

Correlation between Abnormal Pap Smear Finding and Brachial-ankle Pulse Wave Velocity in Korean Women

Yon-Chul Park¹, Hee-Cheol Kang^{2,*}, Duk-Chul Lee², Sung-Hoon Kim³, Jong-Koo Kim¹

¹Department of Family Medicine, Yonsei University Wonju College of Medicine, Wonju, ²Department of Family Medicine, ³Department of Obstetrics and Gynecology, Yonsei University College of Medicine, Seoul, Korea

Background: Cervical cancer is caused by chronic human papilloma virus (HPV) infection. Pap smear is very efficient examination for early detecting cervical cancer. Inflammation reaction due to chronic infection is one of the major causes of atherosclerosis. Pulse wave velocity (PWV) is commonly used in predicting subclinical atherosclerosis. But no study was done about correlation between cervical cancer and PWV.

Methods: The research population, 1,779 people, had been chosen from the patients from Jan. 1st, 2008 to December 31st, 2010, visited health exam center who had done both PWV test and pap smear without any medical history of obstetrics and gynecological disease. The group was divided into two respective groups, 45 people with abnormal finding and 228 people with normal finding. The correlation was analyzed between risk factor of cervical cancer and brachial-ankle PWV. Multiple regression analysis was performed with associated variables.

Results: Average PWV of normal group was $1,313.06 \pm 264.19$ and $1,497.15 \pm 359.58$ was for abnormal. The PWV of abnormal group was statistically significant ($p = 0.0006$) with association between risk factors of cervical cancer and PWV, age, height, weight, income, gravidity. Multiple regression was done with correcting these variables. PWV was associated with abnormal Pap smear but result, were not found to be significant ($p = 0.054$).

Conclusion: The result was not statistically confident but more mass studies are needed to correcting those limitation.

Key Words: Cervical cancer, Pap smear, Brachial ankle pulse wave velocity, Atherosclerosis

INTRODUCTION

Cervical cancer is one of the most common gynecological cancer in Korea [1]. Pap smear test is efficient and commonly used in early detecting cervical cancer. It is commonly used not only in Korea but all over the world and takes a great part reducing mortality and incident rate of cervical cancer [2,3]. Recently, many studies had concluded association between chronic infection and cancer, and in

them cervical cancer is also known as associated with chronic HPV infection [4]. Chronic infection and inflammatory response are also known as major cause of atherosclerosis and coronary artery disease [5].

Pulse wave velocity, emerging early detection method of atherosclerosis, is simple, noninvasive and less time consuming. This measures earlier function change of arterial stiffness, which deteriorate compliance and elasticity [6]. It is known as index of vessel damage severity [7]. Carotid-femoral pulse wave velocity was used in classic, but in these days brachial-ankle pulse wave velocity is used more common due to relatively invasive, non-reproducible, longer process of carotid-femoral pulse wave velocity. Brachial-ankle pulse wave velocity is highly related and reproducible

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*Corresponding author: Hee-Cheol Kang

Department of Family Medicine, Yonsei University College of Medicine,
50 Yonsei-ro, Seodaemun-gu, Seoul 120-752, Republic of Korea
Tel: 82-2-2228-2332, Fax: 82-2-362-2473
E-mail: kanghc@yuhs.ac

with aortic pulse wave velocity which is measured by direct catheter in central elastic artery [8].

Recently, many studies had been reported about association between cancer and coronary disease [9-11]. Association between atherosclerosis and cervical cancer has been studied actively. But no studies were done on associations between pulse wave velocity, major measuring method of subclinical atherosclerosis and cervical cancer.

MATERIALS AND METHODS

1. Study population

Study was done on 1,779 women without gynecological history who visited health promotion center and performed both pap smear and brachial-ankle pulse wave velocity. Exclusion criteria was past history of gynecological surgery, hypertension, diabetes, pituitary disease, cardiologic problem, peripheral vascular disease, liver disease, thyroid disease, cancer and along with taking oral pill. Among them, 228 people with normal Pap smear result were chosen as "control group" and 45 people with abnormal result were chosen as "case group".

2. Pap smear

Sterilized speculum was putted into examinee's vagina and cell was picked on cervical transformation zone by sterilized cytobrush. Cell was smeared on slide and fixed in 95% alcohol. Pap smear was interpreted by The Bethesda

System 2001. The study was done with normal group and atypical squamous cells of undetermined significance (ASCUS) or higher abnormal group.

3. Brachial-ankle pulse wave velocity

Brachial-ankle pulse wave velocity (baPWV) is measured by automatic waveform analyzer (VP-1000, Colin Co, Komaki, Japan) in supine position after at least 5 minute steady state. Pulse and wave of brachia and ankle was recorded with oscillometric sensed cuff on both arm and ankle. Pulse transmission time (ΔT) was obtained by a formula with time difference of two breakpoint which is automatically analyzed with 2nd dimension differentiation by computer. Length from substernal notch to both ankle (La) and both upper arm (Lb) were obtained by formula based on lots of stature data.

$$\text{baPWV} = (\text{La} - \text{Lb}) / \Delta T \text{ (unit: cm/s)}$$

Average data of both sides were used in the study.

4. Statistics

Wilcoxon's rank sum test, Simple regression analysis, multiple regression analysis was done by SAS 9.2 statistic package (SAS Institute Inc. Cary, NC, USA) ($p < 0.05$) was considered as statistically significant.

Table 1. Baseline characteristics of subjects

Variable	Normal (n=228)	Abnormal (n=43)	Total	p [†]
Age (y)*	50.80 ± 10.22	56.75 ± 11.29	55.99 ± 11.44	<0.001
Height (cm)*	157.15 ± 5.62	156.68 ± 6.32	156.08 ± 5.76	0.582
Weight (kg)*	57.86 ± 8.10	59.27 ± 8.41	57.69 ± 7.92	0.221
baPWV_Rt (cm/s)*	1,305.75 ± 272.88	1,490.30 ± 364.87	1,411.53 ± 322.81	0.001
baPWV_Lt (cm/s)*	1,320.36 ± 263.80	1,504.00 ± 362.40	1,426.26 ± 320.66	<0.001
baPWV_average (cm/s)*	1,313.06 ± 264.19	1,497.15 ± 359.58	1,418.90 ± 319.02	<0.001
PYRs*	11.97 ± 10.95	11.20 ± 6.19	12.26 ± 13.82	0.712
Preg*	2.96 ± 2.16	2.79 ± 2.11	3.10 ± 2.30	0.623
Income				
<100 (10,000 won)	10 (5.3%)	5 (13.5%)	198 (13.5%)	0.194
100-200	28 (14.7%)	6 (16.2%)	249 (16.9%)	
200-300	36 (19.1%)	9 (24.3%)	251 (17.1%)	
≥300	115 (60.9%)	17 (46.0%)	773 (52.5%)	

baPWV: brachial-ankle pulse wave velocity, PYRs: packs per years, preg: pregnancy. *mean ± SD, †p-value by Wilcoxon's rank sum test for continuous variables or Chi-square test for categorical variables.

RESULTS

1. General characteristics of study population

Age, left pulse wave velocity, right pulse wave velocity and average pulse wave velocity were higher in abnormal group compared with normal group ($p < 0.05$). But no differences were shown for height, smoking, pregnancy and income (Table 1).

2. Comparison and distribution analysis of average pulse wave velocity

Before examine average brachial-ankle pulse wave velocity (baPWV-M) differences between each group, distribution examination was done to see whether it follows normal distribution or not. In the result, groups did not follow normal distribution (Table 2).

Wilcoxon rank sum test, which is nonparametric method, was used to see the differences between normal and abnormal groups. The result showed that both groups were statistically different ($p = 0.0006$). Normal group average was $1,313.06 \pm 264.19$ and abnormal group was $1,497.15 \pm 359.58$ (Table 3).

Table 2. Normality test using Shapiro-Wilk test

Variable	Shapiro-Wilk	p
baPWV-M	0.9343	<0.001

baPWV-M: mean brachial-ankle pulse wave velocity.

Table 3. Comparison of two means using Wilcoxon's rank sum test

	Normal (n=228)	Abnormal (n=43)	Total	p
baPWV-M*	$1,313.06 \pm 264.19$	$1,497.15 \pm 359.58$	$1,418.90 \pm 319.02$	<0.001

baPWV-M: mean brachial-ankle pulse wave velocity. *mean \pm SD.

Table 5. Comparison of baPWV according to the categorical variables

Income (10,000 won)	< 100 (n=198)	100-200 (n=249)	200-300 (n=251)	≥ 300 (n=773)	Total	p [†]
baPWV average*	$1,624.43 \pm 313.27$	$1,502.15 \pm 334.87$	$1,387.27 \pm 311.97$	$1,334.65 \pm 288.09$	$1,418.90 \pm 319.02$	<0.001

baPWV: brachial-ankle pulse wave velocity. *mean \pm SD. [†]p-value by Kruskal-Wallis test.

3. Association between each variables and average pulse wave velocity

To see the association between each variables and average pulse wave velocity, simple regression analysis was used for continuity variables and Kruskal-Wallis test for categorical variables were done before multiple regression. Simple regression analysis showed average pulse wave velocity had association with age, height, weight, pregnancy. Among those, height was in negative correlation. But smoking history showed no statistical relations ($p = 0.86$) (Table 4).

Difference between Income and average pulse wave velocity were found to be statistically significant by using Kruskal-Wallis test ($p < 0.0001$) (Table 5).

4. Association between abnormal Pap smear result and average pulse wave velocity after multiple regression

Multiple regression analysis was done with brachial ankle

Table 4. Correlations between baPWV and other continuous variables.

Variable	Parameter estimate (β)	Standard error	p*
Age (y)	18.74	0.54	<0.001
Height (cm)	-20.40	1.37	<0.001
Weight (kg)	2.26	1.06	0.032
PYRs	0.40	2.20	0.863
Preg	29.03	3.70	<0.001

baPWV: brachial-ankle pulse wave velocity, PYRs: packs per years, preg: pregnancy. *p-value by simple regression analysis.

Table 6. Factors affecting baPWV

Variable	Parameter estimate (β)	Standard error	p [†]
Age (y)	17.75	1.81	<0.001
Pregnancy	-17.69	7.73	0.023
Group*	-79.97	41.29	0.054

*Group = 1 (normal), Group = 0 (Abnormal), [†]p-value by multiple regression analysis.

pulse wave velocity as dependent variable, abnormal Pap smear finding as dummy variable, and age, height, weight, pregnancy, income as independent variables. The result showed that as brachial ankle pulse wave velocity increases, higher possibilities for abnormal Pap smear observed. But the result was not found to be statistically confident ($\beta = -79.97$, $p = 0.054$) (Table 6).

DISCUSSION

As Korea's living standard grows higher, the incidence is decreasing but still cervical cancer is the most common disease of gynecological cancer in Korea [12]. And as medical health checkup gets popular nowadays, infiltration cancer frequency decreases but precancerous lesion is increasing comparatively. This induces a crucial meaningfulness of which makes cervical cancer in current society. Known risk factors of cervical cancer are first intercourse at age under 16, multiple sex partners, smoking, race, history of multiple pregnancy, low socio-economic status and these seems to be connected with human papilloma virus infection in cervix [13].

There are various causes of classic inflammatory disease like atherosclerosis. Currently well known is the atherogenic formation by cytokine which occurs when recurrent damages are seen on the vessel wall. Other well-known causes are aging, high blood pressure, diabetes, hyperlipidemia, smoking [14]. Major complications of atherosclerosis are cerebral vessel diseases and coronary diseases. So, it is very important to prediction and early diagnosis grades of atherosclerosis for early detecting and treating these serious diseases. Brachial ankle pulse wave velocity is a good indicator of vessel elasticity and stiffness associated with vessel damage. The importance is getting an increased in the meaning of index of early atherosclerogenic generation

[15-18].

To control compounding factor, income, smoking, pregnancy, economical status, which are well known as risk factors of cervical cancer, simple regression analysis were done for continuous variables and Kruskal-Wallis test for categorical variables. The result showed average pulse wave velocity have association with age, height, weight, pregnancy. But smoking history showed no statistical relations, as compared with other known study results ($p = 0.86$). The reason for this could be getting lots of missing data in our survey and also examinee did not answered properly detailed in the questionnaire.

Multiple regression was done with controlling related variables. We were also seen correlation between pulse wave velocity and abnormal pap smear result, but it was not found to be statistically significant ($p = 0.054$).

There are some limitations to our study. First, the number of examinee was only 273 in total. Second, we couldn't get the data of HPV infection which is a major risk factor and cause of inflammatory response, also could not get the information about the first intercourse age and number of sex partner. Third, history of hypertension, diabetes, pituitary diseases, cardiologic problem, peripheral vascular problem, liver disease, thyroid disease, cancer were investigated by survey that couldn't know about the exact prevalence rate. The selection bias cannot be ruled out because of the population group based on a hospital health checkup center.

Chronic infection and inflammation are known as major risk factor for malignant cancer not only by experimental but also clinical studies [4,20,21]. Helicobacter [19-21], hepatitis B virus and human papilloma virus infection are well known independent factor of malignant cancer [4]. Especially HPV is the major cause of cervical squamous cancer. The fact that atherosclerosis is also caused by chronic infection and inflammation that was reported by many studies. The result was not found to be significant but needed more mass studies in order to correcting those limitations.

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