

## Gender Difference in Skin Reactivity to Purified Protein Derivative Among Carriers of HTLV-I in Japan

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**Summary:** The incidence of malignancies due to oncogenic virus infections tends to be higher in men than in women. Gender-related differences in cell-mediated immunity, which plays a role in viral pathogenesis, may explain this observation. To explore this possibility in the context of HTLV-I infection, we examined skin reactivity to purified protein derivative (PPD) among 128 residents of an HTLV-I endemic area in Japan, who were born before 1921 and are assumed to have been exposed to *M. tuberculosis* bacilli. The odds ratio (OR) for reduced PPD reactivity (erythema <10 mm in diameter) was calculated by multiple logistic regression analysis. Men were significantly less likely than women to have reduced PPD reactivity among HTLV-I-negative individuals (26% versus 59%;  $p < .01$ ); whereas this gender difference was not apparent among HTLV-I carriers (63% versus 62%;  $p = .87$ ). HTLV-I positivity was strongly associated with reduced PPD reactivity in men, but not in women (odds ratio [OR], 7.3 versus 1.2;  $p = .05$ ). Although this observation may be due, in part, to a longer average duration of HTLV-I infection in men compared with women, the finding also raises the possibility that men may be inherently more susceptible to loss of PPD reactivity by HTLV-I infection.

**Key Words:** Gender difference; HTLV-I; Purified protein derivative

HTLV-I is a lymphotropic retrovirus that can cause adult T-cell leukemia (ATL), HTLV-I-associated myelopathy/tropical spastic paresis (HAM/TSP) and several other disorders including infective dermatitis (ID) and HTLV-I-associated uveitis (HU) (1). Interesting gender differences have been identified in the natural history of HTLV-I infection and the host-virus relationship. Among HTLV-I carriers, men are more likely than women to have a high proviral load (2) and to have detectable mRNA of the tax/rex gene (3), a marker of an enhanced level of viral transcription (4,5). Within each level of proviral load, men are also more likely to have higher levels of circulating abnormal lymphocytes (Aby) (6), which resemble the malignant cells of ATL. Furthermore, the incidence of ATL is reported to be higher in men than in women (7-9). In contrast, the incidence of nonmalignant HTLV-I-associated diseases such as HAM/TSP, ID, and HU appear to be higher in women than in men (10-12).

The host-virus relationship of oncogenic viruses such as HTLV-I is believed to be largely determined by the host's cell-mediated immunity (13). Thus, a higher proviral load and a higher susceptibility to ATL in male HTLV-I carriers compared with female carriers may be explained by difference in the host's cell-mediated immune response to HTLV-I infection. In population-based prospective studies

of asymptomatic HTLV-I carriers, we previously have shown that reactivity to purified protein derivative (PPD) is a useful marker of cellular immune response and strongly correlates with reactivity to phytohemagglutinin (PHA) (14,15). Reduced PPD reactivity observed among HTLV-I carriers appears to be more profound among those with a detectable level of Ably, who are presumably a step closer to ATL (16), compared with those without Ably (17). These findings support the hypothesis that cell-mediated immune response is more likely to be suppressed in men relative to women, which may explain the observed susceptibility to ATL in men.

To test this hypothesis, the present study examined the gender differences in PPD reactivity within a well-defined, older Japanese population endemic for HTLV-I.

## MATERIALS AND METHODS

### Study Subjects

The prospective, population-based Miyazaki Cohort Study was established in 1984 to study the natural history of HTLV-I in an endemic Japanese population (6). As of April 1998, 2014 adult residents of two villages in Miyazaki Prefecture had been enrolled in the cohort. Study protocols were approved by the Institutional Review Boards of the Harvard School of Public Health and the Miyazaki Medical School. Informed consent has been obtained from all study participants. The study subjects receive follow-up during annual visits with physical and other routine health examinations. The baseline questionnaire collects information on occupational, residential, medical, marital, and reproductive history, as well as on smoking behavior and alcohol use. Health history and symptoms and current smoking and alcohol data are updated by a shorter instrument completed at each follow-up screening.

In areas such as Japan where infection with *Mycobacterium tuberculosis* was highly endemic through the 1950s, PPD reactivity has been used as a standard marker to screen individuals for prior exposure to *M. tuberculosis*. Since 1951 all PPD-negative individuals <30 years of age; that is, those who were born after 1921, have been immunized with bacille Calmette-Guérin (BCG) antigen through a nationwide campaign, resulting in their PPD conversion following vaccination. Approximately 75% of the Japanese population prior to the nationwide BCG immunization campaign are reported to have been PPD-positive by age 30 years (18). Thus, positive PPD reactivity only among those who had been unexposed to BCG immunization would be likely evidence of natural exposure to *M. tuberculosis*. Lack of PPD reactivity among these individuals would likely reflect secondary loss of reactivity rather than lack of lifetime exposure.

During the 1987 to 1991 health screenings in the Miyazaki Cohort Study, in total, 597 study subjects were tested for reaction to PPD antigen (14). Because PPD reactivity following BCG immunization may wane differently over time than that following natural *M. tuberculosis* infection, the present analysis was restricted to 128 PPD-tested study subjects who were born before 1921 and would not therefore have been exposed to BCG.

### Laboratory Methods

PPD-positivity was assessed in a standard one-step procedure, 48 hours after an intradermal challenge with 0.05 µg of PPD recall antigen on the volar aspect of the forearm. The injection site was scored by study personnel blinded to the study subject's HTLV-I status. Reactivity to PPD was classified into four levels by the tuberculosis prophylaxis rule of Japan: (–), if erythema was <10 mm

in diameter; (+), if  $\geq 10$  mm without induration; (++) , if induration was present; and (+++), if necrosis or vesicles was present.

The presence of HTLV-I antibody was determined using a passive particle agglutination assay (Serodia-HTLV, Fujirebio, Tokyo, Japan) at a 1:16 dilution and confirmed with a Western blot assay (Problot HTLV-I, Fujirebio, Tokyo, Japan). HTLV-I status was determined at the screen when PPD reactivity was tested.

### Statistical Analysis

The level of PPD reactivity was dichotomized in accordance with clinical criteria: positive (+, ++, +++) versus negative (-). HTLV-I status was categorized as positive versus negative. Potential modifiers of immune function were also evaluated, including age, smoking, alcohol consumption, and reported history of diabetes and renal disease, as well as parity in women. This information was taken from the study questionnaire administered when the PPD testing was performed.

Comparisons of demographic characteristics across PPD reactivity levels were made using  $\chi^2$  statistics and Wilcoxon rank-sum tests. The odds ratio (OR) and Wald-type 95% confidence interval (CI) for an association with lack of PPD reactivity, PPD (-), were estimated by multiple logistic regression (19). For age, the OR for a 10-year increase is presented. Current and exsmokers were combined as ever-smokers. Alcohol use was dichotomized in the same manner. Reported history of diabetes and renal disease was categorized as yes or no. Parity was treated both as continuous as well as dichotomous at the median of the lifetime number of pregnancies  $\geq 4$  versus  $< 4$ ) and was included in the model only in the analyses of the data from women. The *p* values for a significant difference in the OR across groups were calculated using the likelihood ratio test. Statistical significance was based on two-sided tests at the 0.05 level.

## RESULTS

The characteristics of the 128 study subjects analyzed (50 men, 78 women) by gender and HTLV-I status are summarized in Table 1. In total, 60 study subjects (47%) tested positive for HTLV-I. HTLV-I positivity was higher among women than men (53% in women versus 38% in men; *p* = .11). The mean age was similar across HTLV-I status (*p* = .66) and gender (*p* = .84). Seventy-seven (64%) of the 128 study subjects were PPD-negative. Men were less likely than women to be PPD-negative among HTLV-I–negative study subjects, whereas the difference was not apparent among HTLV-I carriers. Cigarette and alcohol use was higher in men than in women, but similar by HTLV-I status (*p* = .26). Few subjects reported history of diabetes or renal disease, and the prevalence of these diseases was similar by gender and by HTLV-I status. Of the 69 women (88%) for whom parity data were available, the mean number of pregnancies was similar across HTLV-I status (5.2 for HTLV-I–positive versus 4.5 for HTLV-I–negative; *p* = .25).

Variables	HTLV-I positive		p Value <sup>a</sup>	HTLV-I negative		p Value
	Men (n = 38)	Women (n = 42)		Men (n = 12)	Women (n = 36)	
Mean age (SD)	56.0	56.0	.66	56.0	56.0	.84
Smoking	11 (29%)	16 (38%)		12 (100%)	14 (39%)	<.001
Alcohol	13 (34%)	19 (45%)	.03	8 (67%)	13 (36%)	<.001
Diabetes	4 (11%)	5 (12%)	.84	4 (33%)	11 (31%)	.66
Renal disease	10 (26%)	11 (26%)	.84	11 (92%)	11 (31%)	.001
History of diabetes	11 (29%)	16 (38%)	.08	12 (100%)	14 (39%)	<.001
Sex	12 (32%)	14 (33%)	.39	10 (83%)	14 (39%)	.001
History of renal disease	11 (29%)	16 (38%)	.08	12 (100%)	14 (39%)	<.001
Parity	11 (29%)	16 (38%)	.08	12 (100%)	14 (39%)	<.001
Number of pregnancies <sup>b</sup>	4.5	4.5	.25	5.2	4.5	.25
Sex	11 (29%)	14 (33%)	.39	10 (83%)	14 (39%)	.001
Parity	11 (29%)	16 (38%)	.08	12 (100%)	14 (39%)	<.001

**TABLE 1.** Characteristics of the 128 study subjects, by gender and by HTLV-I status, in the Miyazaki Cohort Study

On univariate analysis, HTLV-I positivity was significantly associated with the lack of PPD reactivity (Table 2). Men and those who ever used alcohol were in general less likely to be PPD-negative. However, the association of HTLV-I positivity and lack of PPD reactivity was more than four times higher among men than among women (OR, 4.9 versus 1.1;  $p = .05$ ). The difference in this association by gender was enhanced by adjustment for age, smoking and alcohol use (OR, 7.3 versus 1.2;  $p = .05$ ; Table 2).

Variables	All subjects (OR, 95% CI)	Men (OR, 95% CI)	Women (OR, 95% CI)	$p$ Value <sup>a</sup>
Unadjusted				
Age	1.0 (0.97-1.0)	1.1 (0.75-1.5)	1.0 (0.76-1.3)	.65
HTLV-I positivity	1.0 (1.0-1.0)	4.9 (1.4-16.9)	1.1 (0.45-2.8)	.05
Sex	0.48 (0.19-1.2)	—	—	.16
Smoking	0.85 (0.45-1.7)	1.1 (0.75-1.6)	1.0 (0.45-2.3)	.86
Alcohol use	0.49 (0.19-1.3)	0.77 (0.25-2.4)	0.28 (0.07-1.2)	.01
Adjusted <sup>b</sup>				
Age	1.0 (0.97-1.0)	1.1 (0.75-1.6)	1.0 (0.45-2.3)	.65
HTLV-I positivity	1.0 (1.0-1.0)	7.3 (1.8-30.3)	1.2 (0.45-3.2)	.05
Sex	0.48 (0.19-1.2)	—	—	.16
Smoking	1.1 (0.76-1.6)	1.1 (0.75-1.6)	1.0 (0.45-2.3)	.86
Alcohol use	0.48 (0.19-1.2)	1.1 (0.28-4.2)	1.2 (0.48-3.0)	.86

**TABLE 2.** The association of HTLV-I positivity, gender, and the lack of purified protein derivative reactivity among 128 subjects in the Miyazaki Cohort Study

<sup>a</sup> The  $p$  values are for the difference in the OR across gender, by the likelihood ratio test.  
<sup>b</sup> The model adjust for all variables shown. The reference category was parathick skin, never or age, HTLV-I negativity, female, never smokers, never alcohol users.  
 $p < .05$ .  
 OR, odds ratio; CI, confidence interval.

Among women, an increasing number of pregnancies was marginally associated with a lack of PPD reactivity (OR, 1.2; 95% CI, 0.96–1.4). Women with four or more pregnancies were nearly three times more likely to be PPD-negative compared with women with fewer pregnancies (OR, 2.7; 95% CI, 0.93–7.7). The association of higher parity with lack of PPD reactivity was overwhelmingly evident among HTLV-I-positive women (OR, 5.6; 95% CI, 1.0–30.3), but not among HTLV-I-negative women (OR, 1.5; 95% CI, 0.37–6.1). These associations were unchanged after adjustment for age, smoking, and alcohol use (data not shown). The lack of association between HTLV-I positivity and reduced PPD reactivity in women (Table 2) was unchanged after adjustment for parity (data not shown).

## DISCUSSION

Latent oncogenic viral infections generally induce strong cell-mediated immune response (13). Therefore, the magnitude of the cell-mediated immune response to such an infection likely determines the host-virus relationship, including the host's susceptibility to virus-associated malignancies (20). A male predominance has been found for many virus-associated malignancies, including hepatocellular carcinoma (21,22), nasopharyngeal carcinoma (23), and Hodgkin's disease (24). This observation supports the proposal of inherent gender differences in the immune response to virus infections, and leads to the hypothesis that the higher risk of malignancies associated with an oncogenic infection among men may be due to a less rigorous cell-mediated immunity in men than in women.

The present study examined reactivity to PPD as a marker for cellular immune response in a HTLV-I endemic population with ubiquitous exposure to *M. tuberculosis*. The presence or absence of PPD skin reactivity is generally difficult to interpret, in that the lack of PPD reactivity may either indicate a lack of exposure to *M. tuberculosis* or a waning antigenic challenge over time due to age-related changes in cellular immune response. Although the identification of anergy ideally involves a battery of skin tests other than PPD, the use of PPD response has been shown to correlate with reaction to PHA in an elderly Japanese population (15). In addition, a wide-spread exposure to *M. tuberculosis* among these older Japanese subjects made it possible to use this marker as a surrogate for the presence of cellular immune suppression (14,15,17). The problem of potential differential waning of PPD response following tuberculosis infection versus BCG immunization was avoided by restricting the analysis to those study subjects who were likely not to have been exposed to BCG. Although unconfirmed by vaccination records, our classification of BCG exposure based on the historic

evidence of vaccine availability was thought to be a good proxy for actual BCG exposure in this population.

We compared PPD reactivity between the genders adjusting for known correlates of immune response including age, smoking, alcohol use, history of other immune suppressive conditions such as diabetes and renal disease, and parity, as well as antibody positivity for HTLV-I. We found an association of increasing age with a lack of PPD reactivity, providing evidence for progressive cellular immune suppression with age. The magnitude of the age effect in this population (14,15) is comparable with what has been reported by other investigators (25).

In addition, we found that higher parity was associated with the lack of PPD reactivity among women. Manifestations of generalized immune suppression such as loss of PPD reactivity and changes in cytokine production do occur during pregnancy (13,26,27), but the duration of postpartum immune suppression remains unknown. A significant association of parity with a lack of PPD reactivity was present only in HTLV-I carriers, suggesting that coexisting HTLV-I infection during pregnancy may play a role in persistent cellular immune suppression. The female study subjects in the present analysis are primarily  $\geq 50$  years in age, raising the possibility that postpartum suppression in cell-mediated immunity may persist for decades after the reproductive ages, in the presence of an immunosuppressive infection. The effect of cytokine-regulating sex steroids (20,28–31) has yet to be investigated in the context of HTLV-I infection.

As would be expected from previous reports (25), we found that men in general were less likely to be PPD-negative, and thus are more likely to be PPD-positive, than women. Because smoking was associated with gender and PPD positivity in our previous study (17), we adjusted for smoking in the logistic regression model, but the strong association of male gender and lack of PPD reactivity was unchanged. Based on available data, coexisting immunosuppressive conditions such as diabetes and renal disease or alcohol use did not seem to explain the observed difference in PPD response by gender.

Because incidence of active tuberculosis is generally higher in men (32–34), a differential exposure to *M. tuberculosis* between men and women may have biased the association of gender and PPD positivity. However, exclusion of 9 study subjects (4 men, 5 women) with a reported history of active tuberculosis did not change the estimates in the logistic regression models (data not shown), indicating that a higher incidence of tuberculosis in men is unlikely to explain our findings.

Counter to the finding of a strong inverse association between male gender and lack of PPD reactivity, HTLV-I infection itself was more likely to be associated with lack of PPD reactivity in men than in women (OR, 7.3 versus 1.2, respectively). These results imply that despite competent reactivity to PPD antigen in the absence of HTLV-I infection, men are more susceptible to acquired loss of PPD reactivity when infected with HTLV-I. The seemingly paradoxical effect of gender may indicate a failure among men to effectively respond to and contain their HTLV-I infection. This finding and other manifestations of a gender difference in HTLV-I disease pathogenesis in our study cohort; a higher viral load, mRNA for tax, and Ably levels among men (Table 3) (6) are consistent with a higher viral activity and an increased risk of ATL among men. Not all of the 60 HTLV-I-positive study subjects in the present analysis had data on proviral load and Ably level. Therefore, we were unable to examine the effect of these viral markers on the association of PPD response with HTLV-I status sufficiently.

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Male	Female

**TABLE 3.** *Summary of gender differences in HTLV-I disease pathogenesis*

Because HTLV-I is more efficiently transmitted from men to women than the reverse, most HTLV-I seroconversions within our cohort have been observed among elderly women (35). Thus, a larger number of HTLV-I-positive women than men are expected to have acquired infection later in life (6,35). The observed gender effect, therefore, may partly be explained by a longer average duration of HTLV-I infection among men. In general, the role of gender independent of the effect by age of infection is difficult to evaluate unless age of infection is known for all HTLV-I carriers. Within the same study cohort, we have estimated gender-specific mortality from ATL attributable to perinatal HTLV-I infection and found a significantly elevated risk in men compared with that in women (Hisada M, et al., unpublished data). This finding suggested that the male predominance in the occurrence of ATL may not be entirely due to an earlier age of infection among men.

Two other studies have examined the association between HTLV-I and PPD response in populations from Barbados and the United States (36,37). Neither study detected an association based on a small number of study subjects (OR, 1.5), nor did the investigators examine the association by gender. Differences in age, prevalence of tuberculosis infection, and BCG immunization practices in these populations versus those in Japan may partly explain the inconsistent findings. Of note, an analysis of data from 469 younger subjects in our study cohort, who presumably have been exposed to BCG immunization, revealed similar gender differences with regard to HTLV-I infection and PPD reactivity as observed in the older study subjects (data not shown).

The results of the present analysis support our contention that there are inherent gender differences in the biologic response to HTLV-I infection. Factors that contribute to sustained immune suppression in the presence of HTLV-I in men, as with parity in women, are yet unidentified. The use of PPD reactivity as a sole index of cell-mediated immunity somewhat limits the interpretation of our findings. Concurrent measurement of the host's cell-mediated immunity, including cytotoxic T-lymphocyte response against HTLV-I, would be useful for understanding the mechanism of the observed gender differences.

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