



” , , - ”

-

-

p16INK4a Ki-67
HPV-

” ”

:

03.01.35

:

. - , .
. - , .
:
. - . .
. - . .

-
-
- 1.
- 2.
- 3.
- 3.1.
- 3.2.
- 3.3.
- 3.4.
- 3.5.
- 4.
- 5.
- 6.

:

IARC –

HBV – B

HCV – C

EBV – -

HR HPV –

ICTV –

VLP –

PCR –

ISH –

–

UICC –

CIN –

–

SEER –

ELISA –

–

–

–

1.

:

” - . ” . , , HPV
p16INK4a , Ki-67. -

HPV-

:

1. HPV-

2. .

HPV-

3. .

,

4. .

HPV-

.

РАЗПРОСТРАНЕНИЕ НА HPV

HIV

HBV, HCV

HSV-1, HSV-2

HPV

HPV инфекциите – най-разпространените вирусни полово-предавани инфекции

50% от сексуално-активното население е HPV инфектирано (*Bosch et al., 1995*)

.1

HBV, HCV, EBV, Polyoma
HPV.

157 879

HPV

78

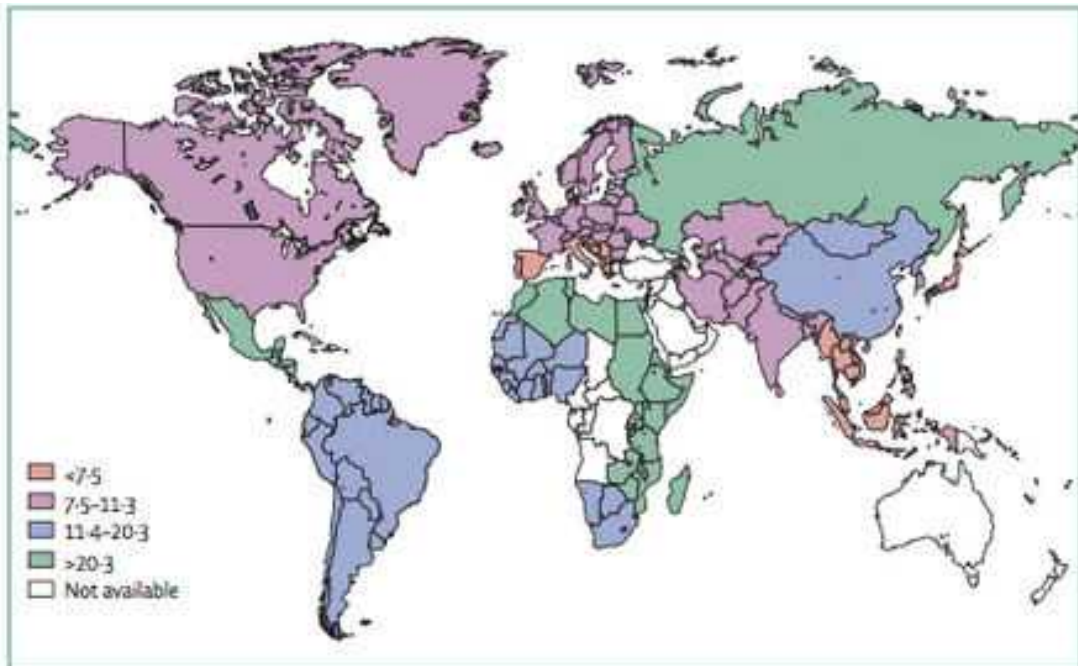


Figure 1: Estimated HPV DNA prevalence in the world regions
 Estimates are based on a meta-analysis of 78 studies including 157 879 women with normal cytology. Colours represent the adjusted prevalence in the region and denote the quartile distribution of all the estimates.

.2

HPV

/ / p16INK4a Ki-67

2012 .–2013 .

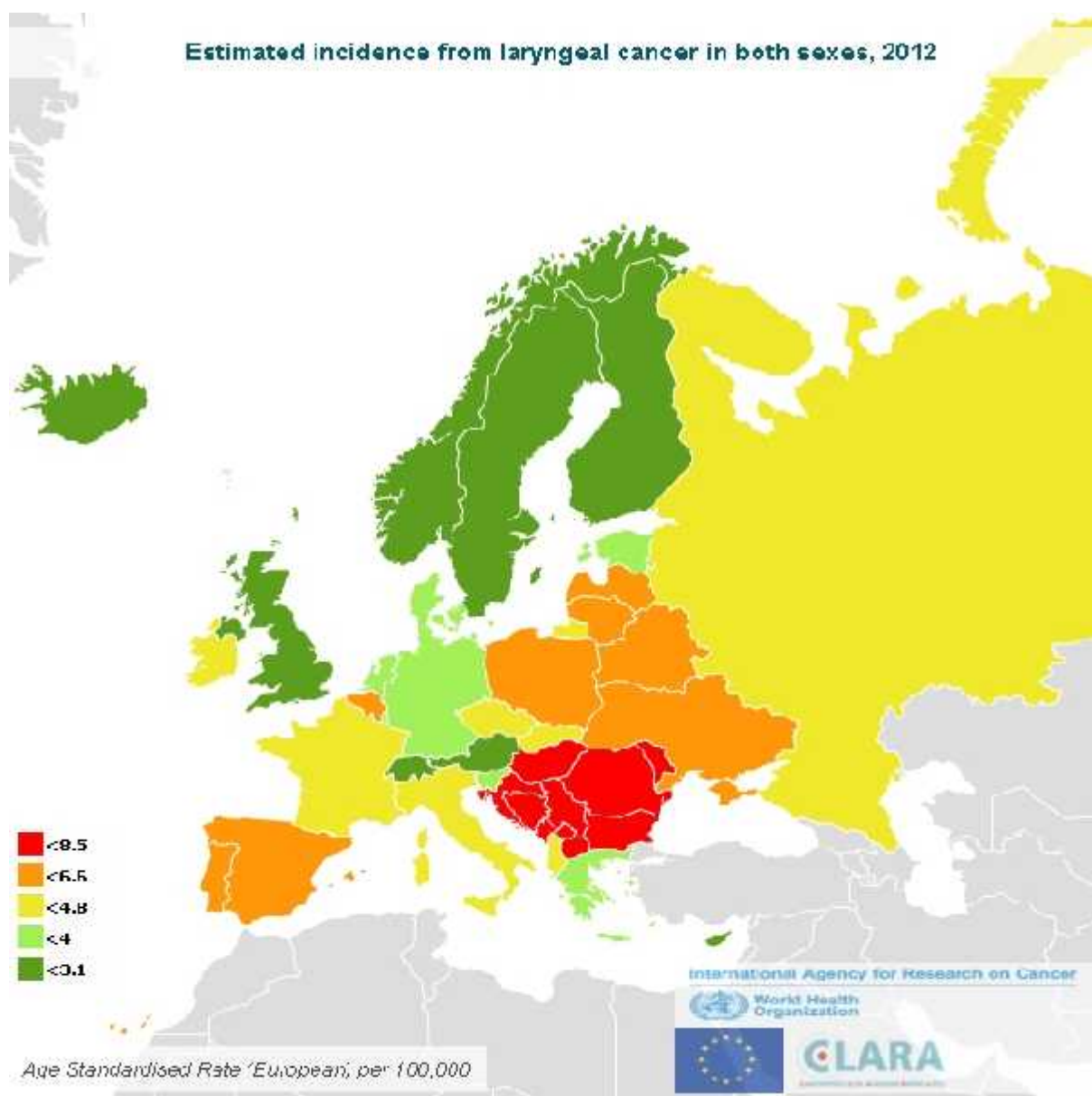
” - HPV ”

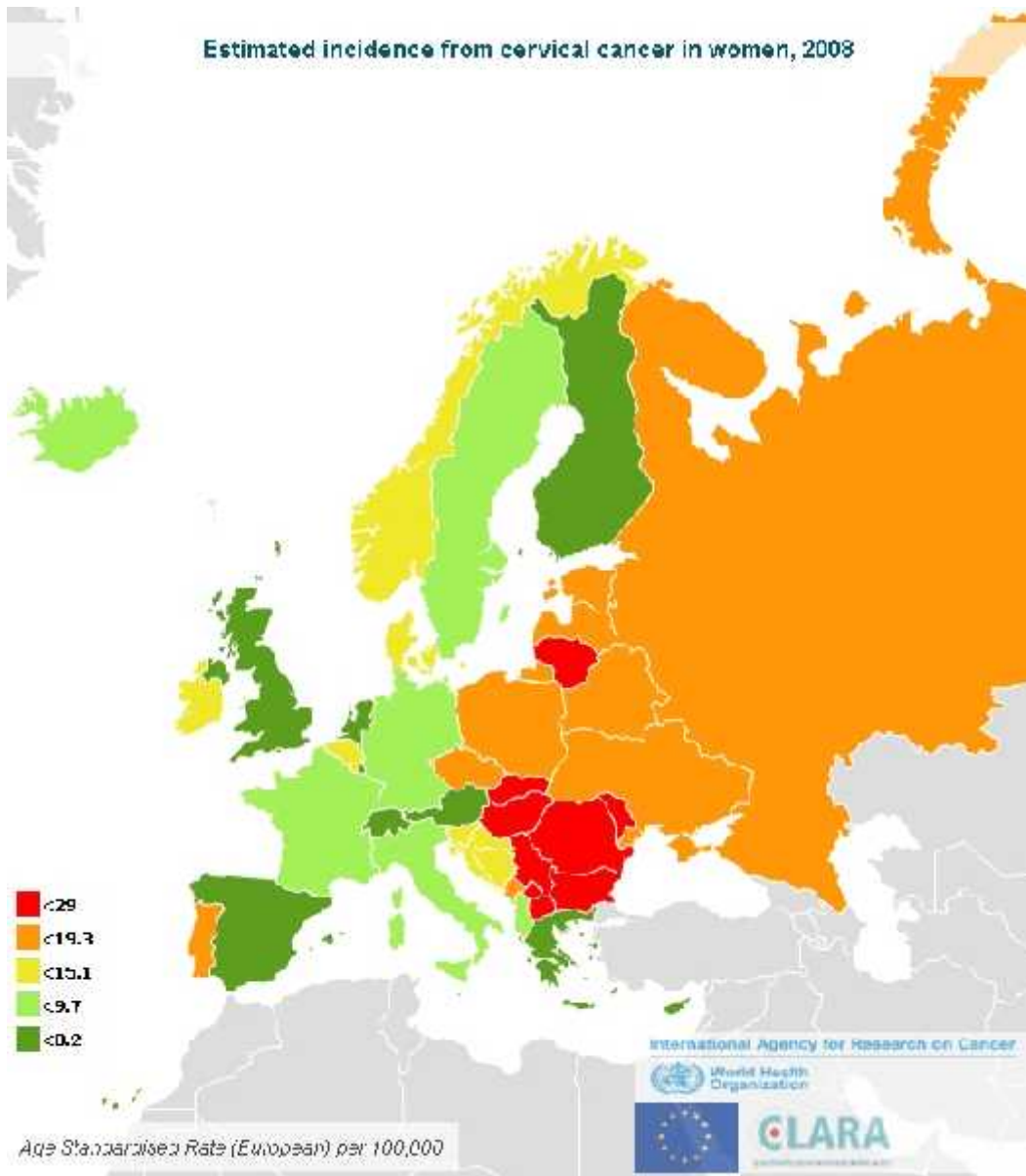
HPV-

.42

IARC /

2012 .





.43

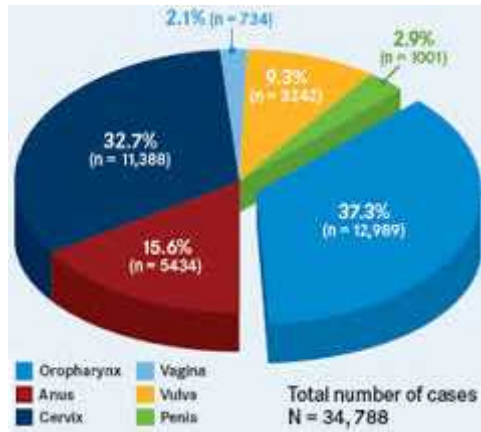
HR-HPV,

2014

HPV-

2020 .

HPV-



.3

(131)

HPV-

1977-2012 . HPV 12 HPV 37 – 44 %.

HPV HPV

5

50 % (26,27,201)

- 21,6

7 HPV

(201, Trosman 2014)

« » -

HPV-

HPV

,

,

98 %

2%

, HPV-

HPV-

HPV

43

15

2.

, 15

73

43

. 15

” -

“

2012 2013 .

:

-
-
-

1.2.

1.3.

1.4.

– p16INK4a Histology kit, En Vision Flex(High pH).
Ki-67 Flex Monoclonal a Hu Ki-67 Antigen.
- Clone MIB-1.

2013 .

30

(pH-6) 5min. 1/50
p16INK4a (CIN tec Histology kit). En Vision Flex

– 2012-

4

3%

2.

2.1.

- / /.
- .
- .
- .

2.2.

-
-Isoprinosine

2.3.

3.

, 5%.
(Exact test).
Statgraph.
:
() –
(one-way ANOVA, t-test for mean differences)
(,
) ,
,

3.

3.1.

HPV

15

, HPV

HPV

-

HPV

HPV

-

HPV

-

(29,31).

3-10%.(9,15)

HPV

,

(35-45 .),

-

HPV

.(24,27).

HPV

HPV

-

HPV.

HPV

HPV

40%.(32,49,61,67,91).

HPV

10

HPV PCR
 HPV.
 HPV

HPV.

11). - , HPV 11, (HPV

2010 .

13 - 18 PCR

” HPV ”
 p16INK4a.

(53,99,112,122,123,129,133)

HPV -

HPV. E₇ p16^{INKa}, Rb S

S Rb 7 -

p16INK4a.
 p16INK4a 100%

p16INK4a,

.(128,133,154,140)

HPV

p16INK4a

– Isoprinosine,

16 18 HPV

– 1

– 6, 11,

5

/.

45, 50, 51, 53, 55, 56, 58, 59, 64, 68,

4,

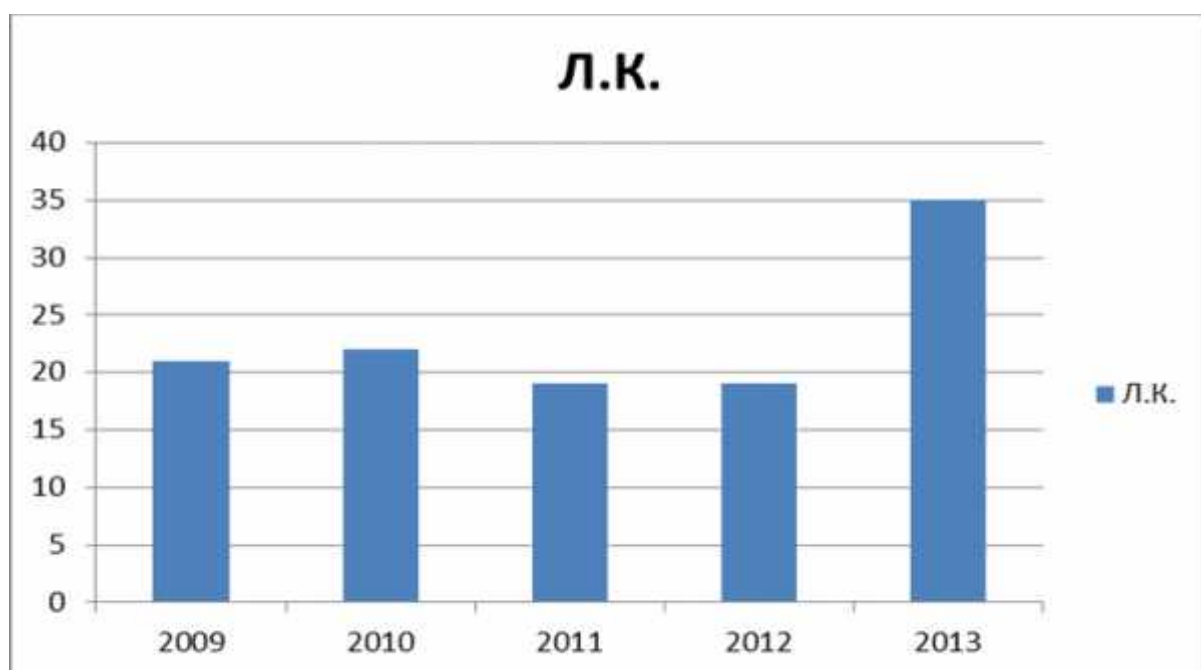
20 – 16, 18,26,30, 31, 33, 35, 39,

HPV

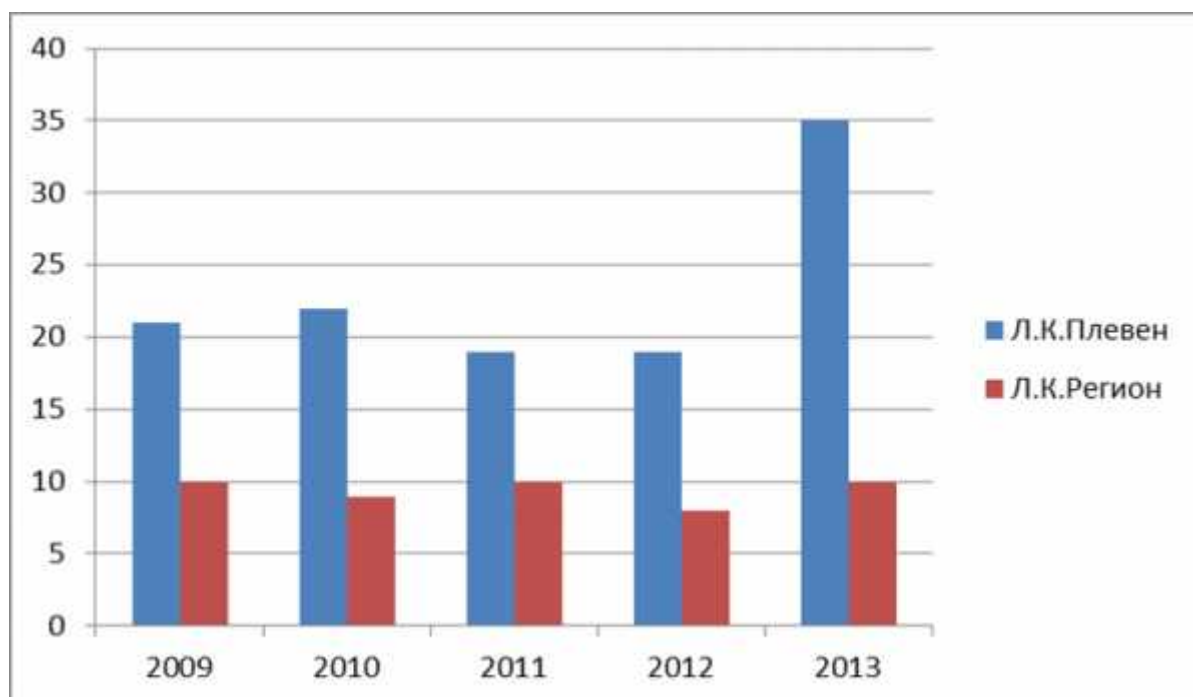
”

“

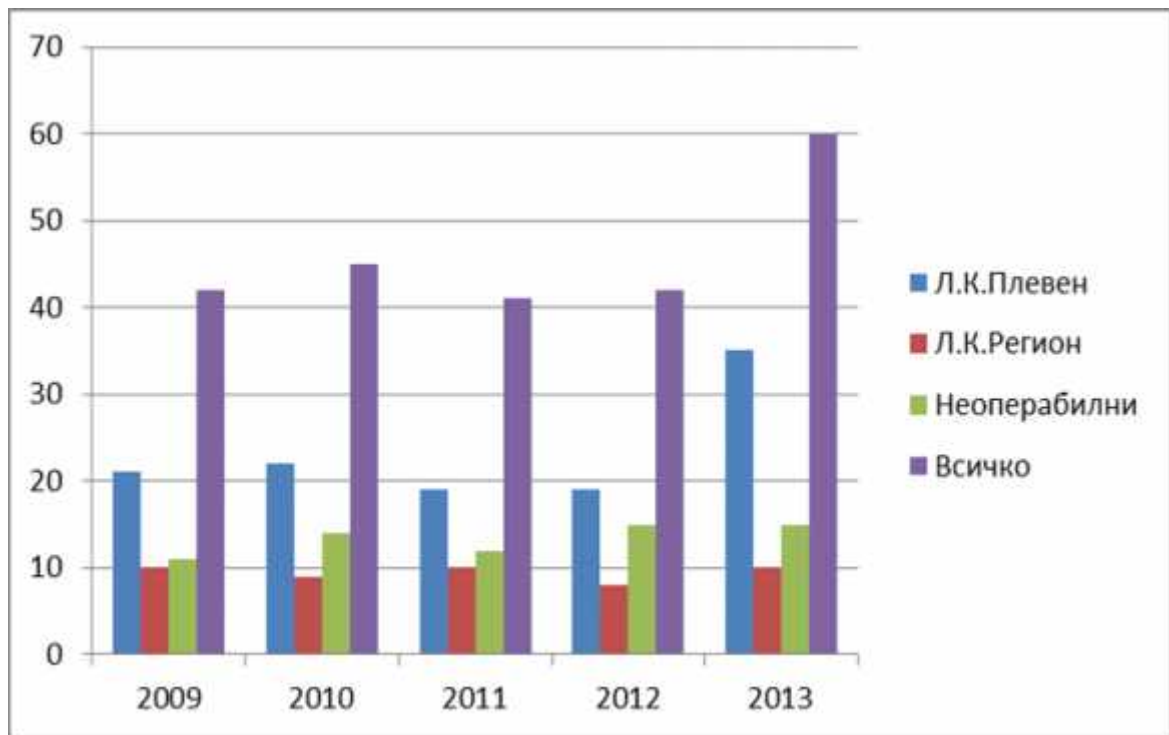
.1



.2



.3



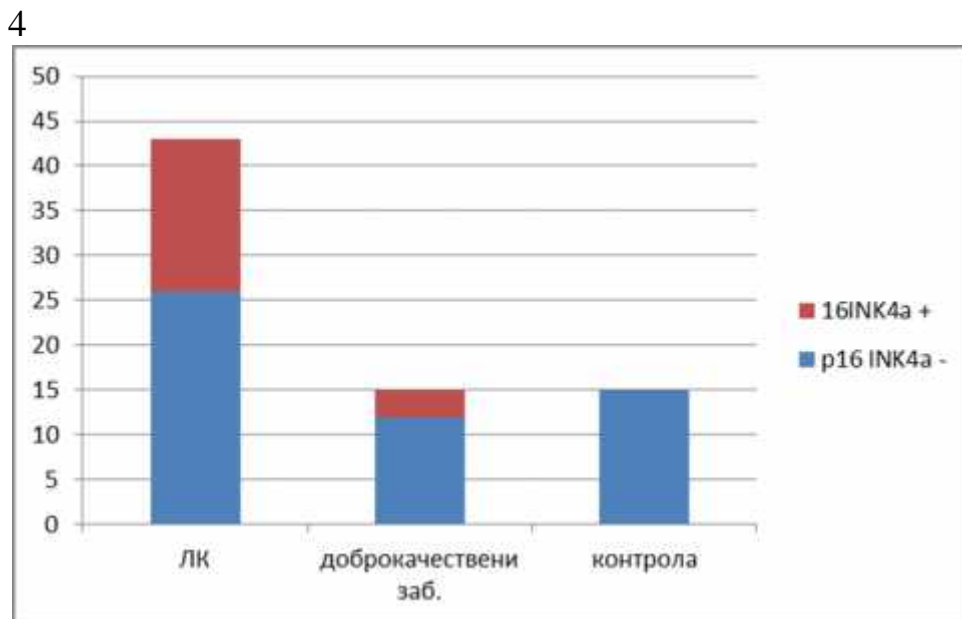
42 2009 .
2009 – 2012 .
60 2013 .
2013 .
5 .,
230
2013 .
40%
5 . 230
HPV
, 92

3.2.

HPV-

“ - . ” . 2012- 2013 .

INK 4a Ki-67, 43 p16 HPV

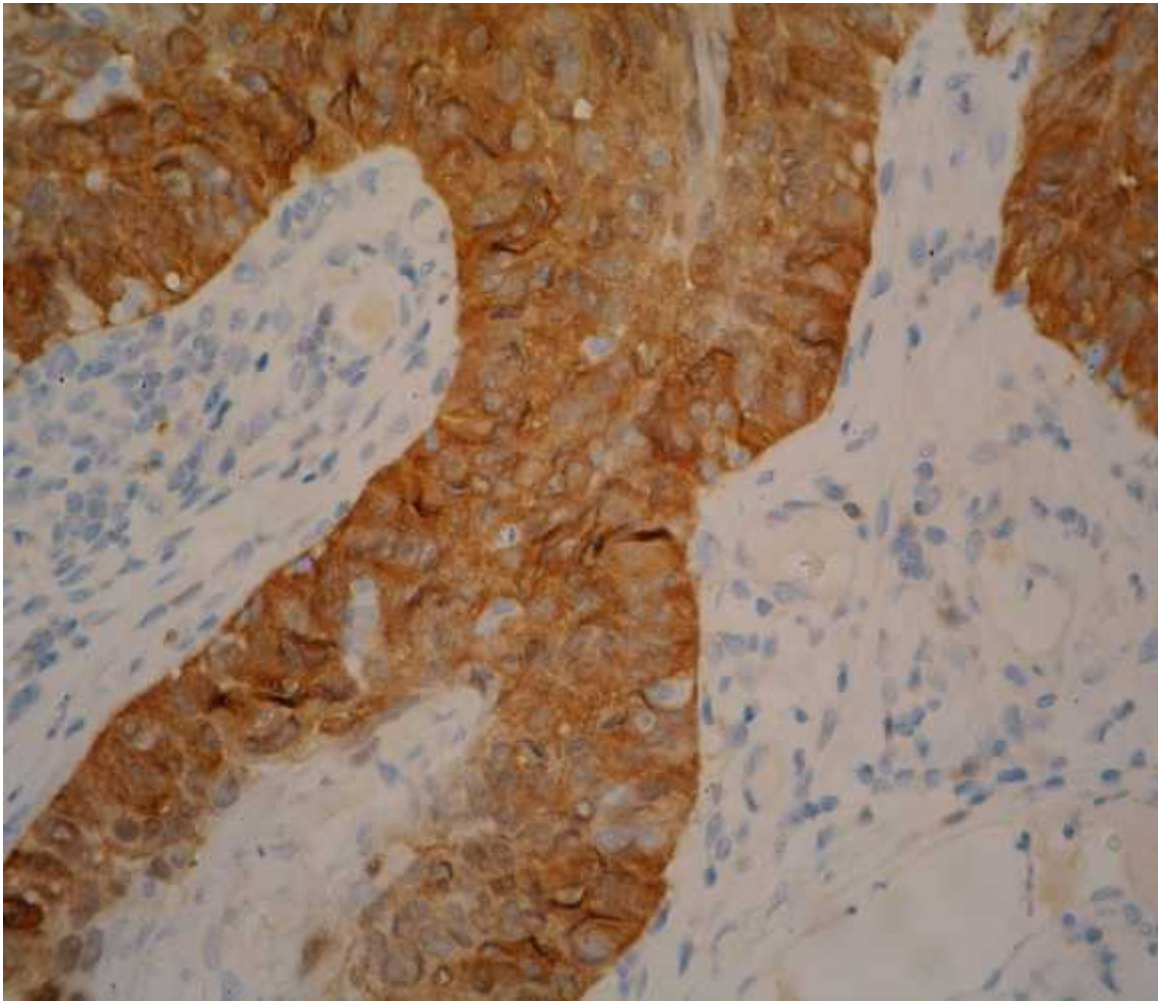


73 , 58,9 % (n=43) ,
20,55 % (n=15) -

20,55 % (n=15)
p16 INK 4^a

HPV

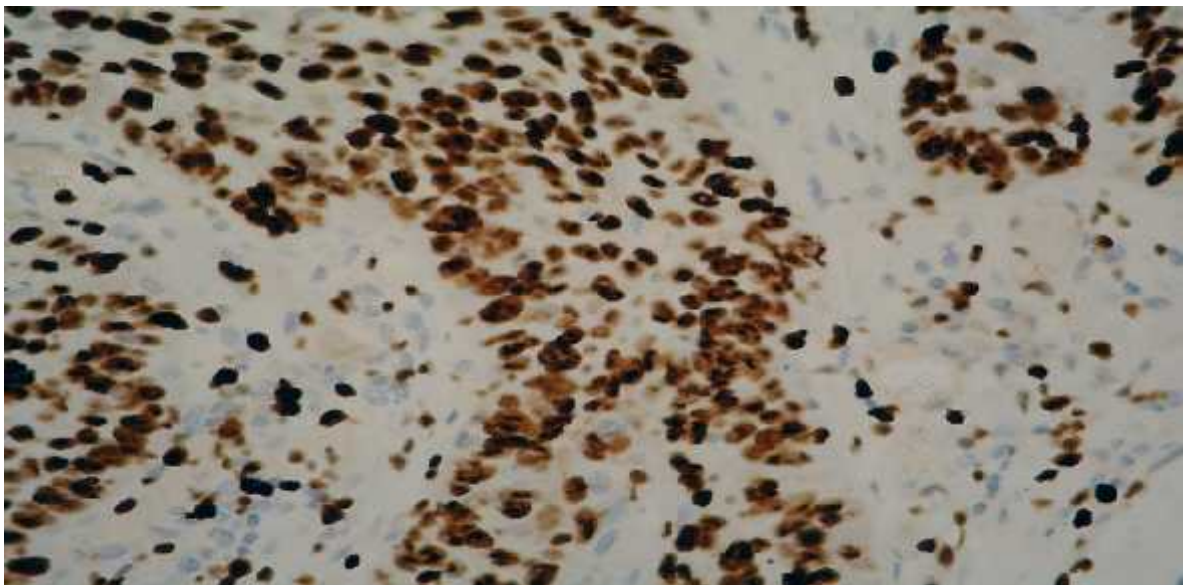
100%



p16INK4

.53

p16CIN tec.

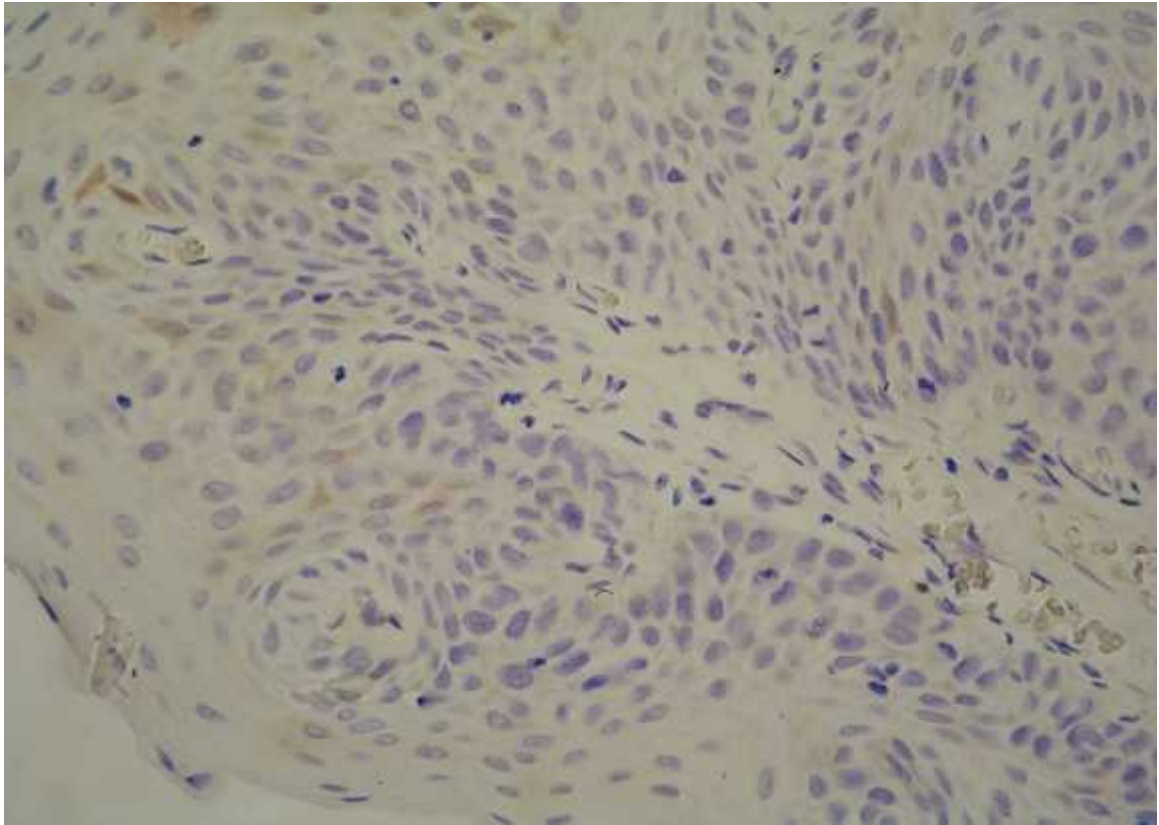


.54

39,5% (n=17)
p16 INK 4^a,

. 60,5 % (n=26)

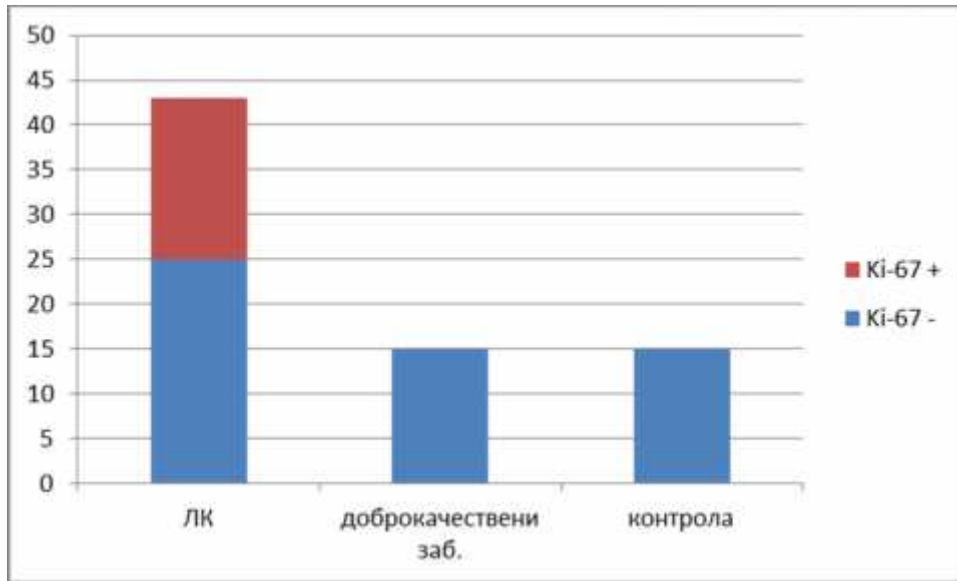
p16 INK 4^a.



.55

20%(n=3) p16 INK 4^a 80 % (n=12) n=15
n=15 p16 INK 4^a
R= - 0,34
(=0,01).
58,1% (n=25) : Ki-67 (n=43) -
Ki-67 41,9% (n=18)

5.



(n=15)

50%

43

-4,6% (n=2)

95,3% (n=41)

6,7% (n=1)

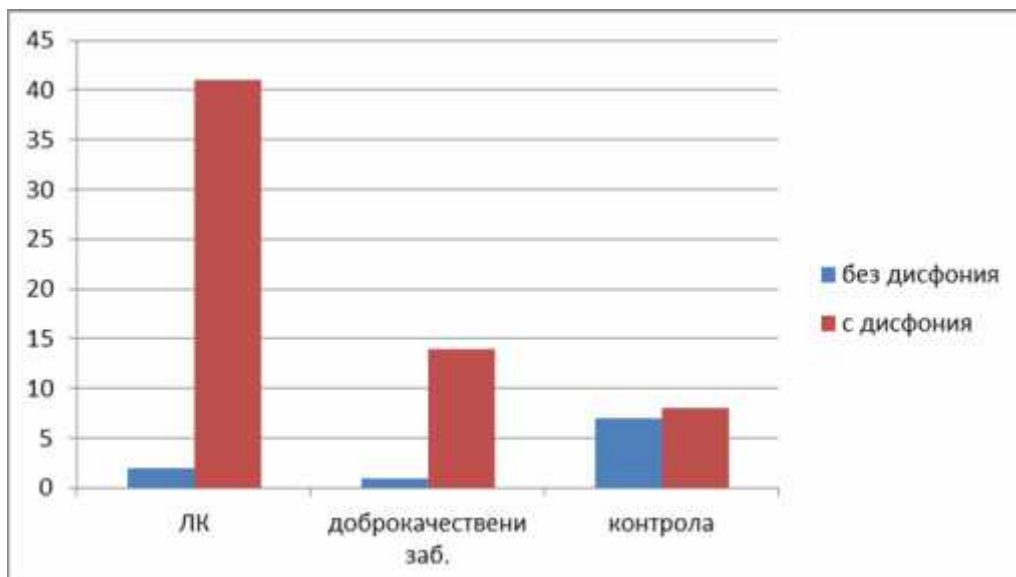
93,3 % (n=14)

46,7 % (n=7)

53,3% (n=8)

R= - 0,44 (=0,0002).

6



3

/n=43/

18,6 % (n=8)
32,6% (n=14)
(n=20)

46,5 %

2,3% (n=1)

R= - 0,65 (=0,0001).

HPV-

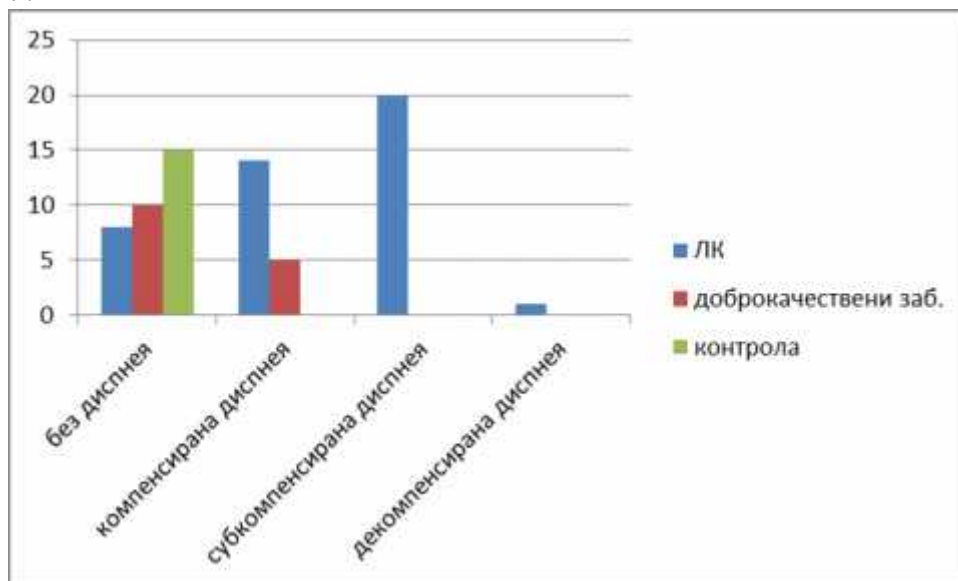
9,3% (n=4)

28,6% (n=8)

9,3% (n=4)

2,3% (n=1)

7.



:

(n=43) 11,6% (n=5)

62,8% (n=27)

18,6% (n=8)

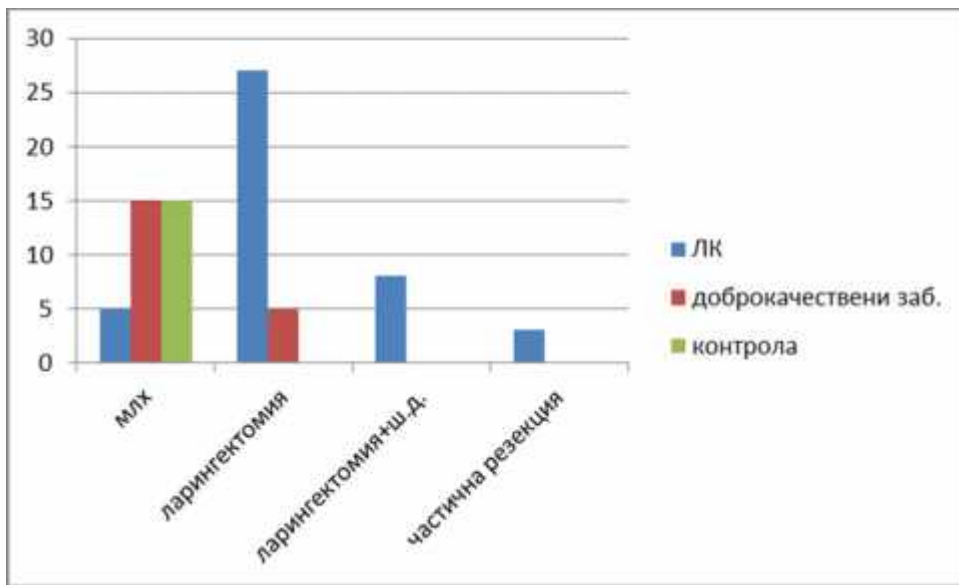
7,0 %

(n=3).

R= - 0,67

(=0,0001).

8

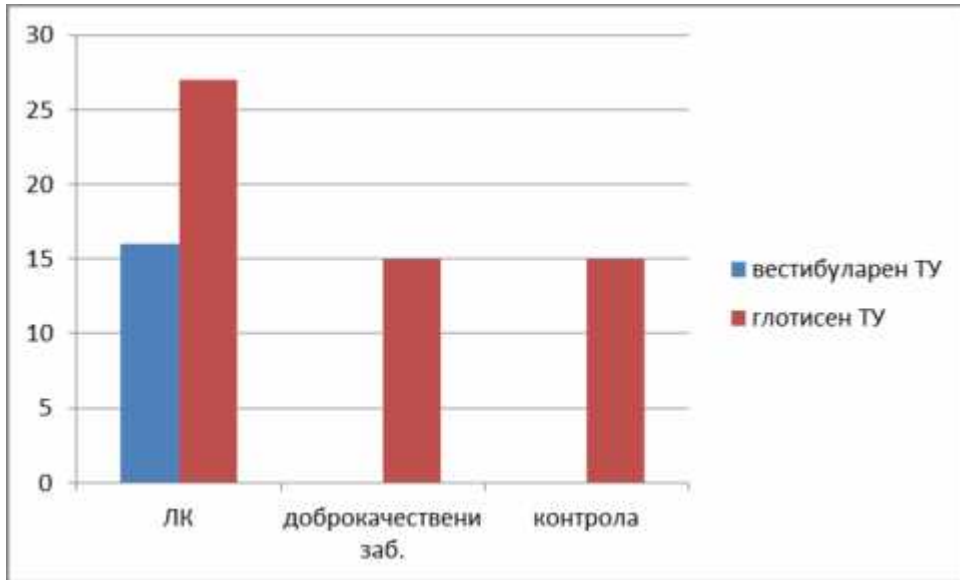


(p<0,05)

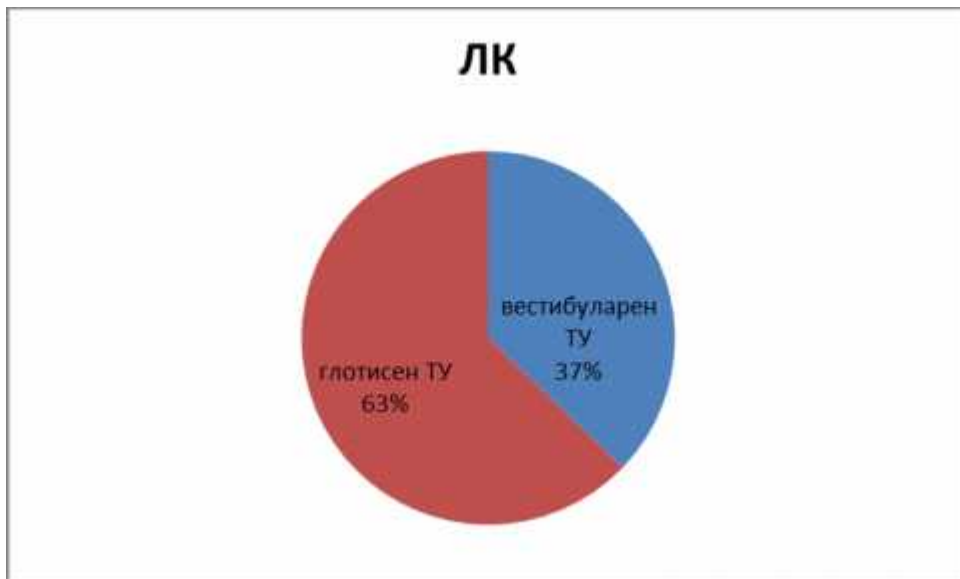
37,2% (n=16)

62,8% (n=27)

9

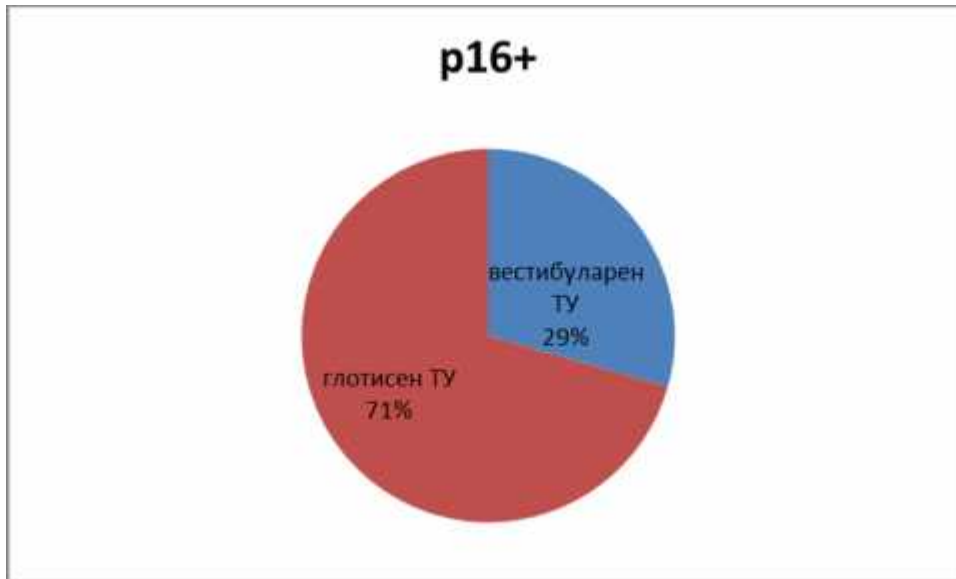


10



p16 INK 4^a HPV R=0,41 (=0,0008).

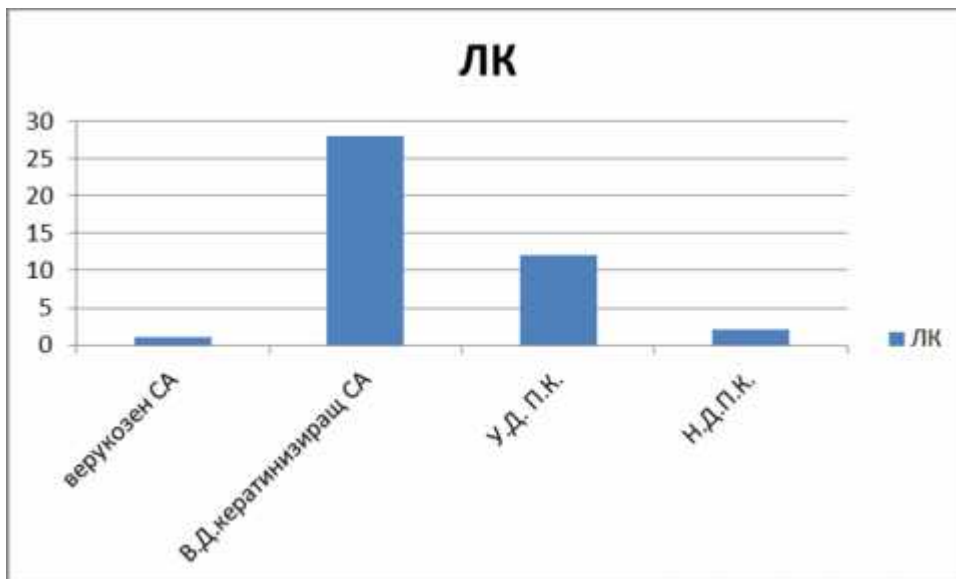
11



HPV-
(n=5), HPV-

29,4%
70,6 % (n=12).

12



65,1% (n=28)

, 27,9% (n=12)
, 4,7% (n=2)

(n=1)

. R=0,96 (=0,0001).

2,3%

HPV

16INK4a

: 82,3% (n=14)

HPV-

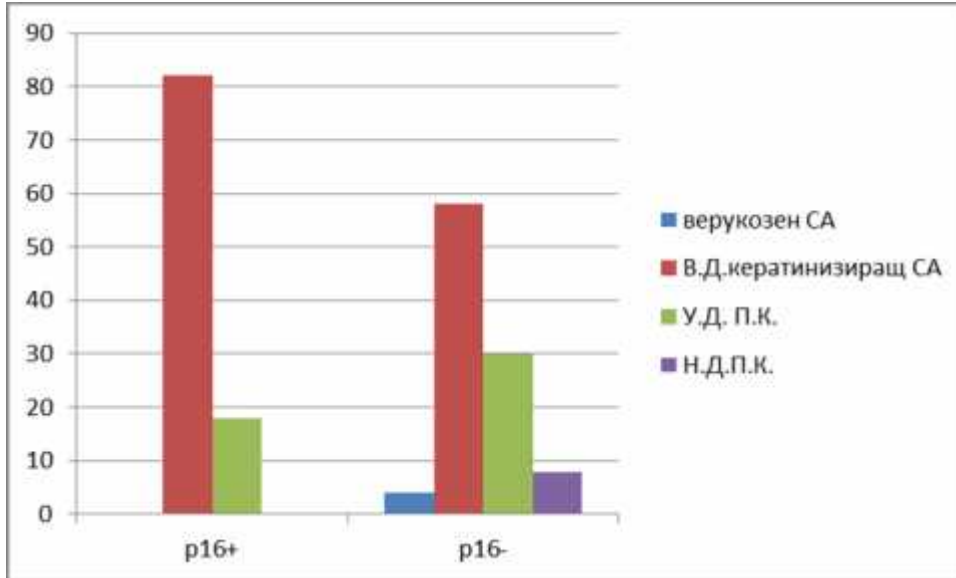
-

HPV

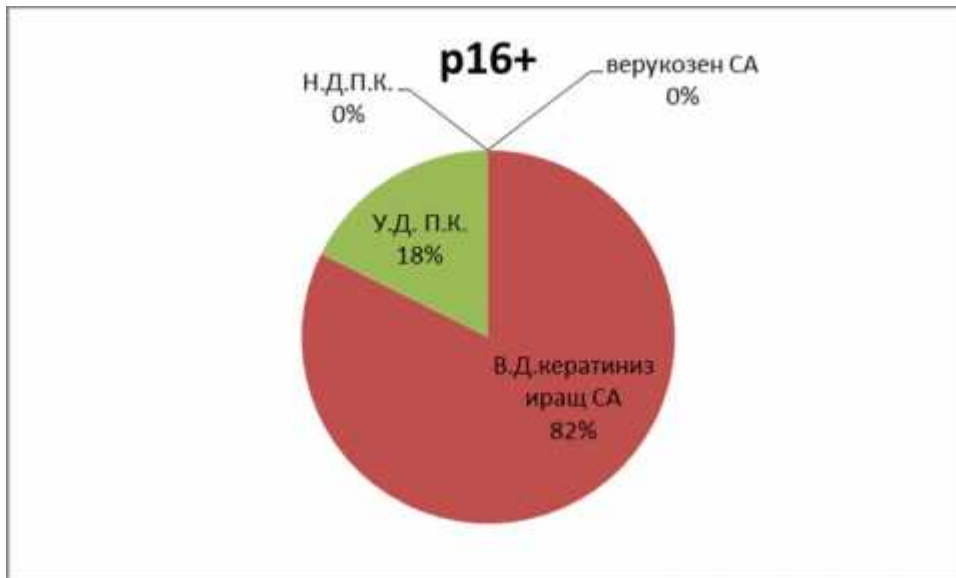
. 17,7% (n=3)

p16INK4a

13



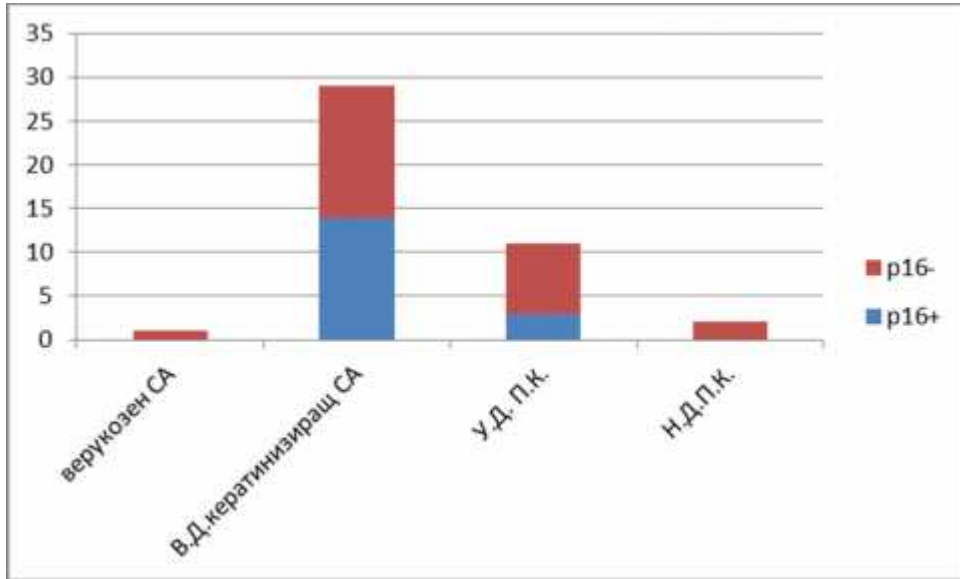
14



-

HPV-

p16INK4a



- R=0,96 (n=0,0001)

HPV

. 7% (n=3) HPV

Carcinoma in situ, 7% (n=3)

HPV-

I, 18,5 % (n=8) HPV

II 7% (n=3)

HPV-

III

HPV

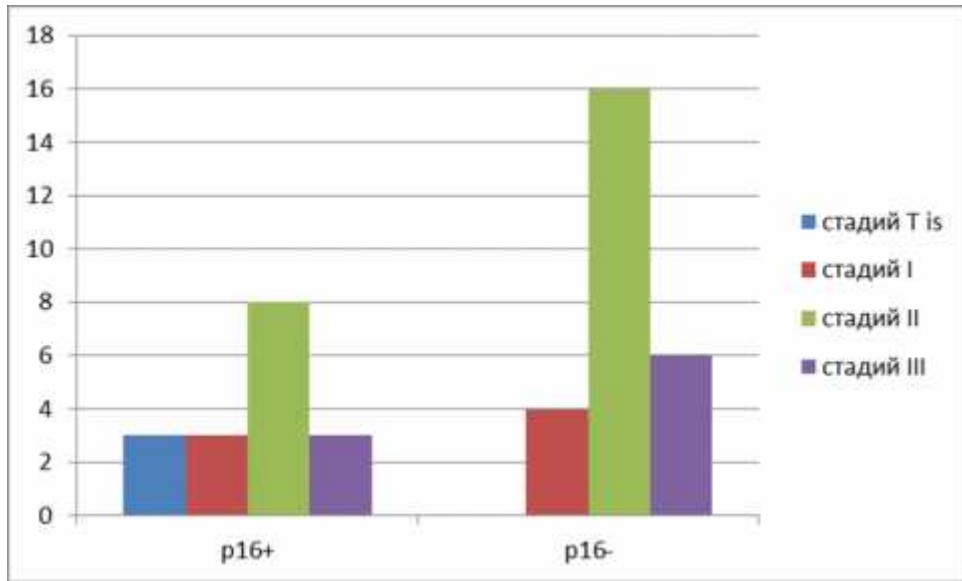
is, 9,3% (n=4)

I , 37,2% (n=16)

- 0%

II 14% (n=6) III .

.16



7,0 % (n=3)

Carcinoma in situ.

HPV

14% (n=6)

HPV

37,2% (n=16)

HPV

18,6% (n=8) HPV

16,2%

(n=7)

14%

3.3.

HPV-

HPV-

(n=43)

9,3% (n=4) HPV

0%

HPV

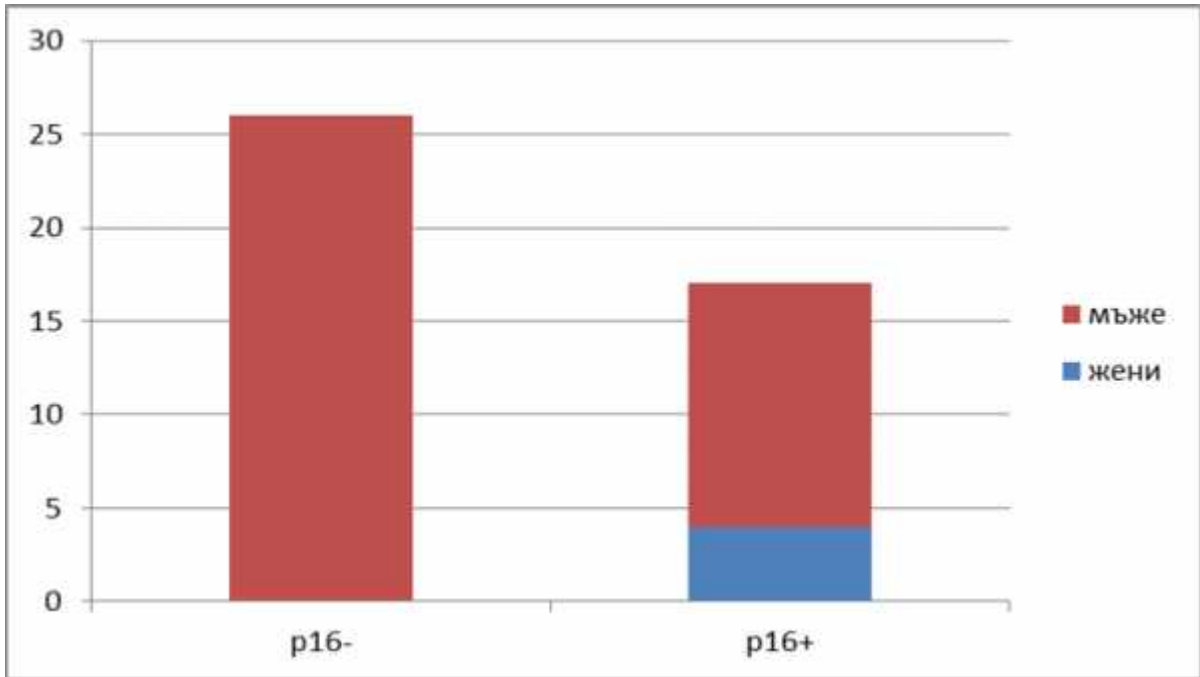
30,2% (n=13)

HPV

60,5% (n=26)

HPV

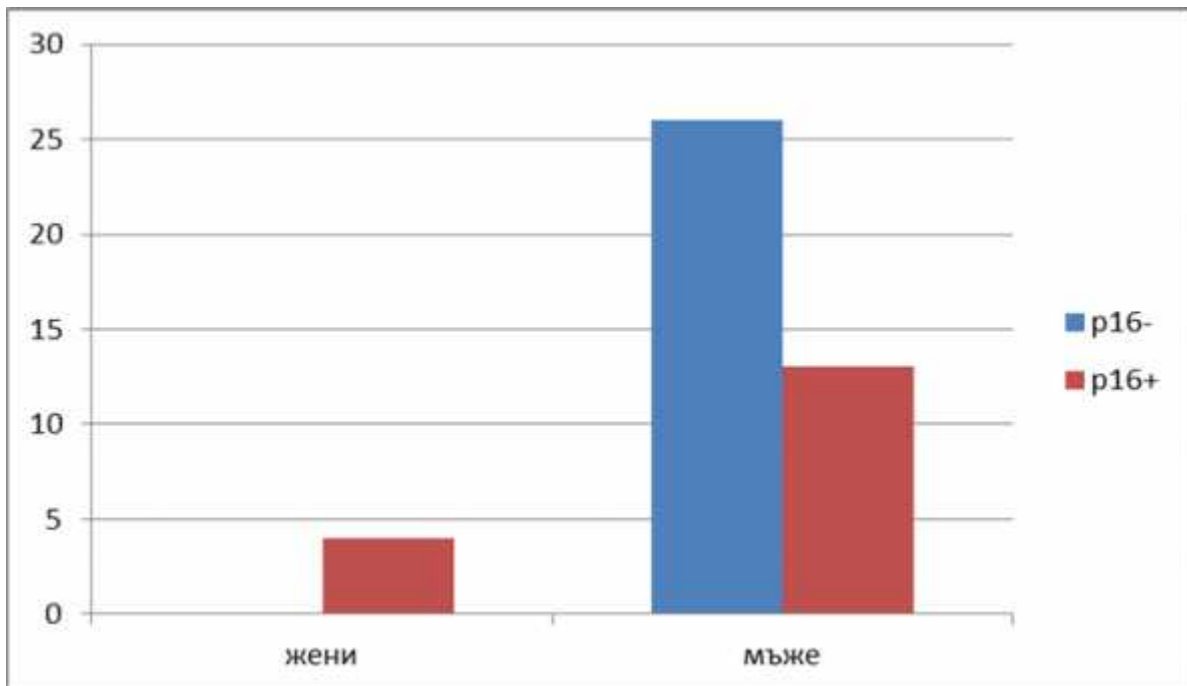
17



– 90,7% (n=39)

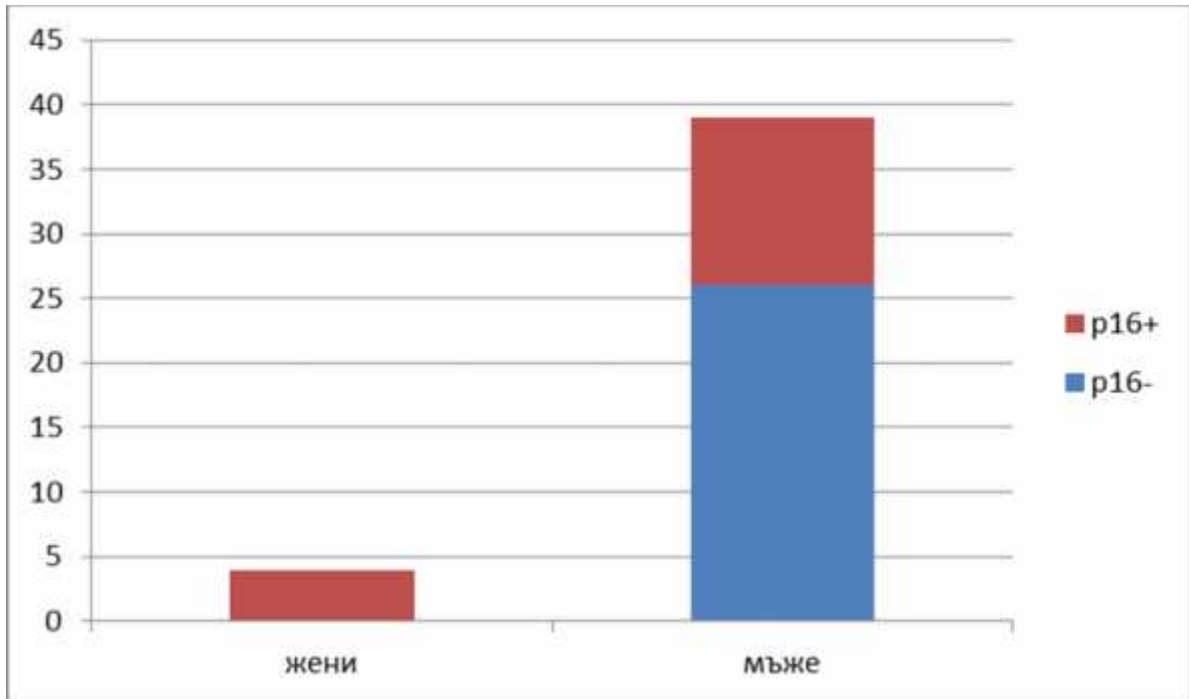
9,3% (n=4).

.18



HPV-
 – 23,5% (n=4) 76,4% (n=13) . r=0,39 (p=0,009)

19



HPV (n=43)

HPV 64,9 .

HPV 27 .

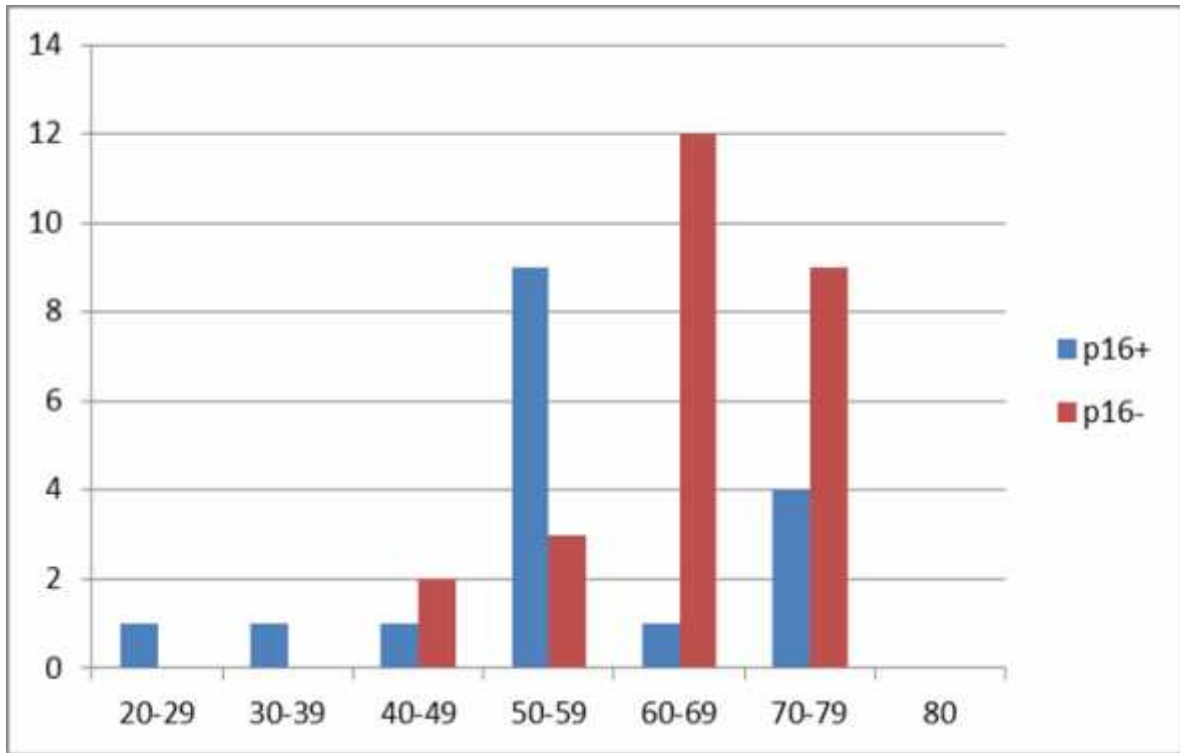
HPV 79 .

HPV 56,9 .

HPV 43 .

HPV 77 .

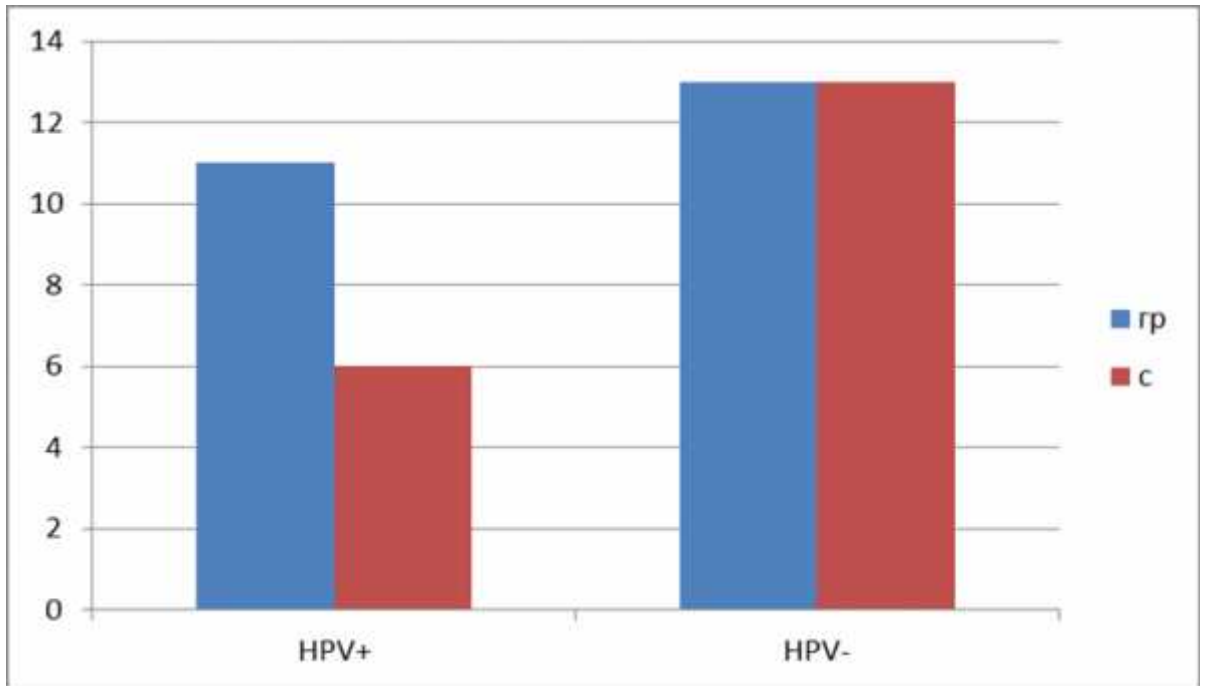
HPV



HPV : HPV
 50-59 .. HPV
 60-79 . HPV-
 8 . -
 HPV - 1 HPV
 27 . 37 .
 .. -

HPV
 30,2% (n=13) HPV
 30,2% (n=13) HPV
 25,6% (n=11)
 , 13,9% (n=6)

.21



, HPV , (p>0,05). ,
, HPV
- HPV ,
44,2% (n=19) 55,8% (n=24),
44,2% (n=19) . 55,8% (n=24)
, HPV - HPV-
35,3% (n=6) . 64,7% (n=11) HPV

HPV

58,1%(n=25),

– 52,9%(n=9)

47,1% (n=8).

41,9% (n=18).

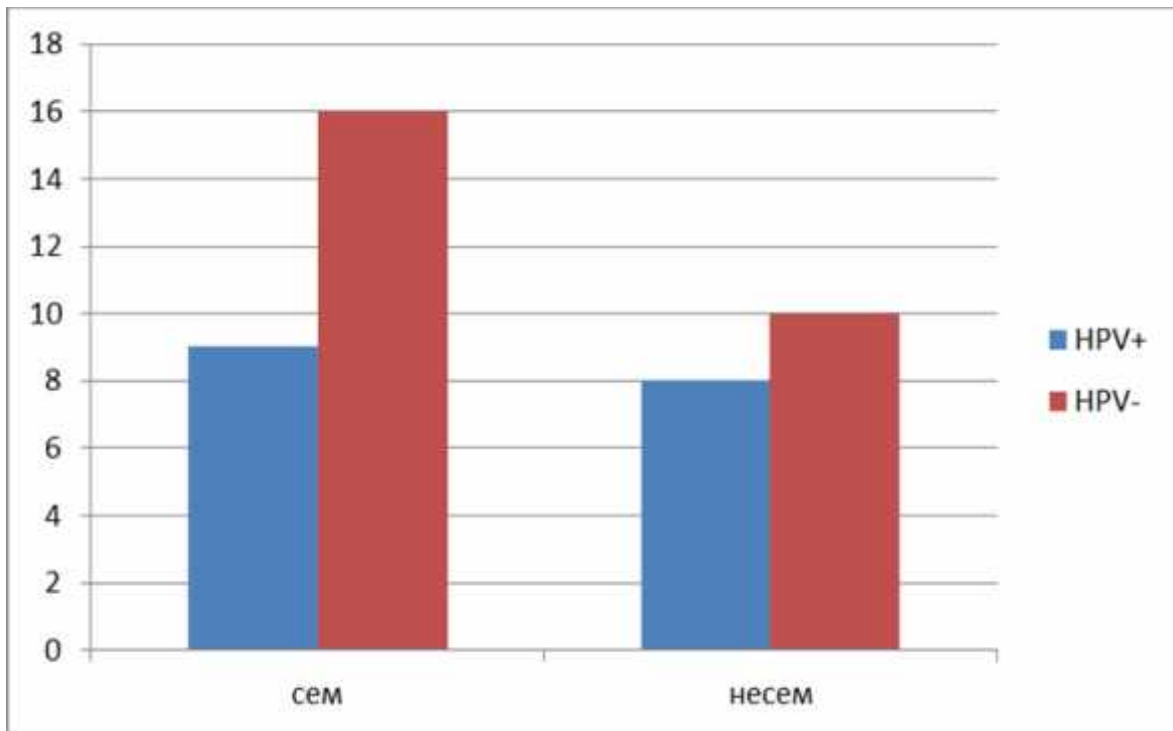
HPV

HPV

HPV-

(p>0,05)

22



HPV –

43

2,3%(n=1)

65,1%(n=28)

27,9%(n=12)

4,6%(n=2)

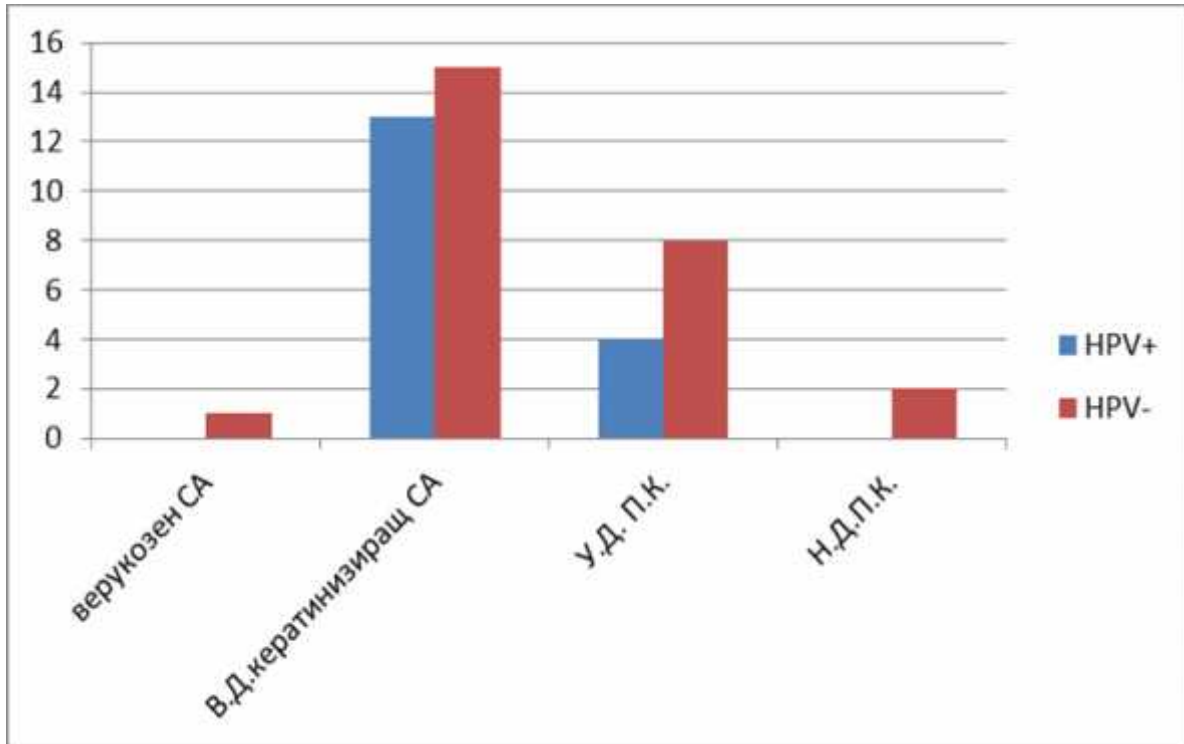
p16INK4a

HPV-

30,2%(n=13) HPV

9,3%(n=4) HPV

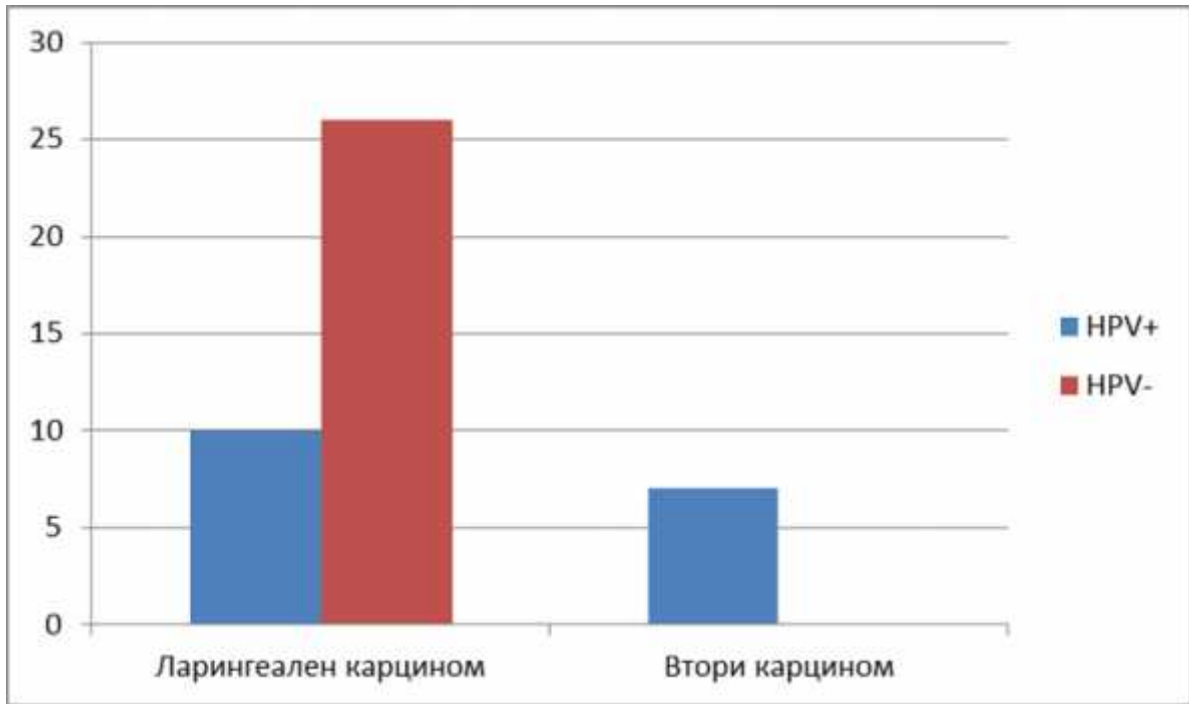
23



HPV –

HPV –

16,3 % (n = 7)



43

16,3 %

/

HPV-

$r = 0,55$ $p=0,0003.$

Ki-67

43

,7

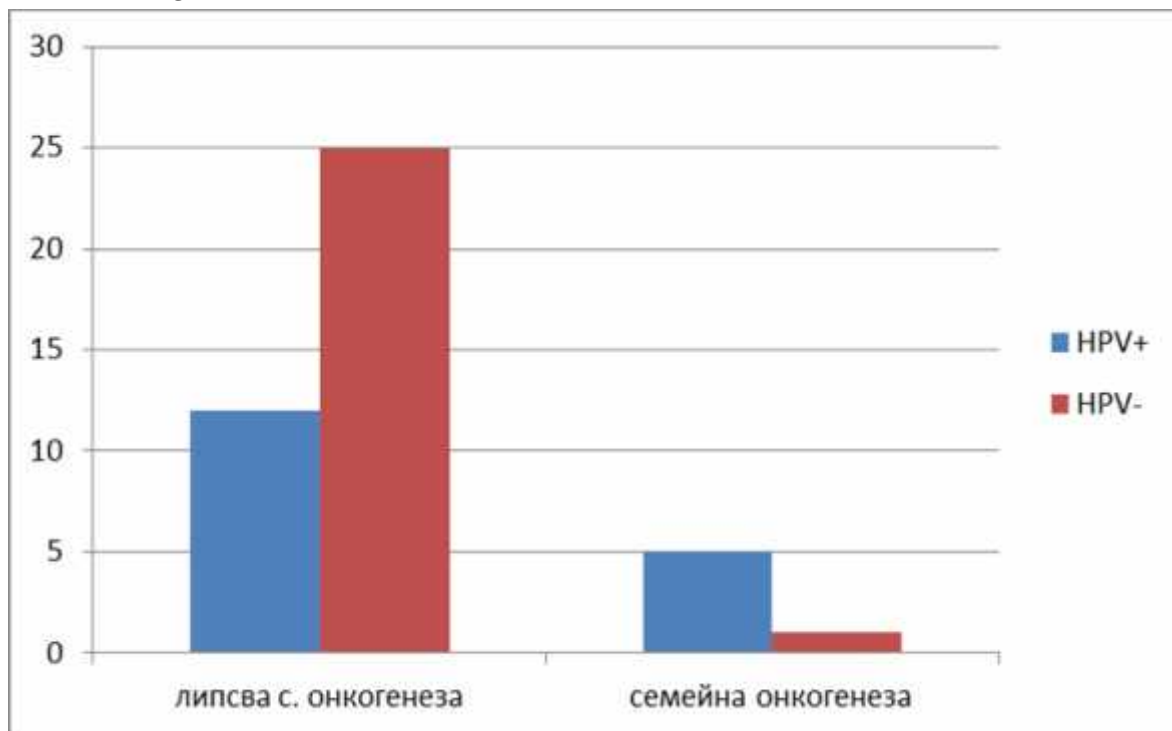
Ki-67 $r=0,39$ ($p=0,01$)

7

(2 , 3)

HPV

25



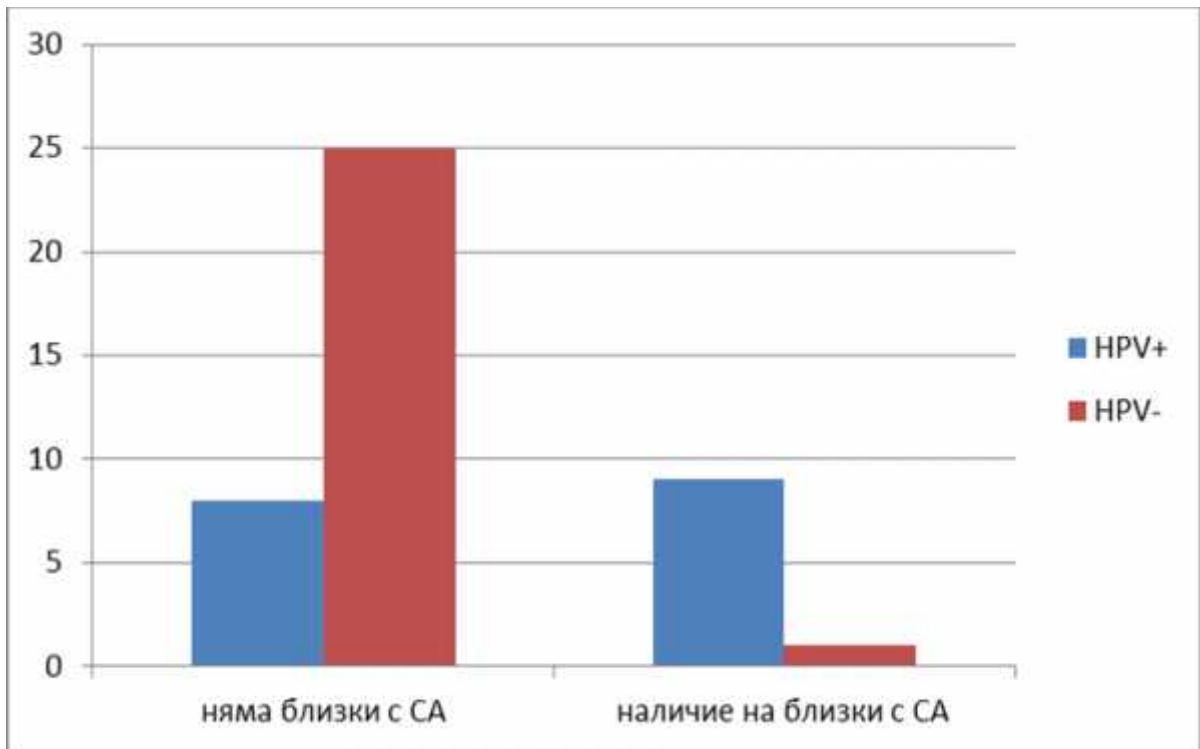
43- 86,1% (n=6)
13,9% (n=6)
()

6-
“ - 5- HPV ” HPV-

r=0,36 (p=0,02).

HPV (, ,).
 , HPV - ,
 43- 23,3% (n=10),
 (- -
 7 10-).

26



$r=0,57$ ($p=0,0002$).
 12 .

HPV

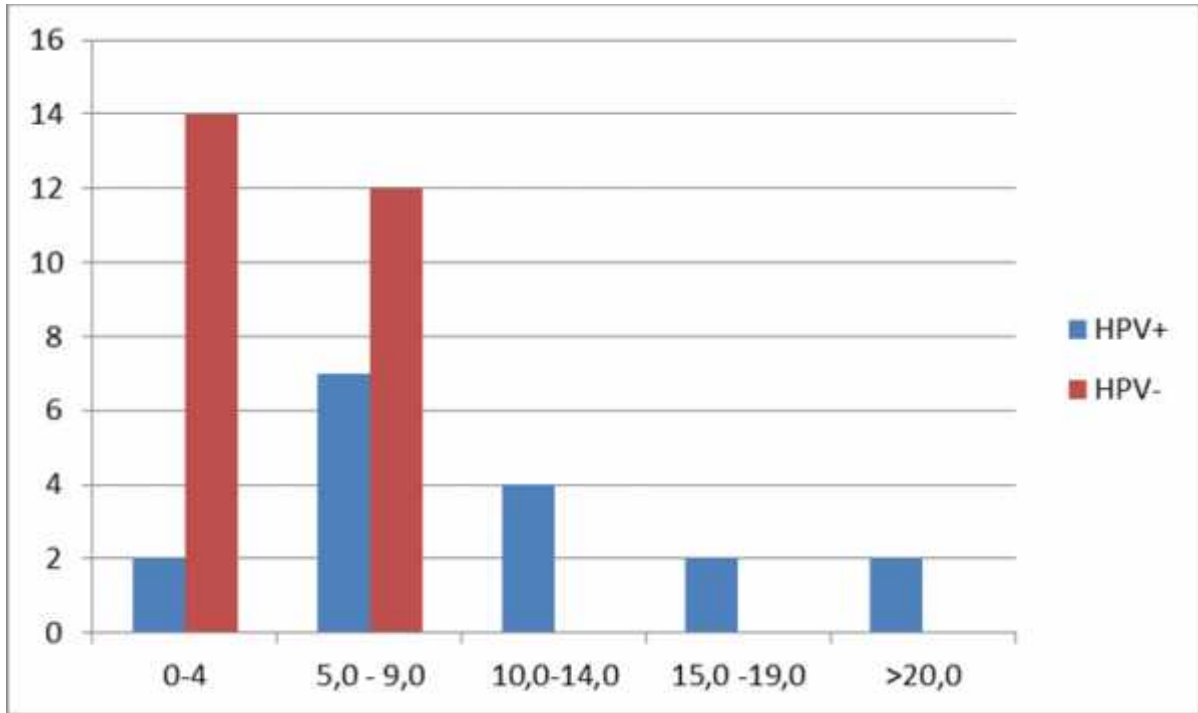
25.

8,8 , HPV

3,9

,
2,

.27



HPV-

p=0,0001,

HPV

2

HPV

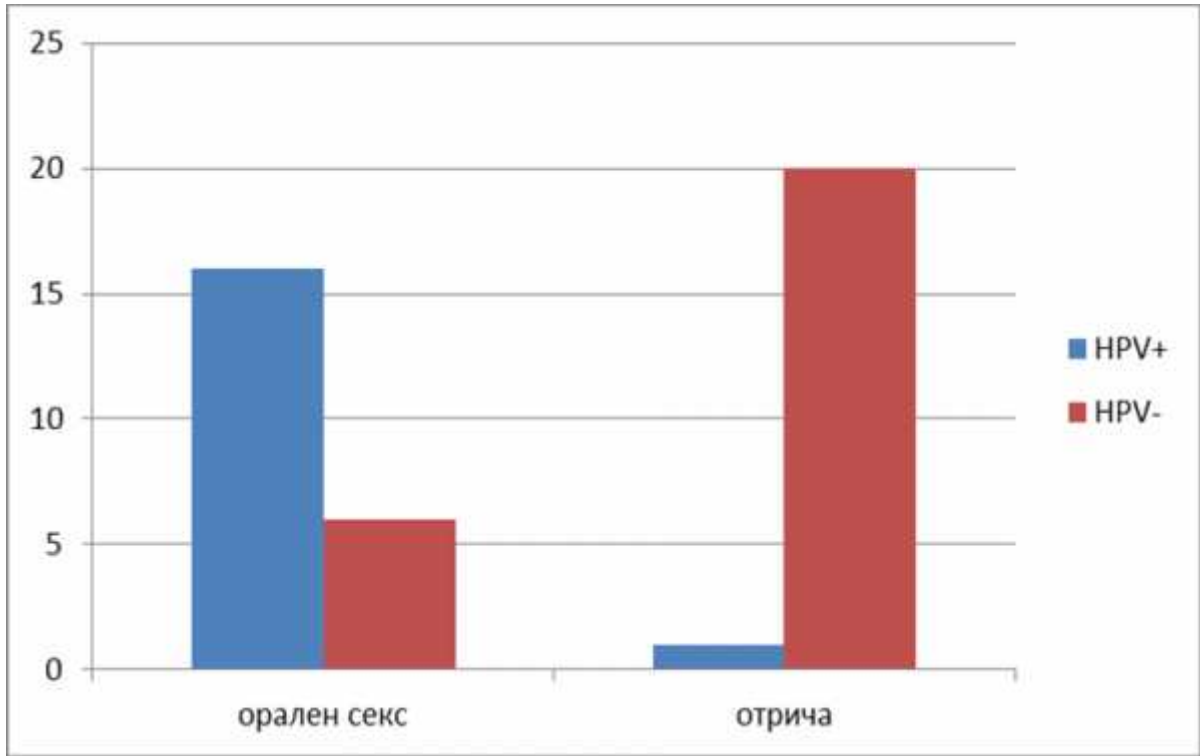
HPV

43-

- 48,8% (n=21)

51,2 % (n=22)

HPV-



HPV
46,5% (n=20)

HPV
37,2% (n=16)

HPV
2,3% (n=1)

HPV
- 13,9% (n=6)

HPV
r=0,69 (p=0,0001)

50

30,9

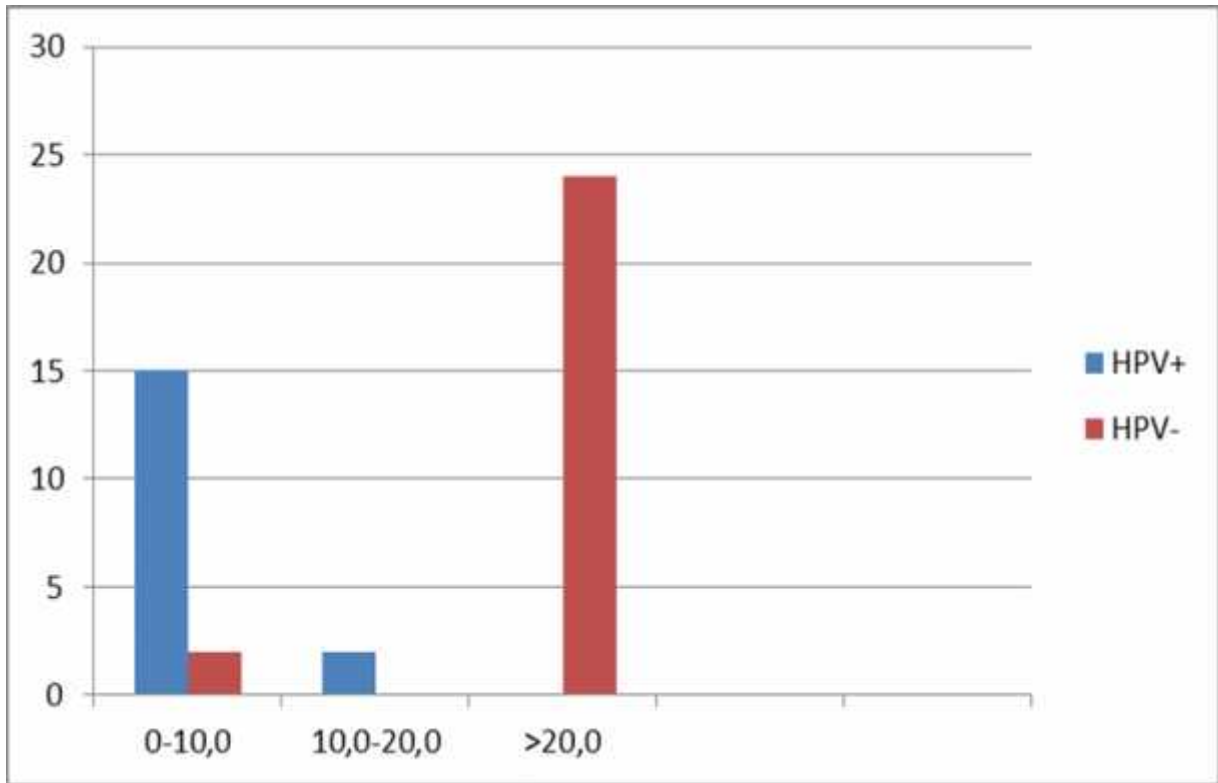
26 HPV

17-

HPV

19,6

2.4



HPV

HPV

76,7%(n=33)

23,3%(n=10)

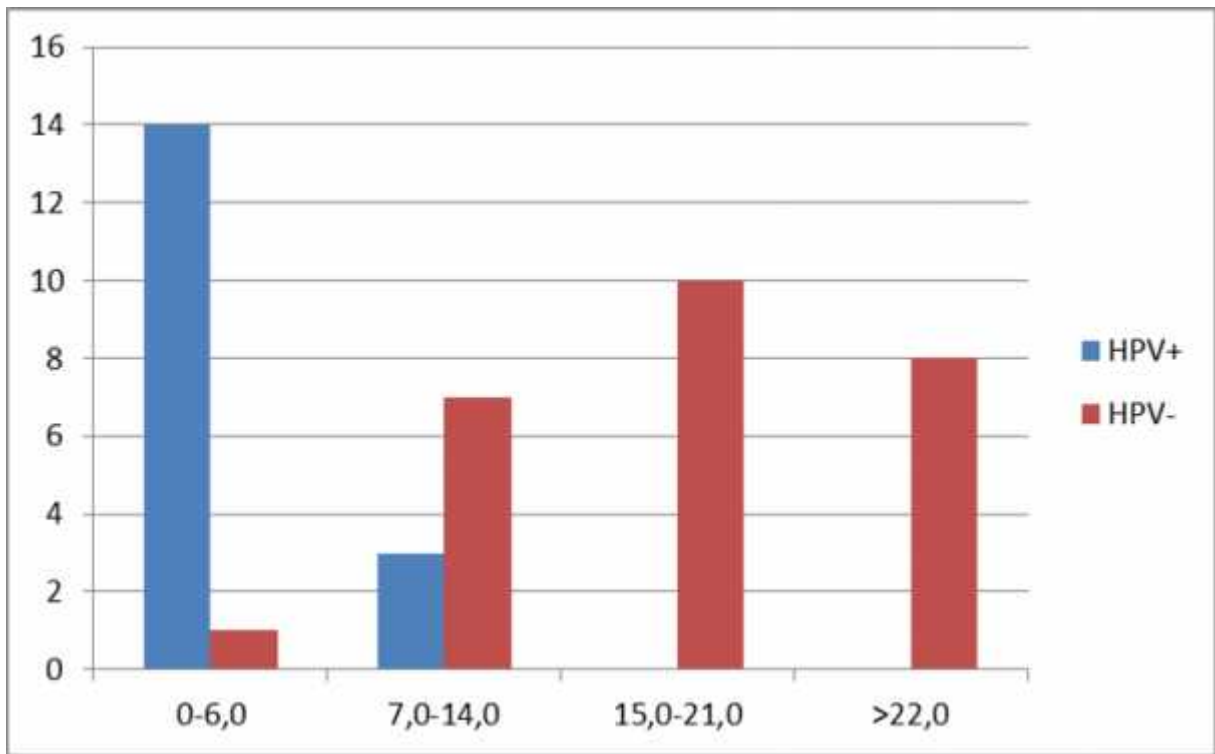
HPV

. P=0,0001 K-W=30,7

HPV-

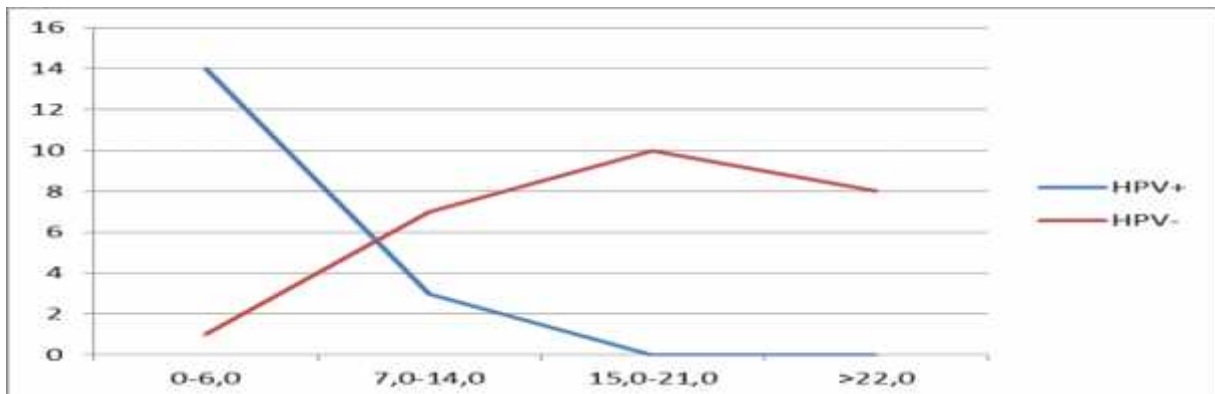
HPV

.32



43-
 (, , 50ml)
 , 83,7% (n=36)
 . 16,3% (n=7)
 (n=10) (n=17), 41,1% (n=7)
 HPV
 58,9%
 HPV
 15,3
 HPV
 HPV
 -2,8
 23,4

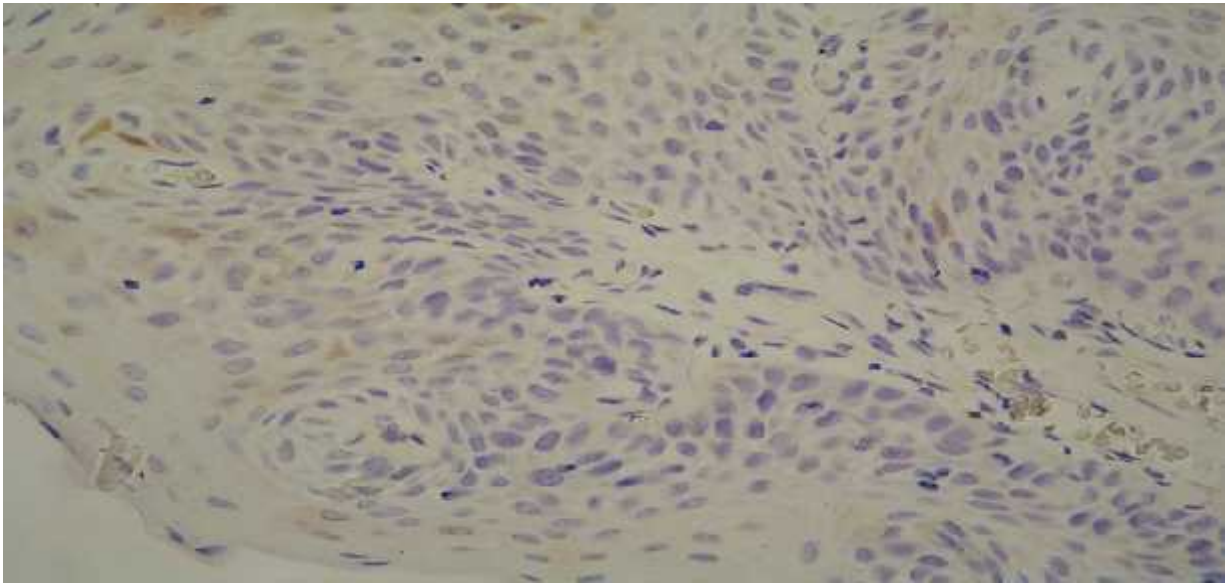
.33



HPV HPV 8 - HPV
 ,
 .
 p=0,0001).

3.4.

15 - 10 5 6
 , 9
 (n=3) HPV 15 p16INK4a HPV 20%
 , . . p16INK4a HPV
 p16INK4a ,
 HPV
 :
 , , .
 p16INK4a ,
 .
 ,
 - p16INK4a.



.56

p16INK4a

6 7

p16INK4a,

p16INK4a.

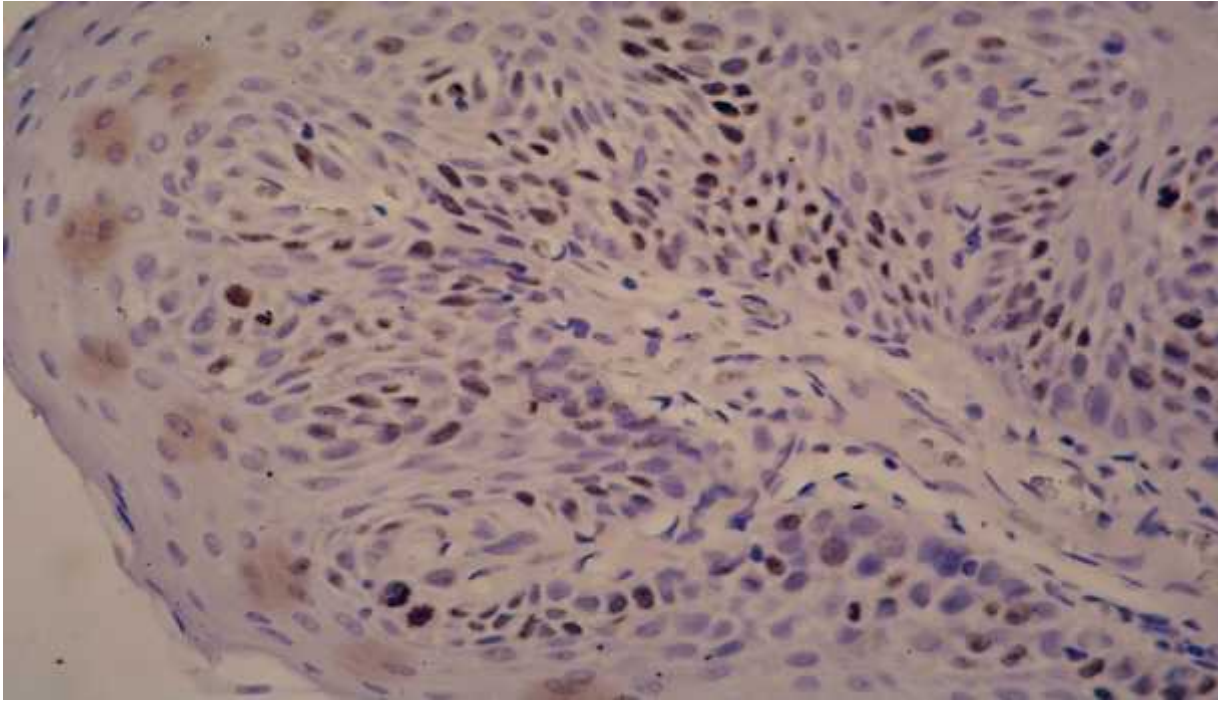
HPV

p16INK4a.

p16INK4a.

50%

p16INK4a

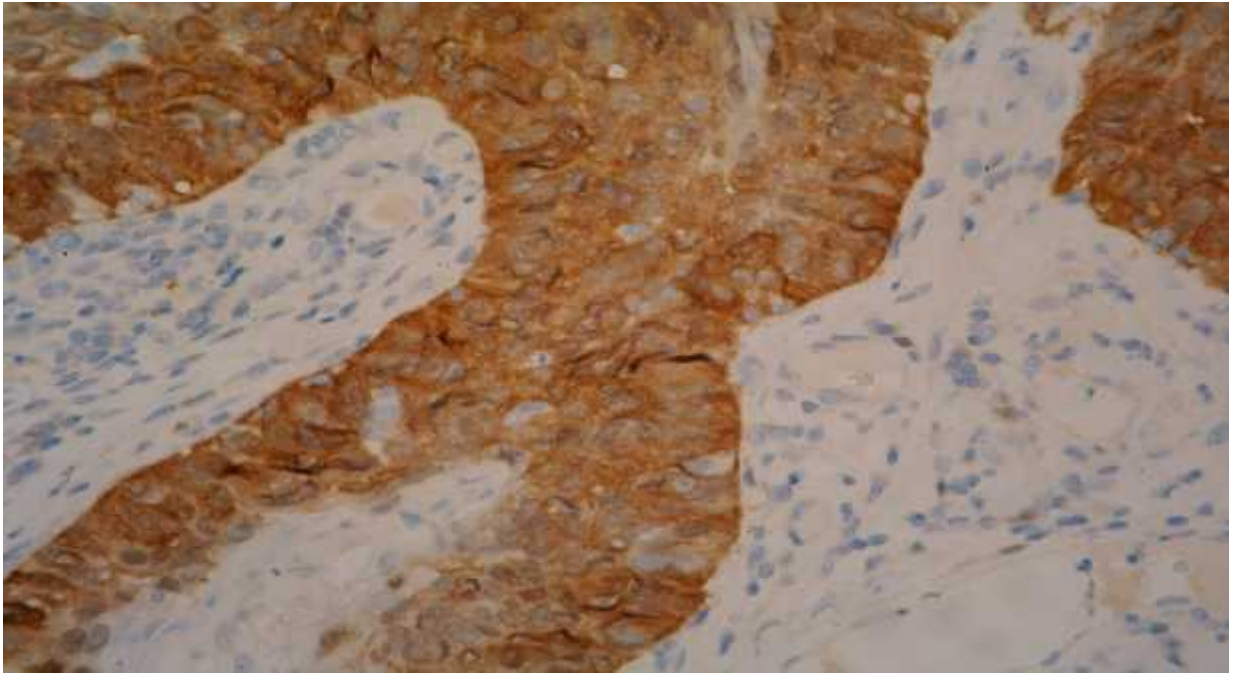


.57

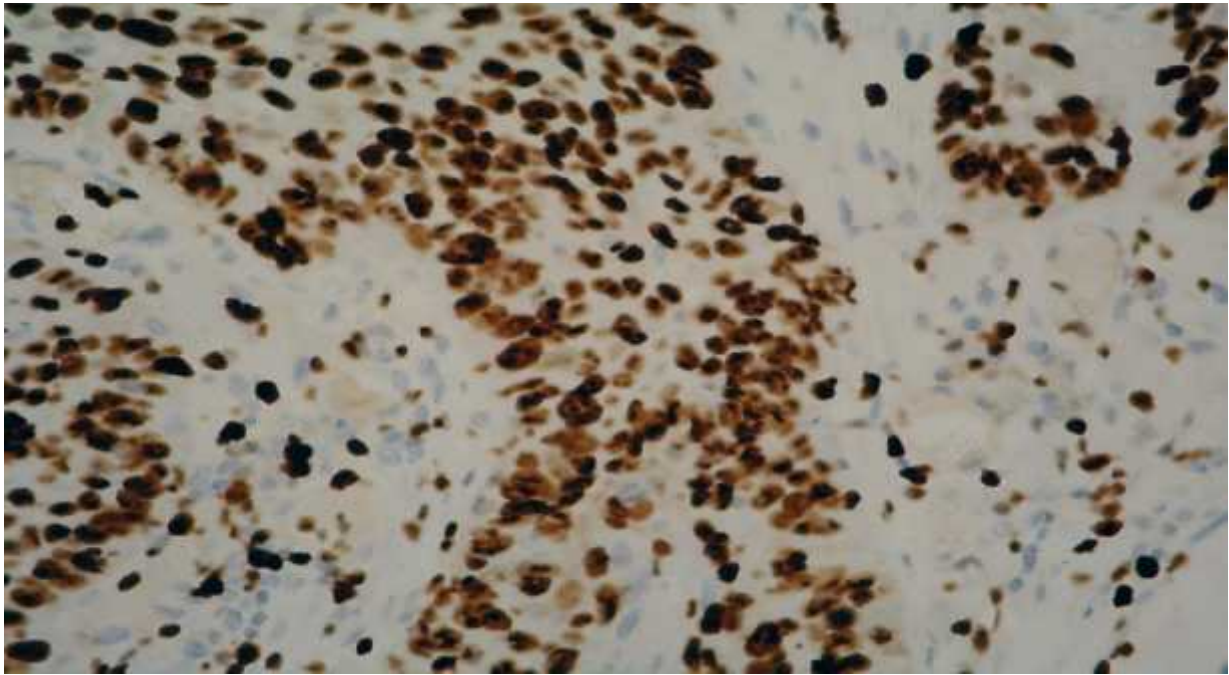
()

– 50%

p16INK4a.



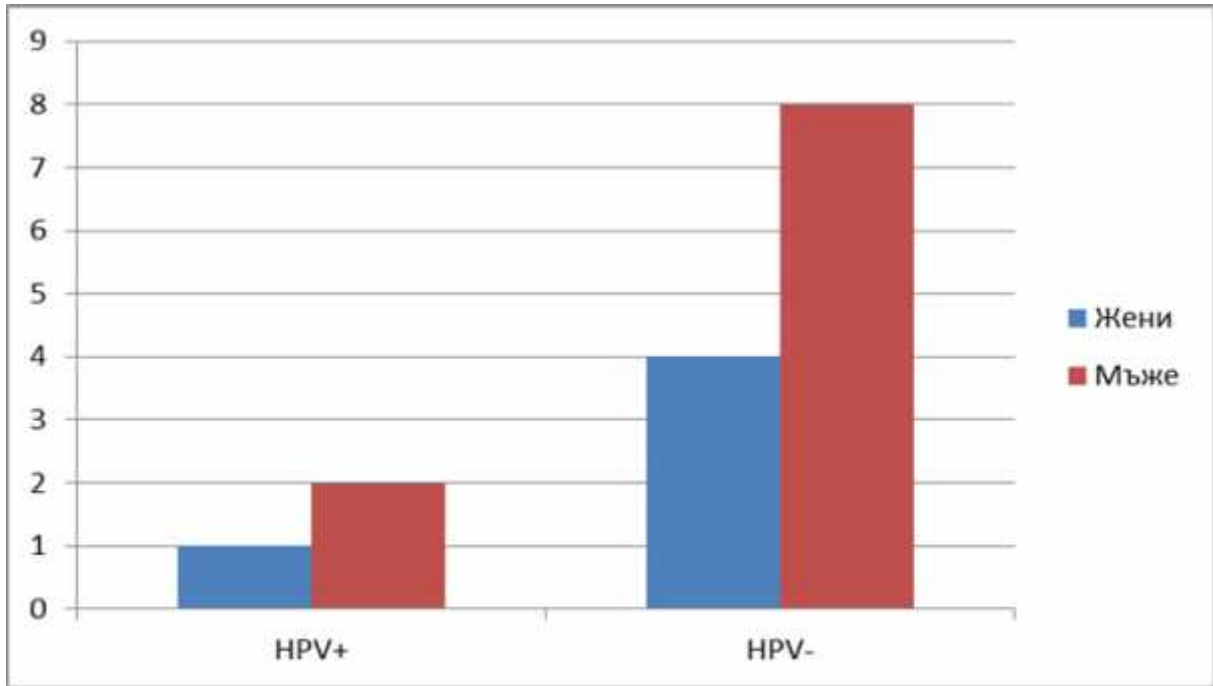
.58



.59

,
3,
15
,
. P16INK4a

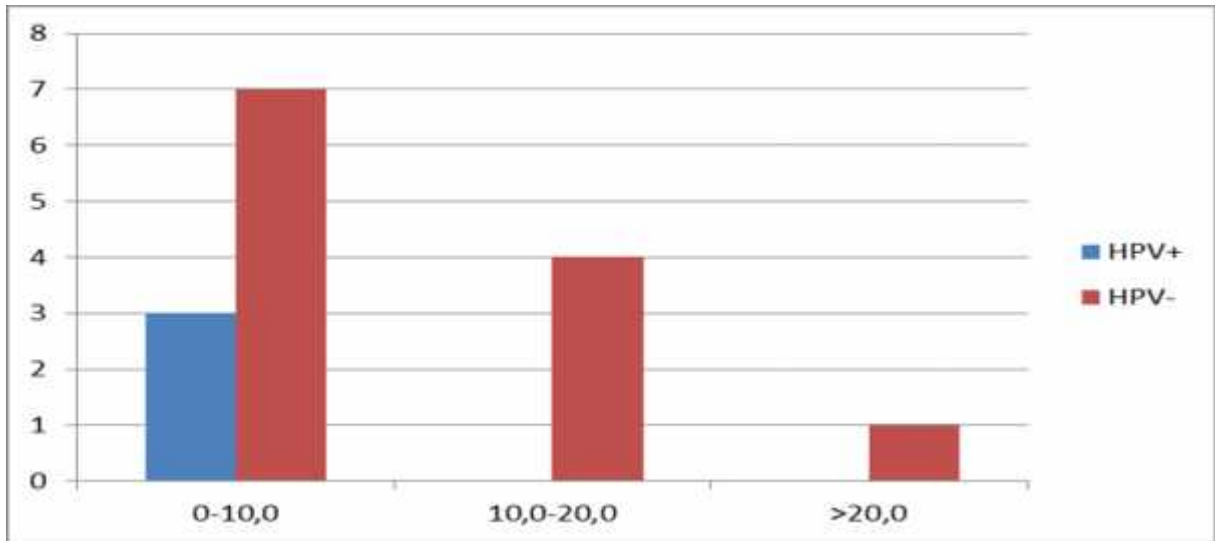
(n=10), 20% (n=3).
 HPV 33,3% (n=3)
 HPV 13,3% (n=2)
 HPV 66,7% (n=10)
 , p16INK4a 6,7%
 p16INK4a



, p>0,05.

86 ; - 42 .,
56,9 ; -
P>0,05 -
HPV , p16INK4a
56,6 ., HPV
58,2 .
- .
40. , 0,
HPV ,
HPV - p16INK4a .

.35

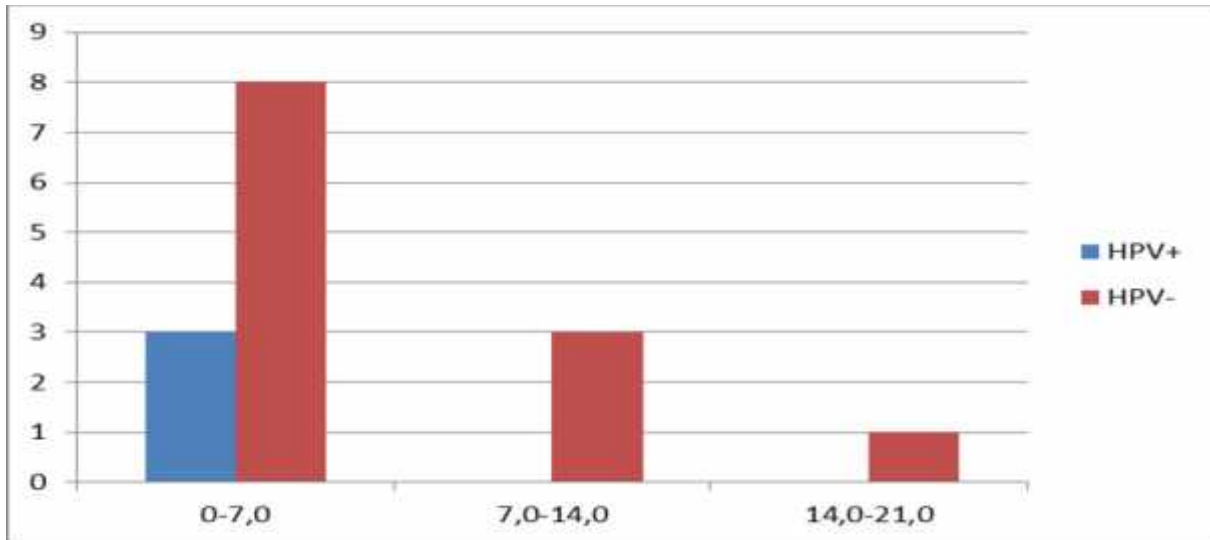


$p > 0,05$,

0 21

HPV

.36



HPV
7

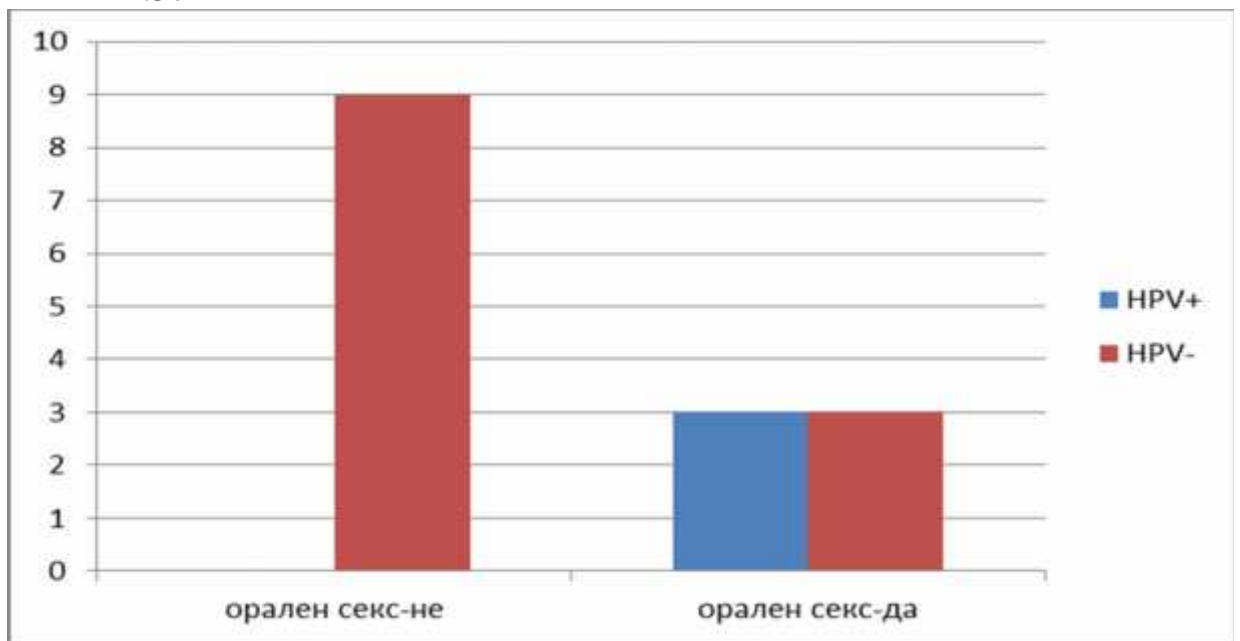
HPV

HPV

. HPV

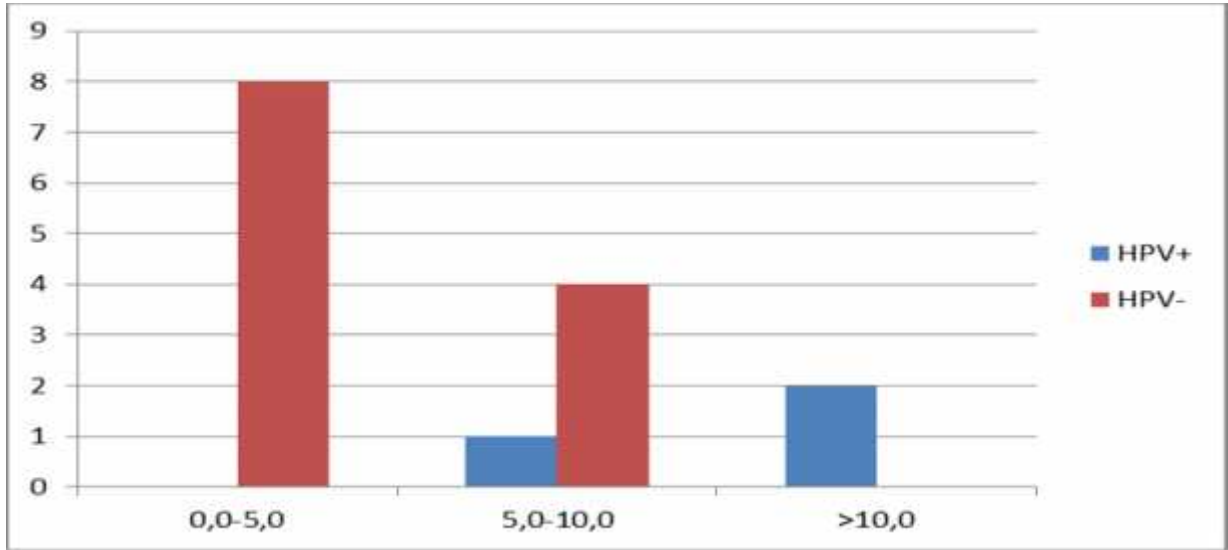
(-)

HPV
P>0,05.,
HPV 75%(n=9)
HPV 25%(n=3)
HPV
.37



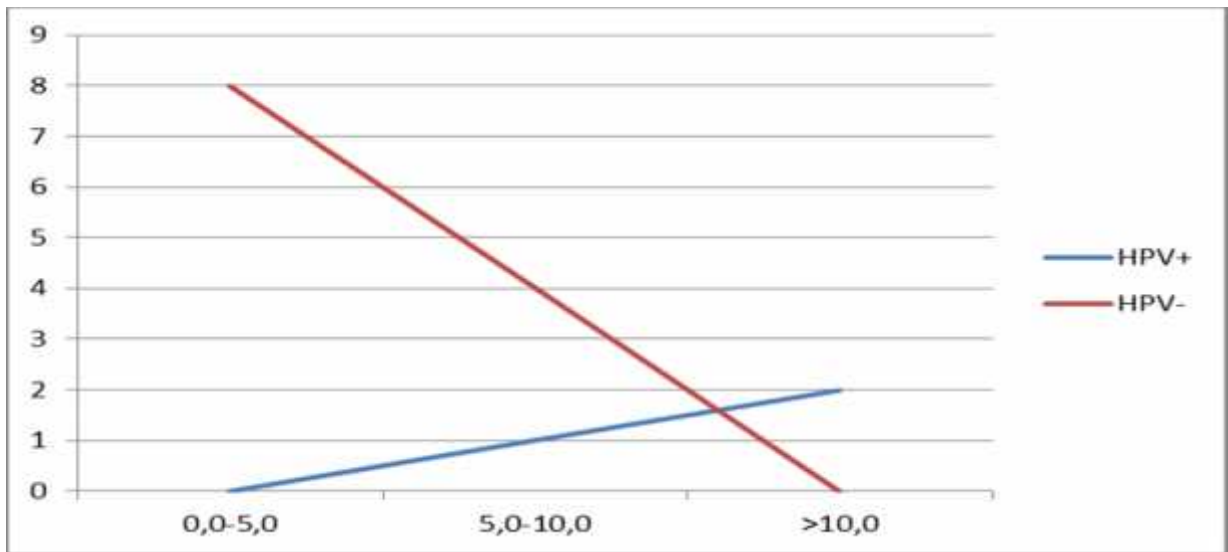
HPV
HPV
15 , 2 15

.38



(53,3%)
HPV
0 5
5 10 10

.39



93,3% (n=14)
HPV
6,7% (n=1)
66,7(n=10)

. 33,5 (n=5)

HPV

3.5.

—

HPV-

PCR.

, HPV

90%

HPV.

PCR

HPV

HPV

PCR

PCP

5

HRHPV

20.

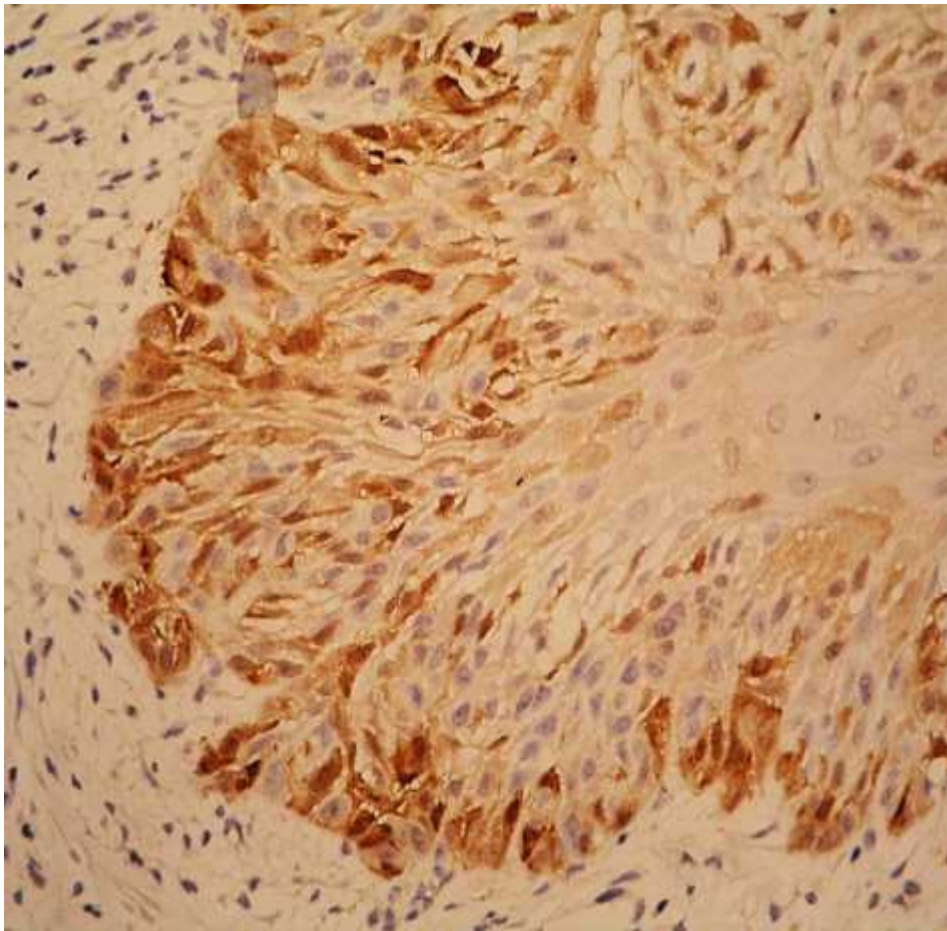
HPV

PCR

6 7

PCR

6 7 HPV p16INK4a p16INK4a 100%



.60

p16INK4a

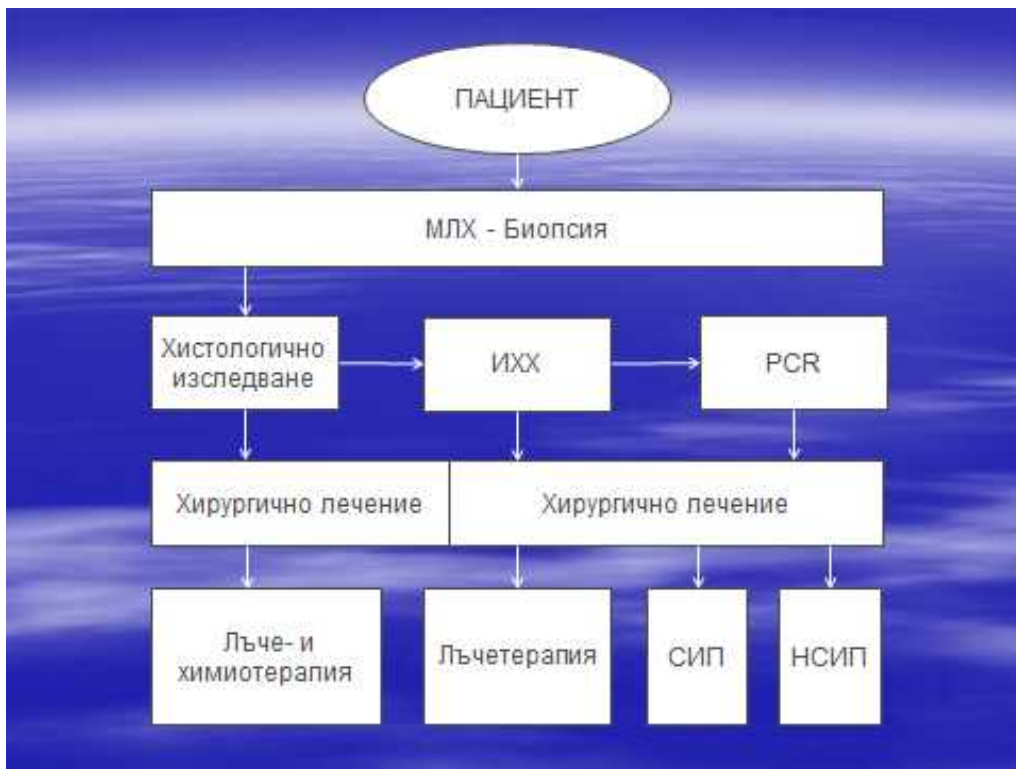
p16INK4a ,

58-80%

90-98%

85%.

HPV –



.61

Kleinzasser,

PCR

– p16INK4a Ki-67.

HPV 16,18,11,6. PCR. HPV 16 18

Nk - / - Isoprinosine

1

: -72 . : 21. 07.
2012 .

: Ly – 41.02%; – 0.97%; Sg – 55.93%;

	CD		(%)
–	CD3+	72.21%	67 – 76
-	CD3+DR+		8.0 – 15
-	CD4+	31.66%	36 – 46
- /	CD8+	38.02%	31 – 40
h/ s		0.83	1.0 – 1.5
–	CD19+	4.08%	5 – 16
- .	CD19+5+		
NK–	CD3- /CD16+56+	17.02%	5 – 19

_____ :

1. - - ;
2. / -
- / -
3. - - ;
4. NK - ;

2

: -72 .

2012 . : : 20. 09.

: Ly - 22.55%; - 2.33%; Sg - 68.08%;

	CD		(%)
-	CD3+	79.45%	67 - 76
-	CD3+DR+		8.0 - 15
-	CD4+	39.35%	36 - 46
- /	CD8+	34.24%	31 - 40
h/ s		1.14	1.0 - 1.5
-	CD19+	6.21%	5 - 16
- .	CD19+5+		
NK-	CD3- /CD16+56+	8.20%	10 - 19

_____:

1. - - ;
2. / -
- / - ;
3. - - ;

4. NK – ;

HPV-

Isoprinosine.

Th.

/

HPV

HPV

„HPV-

”

HPV

80%

20%

8

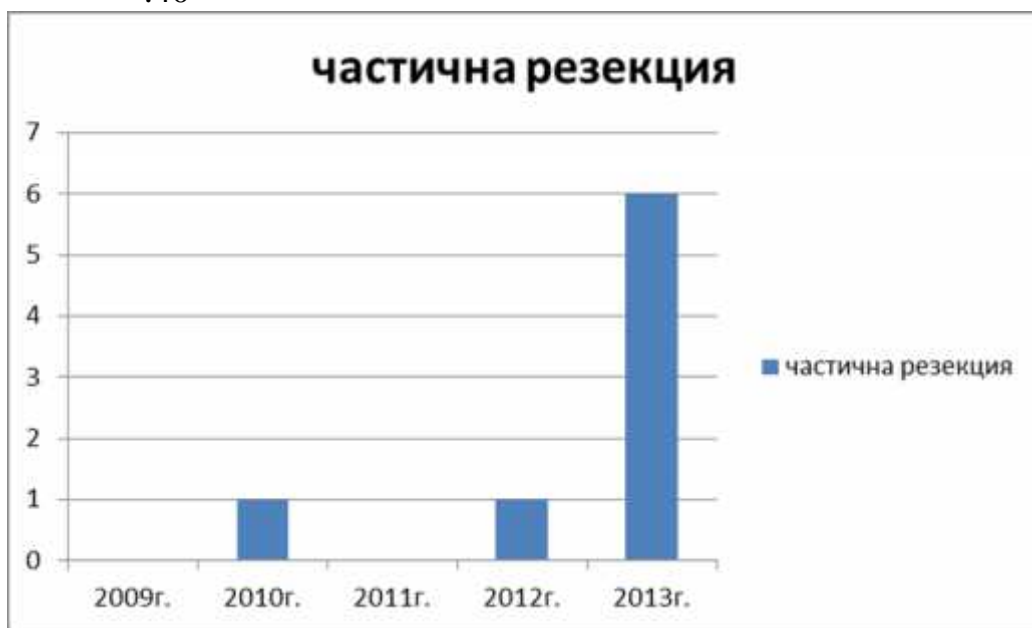
5

8

.3

	частична резекция
2009г.	0
2010г.	1
2011г.	0
2012г.	1
2013г.	6

.40



/ 3, 4/

HPV

HPV-

HPV

HPV

HPV

HPV

HPV

p16INK4a

P16INK4a e

p16INK4a

p16INK4a

6

7

p16INK4a.

3

5

p16INK4a

p16INK4a

CIN.

HPV

HPV -

5.

HPV

HPV
80%

50 80% (7, 8, 203, 205).

1 3

20%

HPV

3% HPV

35-45 .

, HPV

HPV

.(

)

6
9 -

16,1 100 000.
-2,6 100 000
15 100 000

HPV
HPV

- p16INK4a.

6 7.

HPV.

6 7

53, 7 6

P16INK4a,
- pRb.
p16INK4a
HPV.
100%
p16INK4a.

(183,99).

HPV

p16INK4a
 (p16CINtec),
 E2F⁷
 Rb-E2F
 p16INK4a (196,199).
 p16INK4a
 HPV
 CIN.
 CIN
 HPV
 39,5% p16INK4a
 p16INK4a
 (167,99,133,35,53,196).
 HPV,
 HPV
 p16INK4a
 PCR ISH.
 Pub Med.
 PCR ISH.
 p16INK4a 94 100% 79 – 90%.
 HPV
 p16INK4a
 ” “
 p16INK4a PCR
 ISH
 4

Study	Cases	Gold standard	Combined with PCR, %	Combined with ISH, %	Compared with single
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			Both positive		Both positive		Either positive			
			Sens.	Spec.	Sens.	Spec.	Sens.	Spec.	Sens.	Spec.
1.										
Smeets <i>et al</i>	48	HPV E6/E7 mRNA	100	100	–	–	–	–	100	79 ^a
Rotnaglova <i>et al</i>	109	HPV E6*I mRNA	100	88	–	–	–	–	96	94 ^a
Schache <i>et al.</i>	108	HPV E6 mRNA	97	94	88	90	–	–	94	82 ^a
Jordon <i>et al</i>	232	HPV E6/E7 mRNA	–	–	86.1	97.3	98.7	81.1	97	84 ^a
Gao <i>et al</i>	150	HPV E6/E7 mRNA ISH	–	–	69	100	95	85	95	90 ^a

Human papillomavirus (HPV) status detection using p16^{INK4A} immunohistochemical (IHC) staining in combination with HPV DNA PCR or *in situ* hybridization (ISH) assay

HPV , p16INK4a

PCR , p16INK4a .

2 10%

HPV (68,187,192). , 3

16% PCR.

HPV , PCR

p16INK4a .

p16INK4a ,

(122,123,125).

2013 .

p16INK4a

HPV

“

“

p16INK4a

(196).

1.

2.

p16INK4a ,
6 7

HPV.

3. PCR

HPV

(171, 129, 43, 39,21)

Tavanaj et al,

p16INK4a

PCR ISH.

p16INK4a

>50%

0 25%
25 50%

1+,

50%

2+. 75%

3+.

Tavanaj

142

96%,

Nissman et al -89%, Holzinger et al -

86%

(196)

PCR.

HPV

6

7.

PCR

HPV

, p16INK4a

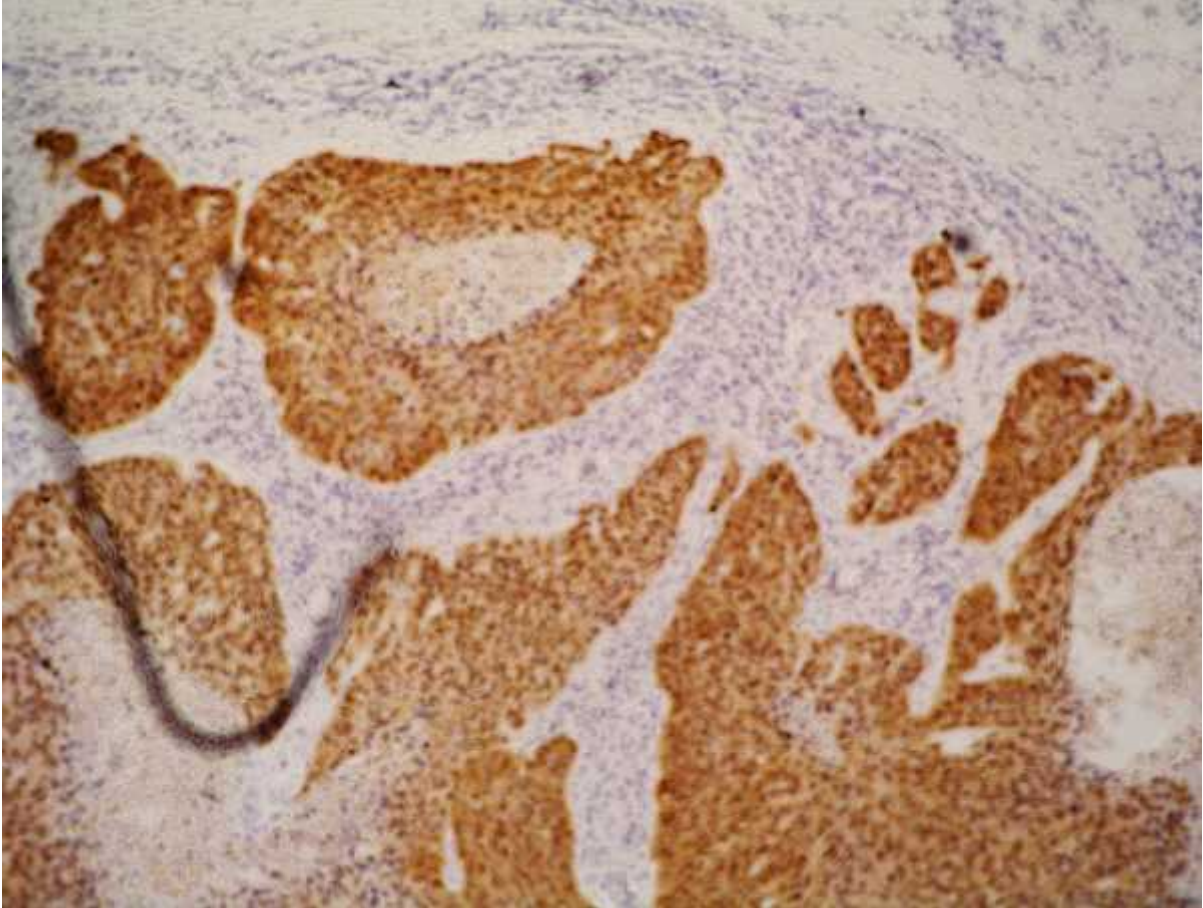
(196).

Wang et al

p16INK4a

HPV

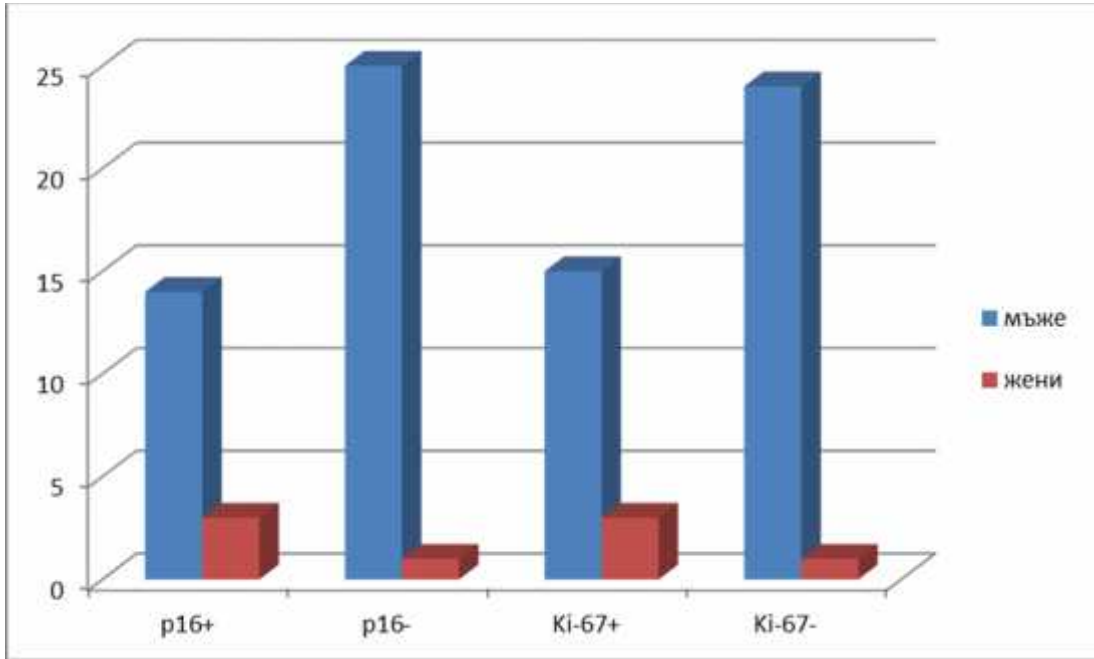
Ki-67 43- 17 p16INK4a 18
 75%, 1 100% 50% 6



.62

39,5% p16INK4a
 41,9% Ki-67
 HPV
 HPV- 25,9% 35,6%.
 Matzow et al 5% HPV
 HPV , 4 13
 23,5% 76,5% 43
 9,3% 90,7% HPV
 HPV

HPV
.41



HPV

67,4%

29,4%
70,4%
32,6%

HPV 1%

HPV

65

57

HPV

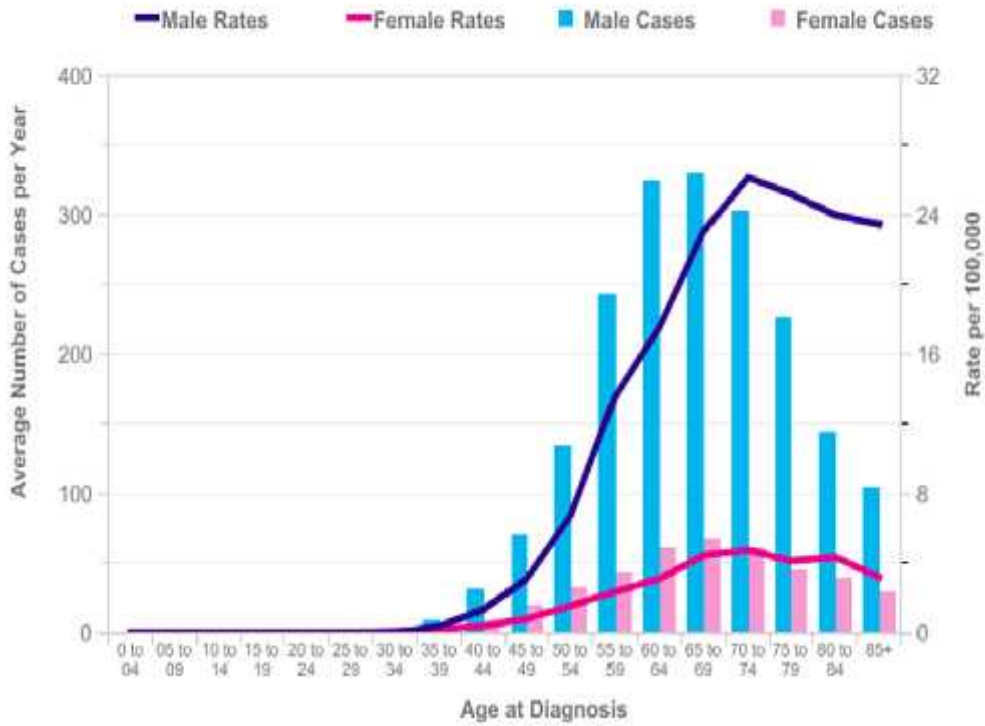
HPV

8

27

50-70 (4,6,15,18,24,45,51)

42



2011 . UK. 2009-

et al.(6) 6-7

40 55-66

35 HPV

(56,67,75,82,91,97,173). Clayman et al. 1435

HPV Chernok (53)

57 . HPV 57,5 .

19 HPV 24

HPV , 11 HPV 6

HPV

53

HPV.(206). HPV „ “ 1

(206),

300

10302

IARC –

100

2

IARC –

HPV

IARC

HPV

HPV

1 –

HPV.(24,71).

(142).

(3,4

),

HPV 58,8%.

12

HPV (145, 152, 155, 160, 175, 189, 201).

50ml

7

HPV+ 2,8.

(83,3%).

HPV- 15,3 23,4

7 (16,3%).

HPV 36

HPV 27,7% (n=10)

HPV 72,3% (n=26)

HPV 86,6% (n=13),

13,4% (n=2).

10244

Hashibe M et al 3

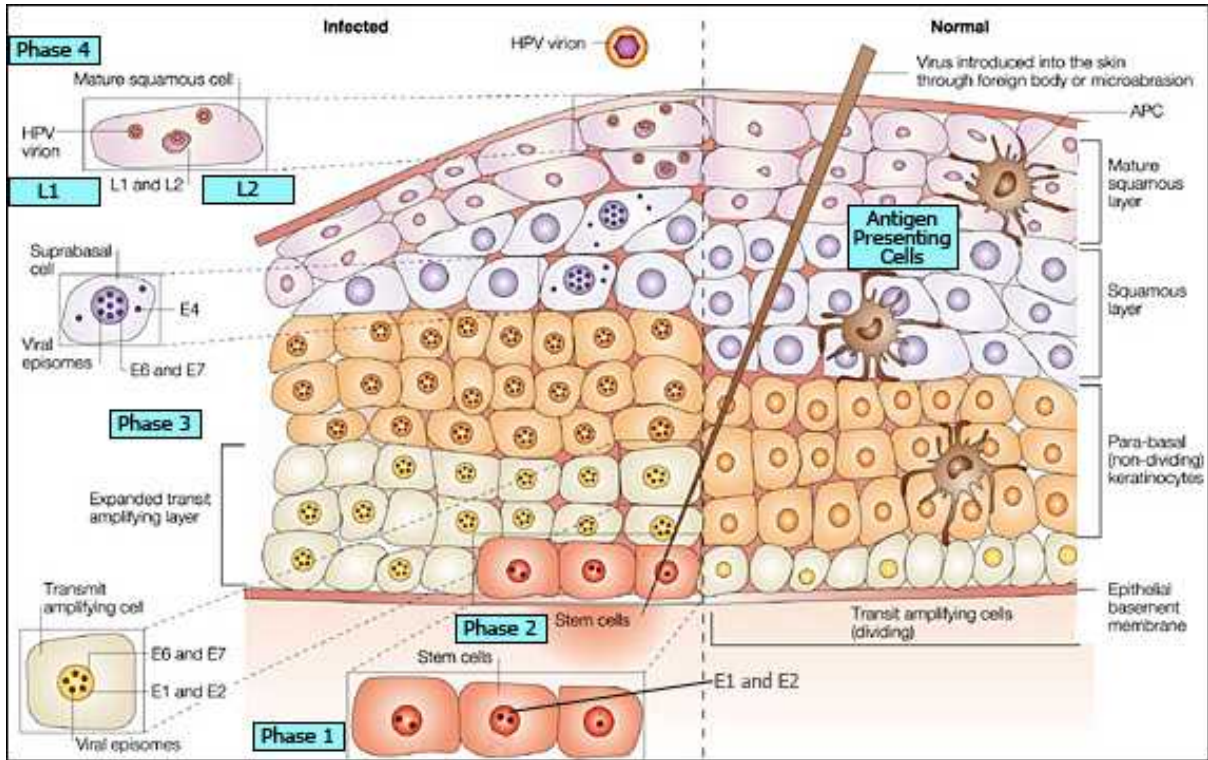
15

7%

600000

300000

HPV,



.63

HPV

HPV

HPV

HPV-

HPV-

HPV-

39,5% (n=17).

23,5% (n=4)

76,5%

(HPV).

. 16 HPV+
1 HPV
94,1% HPV
21 HPV
HPV

23%. Epidemiology, pathogenesis and prevention of the head and the neck cancer – M.L. Gillison

HPV-

Multidisciplinary management of Head and Neck cancer (L. Licitra et al)

HPV-
Cancer-causing viruses and their inhibitors (S. Prakash)
HPV- 26

HPV

43-

2- , - 25.

HPV

8,8

. HPV

(p=0,0001) 3,9 HPV

Cancer research UK

100

8,6.

32

HPV

3-

- 2.5 .

43-

2- , - 25.

HPV

(173). HPV

foundation – 7- () HASUMI

HPV-

(n=10) – 7 10- (59). 23,3% (p=0,0002).

7 – 41,1% HPV (42)

HPV HPV

HPV-

HPV

p16INK4a 15 20%. p16INK4a
 p16INK4a
 - p16INK4a.
 p16INK4a 5 7 p16INK4a
 p16INK4a 50%
 5 6
 p16INK4a
 p16INK4a
 p16INK4a (31).
 p16INK4a (27).
 (53,35,99,106,119,122,133).
 p16INK4a
 CIN (129).

PCR, HPV p16INK4a.
p16INK4a HPV
HPV HPV-

Kleinsasser p16INK4a.
PCR. HPV
p16INK4a HPV PCR

HPV16 PCR 3% 5%
HPV HPV
HPV HPV

HPV HPV /
(42). PCR.

HPV- PCR.
PCR
5 2012

2012

8

1

6

6.

:

1.

39,5% (n=17)

43-

2.

p16INK4a

:

HPV

()

•

•

•

-

HPV-

•

HPV-

-

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HPV-

•

/

HPV

HPV-

•

-

3.

(20%) p16INK4a

p16INK4a

4.

HPV-

•

•

•

•

•

5.

HPV

(

)

7.

1.

p16INK4a

HPV-

HPV

2.

HPV-

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•

•

3.

p16INK4a

4.

HPV

5.

6.

· · · ”

“

HPV

·

1. , PCR
 HPV –
 HPV
 ,
 15-17
 2011 .
2. , , ,
 .MEDINFO 03.2012 .
3. , , , , –
 HPV –
 . .GP news 2013.
 .14. .10-11
4. 9-th Balkan Congress of Otorhinolaryngology. Topics in the Field of
 Otorhinolaryngology head and neck surgery. Budva. Montenegro. 01-05 June 2014.
 -Nikolov G, Valkov Al, Atanasova Kr, Todorova Y, Duhlensky B, Nikolov D,
 Hvarchilkova A – Carcinoma of the Larynx and HPV.
5.
 15-17 2011 .
 - , , PCR
 HPV –
 HPV
 ,
6. XII PCR 7 – 9 2011 .
 - , ,
 HPV-
 HPV
 ,
7. I international medical scientific conference for students and young doctors 12-
 15.10.2011.MU-Pleven HPV – associated carcinomas of the head and neck.
- 8.XIII 28-30 2012 .
 - , , ,
 ISOPRINOSINE .
- , , , HPV –
 .

9.XIV 20-22 2013 . HPV –

10. “ 28-30 2014 . HPV –

11. 7- 24-26 2013 „ „

12. 29-21 2014 . 16INK4a