



**HAL**  
open science

## **Predictors of Human Papilloma Virus (HPV) infection in Italian women**

Maria Cecilia Cercato, Luciano Mariani, Amina Vocaturo, Angela Carrone,  
Irene Terrenato, Giuseppina Morano, Maria Benevolo, Francesca Rollo,  
Chiara Germelli, Francesca Paolini, et al.

► **To cite this version:**

Maria Cecilia Cercato, Luciano Mariani, Amina Vocaturo, Angela Carrone, Irene Terrenato, et al..  
Predictors of Human Papilloma Virus (HPV) infection in Italian women. *Journal of Medical Virology*,  
2010, 82 (11), pp.1921. 10.1002/jmv.21887 . hal-00577347

**HAL Id: hal-00577347**

**<https://hal.science/hal-00577347>**

Submitted on 17 Mar 2011

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



## Predictors of Human Papilloma Virus (HPV) infection in Italian women

Journal:	<i>Journal of Medical Virology</i>
Manuscript ID:	JMV-10-1881.R1
Wiley - Manuscript type:	Research Article
Date Submitted by the Author:	01-Jun-2010
Complete List of Authors:	Cercato, Maria Cecilia; Regina Elena National Cancer Institute, Department of Epidemiology Mariani, Luciano; Regina Elena National Cancer Institute, Department of Gynaecologic Oncology Vocaturro, Amina; Regina Elena National Cancer Institute, Department of Pathology Carrone, Angela; "Sapienza" University of Rome, Department of Gynecology and Obstetrics Terrenato, Irene; Regina Elena National Cancer Institute, Department of Epidemiology Morano, Giuseppina; "Sapienza" University of Rome, Department of Gynecology and Obstetrics Benevolo, Maria; Regina Elena National Cancer Institute, Department of Pathology Rollo, Francesca; Regina Elena National Cancer Institute, Department of Pathology Germelli, Chiara; Regina Elena National Cancer Institute, Department of Gynaecologic Oncology Paolini, Francesca; Regina Elena National Cancer Institute, Laboratory of Virology Venuti, Aldo; Regina Elena National Cancer Institute, Laboratory of Virology
Keywords:	HPV, Cervical cancer, risk factors, sexual behaviour, questionnaire



1  
2  
3 **PREDICTORS OF HUMAN PAPILLOMA VIRUS (HPV) INFECTION IN**  
4  
5 **ITALIAN WOMEN**  
6  
7  
8  
9

10 M.C. Cercato<sup>\*</sup>, L. Mariani<sup>§</sup>, A. Vocaturo<sup>#</sup>, A. Carrone<sup>+</sup>, I. Terrenato<sup>\*</sup>, G. Morano<sup>+</sup>, M.  
11 Benevolo<sup>#</sup>, F. Rollo<sup>#</sup>, C. Germelli<sup>§</sup>, F. Paolini<sup>¶</sup>, A. Venuti<sup>¶</sup>.  
12  
13  
14  
15  
16

17 *Authors Affiliations:*

18  
19  
20 <sup>\*</sup>Department of Epidemiology, “Regina Elena” National Cancer Institute”, Via E.  
21 Chianesi 53, 00144 Rome, Italy.  
22  
23

24 <sup>§</sup>Department of Gynaecologic Oncology, “Regina Elena” National Cancer Institute, Via  
25 E. Chianesi 53, 00144 Rome, Italy.  
26  
27

28  
29 <sup>#</sup> Department of Pathology, “Regina Elena” National Cancer Institute, Via E. Chianesi  
30 53, 00144 Rome, Italy.  
31  
32

33  
34 <sup>+</sup>Department of Gynecology and Obstetrics "Sapienza" University of Rome, Viale del  
35 Policlinico 155, 00155 Rome, Italy.  
36  
37

38  
39 <sup>¶</sup>Laboratory of Virology, “Regina Elena” National Cancer Institute, Via E. Chianesi 53,  
40 00144 Rome, Italy.  
41  
42  
43  
44  
45

46 *Corresponding Author:*

47  
48 Cercato Maria Cecilia, Department of Epidemiology, “Regina Elena” National Cancer  
49 Institute, Via Elio Chianesi 53, 00144 Rome, ITALY. Tel.: +39-06-52666913; Fax:  
50 +39-06-52662732 (e-mail: [cercato@ifo.it](mailto:cercato@ifo.it))  
51  
52  
53  
54  
55  
56

57 **Shortened title:** HPV infection risk factors

58  
59 **Grants :** The Italian Ministry of Health partially funded the study.  
60

## ABSTRACT

**Background:** HPV infection is a “necessary cause” of cervical cancer and it is sexually transmitted. Due to upcoming mass vaccination investigation on risk factors for infection is the basis to implement prophylactic strategy even in older women.

**Objective:** The aim of the study was to evaluate predictors of high-risk HPV infection in adult women.

**Methods:** Between 2006 and 2008, one hundred women aged >18 years, with no previous treatment for cervical lesions, were screened for high-risk HPV infection in Rome, Italy. Risk factors for HPV infection were investigated through a questionnaire including: ethnicity, religion, education, marital status, sexual behaviour, gynaecological and obstetrical history, smoking and alcohol intake.

**Results:** Multivariate analysis identified the “never married-separated/divorced” status (OR: 3.38; 95% CI: 1.14-10.12) as predictor of HPV infection, while having a higher age at the first sexual intercourse shows a protective effect (OR: 0.84; 95% CI: 0.71-1.00). A trend for the association between the infection and having more than three lifetime partners was also observed (OR: 2.57; 95% CI: 0.86-7.71). No significant association was found for other demographic characteristics investigated.

**Conclusions:** These findings provide a contribution in the knowledge of an adult population defining a “high risk” sexual behavioural profile and could be helpful to target prophylactic strategies in older woman.

### Keywords

HPV, cervical cancer, epidemiology, risk factors, sexual behaviour, questionnaire.

## INTRODUCTION

Cervical cancer (CC) is associated with Human Papillomavirus (HPV) infection, which is transmitted during sexual intercourse [Walboomers et al., 1999; American Cancer Society, 2008]. CC is the second most common cancer in woman worldwide and is more frequent in socio-economically deprived regions where proper screening and/or vaccination programs are not easily available [World Health Organization, 2006; Almonte et al., 2008].

Over one hundred HPV genotypes have been identified and classified into low-risk (LR) (e.g. type 6,11) and high-risk (HR) (e.g. type 16,18,31,33,45) groups, according to their potential oncogenic effects [Muñoz et al., 2006]. In the U.S.A., 75% of women aged between 14 and 50 years become infected during their lives, but the great majority of HPV genital infections are transient and are cleared within 2 years by host immune response [World Health Organization, 2006]. Persistent infections with HR-HPV is involved in the pathogenesis of cervical intraepithelial neoplasia and in the progression to cervical cancer [Snijders et al., 2006].

HPV DNA prevalence varies by continent and by age: it is high (up to 30%) in young women (<25 years) all over the world except for Asia, decreasing in the middle-age group, even though a second rise among in perimenopausal women has been recently observed [Almonte et al., 2008; Bosch et al., 2008; Smith et al., 2008].

Contracting HPV genital infection appears to be associated with increased sexual activity and thus with number of partners; other involved factors are age at the first sexual intercourse, marital status, cigarette smoking and contraceptives use [Vaccarella et al., 2006; Almonte et al., 2008; Herbert and Coffin, 2008]. However epidemiological studies investigating risk factors for HPV infection have not been entirely consistent, due to the differences in population characteristics (demographic

1  
2  
3 growth rate, sexual habits, HPV prevalence) as well as to the potential misclassification  
4 involved in the assessment of sexual history [Schlecht et al., 2001; Schroder et al.,  
5  
6  
7  
8 2003].  
9

10  
11 Despite increasing effort, the burden and natural history of HPV infection is not  
12 completely understood and the upcoming mass vaccination will certainly change HPV  
13 epidemiology. Therefore baseline (i.e. pre-vaccine) epidemiological investigations on  
14 risk factors for infection should be encouraged to provide the basis to implement  
15 prophylactic strategies.  
16  
17  
18  
19  
20  
21

22 The aim of the present study was to investigate predictors of HR-HPV infection  
23 in women referred as outpatients to the “Regina Elena” National Cancer Institute and to  
24 the University “La Sapienza” in Rome, Italy, for HPV DNA detection and cervical  
25 cancer prevention.  
26  
27  
28  
29  
30  
31  
32  
33

## 34 MATERIALS AND METHODS

### 35 Population and study design

36  
37  
38 This study was part of a cooperative project conducted from April 2006 to  
39 December 2008, supported by the Italian Ministry of Health and coordinated by the  
40 “Regina Elena” National Cancer Institute. The study population were women who  
41 consecutively attended the Department of Gynaecologic Oncology of the “Regina  
42 Elena” National Cancer Institute and of the University “La Sapienza” of Rome, as  
43 outpatients for HPV DNA detection and cervical cancer prevention. Exclusion criteria  
44 were: age <18 years, positive history for cancer, previous surgical treatment for cervical  
45 lesions, presence of immunological disorders, pregnancy or cognitive impairment.  
46  
47  
48 Eligible patients were asked to participate and a written informed consent obtained. The  
49 study was approved by the Local Medical Ethical Committee.  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3 At enrolment a baseline questionnaire investigating common risk factors for  
4 HPV infection and for cervical cancer was given by the physician just before the clinical  
5 examination. A gynaecologist collected clinical data and during the scheduled clinical  
6 procedures collected cervicovaginal specimens for HPV DNA analysis to be delivered  
7 to the Department of Pathology.  
8  
9

#### 10 11 12 13 14 15 Questionnaire

16  
17 The questionnaire, to be filled in by the patient, consisted of multiple choice questions  
18 addressing: ethnicity, religion, educational level, marital status, gynaecologic and  
19 obstetric history, sexual behaviour (age at first intercourse, lifetime number of partners,  
20 frequency of intercourse), contraceptive use, alcohol use and smoking. Knowledge  
21 about Pap test and frequency of testing was also investigated.  
22  
23  
24  
25  
26  
27

#### 28 29 HPV DNA Detection and Genotyping

30  
31 Cervico-vaginal specimens were collected by cytobrush (Cytoc, Rome, Italy) and Ayre  
32 spatula (Cytoc), in 20 mL of PreservCyt solution (Cytoc), stored at 4°C until the use.  
33

34  
35 HR HPV test was performed according to scientific evidence by means of the HC2  
36 technique (Qiagen, Milan, Italy), a semi-quantitative signal-amplified hybridization  
37 assay for the chemiluminescent detection of the 13 most common HR HPV types  
38 (genotypes: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 68), as described by the  
39 manufacturer [Leinonen et al., 2009]. Before the HC2 testing, 4 ml of PreservCyt  
40 solution were processed by means of the HC2 Sample Conversion Kit (Qiagen). The  
41 positive cut-off (CO) value was considered the average of the positive control samples.  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
The results were considered positive when the ratio between the specimen's light  
emission units (RLU) and the chosen positive CO (RLU/CO) was 1 or greater.

HPV DNA genotyping was carried out by using Linear Array HPV Genotyping Test  
(LA Roche Molecular System, Rome, Italy). 250 µl of PreservCyt sample were taken

1  
2  
3 for DNA extraction, as described by the manufacturer. The assay involves the  
4  
5 amplification of a 450 bp amplicon, generated by a consensus PGMY primer set,  
6  
7 targeting the conserved L1 region [Gravitt et al., 2000; Coutlée et al., 2002]. The  
8  
9 detection of amplified products was achieved by the hybridization to a nylon strip,  
10  
11 containing two levels of  $\beta$ -globin control probes and 37 LR and HR anogenital HPV  
12  
13 types probes (types 6, 11, 16, 18, 26, 31, 33, 35, 39, 40, 42, 45, 51, 52, 53, 54, 55, 56,  
14  
15 58, 59, 61, 62, 64, 66, 67, 68, 69, 70, 71, 72, 73, 81, 82, 83, 84, IS39 and CP6180).  
16  
17  
18

### 19 20 Statistical analysis

21  
22 For the analysis the patients were categorized as “HPV-positive” when at least one of  
23  
24 the two basal HPV DNA tests were positive for high risk genotypes and as “HPV-  
25  
26 negative” when it tested negative to both tests.  
27  
28

29 Descriptive statistics were computed for all variables. Continuous data were reported as  
30  
31 the mean and standard deviation or the median and range; categorical data were  
32  
33 represented by frequencies and percentage values. The Student’s T-test was used to  
34  
35 compare continuous variables; the Pearson’s Chi-Squared and Fisher’s Exact test, when  
36  
37 appropriate, were used to detect potential differences between categorical variables.  
38  
39 Cohen’s Kappa and its relative 95% Confident Interval (95% CI) was used to assess the  
40  
41 concordance the between HC2 and Linear Array HPV Genotyping Test in detecting the  
42  
43 HPV status. P-values less than 0.05 were considered statistically significant.  
44  
45  
46

47  
48 Odds ratios (ORs) and their relative 95% CIs were computed through univariate and  
49  
50 multivariate logistic regression models in order to evaluate the association between  
51  
52 HPV infection and socio-demographic and behavioural variables. Data of some  
53  
54 variables were grouped due to the small number. “Primary” and “secondary school”  
55  
56 educational levels were grouped together. Furthermore, “marital status” was divided  
57  
58 into two categories “never married-separated/divorced” and “married-living together-  
59  
60



widow”, because, according to the “marriage protection hypothesis”, family life is considered to be associated with healthier behaviour and because widowhood is similar to cohabitation in sociologic terms [Contoyannis and Jones, 2004; Sellors et al., 2003].

The number of lifetime sexual partners was categorized into up to three and more than three according to the median value. The multivariate logistic regression model was developed using stepwise regression (forward selection) with predictive variables that were significant in the univariate analyses. The enter and remove limits were  $p = 0.10$  and  $p = 0.15$ , respectively

The data were analysed by using the SPSS version 11.5 (SPSS, Inc., Chicago, IL).

.

## RESULTS

Ninety-four out of the 100 consecutive eligible women submitted to the HPV DNA detection and genotyping tests agreed to complete the questionnaire.

According to the results of detection and genotyping HPV DNA tests 54 (57%) women were classified as “HR-HPV-positive” and 40 (43%) as “HPV-negative”. The agreement between the two tests was 91% (Cohen’s K: 0.83 95% CI[0.63 -1.00] ).

Overall, twenty-five different genotypes were identified: the most common high-risk types were 16 (28%), 31 (16%), 51 and 52 (14%) (Figure 1). No single low-risk infection was found. Multiple HPV types were detected in 26 (50%) out of the 52 positive women at the Linear Array HPV Genotyping Test. Co-infection by two viruses were found in 25% of the positive cases, by three viruses in 15% and by more than three viruses in 10%. Co-infection by three or more genotypes were more frequent in young (>35 years) woman (33% vs 9%).

1  
2  
3 Table I shows the characteristics of the population. All except one were Caucasian and  
4 the great majority (90%) belonged to the Christian faith (data not shown). The  
5 “positive” women were slightly younger but the mean age values did not differ  
6 significantly in the two groups. The “positive” women were more frequently “never  
7 married-separated/divorced”, reported a lower age at their first sexual intercourse (FSI)  
8 (17,9 vs 20.3 years), a higher number of lifetime partners (5.3 vs 3.0), smoking habits  
9 and alcohol consumption. No differences in educational level, number of pregnancies  
10 and of childbirths, frequency of intercourse, and use of estroprogestinic as well as  
11 condoms were observed. Almost all women reported to have knowledge of the Pap test  
12 and to undergo it regularly or occasionally.  
13  
14

15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27 At univariate analysis marital status, age at the FSI, lifetime numbers of sexual partners,  
28 past or current smoking habits, years of smoking, number of cigarettes, and regular use  
29 of alcohol were all factors predicting HPV infection (Tab.II). Multivariate analysis  
30 confirmed that the “never married-separated/divorced” status and a lower age at the first  
31 sexual intercourse were independent factors predicting HR-HPV infection (Tab.II). A  
32 trend for the association between the infection and having more than three lifetimes  
33 partners was also observed. No association was found for other variables included in the  
34 logistic regression model.  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47

## 48 **DISCUSSION**

49  
50 Cervical cancer is the second most common cancer in women worldwide and the  
51 estimate of the attributable fraction due to HPV infection range from 90% to 98%  
52 [Bosch and de Sanjosé, 2003]. HPV 16 and 18 are the most frequent types associated  
53 with CC and two prophylactic vaccines against these high-risk variants have been  
54  
55  
56  
57  
58  
59  
60

1  
2  
3 recently introduced in several countries mainly in young women (up to 26 years)[Ault  
4 and the FUTURE II Study Group, 2007; Harper and Paavonen, 2008].  
5  
6

7  
8 This study describes the predictors of HR-HPV infection in a sample of Italian  
9 women. The results highlight the behavioural characteristics that identify a “high-risk”  
10 profile for HPV infection, providing useful information to widen future prophylactic  
11 strategies also in older age-classes.  
12  
13  
14  
15

16  
17 The high compliance obtained (94%) confirmed the practicable features of the  
18 questionnaire employed and showed a positive attitude towards cervical cancer  
19 prevention of these women who, once informed about the aim of the study, agreed to  
20 disclose information on their sexual behaviour.  
21  
22  
23  
24  
25

26  
27 The results of the multivariate analysis showed that having a “never married-  
28 separated/divorced” status and an early age at the FSI are independent risk factors for  
29 HR-HPV infection. A trend, although not significant probably for the small size of the  
30 population, was also observed for having more than three lifetime partners. These  
31 findings are in agreement with previous studies showing that having a “never married”  
32 or a “separated/divorced” status, an early age at the FSI or a higher “sexual age” (i.e.  
33 years of being sexually active) are all factors associated with HPV infection [Almonte et  
34 al., 2008; Sellors et al., 2000; Lenselink et al., 2008; Tonon et al., 1999]. According to  
35 other authors age at the FSI is more likely to be a predictor of the total number of  
36 partners in a lifetime than a factor independently associated with the infection  
37 [Hildesheim et al., 2001; Burchell et al., 2006].  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52

53 Sexual activity with changing partners represents an additional well-known  
54 predictor of infection [Almonte et al., 2008; Herbert and Coffin, 2008; Vaccarella et al.,  
55 2006; Chan et al., 2009; Sellors et al., 2000; Sellors et al., 2003; Lenselink et al., 2008;  
56 Shields et al., 2004; Venuti et al., 1994]. A pooled analysis of the IARC HPV surveys of  
57  
58  
59  
60

1  
2  
3 11,337 women of nine countries (including areas Latino America, South-Eastern Asia,  
4 Spain and Africa) reported a significant increased risk of HPV infection (any type) for  
5 women with two or more lifetime partners vs one (OR: 1.86; 95%CI: 1.63-2.11)  
6 [Vaccarella et al., 2006]. In several case-control and cross sectional studies conducted in  
7 countries at different HPV prevalence the lifetime number and the number of sexual  
8 partners in the last 6-12 months were strongly associated with the presence of the  
9 infection [Almonte et al., 2008; Lenselink et al., 2008; Winer et al., 2003].

10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20 In this study the multivariate analysis showed no association between the risk of  
21 infection and the use of oral contraceptives, the use of condom, smoking and alcohol  
22 intake. The findings are consistent with the results of other studies, however no  
23 conclusive data are available [Lenselink et al., 2008; Sellors et al., 2003; Sellors et al.,  
24 2000; Winer et al., 2003]. In fact, the protective effect of a condom against HPV  
25 infection is not well established and does not seem to be as strong as for other sexual  
26 transmitted infections because of its transmission by skin-to-skin contact [Vaccarella et  
27 al., 2006; Burchell et al., 2006]. Data on the role of smoking is still debated and some  
28 studies show a positive association with current or past smoking habits [Sellors et al.,  
29 2000; Winer et al., 2003; Chan et al., 2009]. Smoking has been independently  
30 associated with an increased risk of cervical cancer and therefore has an acting role as a  
31 HPV co-factor in the cancerogenesis process [International Collaboration of  
32 Epidemiological studies of Cervical Cancer, 2007].

33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51 The study was not aimed to assess the prevalence of HPV infection. The high  
52 prevalence of the HR-HPV DNA infection observed in this population is probably due  
53 to the sample selection among patients referred by their general practitioners to two  
54 qualified Institutions for Research for HPV detection and cervical cancer screening, and  
55 could represent a limitation of the study. Other limitations are the small size of the  
56  
57  
58  
59  
60

1  
2  
3 sample that does not allow to investigate the role of a specific HR-HPV type, and, as  
4  
5 highlighted by other authors, the potential misclassification involved in reporting sexual  
6  
7 history due to the recall biases or to intentional under-reported number of partners  
8  
9 [Schroder et al., 2003; Schlecht et al., 2001]. Finally, previous infections in HPV  
10  
11 negative patients were not assessed by serologic markers taking into account the low  
12  
13 sensibility of the test as well as the scant relevance of the transient infections in the  
14  
15 carcinogenesis [Snijders et al., 2006; Schiffman and Castle, 2003]  
16  
17  
18

19  
20 Epidemiology of HPV infection is going to change because of upcoming mass  
21  
22 vaccination. HPV vaccine trials have established that both vaccines (the bivalent against  
23  
24 16,18 and the quadrivalent against 16,18,6,11) produce a potent immunological  
25  
26 response and are associated with an efficacy rate close to 100% for at least 5 years in  
27  
28 naïve women [Villa et al., 2005; Villa et al., 2006; Harper et al., 2004; Harper et al.,  
29  
30 2006; Ault and the FUTURE II Study Group, 2007; Paavonen et al., 2009]. National  
31  
32 regulatory agencies (i.e. Food and Drug Administration, European Medicines Agency)  
33  
34 have approved the two commercial products (Gardasil<sup>TM</sup> and Cervarix<sup>TM</sup>) in most  
35  
36 countries for use in young women (up to 26 years). Furthermore, because of the  
37  
38 evidence of immunobridging also in women up to the age of 55 years, in selected  
39  
40 regions there are approvals for women aged >26 years [Harper and Paavonen, 2008;  
41  
42 Schwarz et al., 2009; Castellsagué et al., 2009].  
43  
44  
45  
46  
47

48 Taking into account the safety and efficacy data available, increasing  
49  
50 interventions to immunize women of different ages are expected.  
51  
52  
53

## 54 55 **CONCLUSIONS**

56  
57 Prevalence of HR-HPV infection is high in this selected population and is  
58  
59 mainly associated to sexual behaviour. These findings contribute to the knowledge of an  
60

1  
2  
3 adult population in defining a “high risk” behavioural profile and could be helpful to  
4  
5 target prophylactic strategies in older woman.  
6  
7  
8  
9

#### 10 **Conflict of interest statement**

11  
12 The authors have no conflict of interest to disclose.  
13  
14

#### 15 **ACKNOWLEDGMENTS**

16  
17  
18 The authors thank the Italian Ministry of Health that partially funded the study and the  
19  
20  
21  
22 Lega Italiana Lotta Tumori (LILT).  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

**REFERENCES**

Almonte M, Albero G, Molano M, Carcamo C, García PJ, Pérez G. 2008. Risk factors for human papillomavirus exposure and co-factors for cervical cancer in Latin America and the Caribbean. *Vaccine* 26:L16-36.

American Cancer Society. 2008. Detailed guide: cervical cancer. What are the risk factors for cervical cancer? American Cancer Society Web site. Available at: [http://www.cancer.org/docroot/CRI/content/CRI\\_2\\_4\\_2X\\_What\\_are\\_the\\_risk\\_factors\\_f\\_or\\_cervical\\_cancer\\_8.asp](http://www.cancer.org/docroot/CRI/content/CRI_2_4_2X_What_are_the_risk_factors_f_or_cervical_cancer_8.asp).(last accessed: November 15, 2009).

Ault KA, The Future II Study Group. 2007. Effect of prophylactic human papillomavirus L1 virus-like-particle vaccine on risk of cervical intraepithelial neoplasia grade 2, grade 3, and adenocarcinoma in situ: a combined analysis of four randomized clinical trial. *Lancet* 369:1861–1868.

Bosch FX, de Sanjosé S. 2003. Chapter 1 : Human papillomavirus and cervical cancer-burden and assessment of causality. *J Natl Cancer Inst Monogr* 31:3-13.

Bosch FX, Burchell AN, Schiffman M, Giuliano AR, de Sanjosè S, Bruni L, Tortolero-Luna G, Kruger Kjaer S, Muñoz N. 2008. Epidemiology and natural history of Human Papilloma Virus infections and type-specific implications in cervical neoplasia. *Vaccine* 26:K1-K16.

Burchell AN, Winer RL, de Sanjose S, Franco EL. 2006. Chapter 6: Epidemiology and transmission dynamics of genital HPV infection. *Vaccine* 24:S52–S61.

1  
2  
3 Castellsagué X, Schneider A, Kaufmann AM, Bosch FX. 2009. HPV vaccination  
4 against cervical cancer in women above 25 years of age: key considerations and current  
5 perspectives. *Gynecol Oncol* 115:S15-S23.  
6  
7

8  
9  
10  
11  
12 Chan PK, Ho WC, Wong MC, Chang AR, Chor JS, Yu MY. 2009. Epidemiologic risk  
13 profile of infection with different groups of human papillomaviruses. *J Med Virol* 81:  
14 1635-1644.  
15  
16  
17

18  
19  
20  
21  
22 Coutlée F, Gravitt P, Kornegay J, Hankins C, Richardson H, Lapointe N, Voyer H,  
23 Franco E. 2002. Use of PGM1 primers in L1 consensus PCR improves detection of  
24 human papillomavirus DNA in genital samples. *J Clin Microbiol* 3:902-7.  
25  
26  
27

28  
29  
30  
31 P.Contoyannis, A. M Jones. 2004. Socio-Economic Status, Health and Lifestyle. *Journal*  
32 *of Health Economics* 23:965-995.  
33  
34  
35

36  
37  
38 Gravitt PE, Peyton CL, Alessi TQ, Wheeler CM, Coutlée F, Hildesheim A, Schiffman  
39 MH, Scott DR, Apple RJ. 2000. Improved amplification of genital human  
40 papillomaviruses. *J Clin Microbiol* 38:357-61.  
41  
42  
43  
44

45  
46  
47  
48 Harper DM, Franco EL, Wheeler C, Ferris DG, Jenkins D, Schuind A, Zahaf T, Innis B,  
49 Naud P, De Carvalho NS, Roteli-Martins CM, Teixeira J, Blatter MM, Korn AP, Quint  
50 W, Dubin G; GlaxoSmithKline HPV Vaccine Study Group. 2004. Efficacy of a bivalent  
51 L1 virus-like particle vaccine in prevention of infection with human papillomavirus  
52 types 16 and 18 in young women: a randomized controlled trial. *Lancet* 364:1757-1765.  
53  
54  
55  
56  
57  
58  
59  
60



1  
2  
3 Harper DM, Franco EL, Wheeler CM, Moscicki AB, Romanowski B, Roteli-Martins  
4 CM, Jenkins D, Schuind A, Costa Clemens SA, Dubin G; HPV Vaccine Study group.  
5  
6 2006. Sustained efficacy up to 4.5 years of a bivalent L1 virus-like particle vaccine  
7  
8 against human papillomavirus types 16 and 18: follow-up from a randomized control  
9  
10 trial. *Lancet* 367:1247-1255.  
11  
12  
13

14  
15  
16  
17 Harper MD, Paavonen J. 2008. Age for HPV vaccination. *Vaccine* 26:A7-A11.  
18

19  
20  
21  
22 Herbert J, Coffin J. 2008. Reducing patient risk for human papillomavirus infection and  
23  
24 cervical cancer. *J Am Osteopath Assoc* 108:65-70.  
25  
26  
27

28  
29 Hildesheim A, Herrero R, Castle PE, Wacholder S, Bratti MC, Sherman ME, Lorincz  
30  
31 AT, Burk RD, Morales J, Rodriguez AC, Helgesen K, Alfaro M, Hutchinson M,  
32  
33 Balmaceda I, Greenberg M, Schiffman M. 2001. HPV co-factors related to the  
34  
35 development of cervical cancer: results from a population-based study in Costa Rica. *Br*  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

International Collaboration of Epidemiological Studies of Cervical Cancer, Appleby P,  
Beral V, Berrington de Gonzalez A, Colin D, Franceschi S, Goodhill A, Green J, Peto J,  
Plummer M, Sweetland S. 2007. Cervical cancer and hormonal contraceptives:  
collaborative reanalysis of individual data for 16,573 women with cervical cancer and  
35,509 women without cervical cancer from 24 epidemiological studies. *Lancet* 370:  
1609-1621.

1  
2  
3 Leinonen M, Nieminen P, Kotaniemi-Talonen L, Malila N, Tarkkanen J, Laurila P,  
4  
5 Anttila A. 2009. Age-specific evaluation of primary human papillomavirus screening vs  
6  
7 conventional cytology in a randomized setting. *J Natl Cancer Inst* 101:1612-1623.  
8  
9

10  
11  
12 Lenselink CH, Melchers WJ, Quint WG, Hoebbers AM, Hendriks JC, Massuger LF,  
13  
14 Bekkers RL. 2008. Sexual behaviour and HPV infections in 18 to 29 year old women in  
15  
16 the pre-vaccine era in the Netherlands. *PLoS One* 3:e3743.  
17  
18

19  
20  
21  
22 Muñoz N, Castellsagué X, Berrington de González, Gissmann L. 2006. Chapter 1: HPV  
23  
24 in the etiology of human cancer. *Vaccine* 24 (Suppl 3):1-10.  
25  
26

27  
28  
29 Paavonen J, Naud P, Salmerón J, Wheeler CM, Chow SN, Apter D, Kitchener H,  
30  
31 Castellsague X, Teixeira JC, Skinner SR, Hedrick J, Jaisamrarn U, Limson G, Garland  
32  
33 S, Szarewski A, Romanowski B, Aoki FY, Schwarz TF, Poppe WA, Bosch FX, Jenkins  
34  
35 D, Hardt K, Zahaf T, Descamps D, Struyf F, Lehtinen M, Dubin G; HPV PATRICIA  
36  
37 Study Group, Greenacre M. 2009. Efficacy of human papillomavirus (HPV) oncogenic  
38  
39 HPV types (PATRICIA): final analysis of a double-blind, randomised study in young  
40  
41 women. *Lancet* 374:301-314.  
42  
43  
44  
45  
46  
47

48 Schiffman MH, Castle P. 2003. Epidemiologic studies of a necessary causal risk factor:  
49  
50 human papillomavirus infection and cervical neoplasia. *J Natl Cancer Inst* 95 (6):E2.  
51  
52

53  
54  
55 Schlecht NF, Franco EL, Rohan TE, Kjaer SK, Schiffman MH, Moscicki AB, Duffy  
56  
57 SW; Marsh International Collaborative Group. 2001. Repeatability of sexual history in  
58  
59  
60

1  
2  
3 longitudinal studies on HPV infection and cervical neoplasia: determinants of reporting  
4 error at follow-up interviews. *J Epidemiol Biostat* 6:393-407.  
5  
6  
7  
8  
9

10 Schroder KE, Carey MP, Vanable PA. 2003. Methodological challenges in research on  
11 sexual risk behavior: II. Accuracy of self-reports. *Ann Behav Med* 26:104-123.  
12  
13  
14  
15  
16

17 Schwarz TF, Spaczynski M, Schneider A, Wysocki J, Galaj A, Perona P, Poncelet S,  
18 Zahaf T, Hardt K, Descamps D, Dubin G; HPV Study Group for Adult Women. 2009.  
19 Immunogenicity and tolerability of an HPV-16/18 AS04-adjuvanted prophylactic  
20 cervical cancer vaccine in women aged 15-55 years. *Vaccine* 27:581-587.  
21  
22  
23  
24  
25  
26  
27  
28

29 Sellors JW, Mahony JB, Kaczorowski J, Lytwyn A, Bangura H, Chong S, Lorincz A,  
30 Dalby DM, Janjusevic V, Keller JL. 2000. Prevalence and predictors of human  
31 papillomavirus infection in women in Ontario, Canada. Survey of HPV in Ontario  
32 Women (SHOW) Group. *CMAJ* 163:503-508.  
33  
34  
35  
36  
37  
38  
39  
40

41 Sellors JW, Karwalajtys TL, Kaczorowski J, Mahony JB, Lytwyn A, Chong S, Sparrow  
42 J, Lorincz A; Survey of HPV in Ontario Women Group. 2003. Incidence, clearance and  
43 predictors of human papillomavirus infection in women. *CMAJ* 168:421-425.  
44  
45  
46  
47  
48  
49  
50

51 Shields TS, Brinton LA, Burk RD, Wang SS, Weinstein SJ, Ziegler RG, Studentsov  
52 YY, McAdams M, Schiffman M. 2004. A case-control study of risk factors for invasive  
53 cervical cancer among U.S. women exposed to oncogenic types of human  
54 papillomavirus. *Cancer Epidemiol Biomarkers Prev* 13:1574-1582.  
55  
56  
57  
58  
59  
60

1  
2  
3 Smith JS, Melendy A, Rana RK, Pimenta JM. 2008. Age-specific prevalence of  
4 infection with human papillomavirus in females: a global review. *J Adolesc Health*.  
5  
6 43:S5-25, S25. e1-41.  
7  
8  
9

10  
11  
12 Snijders PJ, Steenbergen RD, Heideman DA, Meijer CJ. 2006. HPV-mediated cervical  
13 carcinogenesis: concepts and clinical implications. *J Pathol* 208:152-164.  
14  
15  
16  
17

18  
19  
20 Solomon D, Davey D, Kurman R, Moriarty A, O'Connor D, Prey M, Raab S, Sherman  
21 M, Wilbur D, Wright T Jr, Young N; Forum Group Members; Bethesda 2001  
22 Workshop. 2002. The 2001 Bethesda System: terminology for reporting results of  
23 cervical cytology. *JAMA* 287:2114-2119.  
24  
25  
26  
27  
28  
29

30  
31  
32 Tonon SA, Picconi MA, Zinovich JB, Liotta DJ, Bos PD, Galuppo JA, Alonio LV,  
33 Ferreras JA, Teyssié AR. 1999. Human Papillomavirus cervical infection and associated  
34 risk factors in a region of Argentina with a high incidence of cervical carcinoma.  
35 *Infectious Diseases in Obstetrics and Gynecology* 7:237-243.  
36  
37  
38  
39  
40  
41

42  
43 Vaccarella S, Franceschi S, Herrero R, Muñoz N, Snijders PJ, Clifford GM, Smith JS,  
44 Lazcano-Ponce E, Sukvirach S, Shin HR, de Sanjosé S, Molano M, Matos E, Ferreccio  
45 C, Anh PT, Thomas JO, Meijer CJ; IARC HPV Prevalence Surveys Study Group. 2006.  
46 Sexual behavior, condom use, and human papillomavirus: pooled analysis of the IARC  
47 human papillomavirus prevalence surveys. *Cancer Epidemiol Biomarkers Prev* 15:326-  
48  
49 333.  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3 Venuti A, Badaracco G, Sedati A, Carbini R, Marcante ML. 1994. Determinants of  
4 human papillomavirus types 16 and 18 infections in the lower femal genital tract in an  
5 Italian population. *Eur J Gynaec Oncol* 15:205-210.  
6  
7  
8  
9

10  
11  
12 Villa LL, Costa RL, Petta CA, Andrade RP, Ault KA, Giuliano AR, Wheeler CM,  
13 Koutsky LA, Malm C, Lehtinen M, Skjeldestad FE, Olsson SE, Steinwall M, Brown  
14 DR, Kurman RJ, Ronnett BM, Stoler MH, Ferenczy A, Harper DM, Tamms GM, Yu  
15 J, Lupinacci L, Railkar R, Taddeo FJ, Jansen KU, Esser MT, Sings HL, Saah AJ, Barr E.  
16  
17 2005. Prophylactic quadrivalent human papillomavirus (types 6, 11, 16, and 18) L1  
18 virus-like particle vaccine in young women: a randomised double-blind placebo-  
19 controlled multicentre phase II efficacy trial. *Lancet Oncol.* 6:271-278.  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30

31 Villa LL, Costa RL, Petta CA, Andrade RP, Paavonen J, Iversen OE, Olsson SE, Høye  
32 J, Steinwall M, Riis-Johannessen G, Andersson-Ellstrom A, Elfgren K, Krogh G,  
33 Lehtinen M, Malm C, Tamms GM, Giacoletti K, Lupinacci L, Railkar R, Taddeo FJ,  
34 Bryan J, Esser MT, Sings HL, Saah AJ, Barr E. 2006. High sustained efficacy of a  
35 prophylactic quadrivalent human papillomavirus types 6/11/16/18 L1 virus-like particle  
36 vaccine through 5 years of follow-up. *Br J Cancer* 95:1459-1466.  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47

48 Walboomers JM, Jacobs MV, Manos MM, Bosch FX, Kummer JA, Shah KV, Snijders  
49 PJ, Peto J, Meijer CJ, Muñoz N. 1999. Human papillomavirus is a necessary cause of  
50 invasive cervical cancer worldwide. *J Pathol* 189:12-9.  
51  
52  
53  
54  
55  
56

57 Winer RL, Lee SK, Hughes JP, Adam DE, Kiviat NB, Koutsky LA. 2003. Genital  
58 human papillomavirus infection: incidence and risk factors in a cohort of female  
59  
60

1  
2  
3 university students. Am J Epidemiol 157: 218-26. Erratum in: Am J Epidemiol 2003  
4  
5 157: 858.  
6  
7  
8  
9

10 World Health Organization, 2006. Initiative for vaccine research (IVR): human  
11 papillomavirus. World Health Organization Web site. Available at:  
12 [http://www.who.int/vaccine\\_research/diseases/viral\\_cancers/en/index3.html](http://www.who.int/vaccine_research/diseases/viral_cancers/en/index3.html). (last  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
accessed: October 22, 2009).

For Peer Review

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

Table I. Characteristics of the 94 patients according to HPV DNA tests results.

Variable	HR-Positive N* (%)	Negative N* (%)	p-value
<b>N of patients</b>	54 (57)	40 (43)	
<b>Age</b>			
mean (sd)	35 (10.2)	39 (11.2)	0.112
<b>Education</b>			0.755
Primary-Secondary school	15 (60)	10 (40)	
High school	27 (54)	23 (46)	
University	12 (63)	7 (37)	
<b>Marital status</b>			<0.0001
Married-Living together-Widow	13 (33)	26 (67)	
Never married-Separated/Divorced	40 (74)	14 (26)	
<b>Age at first sexual intercourse</b>			0.003
mean (sd)	17.9 (2.4)	20.3 (4.9)	
<b>Number of partners</b>			0.004
mean (sd)	5.3 (3.8)	3.0 (3.3)	
<b>Number of pregnancies</b>			0.209
mean (sd)	1 (1.5)	1.3 (1.3)	
<b>Number of childbirth</b>			0.080
media (sd)	0.6 (0.8)	1 (1.2)	
<b>Estroprogestinic contraceptive use</b>			0.128
Yes	33 (63)	19 (37)	
No	18 (47)	20 (53)	
<b>Condom contraceptive use</b>			0.172
Yes	14 (70)	6 (30)	
No	37 (53)	33(47)	
<b>N°sexual intercourse</b>			0.105
Mean (sd) per months	7.9 (6.5)	5.7 (5.7)	
<b>Smoking</b>			0.043
Yes	33 (67)	16 (33)	
No	21 (47)	24 (53)	
<b>Age at first cigarette</b>			0.072
media (sd)	16.8 (2.8)	18.5 (3.0)	
<b>Years of smoking</b>			0.008
media (sd)	9.7 (11.1)	4.3 (7.2)	
<b>Number of smoked cigarettes</b>			0.014
media (sd)	7.3 (7.7)	3.6 (6.1)	
<b>Alcohol consumption</b>			0.026
Yes (regular and occasional drinkers)	23 (26)	8 (74)	
No	31 (50)	31 (50)	
<b>Pap Test knowledge</b>			0.178
Yes	54 (59)	38 (41)	
No	0 (0)	2 (100)	
<b>Pap test frequency</b>			0.930
Every 1-2 years	44 (58)	32 (42)	
Occasionally	7 (58)	5 (42)	
Never	3 (50)	3 (50)	

\* the sum may not add to the total because of missing values.

Table II. Predictors of HR-HPV infection in women: univariate and multivariate logistic regression analysis.

Variables	Univariate OR	95% CI	p-value	Multivariate OR	95% CI	p-value
Age*	0,97	0,93-1,00	0,116			
<b>Education</b>						
Primary-Secondary	0,87	0,26-2,99	0,831			
High School	0,69	0,23-2,03	0,494			
University	1,00	-	-			
<b>Marital Status</b>						
Married/Living together/Widow	1,00	-	<0,0001	1,00	-	0,029
Never married-Separated/Divorced	5,71	2,32-14,08		3,38	1,14-10,12	
Age at first sexual intercourse*	0,82	0,71-0,95	0,007	0,84	0,71-1,00	0,055
<b>Number of partners</b>			<0,0001			
≤ 3	1,00	-		1,00	-	0,092
> 3	5,32	2,09-13,95		2,57	0,86-7,71	
<b>Smoking</b>						
No	1,00	-	0,044	1,00	-	0,131
Yes	2,36	1,02-5,44		2,24	0,79-6,39	
<b>Alcohol consumption</b>			0,029			
No	1,00	-		1,00	-	0,117
Yes (regular and occasional drinkers)	2,88	1,12-7,41		2,56	0,79-8,33	
<b>Estroprogestinic contraceptive use</b>			0,13			
Yes	1,93	0,82-4,52				
No	1,00	-				
<b>Condom use</b>						
Yes	0,48	0,17-1,39	0,178			
No	1,00	-				

\* considered as continuous variables



1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

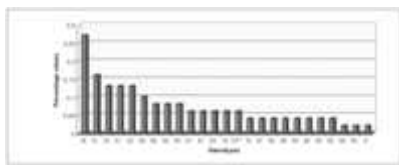


Fig. 1. Distribution of HPV genotypes detected by Linear Array Genotyping Test in the Italian women.  
\* CP6108

8x3mm (600 x 600 DPI)

For Peer Review