month follow-up over expected from the baseline status, according to the levels of alexithymia and perceived social support

		OR_1	95% CI	Wald value	*P* value	OR_2	95% CI	Wald value	*P* value
Alexithymia									
Alexithymics	TAS-20≧61	3.21	1.41–7.28	7.78	.005	2.57	1.13–5.86	5.02	.025
Nonalexithymics	TAS-20<61	1.00				1.00			
Perceived social support									
Available number	SSQ-N≦10	2.45	1.23–4.87	6.50	.011	2.12	1.02–4.41	4.04	.044
	SSQ-N>10	1.00				1.00			
Satisfaction	SSQ-S ≦25	1.63	0.83–3.21	2.00	.157	1.06	0.51–2.21	0.03	.873
	SSQ-S>25	1.00				1.00			

Deterioration of depression at 6-month follow-up over expected from the baseline status is identified when the standardized residual score, the difference between the actual posttest score and the predicted score from the baseline score by using the linear regression analysis, was above the upper quartile.

depression symptoms over the expected from the baseline, although the baseline depression was the strongest factor to predict the presence of depression after 6 months. Use of the residualized gain score enabled us to estimate the independent impacts of alexithymia and reduced social support on the prognosis of depression.

Although alexithymia has been considered as a fairly stable personality trait, some recent studies have demonstrated that alexithymic characteristics can be altered using modified psychotherapeutic techniques [49,50]. From the result of the present study, it seems worth to try whether some interventions for alexithymic individuals would prevent them from developing depression or else helped to improve the prognosis of depressed patients suffering from alexithymia.

Our findings regarding social support may imply the substantial differences between the number of available social support and the degree of satisfaction with it. The SSQ-S showed a stronger association with baseline depression than did the SSQ-N, while only the SSQ-N showed a significant independent association with the deterioration of depressive symptoms. Having adequate quality of support may be effective to keep feelings stable. However, once the individual gets depressed, having adequate quantity of available support may be more important to regulate feelings or affectivity. Further investigations, including observations of multiple situations, will be necessary to clarify the most effective social support factors on the development and prognosis of depression.

In contrast with our recent findings in the Japanese working population [30], there was no interaction between alexithymia and social support in terms of the severity of depression. In this study, those with adequate levels of perceived social support were less depressed regardless of the presence of alexithymia, while in the previous study, beneficial effect of social support was observed only among nonalexithymics. To understand the differences among these observations, we should note that the previous study specifically evaluated the support perceived by the general working population in the work place, while the present one did not specify the sources of support and the subjects were clinically ill. One possible explanation for the different findings of the two studies is that alexithymics may have difficulty in building and maintaining close relationships with others because of their difficulty in communicating their feelings and their poor understanding of other people's emotions [21], especially in environments such as the work place. Once they are in contact with people who help them to buffer strain, alexithymics might benefit from the support provided to a greater extent than nonalexithymic individuals. In fact, Taylor characterized the interpersonal relationships of alexithymic individuals as follows: "[they] tend to employ symbiotic relationships adaptively to compensate for their deficits and to help regulate dysphoric states" [51]. Without being able to depend on such relationships, alexithymic individuals may be vulnerable to developing various disorders. We should also note that in our present study, the subjects were HD patients who tend to be more depressed than the common working population, although their alexithymia scores were comparable. Therefore, the benefits of social support might be strengthened when an alexithymic person is ill or depressed. Further investigation will be necessary to confirm these hypotheses.

We should note some limitations of our current study. First, we used self-reporting measures to evaluate the psychosocial characteristics of the subjects. Depressed patients tend to have a distorted cognitive style and to perceive themselves negatively [52]. Alexithymics also have difficulty in recognizing their own inner feelings as well as those of others. The original authors of the TAS have recommended to measure alexithymia with several tools using different methods [9]. Subic-Wrana et al. [53] compared two alexithymia measures—the TAS-20, a self-rate measure, and the LEAS, an objective measure—and warned that the difference between self-rate and objective measures might be greater in clinical samples than in nonclinical samples. Lumley [54] also remarked that when both alexithymia and depression were assessed by self-reports, the observed relationship between them could be an artifact. Although both the BDI and the TAS-20 have been well validated and have been used to measure depression and alexithymia in a number of previous studies with ESRD patients, our current findings should be confirmed using different measurement tools. Second, depression, as defined

in the present study, was not strictly equivalent to major depression as defined by the *DSM* criteria. The prevalence of depression (43%) observed among the present subjects was comparable to the findings of other studies that have used the BDI as a diagnostic tool [55,56]; however, previous studies that have used the *DSM-IV* criteria have reported much lower frequencies (5–18%) of major depression among HD patients [57–59]. O'Donnell and Chung [60] pointed out the difficulties in applying the *DSM* criteria for major depression to ESRD patients because of the overlap between the physical symptoms of medical illnesses and the neurovegetative symptoms diagnostic of major depression. They suggested that many medically ill patients who might be expected to have improved quality of life after receiving effective treatment for depression were underdiagnosed using these strict criteria and concluded that the BDI is the most appropriate screening tool for detecting ESRD patients with major depression. However, even using criteria including all of the neurovegetative symptoms, one quarter of the depressed patients in our study was overdiagnosed according to their estimates. Third and finally, we limited the subjects of the current study to those who were on regular HD therapy (three times per week) at one of three clinics in an urban area of central Japan and who could complete a battery of questionnaires unaided. Moreover, most of the subjects were living with someone and were fully participating in daily tasks. Therefore, we will need to carry out further investigations with broader samples before making generalizations on the basis of our results.

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RESEARCH COMMUNICATION

Cooking Temperature, Heat-generated-carcinogens, and the Risk of Stomach and Colorectal Cancers

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Abstract

Background: Food change due to cooking temperature and unrecognized heat-formed chemical carcinogens may impact on the risk of stomach and colo-rectal cancers. To test this hypothesis a case-control study was performed.. Methods: A total of 670 cases of stomach and colo-rectal cancers matched with 672 hospital controls for sex and ± 5 years age admitted to three hospitals in Hanoi city in the North Viet Nam from October 2006 to September 2007 were the subjects. Five levels of food change due to cooking temperature were based on food color; white, pale yellow, yellow, dark yellow, and burnt. We asked study subjects to themselves report which of these five colors was their preferable intake before the onset of disease. The present study included; fried fishes-meats-eggs-potato-tofu; grilled foods; roasted foods; sugar, bread, heated wheat, and biscuits. These were cooked at temperatures as high as from 165 to 240°C, based on the literature. Adjusted estimation of odds ratio was conducted controlling for possible confounding factors using STATA 8.0. Results: A high intake of roasted meats, bread and biscuit significantly increased the risk of cancer as much as OR=1.63, 95%CI=1.04-2.54; OR=1.40, 95%CI=1.03-1.90; OR=1.60, 95%CI=1.03-2.46 with probabilities for trend = 0.029, 0.035, and 0.037, respectively. For exposure among controls: 529 (79%) were not exposed at all to roasted meats; 449 (67%) were not exposed at all to bread; and 494 (74%) were not exposed at all to biscuit. Conclusions; Observation of food change due to cooking temperature based on color is practically feasible for detecting associations with risk of developing cancer.

Key Words: Cooking - food colour - risk factor - gastric cancer - colorectal cancer

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Introduction

Except man, all species intake unheated foods and cancer among rarely occurs because carcinogens, like acrylamide, have not been detected in unheated food (Tareke et al., 2002). Man worldwide daily intakes heated foods that are boiled, fried, roasted, grilled, and undergo other types of heating. Moderate levels of acrylamide (5-50 μg/kg) were measured in heated protein rich foods and higher contents (150-4,000 μg/kg) in carbohydrate-rich foods at cooking temperatures from 100°C-240°C (Tareke et al., 2002). Vietnamese foods are commonly heated foods, such as fried fishes-meats-eggs-tofu; grilled foods; roasted foods; bread, biscuit and other heated foods. They were hypothesized to be sources of dietary carcinogens that cause cancer in man. However, very few epidemiological studies have been performed in Viet Nam. The present study aimed to examine the relationship between intakes of heated foods and the risk of stomach and colo-rectal cancers by case-control study in the North Viet Nam.

Materials and Methods

Case-control study was performed for stomach and colorectal cancers admitted to Hanoi Cancer Hospital, Viet Duc Surgery Hospital and Bach Mai General Hospital located in the Hanoi city from October 2006 to September 2007. One incidence case was matched with one incidence control for sex and age ± 5 years. Cases and controls were operated on at these three hospitals and bed-side interview one day before operated on to collect data of demographic and lifestyle questionnaire (DLQ) and semi-quantitative-food-frequency questionnaire (SQFFQ) was done. Blood samples were collected early morning after waked up on the day of operated on. Interviewers were students of bachelor of public health four grade of the Hanoi Medical University. They were trained to interview patients at

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hospitals using the list of selected patients by independent person. Cases and controls were not informed to the interviewers to keep blind data collection using DLQ & SQFFQ.

Development of the SQFFQ

Based on the database of national household survey of food consumption in 2000, the analysis was done basing on surveyed data from Hanoi areas to develop of database SQFFQ for the purpose of the Epidemiological Study of Host and Environmental factors for Stomach and Colorectal Cancers. A total of 158 households (5 clusters multiplying around 30 households per cluster) living in Hanoi participated in a 24- hour recalls survey during September 2000. The unit of survey is a household. 24-hour recalls: The 24-hour recalls survey was carried out on one weekday. Direct interviews were done in the households by 2 investigators from the National Institute of Nutrition. Total time for interview for each subject was around 45 minutes. Investigator interviewed the household about all foods recipes consumed by themselves at their house or outside during last 24 hours.

Nutrients of interest

Based on the Vietnam Food Composition Tables, the following 17 nutrients were selected: energy, protein, fat, carbohydrate, dietary fibber, vitamins (including carotene, vitamin A, C, B1, and B2), and minerals (including calcium, phosphorus, iron and Zinc). In total, 184 kinds of foods were consumed by the subjects. The nutrient intake from food was computed by multiplying the food intake (in grams) with nutrient content per gram of food as listed in the Nutritive Composition Tables of Vietnamese food (revision 2000). Selection of foods/ recipes: According to the contribution analysis and also multiple regression analysis, we choose all food/recipes with up to 90% cumulative contribution for these 17 nutrients, then the foods/ recipes having the apparently the similar nutrient contents are grouped. Afterwards, all foods/recipes with up to 90% cumulative contributions and 0.9 cumulative multiple regression co-efficient were included in the SQFFQ. The number of food items was 63.

Additional food items

We have planned to select some food items regarding further estimation of salt intake, cooking methods and drinking habit. They are rice and cereals (1), beans (1), vegetables (4), oils (1), fishes (9), fruits (7), salted food (18), fried food (9), broiled food (7), and beverages (7), total is 64 food items. These 127 food items are included in the same questionnaire. From each patient, information regarding of frequent intake, size of intake unit and number of intake unit per year was obtained. DLQ & SQFFQ included 184 items.

In order to analyze antibodies to *Helicobacter pylori*, 7 ml aliquots of overnight fasting blood were collected from cases and controls. Syringes were shaken gently several times to mix blood and EDTA-2Na, quickly followed by centrifugation at 3,000 rpm for 20 minutes in a centrifuge with a low temperature control. Using disposable pipettes samples were divided into 4 tubes for plasma, one tube for Buffy coat and one tube for RBCs. These were all to be kept frozen in a deep freezer. The name, number and the date sampled was clearly marked on the tubes, with different colors of tube caps for plasma, lymphocytes and RBCs. Each disposable kit was used for only one person and then discarded. DNA was extracted from the Buffy coat for two candidate genes of GSTM1 and CYP1A1.

Food change due to cooking temperature:

Milk-pork (Two month-old) was roasted and it has been colored and smoked gradually. In community, very yellow indicated that foods be cooked, such as fried fishes-meats-eggs-tofu; grilled foods; roasted foods; bread, heated wheat, biscuit and other heated foods. Five levels of food change due to cooking temperature were based on colors from food done to; off-white, pale yellow, yellow, dark yellow, and burnt (Figure 1). We asked study subjects to report by themselves which of these five colors was their preference before the onset of the present ill condition.

Un-recognized heated chemical forming carcinogens:

Reference to acrylamide levels among fried foods: Concentrations of acrylamide at 120-160-200°C are reproted to be 217-808-3479 μg/kg, respectively (Tareke et al., 2002). The present study included fried fishes-meats-eggs-potato-tofu; grilled foods; roasted foods; make color by heating sugar, bread, heated wheat, and biscuit that have been heated as high temperatures as from 165 to 240°C (Masako, 1984; Stephanie et al., 2001). Therefore, number of un-recognized heated chemical forming carcinogens was hypothesized to be sources of dietary carcinogens that cause stomach and colo-rectal cancers.

Identify the risk of stomach and colo-rectal cancers: For seven food items of fried fishes-meats-eggs-potato-tofu, grilled foods, roasted foods, three levels of exposures were grouped, such as never intake, medium intake and high intake. For other five food items of make color by heating sugar, bread, heated wheat, and biscuit, three levels of exposures were grouped, such as some time per year or never intake (Low), monthly intake (Medium) and daily or weekly intake (High) exposed. Three cancer sites of stomach and colorectal cancers were coded as cancer to do analysis. Data were computer-inputted and tabled for 184 question-items to describe for cases and controls for three levels of exposures. Then we estimated crude odds ratios for items suggested a moderated exposure to the individual factor. Final adjusted estimation of odds ratio was done for crude odds ratios with significantly increased risk of cancer in controlling for a possible confounding factors using STATA 8.0.

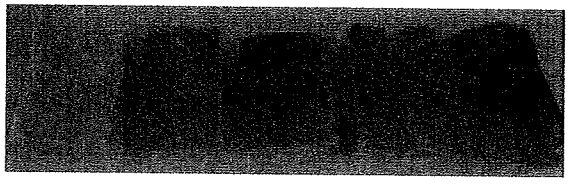

Figure 1. Color Gradation from Off-white to Burnt

Results

The number of stomach and colo-rectal cancers was 670 and there were 672 controls for the final analysis. There was 162 cases of stomach cancer (64.3%) and 309 cases of controls (65.5%) positive for *Helicobacter pylori* infection. There was also GSTM1 positive from 29.5 to 31.1% among controls, stomach cases, colon cancer cases and rectal cancer cases; CYP1A1 positive from 73.6 to 87.3%. There were not significantly differenced between cases and controls for these factors in the present study.

Table 1. Odds Ratios by Exposure Level

Items/Exposure	Number Controls	Cases	Odds Ratio	95% Confidence Interval	P
Q55: Fried fishes					
Low #	170	211	1.00		
Medium	462	416	0.73	0.57-0.92	-
High	38	45	0.95	0.59-1.54	-
Q56: Fried Meats					
Low	313	367	1.00		
Medium	312	232	0.63	0.50-0.80	
High	45	73	1.38	0.93-2.07	-
Q57: Fried eggs					
Low	202	217	1.00		
Medium	459	432	0.88	0.69-1.11	
High	9	23	2.38	1.08-5.26	-
Q58: Fried potatoes					
Low	263	313	1.00		
Medium	388	339	0.73	0.59-0.91	
High	19	20	0.88	0.42-1.69	-
Q59: Fried tofu					
Low	163	191	1.00		
Medium	492	461	0.80	0.63-1.02	
High	15	20	1.14	0.56-2.29	-
Q60*: Grilled foods (200-240°C)					
Low	434	443	1.00		
Medium	150	100	0.65	0.49-0.87	
			0.50*	0.35-0.73	
High	86	129	1.47	1.09-1.90	0.023
			1.21*	0.85-1.72	0.392
Q61 *: Roasted meats (240°C)					
Low	529	502	1.00		
Medium	96	90	0.99	0.72-1.35	
			1.53*	1.02-2.30	
High	45	80	1.87	1.27-2.75	0.002
			1.63*	1.04-2.54	0.029
Q70: Make color by heated sugar					
Low	561	538	1.00		
Medium	76	89	1.22	0.88-1.69	
High	33	45	1.42	0.89-2.26	-
Q80*: Bread (165°C)					
Low	449	405	1.00		
Medium	122	135	1.23	0.93-1.62	
			1.14*	0.85-1.53	
High	99	132	1.48	1.10-1.98	0.007
			1.40*	1.03-1.90	0.035
Q83 *: Heated wheat					
Low	331	274	1.00		
Medium	120	149	1.50	1.13-2.00	
			1.47*	1.09-1.98	
High	219	249	1.37	1.08-1.75	0.017
			1.31*	1.02-1.69	0.106
Q148 *: Biscuit (200°C)					
Low	494	467	1.00		
Medium	139	140	1.07	0.82-1.39	
			1.02*	0.77-1.34	
High	37	65	1.86	1.22-2.84	0.006
			1.60*	1.03-2.46	0.037

Low exposed or never intake-non-exposed; *Adjusted for age, sex, and other factors; P for trend

Based on crude odds ratio, high exposure to five factors included grilled foods, roasted foods, bread, heated wheal, and biscuit have been seen to be significantly increased the risk of cancer. After adjusted for these five factors with age and sex, high intake of roasted meats, bread and biscuit significantly increased the risk of cancer as much as OR=1.63, 95%CI=1.04-2.54; OR=1.40, 95%CI=1.03-1.90; OR=1.60, 95%CI=1.03-2.46 with Probability for trend = 0.029, 0.035, and 0.037, respectively (Table 1). For exposure among control cases, 529 controls (79%) were not exposed at all to roasted meats; 449 controls (67%) were not exposed at all to bread; and 494 controls (74%) were not exposed at all to biscuit.

Discussion

Food change due to cooking temperature has been well known by three observations: i) weight lost from 14.9-55.0% according to cooking temperatures ranked from 100-220°C, ii) Occurred acrylamide-corrected values from 146-2,273 µg/kg (Tareke et al., 2002), iii) Color of food changed from food done to a turn-white; pale yellow, yellow, very yellow, and burnt. Based on these facts and figures, we can observe food changes due to cooking temperature and therefore to develop epidemiological study to promote cancer prevention at household and community.

Unrecognized heated-chemical-forming-carcinogens (HCFC) has been concerned: Man's foods contaminant about 10,000 chemical additives and we have almost no knowledge of the potential danger of any one of these (Adams, 1970). By heating temperature as high as 950°C, there are about 3,800 heated-chemical-forming chemicals included number of carcinogens (IARC, 1985). Dietary carcinogens or heated-chemical-forming-carcinogens (HCFC) should be significantly examined to prevent cancer in human because man in the earth now a day eats almost heated foods.

The risk of developing cancer could be measured: Single chemical carcinogen is induced tumour in rat (Sugimura and Fukimura, 1967). Therefore, chemical carcinogens of HCFC are also presented a similar potential in production of tumour. The present study supported to this hypothesis and confirmed risk of developing stomach and colo-rectal cancers.

In conclusion, observation of food change due to cooking temperature were based on colors of cooked foods is practically, feasible and reliability to detect an association of food change due to cooking temperature, unrecognized heated-chemical-forming-carcinogens (HCFC) and the risk of developing cancer. The present study detected for an association of a high intake of roasted meats, bread and biscuit significantly increased the risk of cancer as much as OR=1.63, 95%CI=1.04-2.54; OR=1.40, 95%CI=1.03-1.90; OR=1.60, 95%CI=1.03-2.46 with Probability for trend = 0.029, 0.035, and 0.037,

respectively.

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Human Genome Epidemiology (HuGE) Review

Meta- and Pooled Analysis of *GSTP1* Polymorphism and Lung Cancer: A HuGE-GSEC Review

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Lung cancer is the most common cancer worldwide. Polymorphisms in genes associated with carcinogen metabolism may modulate risk of disease. Glutathione *S*-transferase pi (GSTP1) detoxifies polycyclic aromatic hydrocarbons found in cigarette smoke and is the most highly expressed glutathione *S*-transferase in lung tissue. A polymorphism in the *GSTP1* gene, an A-to-G transition in exon 5 (Ile105Val, 313A → 313G), results in lower activity among individuals who carry the valine allele. The authors present a meta- and a pooled analysis of case-control studies that examined the association between this polymorphism in *GSTP1* and lung cancer risk (27 studies, 8,322 cases and 8,844 controls and 15 studies, 4,282 cases and 5,032 controls, respectively). Overall, the meta-analysis found no significant association between lung cancer risk and the *GSTP1* exon 5 polymorphism. In the pooled analysis, there was an overall association (odds ratio = 1.11, 95% confidence interval: 1.03, 1.21) between lung cancer and carriage of the *GSTP1* Val/Val or Ile/Val genotype compared with those carrying the Ile/Ile genotype. Increased risk varied by histologic type in Asians. There appears to be evidence for interaction between amount of smoking, the *GSTP1* exon 5 polymorphism, and risk of lung cancer in whites.

Asian continental ancestry group; epidemiology; glutathione *S*-transferase pi; *GSTP1*; lung neoplasms; smoking

Abbreviations: CI, confidence interval; GSEC, Genetic Susceptibility to Environmental Carcinogens; GSTP1, glutathione *S*-transferase pi; OR, odds ratio; PAH, polycyclic aromatic hydrocarbon.

Editor's note: *This paper is also available on the website of the Human Genome Epidemiology Network (http://www.cdc.gov/genomics/hugenet/).*

GENE AND GENE VARIANTS

Glutathione *S*-transferases are a supergene family of phase II enzymes present in many tissues, including lung (1). These enzymes catalyze the detoxification (through conjugation of glutathione) of a variety of reactive electrophilic compounds, including many environmental carcinogens such as benzo [*a*]-pyrene and polycyclic aromatic hydrocarbons (PAHs) (2). The soluble glutathione *S*-transferases comprise 4 main gene classes, alpha (α), mu (μ), pi (π), and theta (θ) (3). Polymorphisms in the glutathione *S*-transferase pi gene, *GSTP1*, located on chromosome 11q13 in humans, have been associated with a reduction in enzymatic activity toward several substrates, including both chemotherapy agents (such as cisplatin, a common agent used in lung cancer treatment) and carcinogens found in tobacco smoke (4–9). Of the several thousand chemicals found in tobacco smoke, at least 50 are known to be carcinogenic, including PAHs, aromatic amines, and nitroso compounds (10).

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GSTP1 detoxifies PAHs and is the most abundant glutathione *S*-transferase isoform in the lungs (1). Two single nucleotide polymorphisms in *GSTP1* that result in a change in amino acids have been identified. A single nucleotide polymorphism in exon 5 (Ile105Val, 313A → 313G), the A-to-G transition that results in an amino acid change from isoleucine to valine, results in significantly lower conjugating activity among individuals who carry one or more copies of the *G* (guanine) allele (Ile/Val or Val/Val) compared with those who have the *A/A* (adenine/adenine; Ile/Ile) genotype (11–13). Having at least one copy of the *G* allele at this locus is also associated with increased levels of hydrophobic adducts in the lung and higher levels of PAH-DNA adducts in human lymphocytes (14). A second single nucleotide polymorphism in exon 6 (Ala114Val, 341C → 341T) results in an amino acid change from alanine to valine, which also appears to confer lower activity (11). Additionally, 3 functional haplotypes have been identified: GSTP1*A (105Ile;114Ala), GSTP1*B (105Val;114Ala), and GSTP1*C (105Val;114Val) (11). A meta-analysis published in 2006 of 5 polymorphisms in glutathione *S*-transferases found no association with *GSTP1* polymorphisms and lung cancer risk in 25 studies published prior to August 2005 (15). The present report includes additional studies published since that time and a pooled analysis examining the association between the *GSTP1* Ile105Val polymorphism and risk of lung cancer.

DISEASE

Lung cancer is the most common cancer worldwide and is responsible for 17.2% of all cancer-related deaths (16). In the United States, overall 5-year survival is about 16% for all stages combined (17). Data from the Surveillance, Epidemiology, and End Results Program indicate that if lung cancer is diagnosed in local stages, survival is significantly better, with overall 5-year survival rates of 49.1%, although fewer than 20% of lung cancers are diagnosed at this stage (17). Along with stage at diagnosis, prognosis also depends on histology type. Because of recent advances in technology that allow a more accurate diagnosis, it is difficult to analyze historic trends in histology types; however, adenocarcinomas of the lung have been increasing in proportion over the last 2–3 decades, especially among women (18). Overall, lung cancer survival rates have not significantly improved with advances in surgical, radiation, or chemotherapy treatments (17).

SMOKING

Cigarette smoking is the greatest risk factor associated with lung cancer development. In the United States and the United Kingdom, approximately 90% of all cases of lung cancer are attributable to current or former cigarette smoking, while the population attributable risks appear to be lower in Japanese populations, especially among women (population attributable risk for men = 67.0%, population attributable risk for women = 14.6%) (19, 20). Other Asian populations report similar risk of lung cancer due to smoking (21, 22). Worldwide, smoking rates have been declining for the past several decades in developed countries and increasing significantly in developing countries. If these trends in smoking rates continue, by 2030, developing countries will account for an estimated 80% of the annual 8 million tobacco-related deaths, many of which will be due to lung cancers (23). Since the induction period for lung cancer appears to be decades, lung cancer will continue to be a major public health issue for generations to come. In addition, the negative health effects of cigarette smoking are not limited to current smokers. In a cohort of former smokers in the United States, 10 years after smoking cessation, the risk of lung cancer is 30%–50% lower than the risk for those who continue to smoke, but lifelong risk remains elevated compared with that for never smokers (24). Furthermore, while cigarette smoking remains the most significant modifiable risk factor, exposure to radon and other occupational and environmental risk factors is associated with development of lung cancer (25, 26).

MATERIALS AND METHODS

Associations and interactions

The association between the exon 5 (Ile105Val, 313A → 313G) polymorphism in *GSTP1* and lung cancer was examined through a meta-analysis of all published papers and a pooled analysis of selected published studies. A MEDLINE search was performed from January 1988 (when the structure of GSTP1 was first described (27)) until March 31, 2007, using different combinations of "glutathione *S*-transferase pi," "GSTP1," "lung," and "lung cancer," restricting the analysis to "human" with no restriction on language. This search was supplemented by examining the reference sections of all selected papers, plus 2 reviews (28, 29) and a pooled analysis of polymorphisms in candidate genes associated with early-onset (<60 years of age at diagnosis) lung cancer (30).

After reviewing all abstracts ascertained from these searches, 34 articles containing information on *GSTP1* polymorphisms and lung cancer were identified. Eligible studies included the frequency of *GSTP1* genotypes or the crude odds ratio for the *GSTP1* exon 5 polymorphism and lung cancer. Both hospital- and population-based case-control studies were included in the analysis. Additionally, 1 study was a nested case-control study from a large cohort of physicians (31). Of the 34 articles selected, 4 were excluded because they were case-only analyses (32–35), 2 because of subject overlap with more recently published studies (36, 37), and 1 because it did not report the genotypes or unadjusted odds ratios (38). Two studies were included in the meta-analysis even though they contained a small number of overlapping subjects (39, 40). Two studies were found in both non-English and, later, English journals; therefore, the data from the English journals were used (41, 42). Only 4 studies reported on the exon 6 (Ala114Val, 341C → 341T) polymorphism, so we restricted the analysis to the exon 5 polymorphism in *GSTP1*. The final number of studies in the meta-analysis was 27, including 8,322 cases and 8,844 controls (31, 39–64) (Table 1).

Table 1. Description of the Studies Included in the Meta-analysis by Ethnicity and Year of Publication

First Author (Reference No.)	Year	No. of Cases	No. of Controls	Country	Mean Age of Cases, Years	Male Cases, %	Histology	Source of Controls	Matching Criteria
Asian studies									
Katoh (47)	1999	47	122	Japan	64.6 (SD, 10.3)	85	SqCC = 51.1%, AC = 25.5%, SCC = 19.1%, LCC = 4.3%	Hospital	None
Kihara (48)	1999	358	257	Japan	62.7 (range, 58–67)	100	SqCC = 33.3%, SCC = 20.4%, AC = 46.3%	Hospital	None
Kiyohara (41)	2000	86	88	Japan	63.8 (range, 35–86)	100	AC = 45.5%, SqCC = 7.9%, SCC = 13.9%, LCC = 4.7%, others = 7.0%	Hospital	None
Lin (51)	2003	198	332	Taiwan	64 (SD, 9)	72.2	AC = 53.0%, SCC = 42.0%, others = 5.0%	Hospital	None
Wang (60)	2003	112	119	China	56.5 (range, 37–75; SD, 8.1)	64.3	AC = 100%	Healthy	Age and gender (frequency matching)
Chan-Yeung (44)	2004	229	197	China	53.8 (SD, 14.3)	67.2	AC = 55.5%, SqCC = 16.6%, NSCLC = 19.2%, others = 8.7%	Healthy	Ethnicity
Chan (43)	2005	75	162	China	63 (no range or SD)	82	AC = 58.7%, SqCC = 41.3%	Hospital	Sex and age
Liang (42)	2005	227	227	China	62.5 (range, 31–86)	74	SqCC = 41.4%, AC = 58.6%	Hospital	Age, gender, and ethnicity (frequency matching)
White studies									
Ryberg (64)	1997	138	297	Norway	62.3 (SD, 10.3)	100	NSCLC = 100%	Healthy	Age, smoking, and ethnicity
Harris (45)	1998	178	199	Australia	66 (range, 38–91; SD, 9.1)	69	SqCC = 43.5%, AC = 18.2%, LCC = 7.7%, SCC = 7.1%, NSCLC = 1.9%, others = 21.6%	Healthy	None
Jourenkova-Mironova (46)	1998	150	172	France	58.4 (no range or SD)	93	SqCC = 65.3%, SCC = 34.7%	Hospital	Age and gender (frequency matching)
Saarikoski (55)	1998	206	293	Finland	62 (SD, 9)	79.8	SqCC = 45.2%, AC = 39.4%, others = 15.4%	Healthy	None
To-Figueras (59)	1999	164	200	Spain	59 (range, 32–87)	88.4	SCC = 34.8%, SqCC = 31.7, AC = 25.6%, LCC = 7.9%	Healthy	Gender
Risch (63)	2001	388	353	Germany	60.9 (range, 28–87)	75.8	SqCC = 44.0%, AC = 39.0%, LCC = 4.9%, SCC = 2.8%, others = 10.8%	Hospital	Ethnicity
Lewis (50)	2002	93	151	United Kingdom	67.4 (SD, 10.4)	63.8	SCC = 16.1%, SqCC = 34.4%, AC = 10.9, others and nonclassified = 38.7%	Hospital	None
Stucker (58)	2002	251	264	France	59.3 (SD, 9.6)	100	SqCC = 46.0%, SCC = 19%, AC = 24.0%, others = 11.0%	Hospital	Age, ethnicity, and gender (frequency matching)
Reszka (54)	2003	138	165	Poland	59.7 (no range or SD)	76.8	SqCC = 44.2%, SCC = 25.4%, NSCLC = 17.4%, AC = 8.7%, others = 4.3%	Hospital	Age and gender (frequency matching)
Wang (61)	2003	362	419	United States	60.9 (SD, 10.1)	52.4		Hospital	Age, gender, ethnicity, and smoking (frequency matching)
Schneider (56)	2004	446	622	Germany	64.4 (SD, 8.7)	90.6	SCC = 15.0%, LCC = 3.6%, AC = 25.1%, SqCC = 41.1%, others = 15.2%	Hospital	None

Larsen (49)	2006	1,095	626	Australia	63.4 (SD, 9.4)	71.9	AC = 45.2%, SqCC = 45.1%, others = 9.7%	Hospital	Age and smoking
Miller (52)	2006	1,921	1,343	United States	66 (no range or SD)	49.7	AC = 43.7%, SqCC = 21.4%, LCC = 7.3%, SCC = 9.2%, others = 18.4%	Healthy	None
Sorensen (57)	2007	429	766	Denmark	No mean age (range, 50–64)	53	SCC = 1.9%, AC = 32%, SqCC = 23%, others = 26%	Healthy	None
Other studies									
Perera (31)	2002	85	163	United States	61.8 (SD, 7.7)	100	AC = 36.0%, SCC = 16.9%, SqCC = 21.3%, LCC = 9.0%, others = 16.8%	Healthy	Smoking, age, and duration of follow-up
Nazar-Stewart (53)	2003	253	487	United States	No mean age (range, 18–74)	100	SqCC = 29.6%, SCC = 19.0%, NSCLC = 12.0%, LCC = 3.3%, AC = 35.0%, others = 1.1%	Healthy	Age and gender (frequency matching)
Yang (62)	2004	235	233	United States			SqCC = 13.5%, SCC = 7.6%, NSCLC = 13.1%, AC = 52.3%, LCC = 3.8%, others = 9.7%	Hospital	None
Cote (39)	2005	317	407	United States	42.1 (no range or SD)	50	SqCC = 11.7%, SCC = 13.2%, AC = 47.7%, LCC = 9.4%, NSCLC = 3.7%, others = 14.3%	Healthy	Race, sex, 5-year age group, and county of residence
Wenzlaff (40)	2005	141	180	United States	62.4 (range, 40–84; SD, 13.9)	57.8	SqCC = 15.7%, SCC = 6.6%, AC = 54.2%, LCC = 7.2%, others = 16.3%	Healthy	Race, sex, county of residence, and age (frequency matching)

Abbreviations: AC, adenocarcinoma; LCC, large-cell carcinoma; NSCLC, non–small cell lung cancer; SCC, small-cell carcinoma; SD, standard deviation; SqCC, squamous-cell carcinoma.

The pooled analysis was performed by using information collected from researchers who submitted information to the Genetic Susceptibility to Environmental Carcinogens (GSEC) database (www.gsec.net). The design of this study is explained in greater detail elsewhere (65). The primary goal of the GSEC project is to examine the associations between various cancers and genetic polymorphisms by using published and unpublished data solicited from collaborating investigators. These data are then cleaned and entered into a main database that is available to interested investigators for analyses related to the overall goals of the study. Each participating center provided information on the study design, source of controls, laboratory methods used for genotyping, source of DNA for genotyping, and response rates for cases and controls.

From the GSEC database, we selected all studies that included information on *GSTP1* and lung cancer. Only 3 studies (46, 55, 62) provided information on the exon 6 (Ala114Val, 341C → 341T) polymorphism; thus, as in the meta-analysis, all analyses reported on in this paper focus on the polymorphism in exon 5 only. Investigators who had not initially participated in the GSEC project were contacted and asked to provide their data for the pooled analysis. We were able to obtain data from 14 of the 27 studies (51.9%) included in the meta-analysis (Wenzlaff et al. (40) and Cote et al. (39), 2 studies from the same principal investigator, combined their data into a single data set, referred to as Cote et al. in the pooled analyses). An additional study not included in the meta-analysis was used in the pooled analysis (32). The number of subjects included in the published reports may differ somewhat from the numbers in this pooled analysis because the GSEC data set includes some unpublished data. The total number of subjects included in the pooled analysis was 4,282 cases and 5,032 controls.

Statistical analysis

For the meta-analysis, study-specific crude odds ratios and 95% confidence intervals were calculated to estimate the association between the exon 5 (Ile105Val, 313A → 313G) polymorphism in *GSTP1* and lung cancer based on the reported frequencies of *Ile/Ile*, *Ile/Val*, and *Val/Val* genotypes in cases and controls. Odds ratios and 95% confidence intervals were calculated for individuals carrying 1 (*Ile/Val*) or 2 (*Val/Val*) valine alleles compared with individuals carrying 2 isoleucine (*Ile/Ile*) alleles. Homogeneity among studies was tested by using the Breslow-Day test for homogeneity, and, when not statistically significant (based on $P > 0.05$), a fixed-effects model was used for the meta-analysis (66). Heterogeneity was also quantified by using the *I*-squared statistic (67). To test for publication bias, both the Begg and Mazumdar adjusted rank correlation test (68) and the Egger et al. regression asymmetry test (69) were performed. Funnel plots were also created to graphically display evidence of publication bias, and sensitivity analyses to examine the influence of each study on the overall estimate were also performed.

Because the frequency of the polymorphism differs by ethnicity, studies were stratified by the reported ethnicity