HPV-associated cancers in Ireland

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National Cancer Registry

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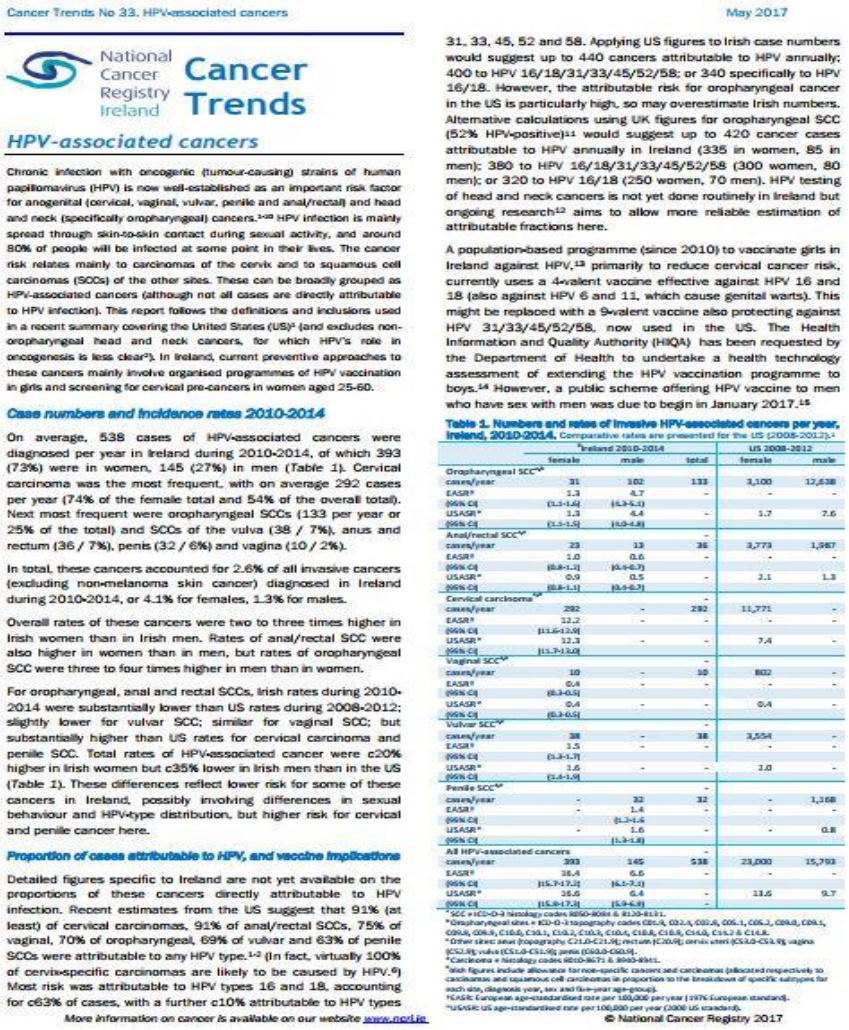

Cancer Trends No 33. HPV-associated cancers

May 2017

National Cancer Registry Ireland **Cancer Trends**

HPV-associated cancers

Chronic infection with oncogenic (tumour-causing) strains of human papillomavirus (HPV) is now well-established as an important risk factor for anogenital (cervical, vaginal, vulvar, penile and anal/rectal) and head and neck (specifically oropharyngeal) cancers.[1-10] HPV infection is mainly spread through skin-to-skin contact during sexual activity, and around 80% of people will be infected at some point in their lives. The cancer risk relates mainly to carcinomas of the cervix and to squamous cell carcinomas (SCCs) of the other sites. These can be broadly grouped as HPV-associated cancers (although not all cases are directly attributable to HPV infection). This report follows the definitions and inclusions used in a recent summary covering the United States (US)[1] (and excludes non-oropharyngeal head and neck cancers, for which HPV's role in oncogenesis is less clear[2]). In Ireland, current preventive approaches to these cancers mainly involve organised programmes of HPV vaccination in girls and screening for cervical pre-cancers in women aged 25-60.

Case numbers and incidence rates 2010-2014

On average, 538 cases of HPV-associated cancers were diagnosed per year in Ireland during 2010-2014, of which 393 (73%) were in women, 145 (27%) in men (*Table 1*). Cervical carcinoma was the most frequent, with on average 292 cases per year (74% of the female total and 54% of the overall total). Next most frequent were oropharyngeal SCCs (133 per year or 25% of the total) and SCCs of the vulva (38 / 7%), anus and rectum (36 / 7%), penis (32 / 6%) and vagina (10 / 2%).

In total, these cancers accounted for 2.6% of all invasive cancers (excluding non-melanoma skin cancer) diagnosed in Ireland during 2010-2014, or 4.1% for females, 1.3% for males.

Overall rates of these cancers were two to three times higher in Irish women than in Irish men. Rates of anal/rectal SCC were also higher in women than in men, but rates of oropharyngeal SCC were three to four times higher in men than in women.

For oropharyngeal, anal and rectal SCCs, Irish rates during 2010-2014 were substantially lower than US rates during 2008-2012; slightly lower for vulvar SCC; similar for vaginal SCC; but substantially higher than US rates for cervical carcinoma and penile SCC. Total rates of HPV-associated cancer were c20% higher in Irish women but c35% lower in Irish men than in the US (Table 1). These differences reflect lower risk for some of these cancers in Ireland, possibly involving differences in sexual behaviour and HPV-type distribution, but higher risk for cervical and penile cancer here.

Proportion of cases attributable to HPV, and vaccine implications

Detailed figures specific to Ireland are not yet available on the proportions of these cancers directly attributable to HPV infection. Recent estimates from the US suggest that 91% (at least) of cervical carcinomas, 91% of anal/rectal SCCs, 75% of vaginal, 70% of oropharyngeal, 69% of vulvar and 63% of penile SCCs were attributable to any HPV type.[1-2] (In fact, virtually 100% of cervix-specific carcinomas are likely to be caused by HPV.[6]) Most risk was attributable to HPV types 16 and 18, accounting for c63% of cases, with a further c10% attributable to HPV types 31, 33, 45, 52 and 58. Applying US figures to Irish case numbers would suggest up to 440 cancers attributable to HPV annually; 400 to HPV 16/18/31/33/45/52/58; or 340 specifically to HPV 16/18. However, the attributable risk for oropharyngeal cancer in the US is particularly high, so may overestimate Irish numbers. Alternative calculations using UK figures for oropharyngeal SCC (52% HPV-positive)[11] would suggest up to 420 cancer cases attributable to HPV annually in Ireland (335 in women, 85 in men); 380 to HPV 16/18/31/33/45/52/58 (300 women, 80 men); or 320 to HPV 16/18 (250 women, 70 men). HPV testing of head and neck cancers is not yet done routinely in Ireland but ongoing research[12] aims to allow more reliable estimation of attributable fractions here.

A population-based programme (since 2010) to vaccinate girls in Ireland against HPV,[13] primarily to reduce cervical cancer risk, currently uses a 4-valent vaccine effective against HPV 16 and 18 (also against HPV 6 and 11, which cause genital warts). This might be replaced with a 9-valent vaccine also protecting against HPV 31/33/45/52/58, now used in the US. The Health Information and Quality Authority (HIQA) has been requested by the Department of Health to undertake a health technology assessment of extending the HPV vaccination programme to boys.[14] However, a public scheme offering HPV vaccine to men who have sex with men was due to begin in January 2017.[15]

Table 1. Numbers and rates of invasive HPV-associated cancers per year, Ireland, 2010-2014. Comparative rates are presented for the US (2008-2012).[1]

	Ireland 2010-2014			US 2008-2012	
	female	male	total	female	male
Oropharyngeal SCC[a,b]					
cases/year	31	102	133	3,100	12,638
EASR[c]	1.3	4.7	-	-	-
(95% CI)	(1.1-1.6)	(4.3-5.1)			
USASR[d]	1.3	4.4	-	1.7	7.6
(95% CI)	(1.1-1.5)	(4.0-4.8)			
Anal/rectal SCC[a,b]			-		
cases/year	23	13	36	3,773	1,987
EASR[c]	1.0	0.6	-	-	-
(95% CI)	(0.8-1.2)	(0.4-0.7)			
USASR[d]	0.9	0.5	-	2.1	1.3
(95% CI)	(0.8-1.1)	(0.4-0.7)			
Cervical carcinoma[a,b]			-		
cases/year	292	-	292	11,771	-
EASR[c]	12.2	-	-	-	-
(95% CI)	(11.6-12.9)				
USASR[d]	12.3	-	-	7.4	-
(95% CI)	(11.7-13.0)				
Vaginal SCC[a,b]			-		
cases/year	10	-	10	802	-
EASR[c]	0.4	-	-	-	-
(95% CI)	(0.3-0.5)				
USASR[d]	0.4	-	-	0.4	-
(95% CI)	(0.3-0.5)				
Vulvar SCC[a,b]			-		
cases/year	38	-	38	3,554	-
EASR[c]	1.5	-	-	-	-
(95% CI)	(1.3-1.7)				
USASR[d]	1.6	-	-	2.0	-
(95% CI)	(1.4-1.9)				
Penile SCC[a,b]			-		
cases/year	-	32	32	-	1,168
EASR[c]	-	1.4	-	-	-
(95% CI)		(1.3-1.6			
USASR[d]	-	1.6	-	-	0.8
(95% CI)		(1.3-1.8)			
All HPV-associated cancers			-		
cases/year	393	145	538	23,000	15,793
EASR[c]	16.4	6.6	-	-	-
(95% CI)	(15.7-17.1)	(6.1-7.1)			
USASR[d]	16.6	6.4	-	13.6	9.7
(95% CI)	(15.8-17.3)	(5.9-6.8)			

[a] SCC = ICD-O-3 histology codes 8050-8084 & 8120-8131.
[b] Oropharyngeal sites = ICD-O-3 topography codes C01.9, C02.4, C02.8, C05.1, C05.2, C09.0, C09.1, C09.8, C09.9, C10.0, C10.1, C10.2, C10.3, C10.4, C10.8, C10.8, C10.9, C15.2 & C14.8.
[c] Other sites: anus (topography C21.0-C21.9); rectum (C20.9); cervix uteri (C53.0-C53.9); vagina (C52.9); vulva (C51.0-C51.9); penis (C60.0-C60.9).
[d] Carcinoma = histology codes 8010-8671 & 8940-8941.
[e] Irish figures include allowance for non-specific cancers and carcinomas (allocated respectively to carcinomas and squamous cell carcinomas in proportion to the breakdown of specific subtypes for each site, diagnosis year, sex and five-year age-group).
[f] EASR: European age-standardised rate per 100,000 per year (1976 European standard).
[g] USASR: US age-standardised rate per 100,000 per year (2000 US standard).

More information on cancer is available on our website www.ncri.ie

- Collects information on all new cases in Ireland
- Monitors trends and outcomes in different cancer types
- Produces annual reports, short reports on trends for different cancer types based on the data we collect
- **Report on HPV-associated cancers published May 2017**

www.ncri.ie

HPV infection & cancer:
A global prespective

National Cancer Registry Ireland

- >100 types of HPV
- HPV16 most frequent type in anal, vaginal, penile and oropharyngeal cancers (Bruni L et al. 2017)

Cervical cancer

- HPV16 and 18, the two vaccine-preventable types covered by current Irish vaccine, contribute to over 70% of all cervical cancer cases
- HPV31, 33, 35, 45, 52 & 58 account for an additional 20% of cervical cancers worldwide (Clifford G et al. 2006)

Oropharyngeal cancers

- Around 50-70% of oropharyngeal cancers are thought to be caused by HPV (mostly type 16) (Marur et al. 2010; Lucas-Roxburgh et al. 2017;Schache et al. 2016)
- HPV-18, 31 or 33 are also causative, but are less common

Background to NCRI report

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- Recent increase in media reporting of HPV and HPV vaccination – increased (negative?) public awareness of HPV
- Reporting period: 2010 – 2014 for 6 HPV-related cancers (plus 1994-2014 trends)
- Trends report & NCR/ICS infographic follow figures and definitions used in a recent U.S report and (oropharyngeal SCC) UK paper

Viens et al 2016 (US): ≥91% of cervical carcinomas, 91% of anal/rectal, 75% of vaginal, 70%* of oropharyngeal, 69% of vulvar and 63% of penile squamous cell carcinomas (SCC) attributable to HPV *52% (UK) used for NCRI report (Schache et al. 2016)

HPV-associated cancers
Cases and deaths

National Cancer Registry Ireland

- **538** cases of HPV-associated cancers diagnosed per yr 2010-2014
  - 393 in women; 145 in men
  - 292† cervical carcinoma cases, 133 oropharyngeal SCCs

  38 vulva SCCs, 36 anus/rectum, 32 penile, 10 vaginal (†262 2013-2015)
- **180** deaths per year from HPV-associated cancers in Ireland during 2010-2014

Applying US estimates (& UK proportion of 52% for oropharyngeal SCC), prop. of cases attributable to HPV:

- Estimated **420** cases are caused by HPV per year
  - 335 in women; 80 in men
  - 265 cervical, 69 oropharyngeal, 32 anus and rectum, 26 vulvar, 20 penile, 8 vaginal
- Estimated up to **130** deaths per year in Ireland from cancers caused by HPV (c100 in women & c30 in men)

Trends in HPV-associated cancers

Oropharyngeal SCC

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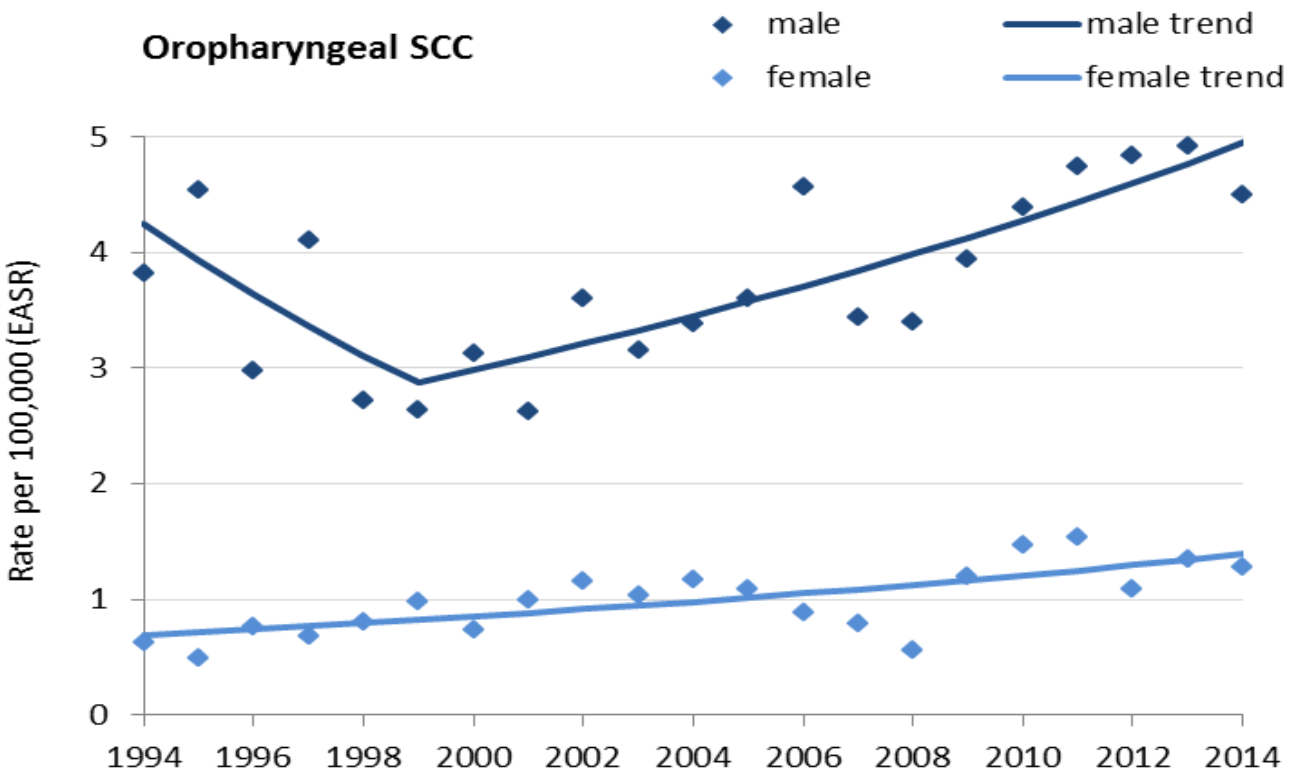
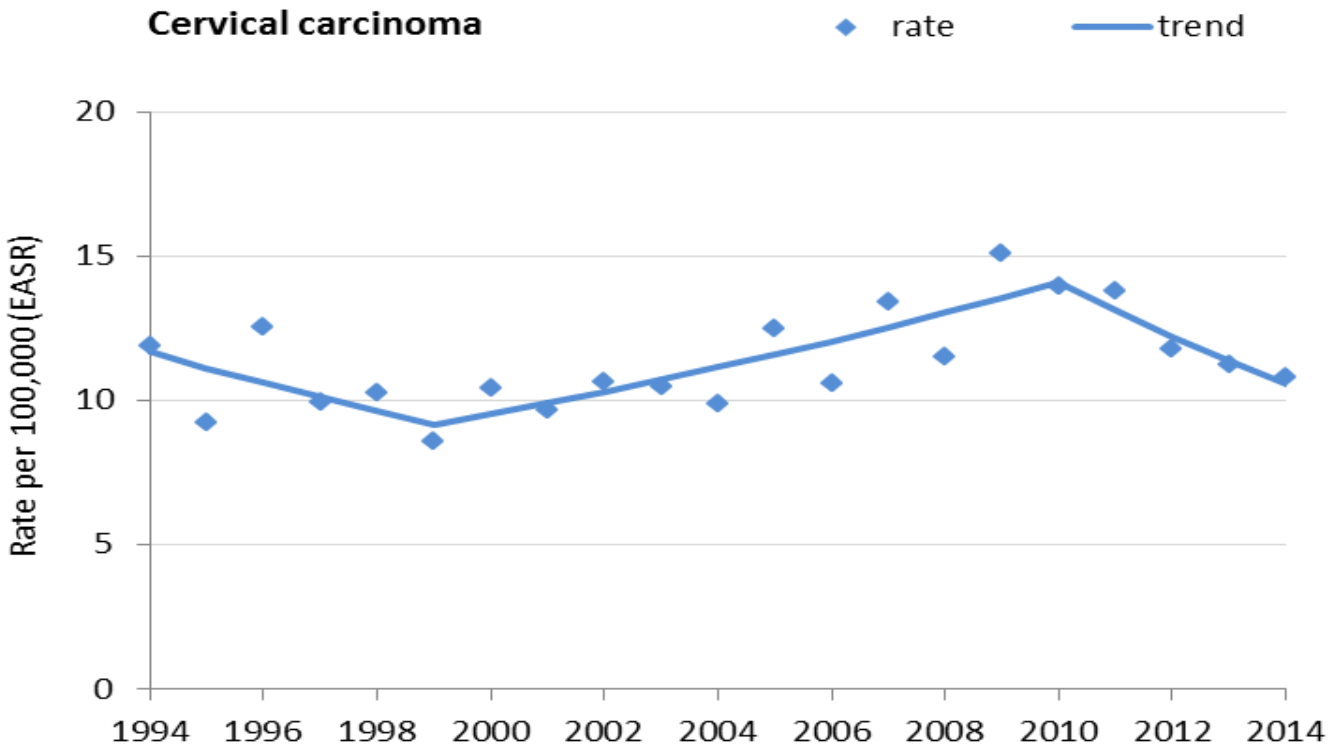


Sex	Period	APC	95% CI	P
Male	1994-1999	-7.5%	(-16.0%, +1.0%)	0.108
	1999-2014	+3.7%	(+2.1%, +5.3%)	<0.001
Female	1994-2014	+3.6%	(+1.9%, +5.2%)	<0.001

Trends in HPV-associated cancers

Cervical carcinoma

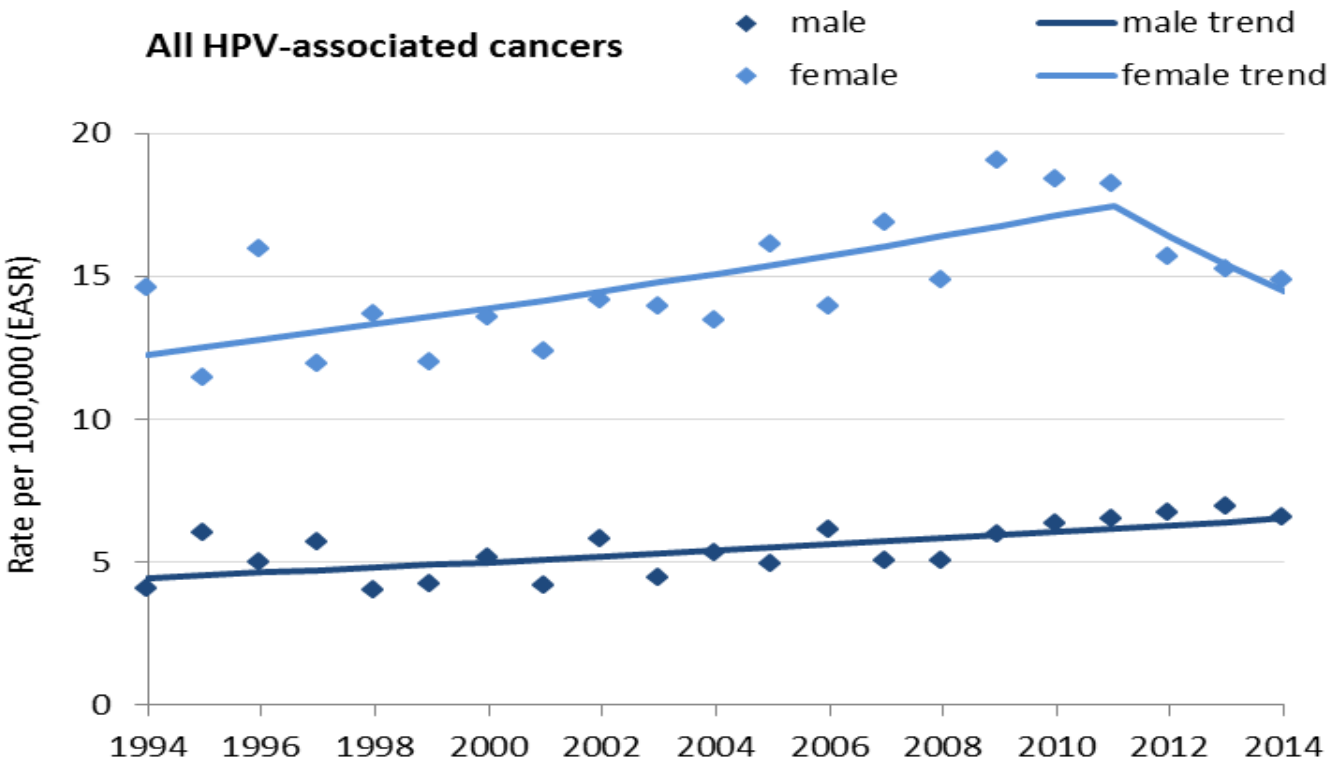


Sex	Period	APC	95% CI	P
Female	1994-1999	-4.7%	(-12.0%, +3.1%)	0.209
	1999-2010	+4.0%	(+1.5%, +6.5%)	0.040
	2010-2014	-7.0%	(-14.8%, +1.6%)	0.021

Trends in HPV-associated cancers

National Cancer Registry Ireland

All HPV-associated cancers



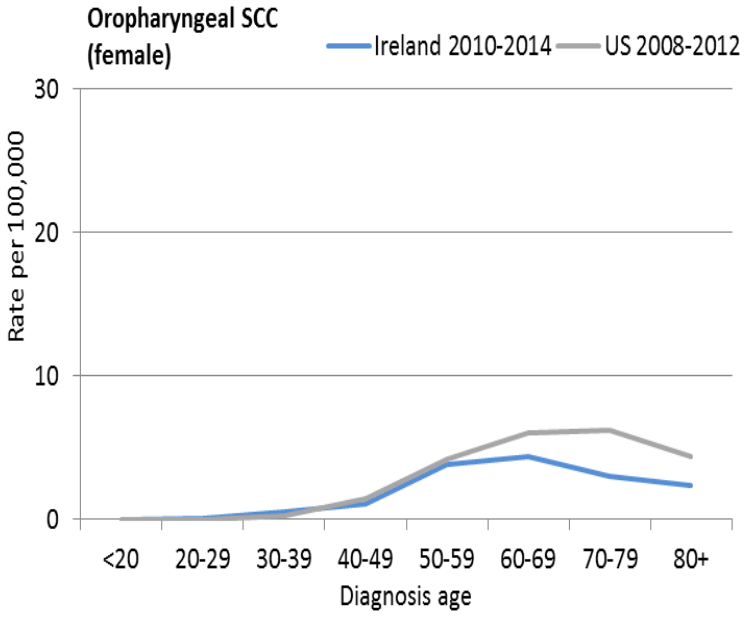
Sex	Period	APC	95% CI	P
Male	1994-2014	+1.9%	(+1.0%, +2.9%)	<0.001
Female	1994-2011	+2.1%	(+1.0%, +3.3%)	0.001
	2011-2014	-6.1%	(-18.7%, +8.5%)	0.238

Rates of HPV-associated cancer*: Ireland v US

Oropharyngeal cancer

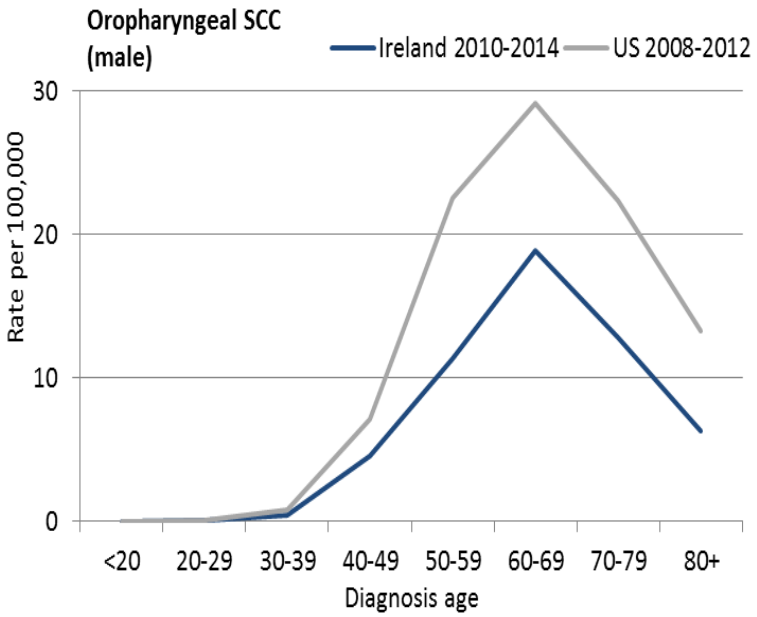
National Cancer Registry Ireland

Females



Overall rate Irl 0.8X < US

Males



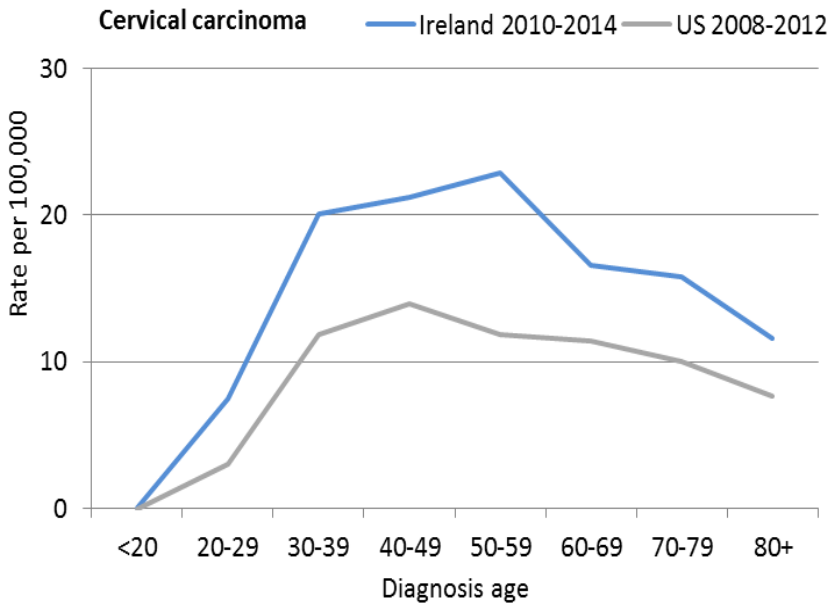
Overall rate Irl 0.6X < US

*Age-specific rates of HPV-associated cancers in Irl, 2010-2014 (and comparison with US, 2008-2012)

Rates of HPV-associated cancer

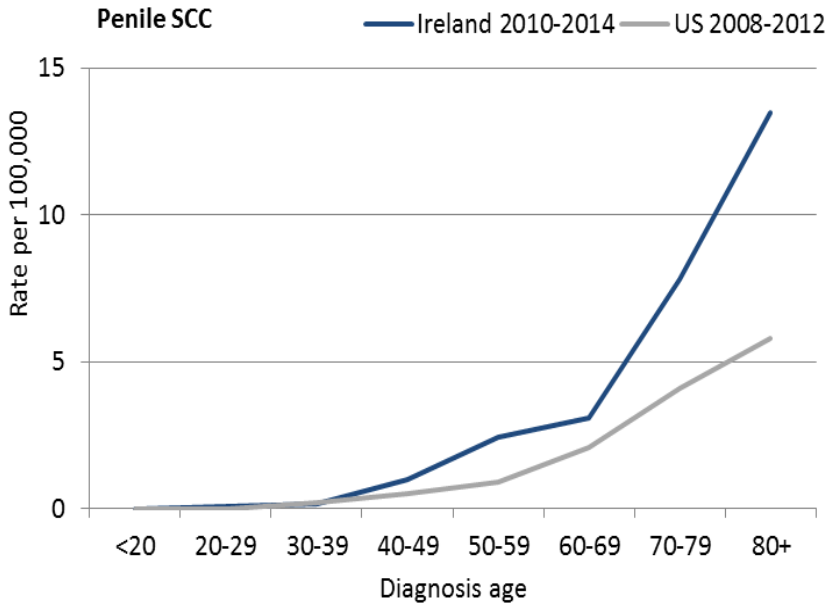
National Cancer Registry Ireland

Cervical carcinoma



Overall rate Irl 1.7X > US

Penile SCC



Overall rate Irl 2X > US

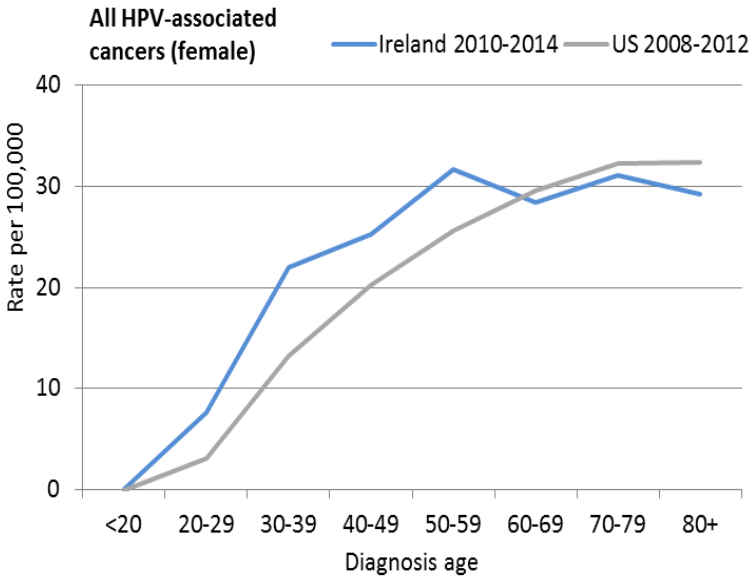
*Age-specific rates of HPV-associated cancers in Irl, 2010-2014 (and comparison with US, 2008-2012)

Rates of HPV-associated cancer

National Cancer Registry Ireland

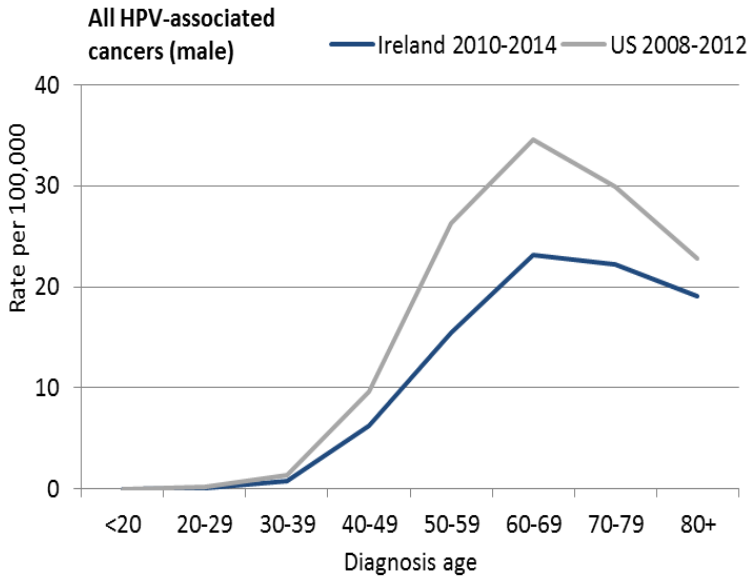
All HPV-associated cancers

Females



Overall rate Irl 1.2X > US

Males



Overall rate Irl 0.65X < US

*Age-specific rates of HPV-associated cancers in Irl, 2010-2014 (and comparison with US, 2008-2012)

Overall conclusions

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- Overall, HPV-associated cancers are increasing in Ireland– changes in sexual behaviours?
- Most of the 420 cancers estimated to be caused by HPV in Ireland every year may potentially be prevented through HPV vaccination
- Need for extension of school-based HPV vaccination programme to cover boys?
- Need for routine collection of HPV status of oropharyngeal or other SCCs by cancer registries?

CERVIVA Approach

CERVIVA aims to through an inter-disciplinary approach, to advance high-quality research that provides the best possible information and guidance in the delivery of services for HPV-related disease

National Cancer Registry Ireland

cerviva ICSRC Promoting quality research in HPV associated diseases

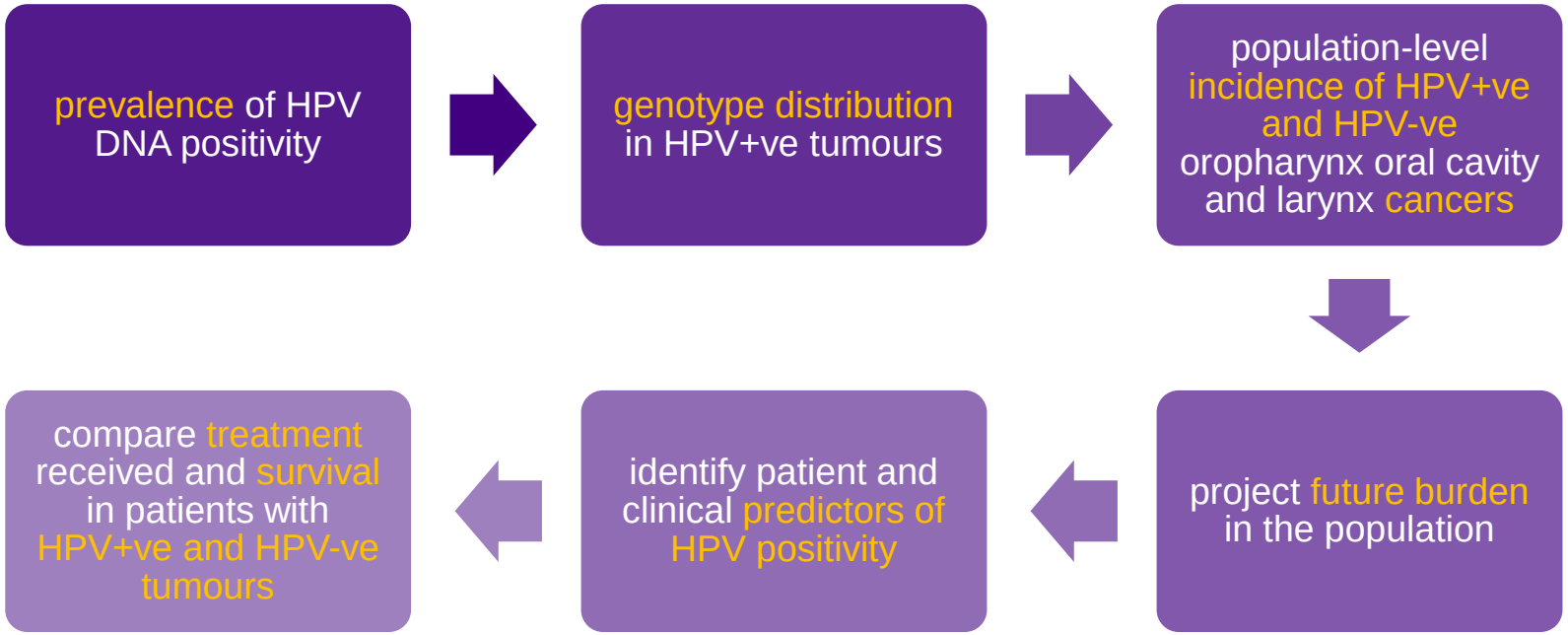
HRB Health Research Board

Design & Objectives of echo

Epidemiology of HPV Infection in Oral Cancer in Ireland

National Cancer Registry Ireland

Retrospective study of HPV infection in oropharyngeal, laryngeal and oral cavity squamous cell carcinoma, diagnosed between 1994 and 2013, in Ireland.



HPV in oral cancer pilot study*

HPV Positive: 44% Genotyping: 95%

HPV-16 (others: 33, 44, 52 and 6).

HPV negative: 56%

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*Woods 2016, TCD thesis

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- Dr Paul Walsh, Epidemiologist, NCR
- All NCR staff
- Hospitals, clinics and their staff – access to patient records, pathology notes etc
- Central Statistics Office and General Register Office – population and mortality data

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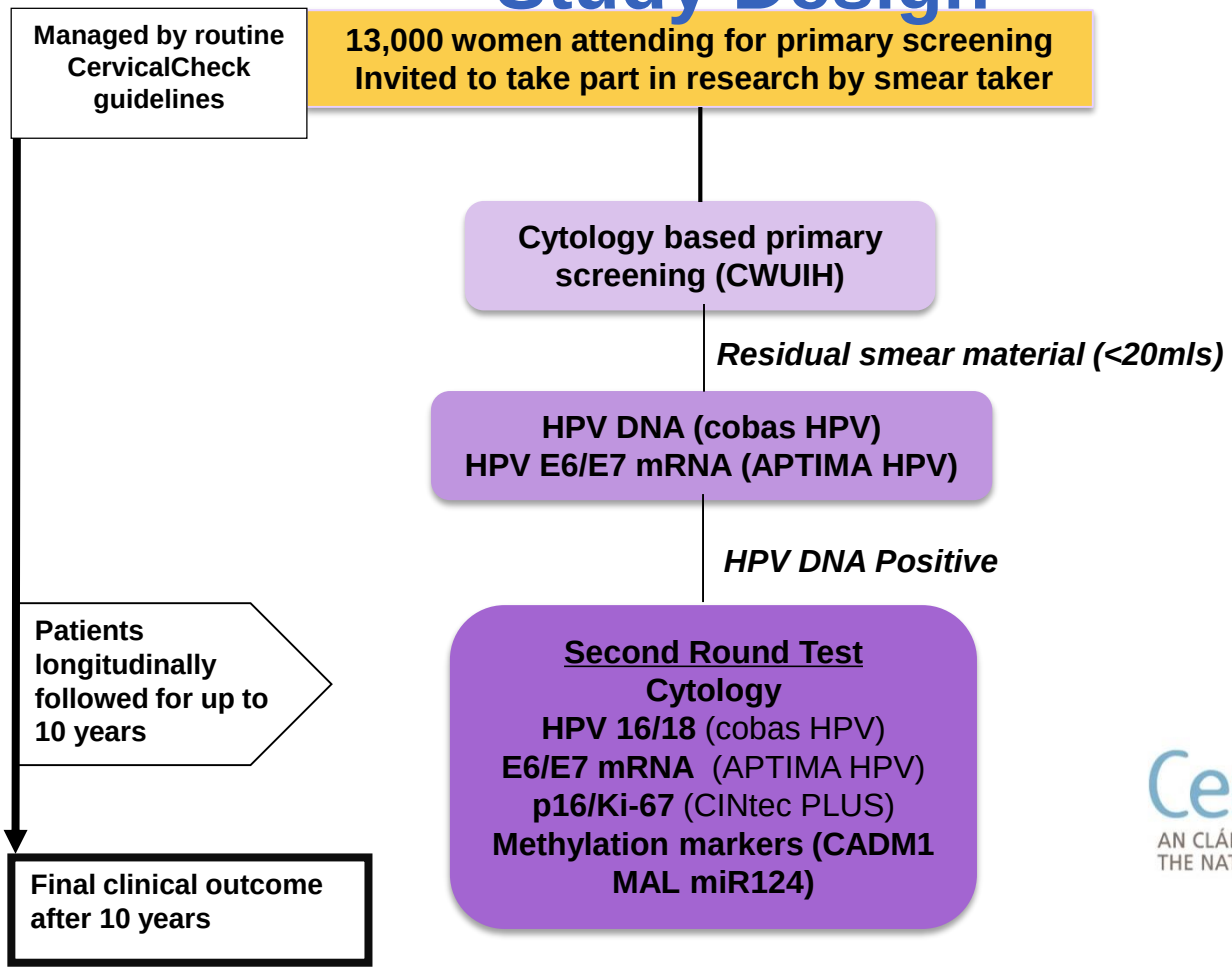
www.cerviva.ie

References

National Cancer Registry Ireland

- Marur, S. HPV-associated head and neck cancer: a virus related cancer epidemic. Lancet Oncology 2010; 11:781-789.
- Lucas-Roxburgh R, Benschop J, Lockett B, van den Heever U, Williams R, Howe L (2017) The prevalence of human papillomavirus in oropharyngeal cancer in a New Zealand population. PLoS ONE 12(10): e0186424.
- Viens LJ, Henley J, Watson et al. Human papilloma-virus associated cancers – United States, 2008-2012. MMWR Mor Mortal Wkly Rep. 2016; 65: 661-666.
- Clifford G et al. Vaccine 2006;24(S3):26-34.
- Bruni L, Barrionuevo-Rosas L, Albero G, Serrano B, Mena M, Gómez D, Muñoz J, Bosch FX, de Sanjosé S. ICO Information Centre on HPV and Cancer (HPV Information Centre). Human Papillomavirus and Related Diseases in the World. Summary Report 27.
- Schache AG, Powell NG, Cuschieri KS et al. HPV-related oropharynx cancer in the United Kingdom: An evolution in the understanding of disease etiology. Cancer Research Cancer Res. 2016; 76: 6598-6606. doi: 10.1158/0008-5472.CAN-16-0633.
- Walsh P, O'Connor M, Clough-Gorr K. Cancer Trends 33 – HPV-associated cancers https://www.ncri.ie/publications/cancer-trends-and-projections/cancer-trends-33-hpv-associated-cancers

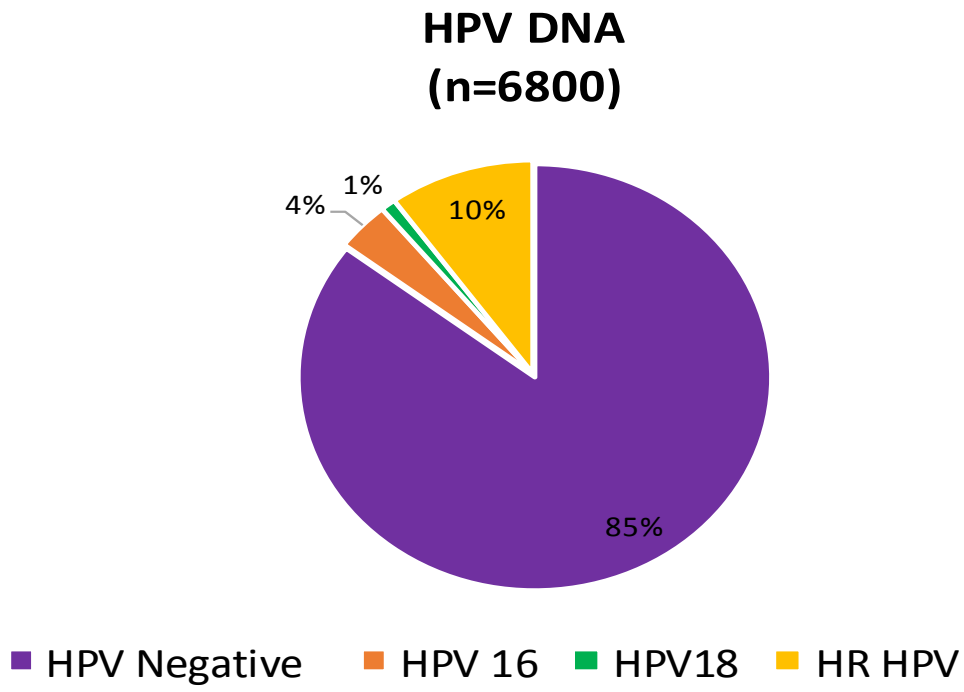
HPV Primary Screening Pilot
Study Design



Aim: evaluate a range of options for stratifying women following an initial HPV DNA positive screening test

HPV Primary Screening Pilot
Prevalence of HPV

National Cancer Registry Ireland



HPV Primary Screening Pilot
Prevalence of HPV in relation to age

National Cancer Registry Ireland

Age	HPV DNA		HPV mRNA			
	% (n)	OR (95% CI)	% (n)	OR (95% CI)	p value	Kappa
<30	**32.8%** (372/1135)	-	**28.8%** (327/1135)	-	<0.0001	0.767
30-39	**15.1%** (380/2522)	0.36 (0.308-0.429)	**12.9%** (325/2522)	0.37 (0.307-0.435)	<0.0001	0.689
40-49	**8.2%** (168/2042)	0.18 (0.150-0.225)	**7.0%** (143/2042)	0.19 (0.152-0.232)	0.035	0.584
50+	**7.1%** (78/1101)	0.15 (0.120-0.203)	**5.8%** (64/1101)	0.152 (0.115-0.202)	0.098	0.534

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