La collaborazione tra Registri Tumori e clinica: i tumori HPV – correlati

Mario Preti**, Leonardo Micheletti**, Silvana Privitera, Carola Libero**, Irene Sobrato*, Niccolò Gallio**, Chiara Benedetto**, Livia Giordano****, Paola Busso* Silvia Patriarca*, Stefano Rosso****

** SSD Registro Tumori Piemonte – Città della Salute e della Scienza di Torino*

*** SC Ginecologia e Ostetricia 1 U - Città della salute e della scienza di Torino*

**** SC Anatomia Patologica - Città della salute e della scienza di Torino*

***** SSD Epidemiologia e Screening – Città della Salute e della Scienza di Torino*

Evento Formativo Residenziale

IL REGISTRO TUMORI PIEMONTE A 50 ANNI DALLA FONDAZIONE: I NUOVI DATI REGIONALI ED IL LORO UTILIZZO

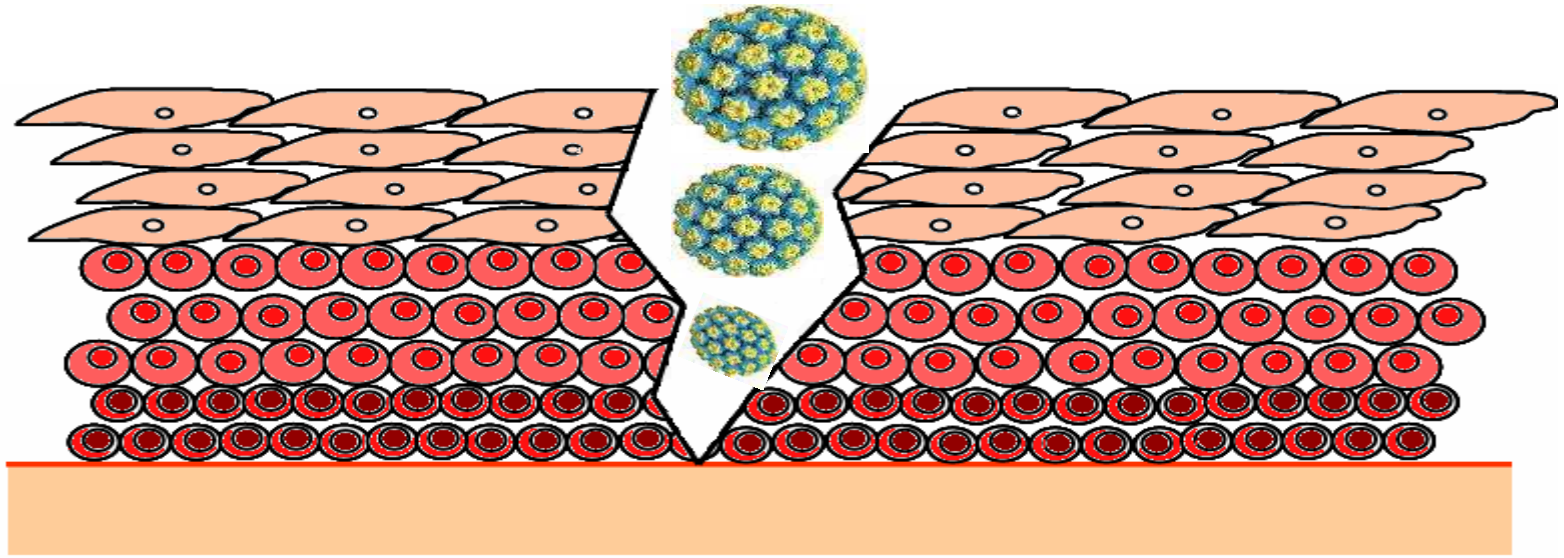
HPV (human papilloma virus) infection is responsible for 5.2% of all cancers

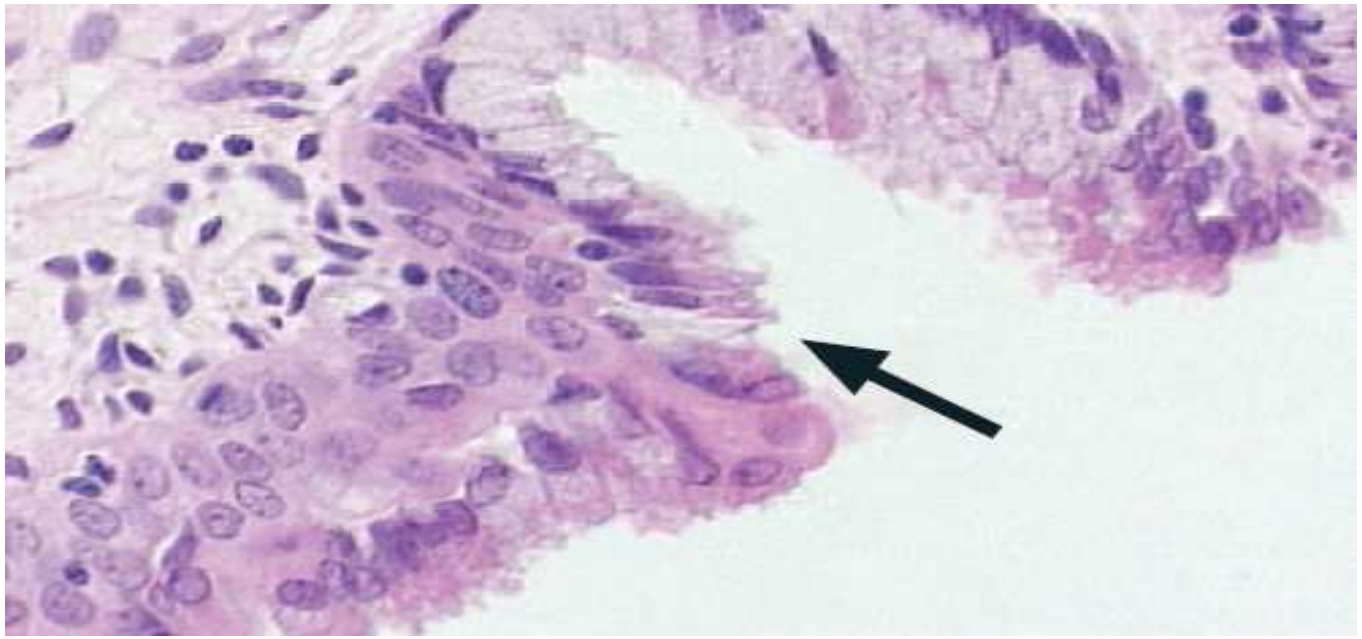
HPV – cervical cancer → well known

HPV - cancers of anus, vagina, vulva, oropharynx, head and neck → only recently been confirmed

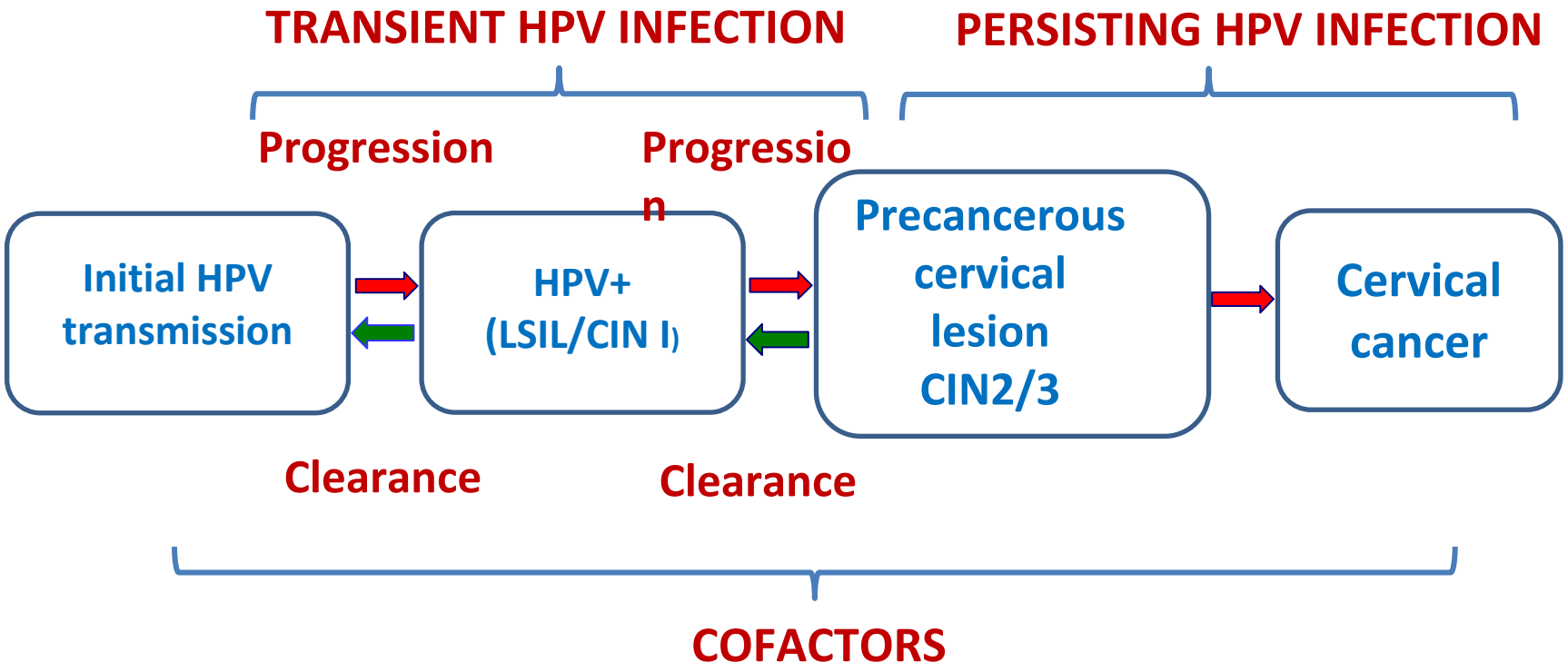
- F.L. Sand et al.; AACR journals; 25(7); 2016
- L. Shack et al.; *CMAJ* open; 2(3); 2014
- F. Neumann et al.; Preventive Medicine 90; 52-58; 2016
- A. Fontánez et al.; J. Low Genit Tract Dis; 22(3); 2018
- M. Gaudet et al. , Gynecologic Oncology,134, 523–526, 2014

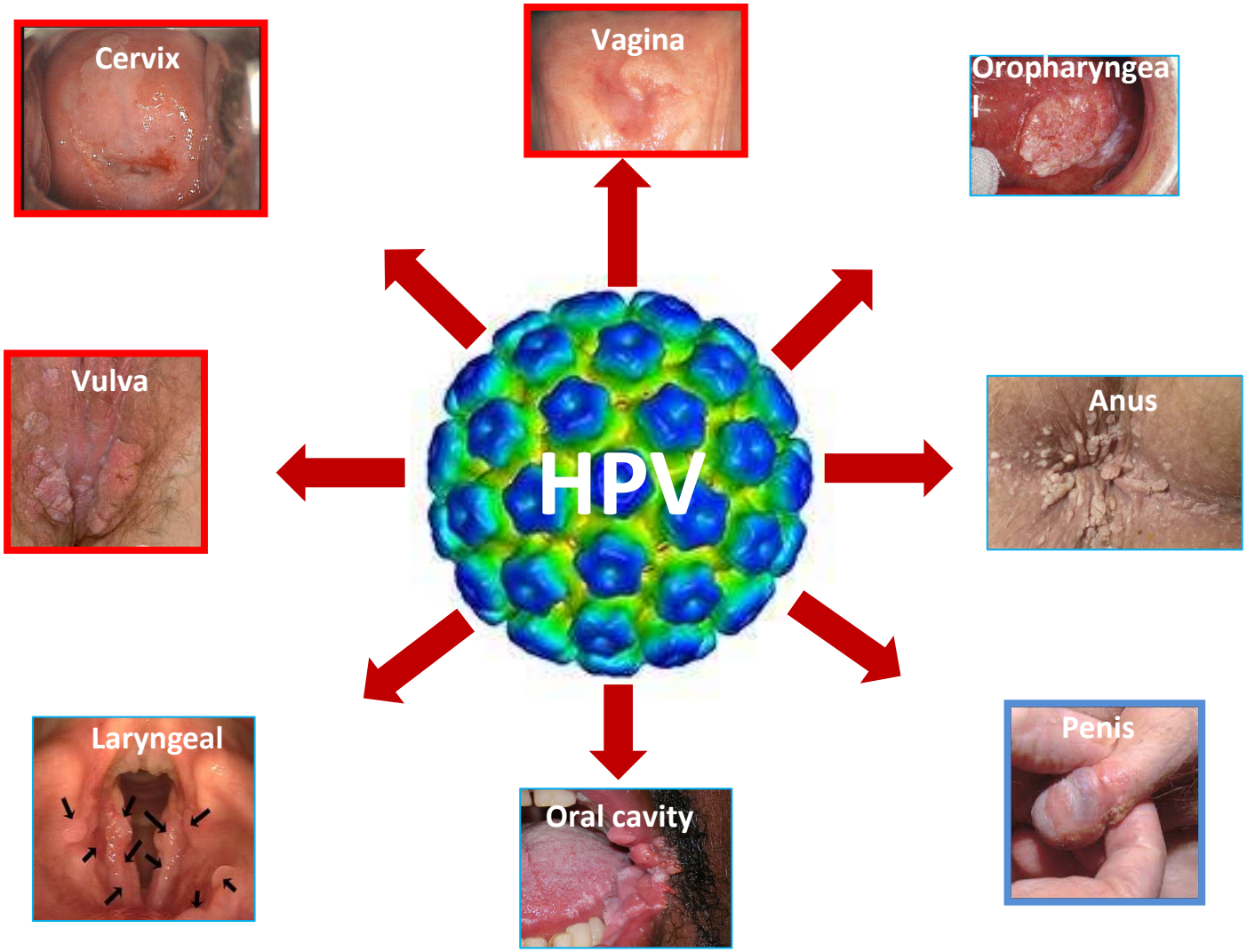
HPV infection



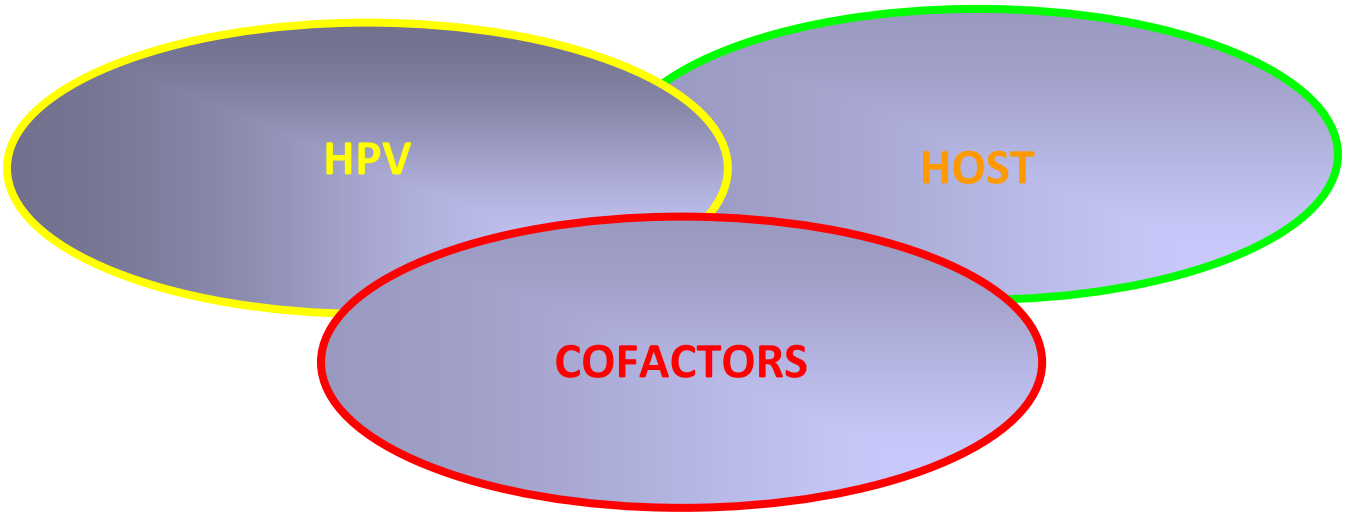


Schiffman M et al. Lancet, 2007 370:890-7


TRANSIENT HPV INFECTION
PERSISTING HPV INFECTION
Progression
Progressio
n
Initial HPV
transmission
HPV+
(LSIL/CIN I)
Precancerous
cervical
lesion
CIN2/3
Cervical
cancer
Clearance
Clearance
COFACTORS


Cervix
Vagina
Oropharyngeal
Vulva
HPV
Anus
Laryngeal
Oral cavity
Penis

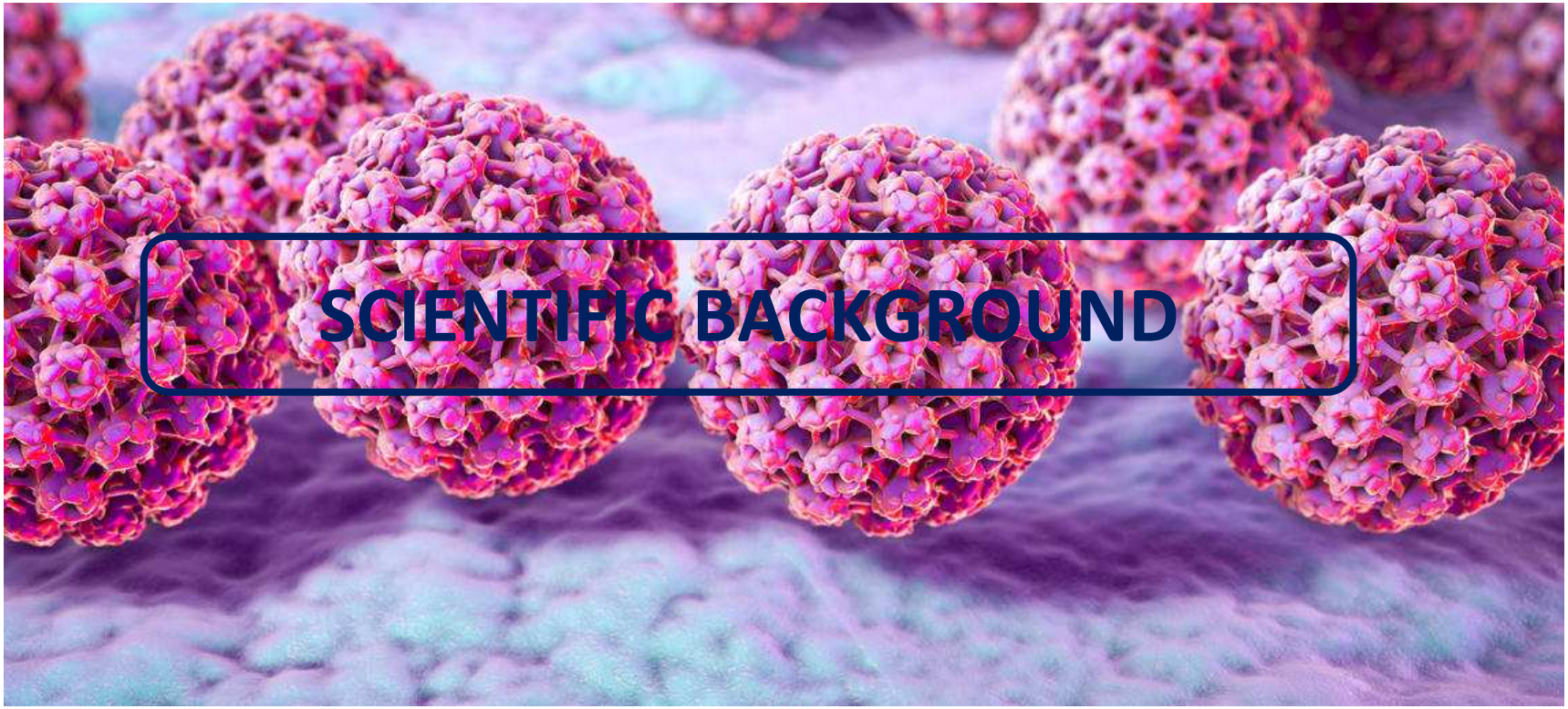
Risk of cancer



HPV is detected in anatomical sites

	HPV (any type) prevalence	16/18 positives of HPV+ cancers
Cervical cancer	100%	70-75%
Anal cancer	84%	> 80%
Vaginal cancer	70%	80-90%
Penile cancer	47%	> 80%
Vulvar cancer	40%	> 90%
Head & Neck cancer		
Oropharyngeal cancer	28%	> 95%
Laryngeal cancer	21%	> 95%
Oral cavity cancer	16%	> 95%

Sources : [1]DE Vuyst Eur J Cancer 2009; [2] De Vuyst Int J Cancer 2009; [3] Miralles-Guri J Clin Pathol 2009; [4] Kreimer Cancer Epidemiol Biomarkers Prev 2005; [5] von Krogh Eur J Dermatol 2001


SCIENTIFIC BACKGROUND

ACADEMIC PRESS

Gynecologic Oncology

Second primary cancers after cervical intraepithelial neoplasia III and invasive cervical cancer in Southeast England

H.S. Evans,[a,*] A. Newnham,[a] S.V. Hodgson,[b] and H. Møller[a,c]

OBJECTIVE: to identify cancers occur more often than would be expected in a cohort of women diagnosed with CIN III and in women with invasive cervical cancer.
METHODS: **59,586** patients, 1960- 1999, **Thames Cancer Registry** was used to identify two cohorts of women diagnosed with either CIN III or invasive cervical cancer. The number of subsequent cancers at other sites was observed and compared to the expected number.
RESULTS:. **They support the hypothesis that cancers of the cervix, anus, vulva, and vagina share common risk factors such as HPV and smoking.**

H.S.Evans et al., Gynecologic Oncology, Vol. 90, 131–136, 2003

Women who were diagnosed with CIN III had a significantly increased risk of developing subsequent cancer at the following six sites:

Subsequent site	Initial diagnosis		
	CIN III		
			95% CI
			0.8 to 1.9
			0.4 to 1.6
			0.8 to 1.8
			0.9 to 1.4
			0.8 to 1.6
			3.7 to 8.8
			0.6 to 1.5
			0.5 to 3.4
			1.5 to 2.1
			0.1 to 1.5
Skin m melanoma	42	1.0	0.8 to 1.4
Breast	512	1.0	0.9 to 1.1
Cervix uteri	194	2.8[b]	2.4 to 3.2

Standardised incidence ratio (SIR), calculated by dividing the observed incidence of second primary malignancies (SPM) by the incidence for the general population, measured from the rest of the registry unaffected by the primary cancer in question

There is an increased risk of invasive cervical cancer after a diagnosis of CIN III and an increased risk of ano-genital cancers after both CIN III and cervical cancer.

H.S.Evans et al., Gynecologic Oncology, Vol. 90, 131–136, 2003

Risk of anogenital cancer after diagnosis of cervical intraepithelial neoplasia: a prospective population-based study

Edgren G, Sparén P

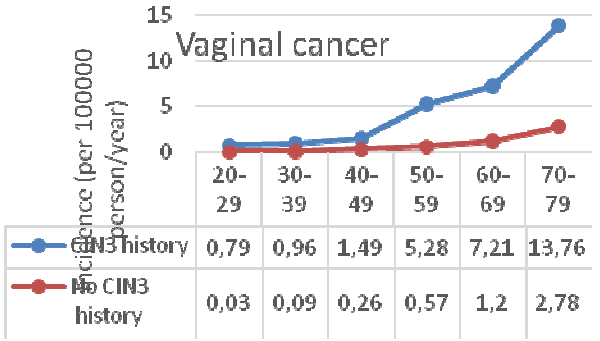
Lancet Oncology (2007) 8(4) 311-316

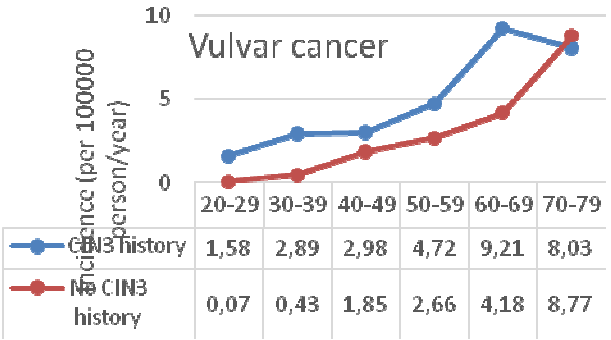
OBJECTIVE: to assess the risks of vaginal, vulvar, anal, and rectal cancer in women with a history of a grade 3 CIN diagnosis.

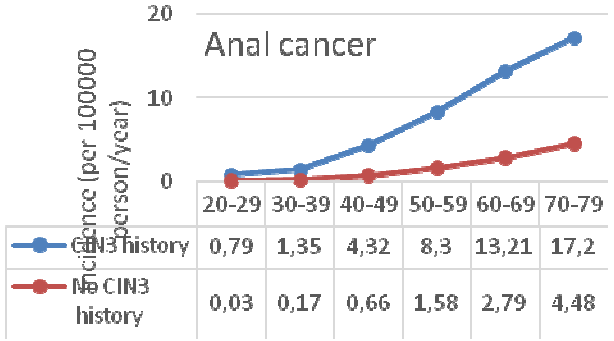
METHODS: it is used the national registration number, date of birth, and date of death for all women who were born between 1918 and 1986 and who were recorded as living in **Sweden** at any time between **1968** and **2004**.

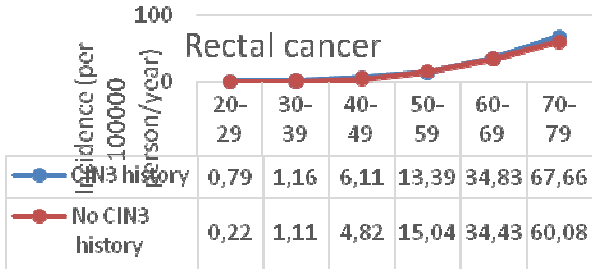
G. Edgren, Lencet Oncology, Vol.8, 311-316, 2007

RESULTS: **Women with a history of CIN3 had increased risks of cancer of the vagina, vulva, and anus**. No excess risk was found for rectal cancer.
For all four anatomical sites, the IRRs varied substantially with the amount of time that had elapsed since the date of first diagnosis of CIN3. Analyses stratified by attained age during follow-up showed that the risk of cancer was highly age dependent.









G. Edgren, Lencet Oncology, Vol.8, 311-316, 2007

Study	Year-Country	Value	SPCs			
			Vulvar	Vaginal	Anal	Head and neck
Evans et al	2003-England	SIR	4,4	18,5	5,9	**1,2
Kalliala et al	2005-Finland	SIR	4,1	12	5,7	* 1,7
Strander et al	2007-Sweden	RR		6,8		
Edgren et al	2007-Sweden	IRR	2,2	6,7	4,7	
Saleem et al	2011-USA Canada	SIR			16,4	
		SIR			6,2	
Tatti et al	2012-USA	OR			1,91	
Gaudet et al	2014-Canada	SIR	1,47	3,61	0,89	0,47
		SIR	3,79	8,53	2,28	0,67
		SIR	2,9	6,65	1,75	0,61
Sand et al	2016-Denmark	RR	2,5	8,1	2,9	
		RR	4	17,1	4,2	
Ebish et al	2017-Holland	IRR	4,97	86,08	3,85	***5,51
Fontanez et al	2018-Puerto Rico	SIR			51,6	
Suk et al	2018	SIR	3,8	17,3	2,3	

** oral/pharingeal
* smoking related cancers
*** Age standardised values

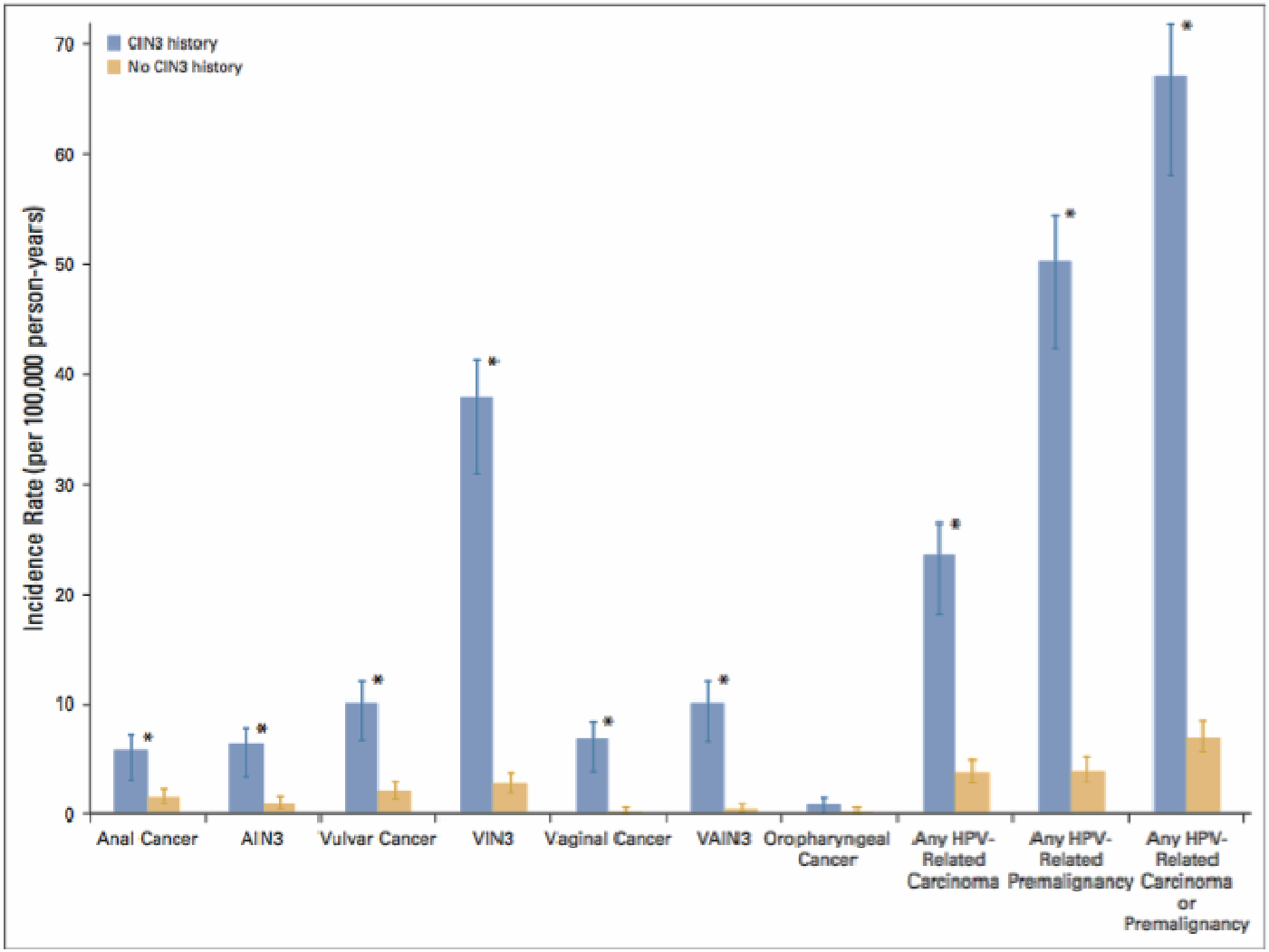
Long-Lasting Increased Risk of Human Papillomavirus–Related Carcinomas and Premalignancies After Cervical Intraepithelial Neoplasia Grade 3: A Population-Based Cohort Study

Renée M.F. Ebisch, Dominiek W.E. Rutten, Joanna IntHout, Willem J.G. Melchers, Leon F.A.G. Massuger, Johan Bulten, Ruud L.M. Bekkers, and Albert G. Siebers

OBJECTIVE: to determine the risk of human papillomavirus (HPV) related carcinomas and premalignancies in women diagnosed with cervical intraepithelial neoplasia grade 3 (CIN3)**.**

RESULTS: 89,018 with a previous diagnosis of CIN3 (average age 35 years) and 89,018 matched control subjects without a history of CIN3 (average age 36 years).
Women with a history of CIN3 showed **increased risk of HPV-related carcinomas and premalignancies**. The increased risk showed a decrease over time with an IRR of 16.44 (95% CI, 8.68 to 31.13) in the first year, and an IRR of 2.57 (95% CI, 1.38 to 5.18) after 20 years. → **decreased over time it was still significantly increased up to 20 years after the CIN3 diagnosis.**

R.M.F. Ebisch et al., J Clin Oncol 35,2542-2550, 2017


CIN3 history
No CIN3 history
Incidence Rate (per 100,000 person-years)
70
60
50
40
30
20
10
0
*
Anal Cancer
AIN3
Vulvar Cancer
VIN3
Vaginal Cancer
VAIN3
Oropharyngeal Cancer
Any HPV-Related Carcinoma
Any HPV-Related Premalignancy
Any HPV-Related Carcinoma or Premalignancy

BJC British Journal of Cancer

www.nature.com/bjc

ARTICLE

Epidemiology

Increased risk of second cancers at sites associated with HPV after a prior HPV-associated malignancy, a systematic review and meta-analysis

Duncan C. Gilbert[1,2], Katie Wakeham[2], Ruth E. Langley[1] and Claire L. Vale[1]

British Journal of Cancer (2019) 120:256–268;

Studies reporting second cancers at anogenital and oropharyngeal sites after prior diagnoses (preinvasive/invasive HPV-associated cancer) were identified.
Studies reporting standardised incidence ratios (SIRs) were included in formal meta-analyses of second cancer risk.

BJC British Journal of Cancer www.nature.com/bjc

Searches returned 5599 titles, including 60 unique, eligible studies. Thirty-two (98 comparisons) presented SIRs for second cervical, anal, vulvo-vaginal, penile, and/or oropharyngeal cancers, included in the meta-analyses.

All studies reported increased cancers in the population with previous HPV-associated cancer when compared to controls. Pooled SIRs for second primary cancers ranged from 1.75 (95% CI 0.66–4.67) for cervical cancer after primary anal cancer, to 13.69 (95% CI 8.56–21.89) for anal cancer after primary vulvo-vaginal cancer.

For patients diagnosed with HPV-associated invasive or preinvasive tumours, the risk of a second HPV-associated cancer at most sites is approximately a fivefold increase as compared with unaffected individuals;

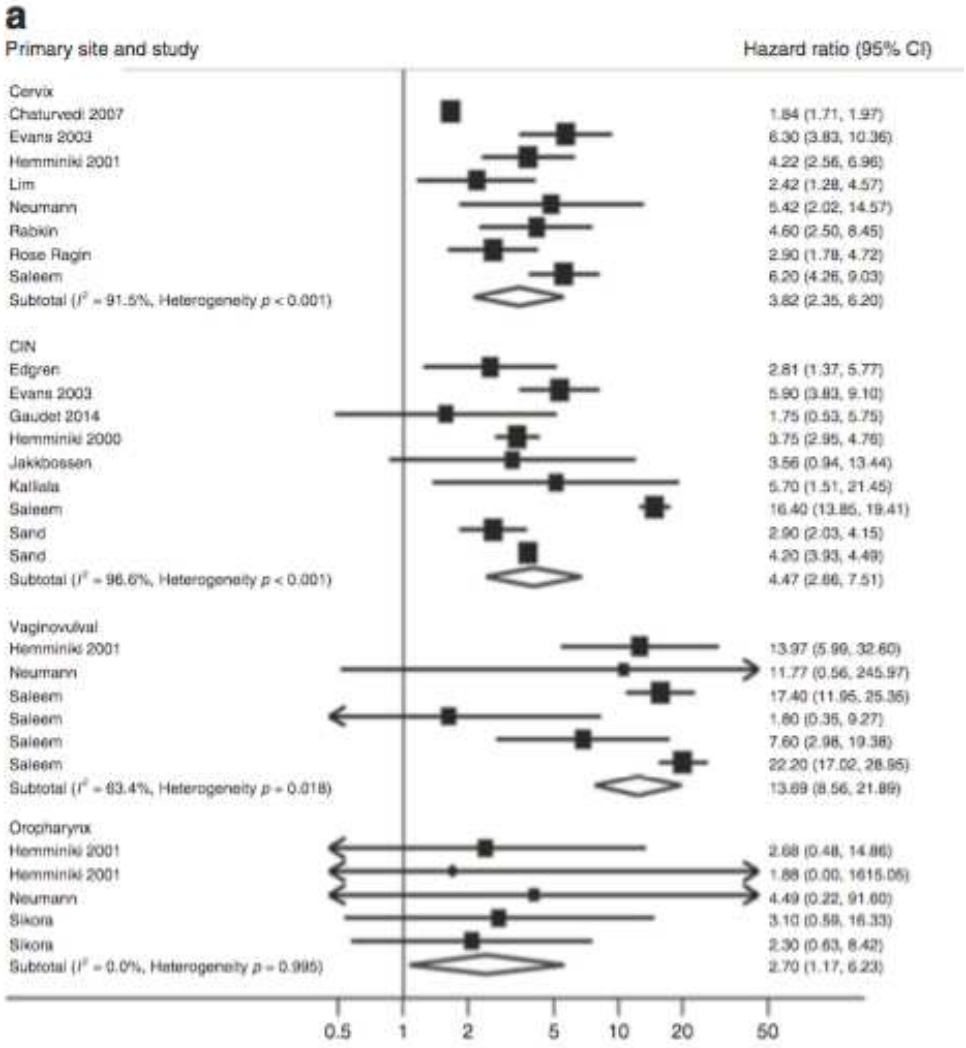


Table 2. Pooled SIRs of second HAC after primary tumours, and basal incidence, Europe and North America

Primary cancer	Secondary cancer, pooled SIR (95% CI)			
	Cervix	Vulvo-vaginal	Anal	Oropharyngeal
Cervix	1.61 (0.39–6.65)	7.76 (5.50–10.95)	3.82 (2.35–6.20)	1.72 (1.36–2.19)
CIN	2.40 (2.15–2.68)	5.09 (3.85–6.73)	4.47 (2.66–7.51)	2.01 (1.41–2.88)
Vulvo-vaginal	5.95 (1.39–25.47)	9.08 (5.46–15.12)	13.69 (8.56–21.89)	4.65 (2.36–9.16)
Anal	1.75 (0.66–4.67)	9.13 (5.84–14.28)	30.81 (23.50–40.39)	4.87 (1.96–6.81)
Penile	NA	NA	—	3.88 (2.21–6.81)
Oropharyngeal	2.21 (1.33–3.66)	3.74 (1.72–8.15)	2.70 (1.17–6.23)	22.45 (12.70–39.68)
Incidence (UK)	10 per 100,000	4.1 per 100,000	2 per 100,000	3–5 per 100,000
Incidence (Europe)[75]	15.2 per 100,000	0.8–4.1 per 100,000	1.2 per 100,000	7.9 per 100,000
Incidence (North America)[75]	8.1 per 100,000	2.5 per 100,000	1.8 per 100,000	6.1 per 100,000

BJC British Journal of Cancer www.nature.com/bjc

CORRESPONDENCE

Comment on "Increased risk of second cancers at sites associated with HPV after a prior HPV-associated malignancy, a systematic review and meta-analysis"

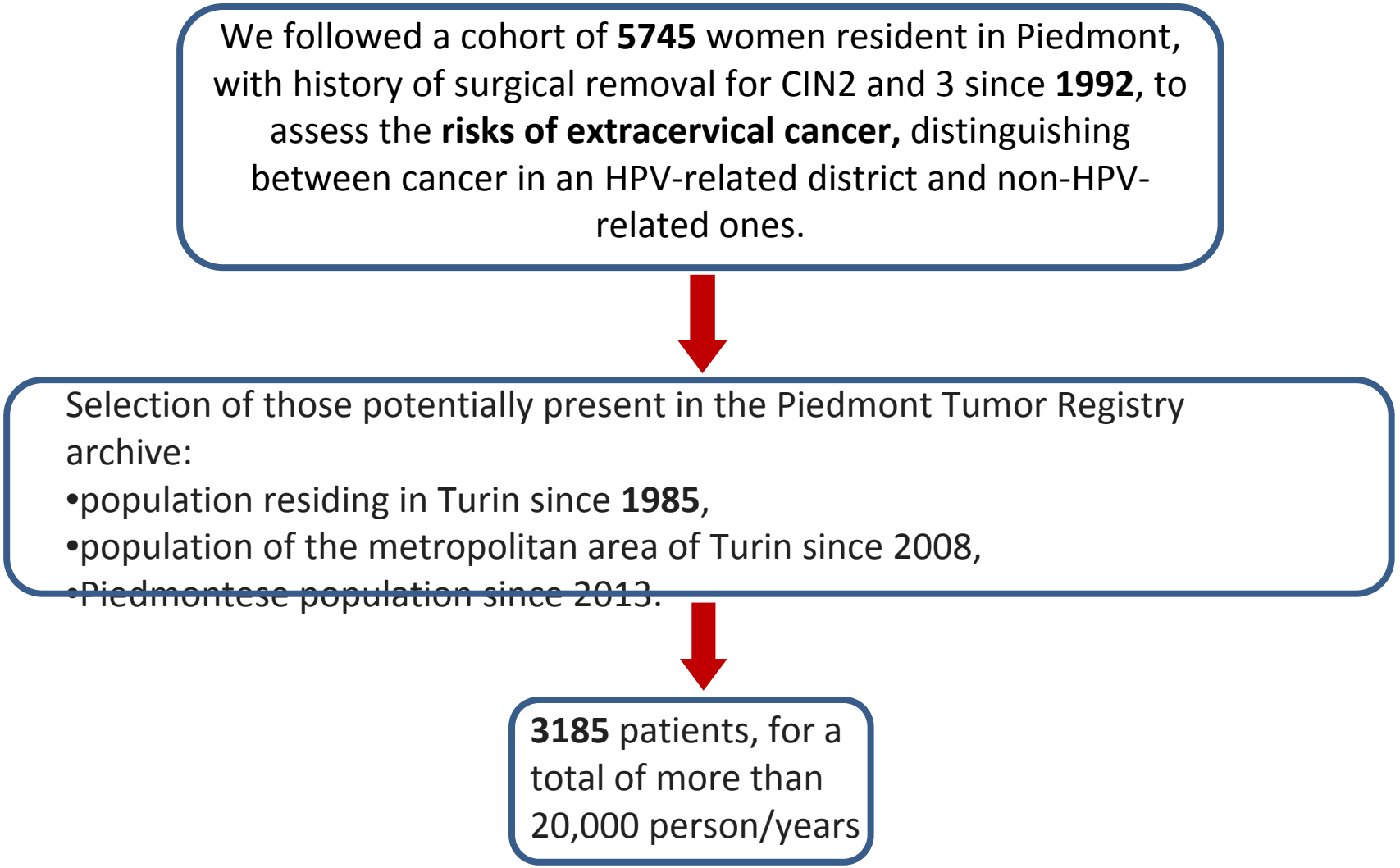
SMALL SAMPLE SIZE AND WIDER CONFIDENCE INTERVAL FOR QUANTITATIVE SYNTHESIS
INDIVIDUAL STUDY WEIGHT AGAINST POOLED ESTIMATED EFFECT SIZE

IS SIRS INTERCHANGEABLE WITH HAZARD RATIO (HRS)?

ESTIMATED VARIATION OF HETEROGENEITY BETWEEN STUDIES

PUBLICATION BIAS IS A CRUCIAL INDICATOR OF META- ANALYSIS IN CLINICAL RESEARCH


La collaborazione tra Registri Tumori e clinica

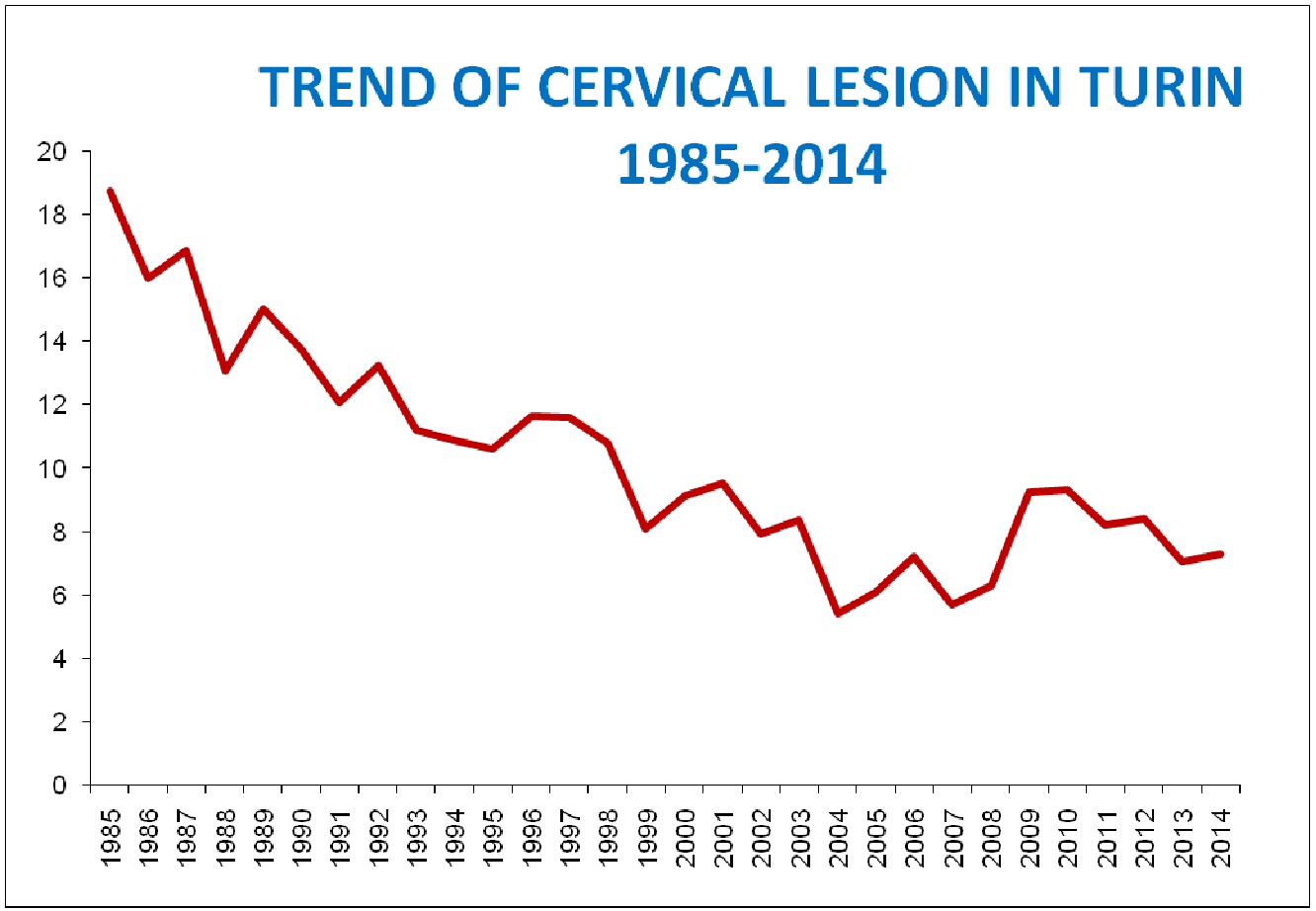

We followed a cohort of **5745** women resident in Piedmont, with history of surgical removal for CIN2 and 3 since **1992**, to assess the **risks of extracervical cancer,** distinguishing between cancer in an HPV-related district and non-HPV-related ones.
Selection of those potentially present in the Piedmont Tumor Registry archive:
•population residing in Turin since **1985**,
•population of the metropolitan area of Turin since 2008,
•Piedmontese population since 2013.
3185 patients, for a total of more than 20,000 person/years

HPV-RELATED CANCER RISK: STANDARDIZED INCIDENCE REPORT (SIR)

- **Expeted incidence rate**: age-specific cancer rate in Turin, metropolitan area and Piedmont population.

- **Confidence intervals (CI)** are calculated using Haenszel formula.

INCIDENCE - Age specific rates (per 100,000, per year)															Rough rates	Std mond
DISTRICT	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	85+		
Mouth C03-06	0,5	0,5	0,4	1,0	0,3	2,2	1,5	3,9	8,3	9,1	7,2	9,5	10,6	17,9	**4,09**	**1,58**
Anus C21	0,0	0,0	0,0	0,3	0,9	0,6	3,5	6,2	5,5	8,0	7,6	6,3	7,7	9,2	**3,24**	**1,29**
Vulva C51	0,0	0,0	0,0	0,3	0,3	0,8	2,4	1,6	4,8	7,7	12,8	10,3	23,7	12,4	**4,18**	**1,28**
Vagina C52	0,0	0,5	0,8	0,7	0,9	1,6	1,5	1,3	1,0	3,1	3,4	1,6	5,8	5,5	**1,57**	**0,68**
Lung C34	1,0	1,9	1,2	4,3	5,4	13,4	27,7	50,2	79,2	97,4	112,6	113,3	125,5	97,5	**41,62**	**15,78**
Bladder C67	0,0	0,5	0,0	2,3	3,1	3,3	10,9	21,6	31,5	44,4	58,9	58,8	86,9	72,2	**21,73**	**7,12**


TREND OF CERVICAL LESION IN TURIN
1985-2014
20
18
16
14
12
10
8
6
4
2
0
1985
1986
1987
1988
1989
1990
1991
1992
1993
1994
1995
1996
1997
1998
1999
2000
2001
2002
2003
2004
2005
2006
2007
2008
2009
2010
2011
2012
2013
2014

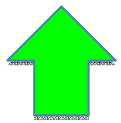
CANCERS in HPV RELATED SITES

VULVA C51

Expected	0,05
Observed	1
SIR	**18,24**
95% Lower lim	0,46
95% Upper lim	101,62

ANUS C21

Expected	0,12
Observed	1
SIR	**8,67**
95% Lower lim	0,22
95% Upper lim	48,28



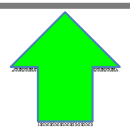
VAGINA C52

Expected	0,04
Observed	1
SIR	**25,24**
95% Lower lim	0,64
95% Upper lim	140,58

CANCERS in HPV RELATED SITES

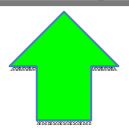
ORAL CAVITY AND PHARYNX C01-C10

Expected	0,26
Observed	4
SIR	**15,26**
95% Lower lim	4,15
95% Upper lim	39,06



TONGUE C01

Expected	0,13
Observed	3
SIR	**23,27**
95% Lower lim	4,79
95% Upper lim	67,95



CANCERS in NON HPV RELATED SITES

LUNG C34

Expected	1,78
Observed	17
SIR	**9,55**
95% Lower lim	5,57
95% Upper lim	15,28

BLADDER C67

Expected	0,74
Observed	4
SIR	**5,40**
95% Lower lim	1,47
95% Upper lim	13,82

? **MAY THEY BE RELATED TO SMOKE** ?

CANCERS in NON HPV RELATED SITES

BREAST C50

Expected	19,23
Observed	60
SIR	**3,12**
95% Lower lim	1,01
95% Upper lim	7,27

THYROID C73

Expected	3,37
Observed	10
SIR	**2,97**
95% Lower lim	0,96
95% Upper lim	6,92

LIVER C22
BILIARY DUCTS C24

Expected	0,64
Observed	3
SIR	**4,66**
95% Lower lim	0,96
95% Upper lim	13,61

CONCLUSIONS

The results support the hypothesis of the study of an increased risk of **non-cervical HPV-related tumors** in patients treated for CIN

Statistically significant risks were also recorded for other cancers (lung and bladder) linked to the possible **common risk factors.**

Women with diagnosis and treatment of high-grade CIN have a higher risk of developing extracervical cancer, this risk remains high even **20 years after treatment** for CIN.

Contents lists available at ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

Prevalence of high-grade anal dysplasia among women with high-grade lower genital tract dysplasia or cancer: Results of a pilot study☆

Joël Fokom Domgue [a,b,c], Craig Messick [d], Andrea Milbourne [a], Ming Guo [e], Mila P. Salcedo [a,f], Kristina R. Dahlstrom [g], Elizabeth Y. Chiao [h], Ashish A. Deshmukh [i], Erich M. Sturgis [g], Kathleen M. Schmeler [a,*]

[a] The Department of Gynecologic Oncology & Reproductive Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

The high prevalence of anal HSIL in this high-risk group supports its inclusion into anal screening guidelines.

- Anal cytology, anal HPV16/18 and high resolution anoscopy should be considered for anal cancer screening.
- Further study is needed to determine what screening strategy is suited to this population.