

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

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Directed by Professor Hee Cheol Kang

The Master's Thesis
Submitted to the Department of Medicine,
the Graduate School of Yonsei University
in partial fulfillment of the requirements for the
degree of Master of Medical Science

Yon Chul Park

June 2013

This certifies that the Master's
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The Graduate School
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June 2013

Acknowledgements

First of all,

Thank you God, who is always along with us.

Also,

Thank you Professor Kang, Professor Lee, Professor Kim
for all the help and encouragement.

And,

Thank you my family, I love you all...

Yon Chul Park

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ABSTRACT

Correlation between abnormal pap smear finding and brachial-ankle pulse wave velocity in Korean women

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(Directed by Professor Hee-Cheol Kang)

Cervical cancer is caused by chronic HPV infection. Pap smear is very efficient examination for early detecting cervical cancer. Inflammation reaction due to chronic infection is one of the major cause 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.

The research population, 1779 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 to groups, 45 people with abnormal finding and 228 people with normal finding. And analyzed correlation between risk factor of cervical cancer and Brachial-Ankle PWV. Multiple regression analysis was done with associated variables.

Average PWV of normal group was 1313.06 ± 264.19 and abnormal was 1497.15 ± 359.58 , that PWV of abnormal group was higher. ($p=0.0006$) Analyzing association between risk factors of cervical cancer and PWV, age, height, weight, income, gravidity were associated. Multiple regression was done with correcting these variables. As a result, PWV was associated with abnormal pap smear result, but not statistically efficient ($p=0.054$) But more study is needed with correcting accurate date about HPV infection and smoking history for massive number of group.

Key Words : cervical cancer, pap smear, brachial-ankle pulse wave velocity, atherosclerosis

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I INTRODUCTION

Cervical cancer is one of the most common gynecological cancer in Korea¹. Pap smear test is efficient and commonly used in early detecting cervical cancer. It is commonly used not only in Korea but also in world wide 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 inflammation response are also know 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 know 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 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 10 11} Association between atherosclerosis and cervical cancer have been studied actively. But no studies were done on associations between pulse wave velocity, major measuring method of subclinical atherosclerosis and cervical cancer.

II MATERIALS AND METHODS

1. STUDY POPULATION

Study was done with 1779 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. And study was done by 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 demension differentiation by computer. Length from substernal notch to both ankle(L_a) and both upper arm(L_a) were obtained by formula based

on lots of stature data.

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

Average data of both side were used in this 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.

III 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]

Table 1. Baseline characteristics of subjects

Variable	Normal (n=228)	Abnormal (n=43)	Total	P-value ‡	
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	0.58	
Weight (kg)	57.86±8.10	59.27±8.41	57.69±7.92	0.22	
baPWV_Rt (cm/s)	1305.75±272.88	1490.30±364.87	1411.53±322.81	< 0.001	
baPWV_Lt (cm/s)	1320.36±263.80	1504.00±362.40	1426.26±320.66	< 0.001	
baPWV_average (cm/s)	1313.06±264.19	1497.15±359.58	1418.90±319.02	< 0.001	
PYRs	11.97±10.95	11.20±6.19	12.26±13.82	0.71	
preg	2.96±2.16	2.79±2.11	3.10±2.30	0.62	
income	<100	10(5.29)	5(13.51)	198(13.46)	0.19
(10,000won	100~200	28(14.81)	6(16.22)	249(16.93)	
/month)	200~300	36(19.05)	9(24.32)	251(17.06)	
	≥300	115(60.85)	17(45.95)	773(52.55)	

baPWV : Brachial-Ankle Pulse Wave Velocity PYRs: packs per years preg : pregnancy

‡ -value by Wilcoxon's rank sum test for continuous variables or Chi-square test for categorical variables.

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-value = 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 value
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 value
baPWV-M	1313.06 ± 264.19	1497.15 ± 359.58	1418.90 ± 319.02	<0.001

baPWV-M : mean brachial-ankle pulse wave velocity

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]

Table 4. Correlations between baPWV and other continuous variables

Variable	Parameter Estimate (β)	Standard Error	P-value \ddagger
Age (y)	18.74	0.54	<0.001
Height (cm)	-20.40	1.37	<0.001
Weight (kg)	2.26	1.06	0.03
PYRs	0.40	2.20	0.86
preg	29.03	3.70	<0.001

baPWV : Brachial-Ankle Pulse Wave Velocity PYRs: packs per years preg : pregnancy

\ddagger -value by simple regression analysis

Difference between Income and average pulse wave velocity were found to be statistically significant by using Kruskal-Wallis test ($p < 0.001$) [Table 5]

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-value \ddagger
baPWV average	1624.43 ± 313.27	1502.15 ± 334.87	1387.27 ± 311.97	1334.65 ± 288.09	1418.90 ± 319.02	<0.001

baPWV : Brachial-Ankle Pulse Wave Velocity

\ddagger -value by Kruskal-Wallis test

4. ASSOCIATION BETWEEN ABNORMAL PAP SMEAR RESULT AND AVERAGE PULSE WAVE VELOCITY AFTER MULTIPLE REGRESSION

Multiple regression analysis was done with brachial ankle 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]

Table 6. Factors affecting baPWV

Variable	Parameter Estimate (β)	Standard Error	P-value \ddagger
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)

\ddagger -value by multiple regression analysis

IV 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 16 17 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.

V CONCLUSION

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 20 21}, hepatitis B virus and human papilloma virus infection are well known independent factor of malignant cancer⁴ 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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ABSTRACT (IN KOREAN)

한국인 여성에서 비정상 자궁 도말 검사 소견과
상완 발목 맥파 속도와와의 관련성

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박 연 철

자궁경부암은 HPV의 만성 감염에 의해 발현되는 것으로 알려져있다. 자궁 경부 도말 검사는 자궁경부암의 조기 진단을 위한 효율적 선별 검사이다. 만성 감염에 의한 염증 반응은 동맥 경화의 주요 기전 중 하나이며, 상완 발목 맥파 속도 측정은 잠재적 동맥경화의 예측에 널리 사용되는 방법이다. 현재 비정상 자궁 도말 경부 검사 소견과 상완 발목 맥파 속도와와의 관련성을 알아본 연구는 없다.

일개 병원의 2008년부터 2010년까지 3년간의 종합 건강 검진 수검자를 대상으로 하여 자궁경부도말검사와 상완-발목 맥파 속도를 모두 검사 받은 수검자 중 산부인과적 병력이 없는 여성 1779명을 대상으로 연구하였다. 각 수검자의 자궁 도말 검사 소견중 비정상인 그룹 45명과 정상인 그룹 228명을 나눈 뒤 자궁경부암의 위험 인자들과 상완-발목 맥파 속도와와의 연관성을 분석 한 후 유의한 연관성을 보인 변수들에 대해 다중 회귀 분석을 시행하였다.

도말 검사 상 정상군의 상완-발목맥파속도의 평균은 1313.06 ± 264.19 이었으며, 비정상군의 평균은 1497.15 ± 359.58 으로 비정상군의 평균이 유의하게 높았다. ($p=0.0006$) 자궁 경부암의 위험 인자들과의 연관성을 분석한 결과 나이, 키, 몸무게, 소득수준, 임신력이 관련성이 있는 것으로 나타났고 이를 보정하여 회귀분석을 시행하였으며.

그 결과 맥파 속도와 비정상 자궁 도말 검사 소견 사이에는 연관성이 있는 것으로 나타났다. 그러나 통계학적으로 유의하지는 않았다 ($p=0.054$)

하지만 HPV 감염 여부 및 흡연력 등에 대한 정확한 데이터 등과 같은 제한점들을 개선하여 대규모 연구 집단을 대상으로 추가적 연구를 시행 할 필요성이 있겠다

핵심되는 말 : 자궁경부암, 자궁경부도말검사, 상완-발목 맥파속도, 동맥경화