Research Article

Human Papillomavirus and Coronary Artery Disease in Climacteric Women: Is There an Association?

Luciane Maria Oliveira Brito,1 Haissa Oliveira Brito,1 Rita da Graça Carvalhal Frazão Corrêa,1 Clariano Pires de Oliveira Neto,1 Joyce Pinheiro Leal Costa,1 Sally Cristina Moutinho Monteiro,1 Flávia Castello Branco Vidal,1 Maria do Desterro Soares Brandão Nascimento,1 José Albuquerque de Figueiredo Neto,1 Rui Miguel Gil da Costa,1,2 Leonardo Victor Galvão-Moreira,1 and Ismael Dale Cotrim Guerreiro da Silva3

1Tumor and DNA Biobank of Maranhão, Federal University of Maranhão, São Luís, Brazil
2Molecular Oncology and Viral Pathology Group, Portuguese Institute of Oncology, Porto, Portugal
3Federal University of São Paulo, São Paulo, Brazil

Correspondence should be addressed to Luciane Maria Oliveira Brito; luciane2406@yahoo.com.br

Received 6 February 2019; Accepted 22 May 2019; Published 20 June 2019

Academic Editor: Francesco Giallauria

Copyright © 2019 Luciane Maria Oliveira Brito et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Background. Cardiovascular diseases are leading causes of death worldwide. Recent studies suggest that infection by some viruses, including the human papillomavirus (HPV), may increase the risk of developing atheromatous lesions on coronary arteries. However, there is a lack of data regarding the possible association between HPV infection and coronary artery disease (CAD) in women. Objective. To investigate whether HPV infection is associated with the occurrence of CAD among climacteric women. Methods. The presence of CAD and cervical HPV DNA was investigated in 52 climacteric women. Social and demographic variables and metabolic profiles were also investigated. Results. Among 27 women with CAD, 16 were positive for HPV, whereas 11 were negative. The presence of cervical HPV was strongly associated with CAD, after adjusting for demographic variables, health and sexual behaviors, comorbidities, and known cardiovascular risk factors. HPV-positive women showed a greater likelihood of having CAD (odds ratio [OR] = 3.74; 95% confidence interval [CI]: 1.16 to 11.96) as compared with HPV-negative women, particularly those infected with high-risk HPV types (OR = 4.90; 95% CI: 1.26 to 19.08). Conclusion. These results support the hypothesis that HPV infection might be associated with CAD among climacteric women, though further studies are needed to investigate the mechanisms involved.

1. Introduction

Cardiovascular diseases are the leading cause of death and constitute a major public health issue worldwide. Globally, they account for millions of deaths and, in Brazil, represent 29.4% of all deaths [1, 2]. Indeed, coronary artery disease (CAD) is characterized by insufficient blood supply to the heart through the coronary arteries, leading to myocardial infarction [3, 4]. Important risk factors for CAD are well established, including hypertension, diabetes, dyslipidemia, and smoking [2, 3, 5]. However, several individuals with CAD display none of these risk factors, thereby instigating the investigation of other determinants or associated variables [4, 5].

Infections with several agents such as HIV, Epstein-Barr virus, cytomegalovirus, and Chlamydia pneumonia have been suggested as risk factors for CAD, possibly by promoting a chronic inflammatory status [6, 7]. In this context, the human papillomavirus (HPV), one of the most common sexually transmitted infections worldwide, may play a significant role. HPV includes more than 200 subtypes, which are etiologically linked to the development of benign and malignant
lesions. HPV 16 and 18 are the most common “high-risk”
types and are strongly associated with cervical cancer and
other malignancies [8]. In the general female population, the
prevalence of HPV infection ranges 2-44% [8]. In developing
countries, the prevalence ranges 21-48%, with high-risk HPV
being detected in 48-53% of infected individuals [9–11]. Over
the years, our group has specialized in HPV-related tumors,
such as penile [12], anal [13], and cervical [14] cancers.

Previous reports [15] have described that women with
vaginal HPV show a threefold increased risk of cardiovas-
cular disease as compared with HPV-negative women. More
recently, HPV DNA and proteins have been detected in 50%
of atheromatous coronary arteries in a small sample of 20
deceased donors [16]. HPV infection is speculated to facilitate
the development of CAD by providing an enhanced systemic
inflammatory stimulus [16], which is also observed in HPV-
transgenic animal models [17]. In fact, chronic unresolved
inflammation plays a key role in CAD [18] and HPV infection
might also contribute to this. Occasional studies claim that
HPV, like other viruses, interferes with lipid metabolism,
which might also contribute to CAD [16, 21]. Therefore,
the present study was aimed at investigating a possible
association between HPV infection and CAD in climacteric
women.

2. Methods

2.1. Ethics and Study Population. A cross-sectional study
was approved by the Federal University of Maranhão Ethics
Committee (approval #195.357). Written informed consent
was obtained from all women. The sample size was calculated
considering a prevalence of 65% of women with coronary
artery disease positive for HPV [15], a power of 80% and a
5% significance level.

2.2. Inclusion and Exclusion Criteria. Volunteers with and
without CAD were included if they were over 35 years
of age and climacteric. Individuals with cardiac catheri-
ization following coronary angioplasty were considered for
enrolment and referred to the Gynecology Service of the
Clinical Research Center/UFMA, where they underwent
clinical examination to confirm eligibility. Exclusion criteria
were previous chemotherapy/ pelvic radiotherapy or having
serum HIV positivity.

2.3. Sociodemographic Variables. Sociodemographic vari-
ables (age, ethnicity, education, family income, professional
activity, marital status, sexual behavior, alcohol consumption,
smoking, and physical activity) were investigated using a
semistructured questionnaire specifically developed for this
study.

2.4. Comorbidities. During clinical examination, volunteers
reported the presence or absence of comorbidities (hyperten-
sion, diabetes, thyroid disorders, and sexually transmit-
ted diseases). Next, blood pressure (BP) and body mass
index (BMI) were determined for each participant. For BP,
volunteers were required to have an empty bladder and
have not exercised or consumed alcohol, coffee or any food
for at least 30 minutes prior to measurement. Systolic and
diastolic BP were measured following the Brazilian Society
of Cardiology guidelines, using a stethoscope and a mer-
cury sphygmomanometer [22]. BP was considered abnormal
when BP was equal to or greater than 130/85 mmHg. The
BMI was calculated as the ratio between body weight in
kilograms divided by the square of height in meters, and
was categorized according to the WHO cut off points [23]:
<18.5 (underweight), 18.5 to 24.9 (normal weight), 25.0 to 29.9
(overweight), and >30.0 (obese).

2.5. Metabolic Profile. Venous blood samples were obtained
from volunteers after a 12-hour fasting period. After col-
lection into tubes with and without anticoagulant, plasma
and serum were separated by centrifugation and stored in
freezer -80°C until further analysis. The samples were used
to perform hemograms, glucose profile (fasting glucose, insul-
in, and glycated hemoglobin), lipid profile (total cholesterol,
triglycerides, High Density Lipoprotein-HDL and Low Den-
sity Lipoprotein-LDL cholesterol), renal profile (creatinine
and urea), and high-sensitivity C-reactive protein (hs-CRP).

2.6. HPV Detection and Genotyping. Cervical material was
collected and submitted to nested polymerase chain reaction
(PCR) for HPV genotyping. Extraction of genetic material
was performed using the QIAamp DNA Mini and Blood Mini
kit (QIAGEN, Valencia, CA) following the manufacturer’s
instructions. Briefly, 400 μL sample solution was added to
400 μL of AL buffer and 20 μL of proteinase. Then, 400μL
of 100% ethanol was added to each tube; the samples were
centrifuged four times and, after a brief incubation period,
were again centrifuged at 8,000 rpm for 5 minutes to elute
the DNA, which was stored at -20 °C. The DNA concentration
was determined using a NanoVue (GE) spectrophotometer. HPV
DNA detection was performed by LI gene amplification using
a PCR-NESTED technique and the primer pairs PGMY 09/11
and GP 5 + / 6 + . Next, the product of the first reaction with
the primers GP5+ / GP6+ was amplified.

Following the PCR reactions, 5 μL of each sample was
submitted to 1.5% agarose gel electrophoresis to verify ampli-
fication. The PCR products were purified and subsequently
sequenced using a MegaBACE 1000 automated sequencer
(GE Healthcare, UK). Chromatograms of the sequences
obtained were analyzed by Chromas software (Technelysium)
and the sequences were submitted to online BLASTn software
for the identification of HPV types. A total of 36 DNA-HPV
samples were analyzed, and HPV types 16, 18, 33, 35, 39, 45,
51, 56, and 58 were defined as posing high oncogenic risk.

2.7. Statistical Analysis. Data are presented as absolute and
relative frequencies. A binary logistic regression model was
used to obtain adjusted odds ratio (OR) and confidence
intervals (CI). Data were analyzed using EpInfo 7 software
(CDC, Atlanta). A p < 0.05 was considered statistically
significant.
Table 1: Association between sociodemographic characteristics of participants and HPV status.

<table>
<thead>
<tr>
<th>Variable</th>
<th>HPV positive (n=23)</th>
<th>HPV negative (n=29)</th>
<th>$p$</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age group</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>37–49</td>
<td>6 (26.1)</td>
<td>4 (13.8)</td>
<td>0.4454</td>
<td>Ref</td>
</tr>
<tr>
<td>50–59</td>
<td>9 (39.1)</td>
<td>19 (65.5)</td>
<td>0.31</td>
<td>0.07-1.40</td>
</tr>
<tr>
<td>60+</td>
<td>8 (34.8)</td>
<td>6 (20.7)</td>
<td>0.88</td>
<td>0.17-4.62</td>
</tr>
<tr>
<td><strong>Marital Status</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single</td>
<td>12 (52.2)</td>
<td>13 (44.8)</td>
<td>0.9336</td>
<td>Ref</td>
</tr>
<tr>
<td>Married</td>
<td>7 (30.4)</td>
<td>15 (51.7)</td>
<td>0.55</td>
<td>0.16-1.85</td>
</tr>
<tr>
<td>Widow</td>
<td>4 (17.4)</td>
<td>1 (3.5)</td>
<td>4.72</td>
<td>0.45-8.77</td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>9 (39.1)</td>
<td>12 (41.4)</td>
<td>0.3268</td>
<td>Ref</td>
</tr>
<tr>
<td>Brown</td>
<td>10 (43.5)</td>
<td>13 (44.8)</td>
<td>1 (0.43-2.30)</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>4 (17.4)</td>
<td>4 (13.8)</td>
<td>0.36</td>
<td>0.11-1.14</td>
</tr>
<tr>
<td><strong>Income</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 MW</td>
<td>12 (52.2)</td>
<td>11 (37.9)</td>
<td>0.1686</td>
<td>1.16 (0.43-2.30)</td>
</tr>
<tr>
<td>2-3 MW</td>
<td>5 (21.7)</td>
<td>11 (37.9)</td>
<td>1 (0.32-3.10)</td>
<td></td>
</tr>
<tr>
<td>4+ MW</td>
<td>6 (26.1)</td>
<td>7 (24.2)</td>
<td>Ref</td>
<td></td>
</tr>
<tr>
<td><strong>Alcoholism</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>4 (17.4)</td>
<td>2 (6.9)</td>
<td>0.3447</td>
<td>0.17 (0.05-0.60)</td>
</tr>
<tr>
<td>No</td>
<td>11 (47.8)</td>
<td>20 (69.0)</td>
<td>Ref</td>
<td></td>
</tr>
<tr>
<td>Ex alcoholic</td>
<td>8 (34.8)</td>
<td>7 (24.1)</td>
<td>0.47</td>
<td>0.20-1.09</td>
</tr>
<tr>
<td><strong>Smoking</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>-</td>
<td>1 (3.5)</td>
<td>0.0022</td>
<td>-</td>
</tr>
<tr>
<td>No</td>
<td>17 (73.9)</td>
<td>24 (82.7)</td>
<td>Ref</td>
<td></td>
</tr>
<tr>
<td>Former smoker</td>
<td>6 (26.1)</td>
<td>4 (13.8)</td>
<td>0.15</td>
<td>0.04-0.50</td>
</tr>
<tr>
<td><strong>Physical activity</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>8 (34.8)</td>
<td>7 (24.1)</td>
<td>0.5937</td>
<td>Ref</td>
</tr>
<tr>
<td>No</td>
<td>15 (65.2)</td>
<td>22 (75.9)</td>
<td>1.67</td>
<td>0.50-5.61</td>
</tr>
<tr>
<td><strong>Beginning of sexual activity</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 – 18</td>
<td>11 (47.8)</td>
<td>18 (62.1)</td>
<td>0.5562</td>
<td>Ref</td>
</tr>
<tr>
<td>19 – 25</td>
<td>8 (34.8)</td>
<td>11 (37.9)</td>
<td>0.6</td>
<td>0.26-1.37</td>
</tr>
<tr>
<td>25 +</td>
<td>4 (17.4)</td>
<td>-</td>
<td>0.13</td>
<td>0.33-0.58</td>
</tr>
<tr>
<td><strong>Sexual partners</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>11 (47.8)</td>
<td>14 (48.3)</td>
<td>0.8445</td>
<td>Ref</td>
</tr>
<tr>
<td>2</td>
<td>6 (26.2)</td>
<td>8 (27.6)</td>
<td>0.46</td>
<td>0.17-1.21</td>
</tr>
<tr>
<td>3</td>
<td>3 (11.5)</td>
<td>2 (6.9)</td>
<td>0.23</td>
<td>0.06-0.80</td>
</tr>
<tr>
<td>4+</td>
<td>3 (11.5)</td>
<td>5 (17.2)</td>
<td>0.30</td>
<td>0.10-0.94</td>
</tr>
<tr>
<td><strong>Actual sexual activity</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>7 (30.4)</td>
<td>14 (48.3)</td>
<td>0.3912</td>
<td>0.46 (0.14-1.47)</td>
</tr>
<tr>
<td>No</td>
<td>16 (69.6)</td>
<td>15 (51.7)</td>
<td>Ref</td>
<td></td>
</tr>
</tbody>
</table>

OR: odds ratio; CI: confidence interval; MW: minimum wage; Ref: reference.

3. Results

Fifty-two women participated in this study, who were divided into two groups, according to the presence or absence of HPV infection: HPV-positive (n = 23) and HPV-negative (n = 29) (Table 1). The profile of HPV-positive volunteers included an age range of 50 to 59 years, single, low socioeconomic status, no drinking or smoking history, sedentary, being with early beginning of sexual activity (12-18 years), having few sexual partners (one), and being without sexual activity. There were no differences between the HPV-positive and HPV-negative groups with regard to sociodemographic variables. Variables related to metabolic risk for developing CAD in the both groups are summarized in Table 2. There was no statistical difference between the two groups regarding the prevalence of diabetes mellitus or metabolic syndrome and values of hs-CRP, body mass index, blood glucose, and triglycerides. However, the HPV-positive group showed
lower blood levels of HDL cholesterol \( (p = 0.008) \) and elevated systemic blood pressure \( (p = 0.002) \) when compared with the HPV-negative group.

Regarding the presence of HPV, 44.2% of all women were positive for cervical HPV DNA, 69.6% of which with CAD, and 30.4% without CAD (Table 2). Among HPV-negative women, the CAD prevalence was 37.9%. The difference in CAD prevalence between the HPV-positive and negative groups was marginally significant \( (p = 0.0467) \) and the OR for CAD was 3.74 for HPV-positive volunteers compared with HPV-negative women.

Sixteen women (30.8%) had high-risk HPV types (16, 18, 33, 39, 45, and 58). These volunteers included 44.5% of the women with CAD and 16.0% of those without CAD (Table 3). After adjusting for age and ethnicity, the presence of high-risk vaginal HPV DNA was statistically associated with CAD \( (OR = 4.90, p = 0.0384) \). The presence of other types of HPV was not associated with CAD in this study.

### 4. Discussion

HPV infection is the cause of multiple benign and malignant lesions, but a possible association with cardiovascular disease has seldom been proposed and remains speculative. Still, some evidence [15] has reported that vaginal HPV infections increase the risk of cardiovascular diseases. One study [16] identified HPV in 55% of atheromatous coronary arteries in a small sample of postmortem donors, and the HPV E7 protein was detected in smooth muscle cells, plasma cells, and foamy macrophages located in those plaques. These observations

<table>
<thead>
<tr>
<th>Variable</th>
<th>HPV positive (n=23)</th>
<th>HPV negative (n=29)</th>
<th>( p )</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BMI, kg/m(^2)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 30</td>
<td>14 (60.9)</td>
<td>21 (72.4)</td>
<td>0.2865</td>
<td>Ref</td>
</tr>
<tr>
<td>( \geq ) 30</td>
<td>9 (39.1)</td>
<td>8 (27.6)</td>
<td>0.57</td>
<td>(0.23–1.36)</td>
</tr>
<tr>
<td><strong>Blood pressure, mmHg</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 130 x 85</td>
<td>4 (17.4)</td>
<td>11 (37.9)</td>
<td>0.002</td>
<td>Ref</td>
</tr>
<tr>
<td>( \geq ) 130 x 85</td>
<td>19 (82.6)</td>
<td>18 (62.1)</td>
<td>4.5</td>
<td>(1.52–12.29)</td>
</tr>
<tr>
<td><strong>Triglycerides, mg/dL</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 150</td>
<td>13 (56.6)</td>
<td>19 (65.5)</td>
<td>0.6767</td>
<td>Ref</td>
</tr>
<tr>
<td>( \geq ) 150</td>
<td>10 (43.4)</td>
<td>10 (34.5)</td>
<td>0.7692</td>
<td>(0.33–1.75)</td>
</tr>
<tr>
<td><strong>HDL Cholesterol, mg/dL</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( \geq ) 50</td>
<td>5 (21.7)</td>
<td>10 (34.5)</td>
<td>0.008</td>
<td>Ref</td>
</tr>
<tr>
<td>&lt; 50</td>
<td>18 (78.3)</td>
<td>19 (65.5)</td>
<td>3.8</td>
<td>(1.41–10.37)</td>
</tr>
<tr>
<td><strong>Blood glucose, mg/dL</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 100</td>
<td>14 (60.9)</td>
<td>16 (55.2)</td>
<td>0.8473</td>
<td>Ref</td>
</tr>
<tr>
<td>( \geq ) 100</td>
<td>9 (39.1)</td>
<td>13 (44.8)</td>
<td>0.92</td>
<td>(0.43 – 1.97)</td>
</tr>
<tr>
<td><strong>HbA1C, %</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 5.4</td>
<td>4 (17.4)</td>
<td>6 (20.7)</td>
<td>0.7665</td>
<td>Ref</td>
</tr>
<tr>
<td>( \geq ) 5.4</td>
<td>19 (82.6)</td>
<td>23 (79.3)</td>
<td>1.23</td>
<td>(0.30–5.04)</td>
</tr>
<tr>
<td><strong>hs-CRP, mg/dL</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 0.3</td>
<td>9 (39.1)</td>
<td>15 (51.7)</td>
<td>0.4042</td>
<td>Ref</td>
</tr>
<tr>
<td>( \geq ) 0.3</td>
<td>14 (60.9)</td>
<td>14 (48.3)</td>
<td>1.55</td>
<td>(0.67 – 3.59)</td>
</tr>
<tr>
<td><strong>Metabolic Syndrome</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>13 (56.6)</td>
<td>18 (62.1)</td>
<td>0.8383</td>
<td>Ref</td>
</tr>
<tr>
<td>Yes</td>
<td>10 (43.4)</td>
<td>11 (37.9)</td>
<td>0.84</td>
<td>(0.34 – 2.04)</td>
</tr>
<tr>
<td><strong>CAD</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>7 (30.4)</td>
<td>18 (62.1)</td>
<td>0.0467</td>
<td>Ref</td>
</tr>
<tr>
<td>Yes</td>
<td>16 (69.6)</td>
<td>11 (37.9)</td>
<td>3.74</td>
<td>(1.16–11.96)</td>
</tr>
</tbody>
</table>

OR: odds ratio; CI: confidence interval; BMI: body mass index; Ref: reference.

<table>
<thead>
<tr>
<th>Variable</th>
<th>With CAD (n=27)</th>
<th>Without CAD (n=25)</th>
<th>( p )</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPV</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>11 (40.7)</td>
<td>18 (72.0)</td>
<td>Ref</td>
<td></td>
</tr>
<tr>
<td>High-risk</td>
<td>12 (44.5)</td>
<td>4 (16.0)</td>
<td>0.0384</td>
<td>4.90 (1.26–19.08)</td>
</tr>
<tr>
<td>Other types</td>
<td>4 (14.8)</td>
<td>3 (12.0)</td>
<td>0.6182</td>
<td>2.18 (0.40–11.64)</td>
</tr>
</tbody>
</table>

OR: odds ratio; CI: confidence interval; Ref: reference.
raise questions concerning the possible mechanisms by which HPV could promote the formation of atheromatous plaques.

The prevailing view is that HPV remains confined to its epithelial lesions, but some authors report the detection of HPV DNA and proteins on endothelial cells [20] and circulating blood leukocytes [19]. If these observations reflect true viral dissemination, they could help explaining the presence of HPV in atheromatous lesions [16]. On the other hand, if HPV remains confined to mucosal lesions, it may be involved in CAD by promoting a systemic inflammatory status [17] and by deregulating the host metabolism, in particular that of lipids [21]. In the present study, we chose to address some of these issues in climacteric women. Menopause is associated with chronic inflammation and has major implications for CAD development [24, 25] and associated lipid disorders [26]. HPV incidence is also higher in this group [27] and might act synergistically with some of these factors to aggravate its cardiovascular risk.

Among climacteric women, we observed a marginally significant association between HPV infection and CAD. Importantly, the high-risk HPV genotypes associated with cancer were selectively associated with CAD, whereas no association with low-risk genotypes was observed. This is in line with previous studies [16] that detected the two most common high-risk HPV types, HPV16 and HPV18, in atheromatous plaques, but not low-risk types. Interestingly, the HPV type observed in endothelial cells and blood leukocytes in previous studies [19, 20] was also the high-risk HPV16.

The present results support the hypothesis that infection with HPV is associated with CAD, and that there is a specific association with high-risk (rather than low-risk) HPV types. If HPV does reach coronary arteries and is present in atheromatous plaques, it might promote their development through its classical cellular targets, p53, and the retinoblastoma protein (pRb). The loss of p53 function in macrophages was found to be strongly associated with the increase of atherosclerotic lesions [28–30]. In addition, knock-out animals for pRb showed increased development of atherosclerosis [31].

The present results also show a lower HDL and higher systemic blood pressure levels in HPV-positive compared with the HPV-negative group. While this could represent a menopause-related change, the statistical correlations with HPV infection were highly significant and call for an explanation, which may involve the interference of HPV on lipid metabolism [21]. However, the reduced number of subjects in our study and the restriction to climacteric women only and the lack of further cardiovascular data do not allow us to draw conclusions in this regard.

5. Conclusions

Overall, in the current study, HPV infection was associated with a greater likelihood of CAD occurrence among climacteric women. Prospective cohort studies are hereby necessary to investigate a potential causal effect of HPV infection on CAD development, and the investigation of biological mechanisms underlying this association is warranted.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Disclosure

The funding agencies had no role in the study design; collection, analysis, and interpretation of data; or the writing and final approval of the manuscript.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Acknowledgments

This study was supported by FAPEMA (grant #BIC-02582/14, Brazil), MCTI/CNPq (grant #460035/2014-2, Brazil), CAPES/PROCAD (grant #PROCAD/NF2009, Brazil), LEPABE/FEDER/COMPETE2020 (grant #POCI-01-0145-FEDER-006939, Portugal), and Fundação para a Ciência e a Tecnologia (grant #SFRH/BPD/85462/2012, Portugal). The authors are grateful to Dr. E.C. Fraga for providing support during HPV-DNA sequencing.

References


[19] C. Foresta, A. Bertoldo, A. Garolla et al., “Human papillomavirus proteins are found in peripheral blood and semen Cd20+ and Cd56+ cells during Hpv-16 semen infection,” *BMC Infectious Diseases*, vol. 15, article 593, 2013.


