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†	1.3	4.7	-	-	-
(95% CI)	(1.1-1.6)	(4.3-5.1)			
USASR*	1.3	4.4	-	1.7	7.6
(95% CI)	(1.1-1.5)	(4.0-4.8)			
Anal/rectal SCC[a,c]			-		
cases/year	**23**	**13**	**36**	3,773	1,987
EASR†	1.0	0.6	-	-	-
(95% CI)	(0.8-1.2)	(0.4-0.7)			
USASR*	0.9	0.5	-	2.1	1.3
(95% CI)	(0.8-1.1)	(0.4-0.7)			
Cervical carcinoma[c,d]			-		
cases/year	**292**	**-**	**292**	11,771	-
EASR†	12.2	-	-	-	-
(95% CI)	(11.6-12.9)				
USASR*	12.3	-	-	7.4	-
(95% CI)	(11.7-13.0)				
Vaginal SCC[a,c]			-		
cases/year	**10**	**-**	**10**	802	-
EASR†	0.4	-	-	-	-
(95% CI)	(0.3-0.5)				
USASR*	0.4	-	-	0.4	-
(95% CI)	(0.3-0.5)				
Vulvar SCC[a,c]			-		
cases/year	**38**	**-**	**38**	3,554	-
EASR†	1.5	-	-	-	-
(95% CI)	(1.3-1.7)				
USASR*	1.6	-	-	2.0	-
(95% CI)	(1.4-1.9)				
Penile SCC[a,c]			-		
cases/year	**-**	**32**	**32**	-	1,168
EASR†	-	1.4	-	-	-
(95% CI)		(1.2-1.6			
USASR*	-	1.6	-	-	0.8
(95% CI)		(1.3-1.8)			
All HPV-associated cancers			-		
cases/year	**393**	**145**	**538**	23,000	15,793
EASR†	16.4	6.6	-	-	-
(95% CI)	(15.7-17.2)	(6.1-7.1)			
USASR*	16.6	6.4	-	13.6	9.7
(95% CI)	(15.8-17.3)	(5.9-6.9)	-		

[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, C10.9, C14.0, C14.2 & 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.
#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).
†EASR: European age-standardised rate per 100,000 per year (1976 European standard).
*USASR: US age-standardised rate per 100,000 per year (2000 US standard).

Incidence trends over time

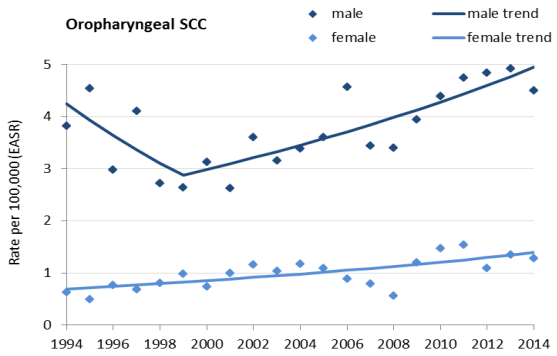
Rates of anal/rectal SCC increased significantly, by on average 3-4% annually, between 1994 and 2014. Other trends were generally upward, though non-significant for vaginal/vulvar and penile SCC and more complex for oropharyngeal and cervical cancers (*Figure 1*).

For oropharyngeal SCC, female rates increased significantly by, on average, 3.6% per year across the whole period, but male rates showed an initial non-significant decrease, followed by a significant 3.7% annual increase from 1999 to 2014. Tobacco and alcohol are also important risk factors for oropharyngeal cancer, and trends in these factors, in additions to HPV exposure, are likely also contributing. Lung cancer rates (mainly influenced by smoking) have fallen significantly in men but increased in women since 1994, while liver cancer rates (likely influenced by alcohol consumption) have increased significantly in both sexes.[16,17]

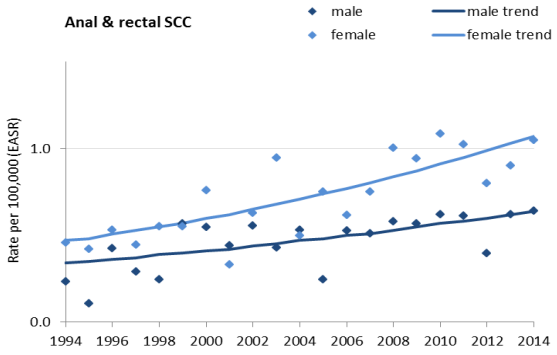
Cervical carcinoma rates showed an initial non-significant decrease, from 1994 to 1999, followed by a significant increase 1999-2010 then a significant decrease 2010-2014. In part, these trends may reflect the influence of the introduction of the CervicalCheck screening programme in 2008.

Overall rates of HPV-associated cancers increased for both sexes by about 2% per year over most of the period examined, but female rates fell from 2011 to 2014, reflecting trends in cervical cancer (*Figure 1*). Trends did not differ significantly between males and females for any site or overall. In comparison, cancer rates as a whole in Ireland have increased more slowly over the

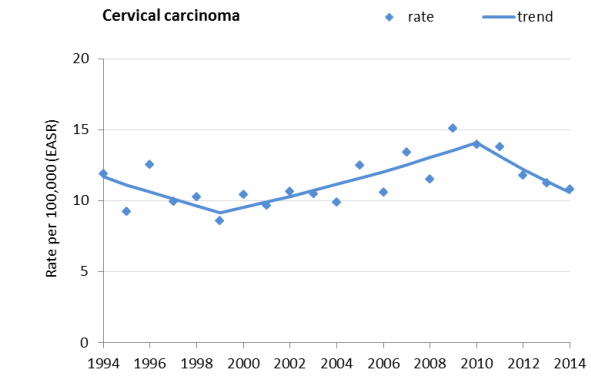
Figure 1. Trends in HPV-associated cancers in Ireland, 1994-2014. The fitted trends are based on Joinpoint analysis.[18-19]



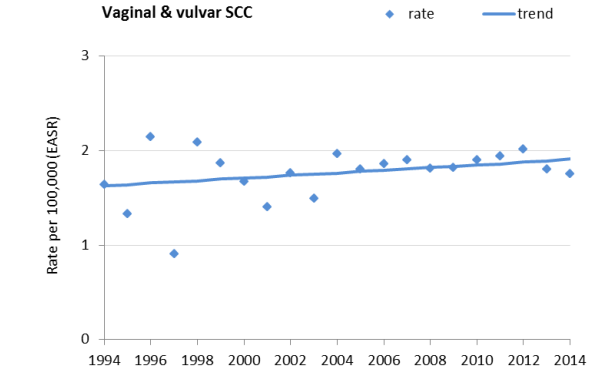
Sex	Period	APC	95% CI	P
Male	1994-1999	-7.5%	(-16.0%, +1.0%)	0.108
	1999-2014	**+3.7%**	(+2.1%, +5.3%)	<0.001
Female	1994-2014	**+3.6%**	(+1.9%, +5.2%)	<0.001



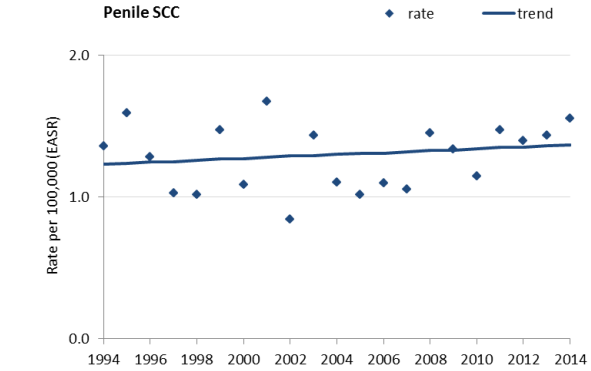
Sex	Period	APC	95% CI	P
Male	1994-2014	**+3.2%**	(+1.1%, +5.5%)	0.005
Female	1994-2014	**+4.3%**	(+2.7%, +5.9%)	<0.001



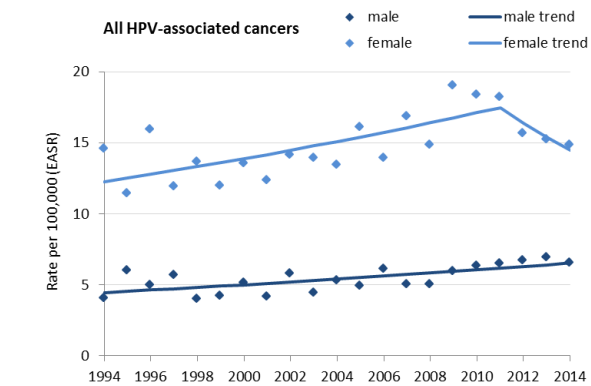
Sex	Period	APC	95% CI	P
Female	1994-1999	-4.7%	(-12.0%, +3.1%)	0.209
	1999-2010	**+4.0%**	(+1.5%, +6.5%)	0.040
	2010-2014	**-7.0%**	(-14.8%, +1.6%)	0.021



Sex	Period	APC	95% CI	P
Female	1994-2014	+0.8%	(-0.4%, +2.0%)	0.179



Sex	Period	APC	95% CI	P
Male	1994-2014	+0.5%	(-0.8%, +1.8%)	0.413



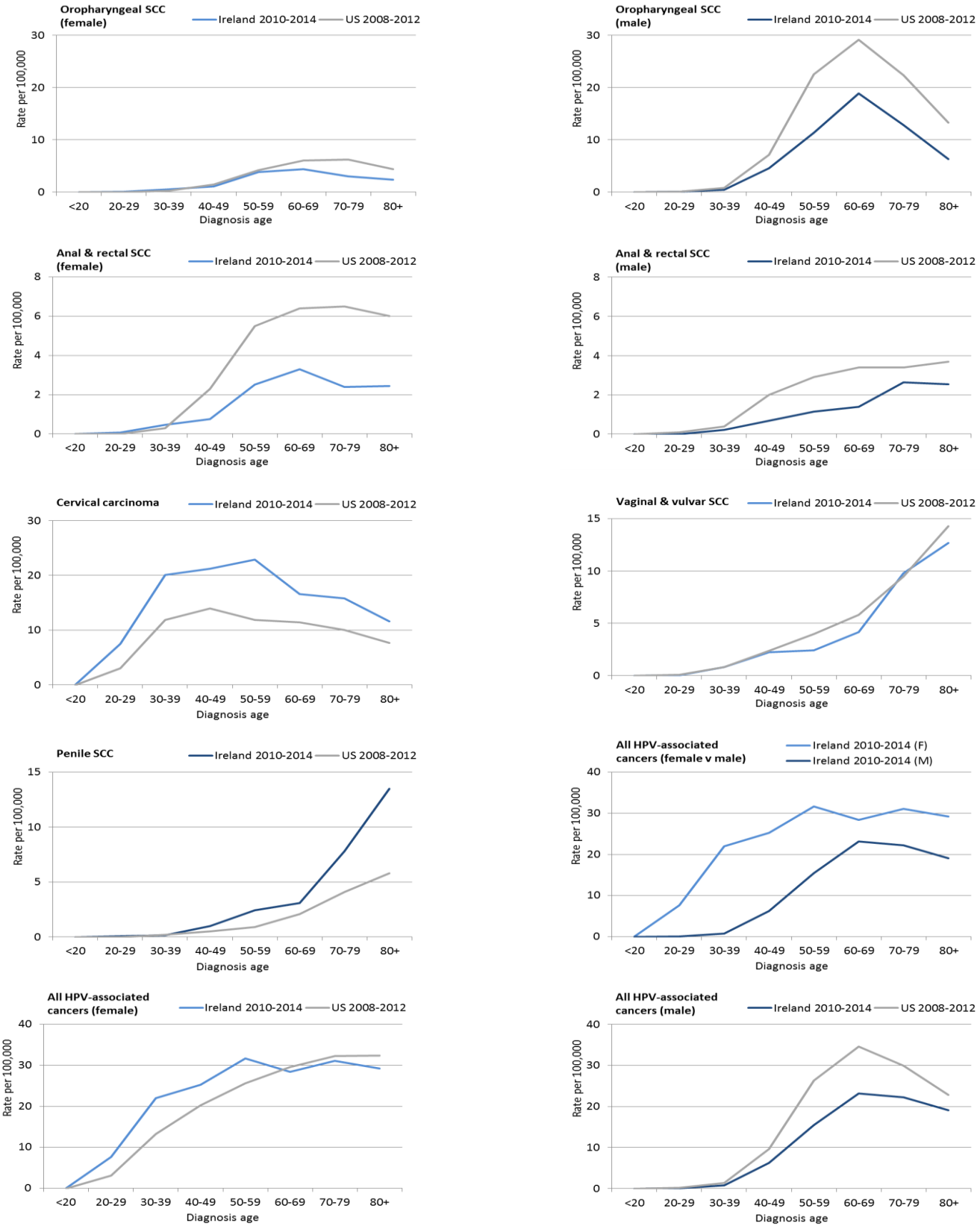
Sex	Period	APC	95% CI	P
Male	1994-2014	**+1.9%**	(+1.0%, +2.9%)	<0.001
Female	1994-2011	**+2.1%**	(+1.0%, +3.3%)	0.001
	2011-2014	-6.1%	(-18.7%, +8.5%)	0.238

Age at diagnosis

Age-specific rates are summarised in *Figure 2* for the period 2010-2014 for Ireland and, for comparison, for 2008-2012 for the US.[1] Cervical carcinomas showed the youngest age-profile, penile and vaginal/vulvar SCCs the oldest, with oropharyngeal and anal/rectal SCCs intermediate. Rates of cervical carcinoma and penile SCC were higher in most age-groups in Ireland than in the US, but the opposite pattern was seen for oropharyngeal and anal/rectal SCCs.

Overall female rates of HPV-associated cancer were higher in Ireland than the US for all age-groups under 60 (reflecting the high rates of cervical carcinoma in Irish women) and substantially higher than rates in Irish men. In contrast, overall male rates were higher in the US in most age-groups.

Figure 2. Age-specific rates of HPV-associated cancers in Ireland, 2010-2014 (and comparison with US rates, 2008-2012[1]). SCC = squamous cell carcinoma. Irish figures include allowance for non-specific cancers and carcinomas (see footnote to Table 1).



Tumour-directed treatment

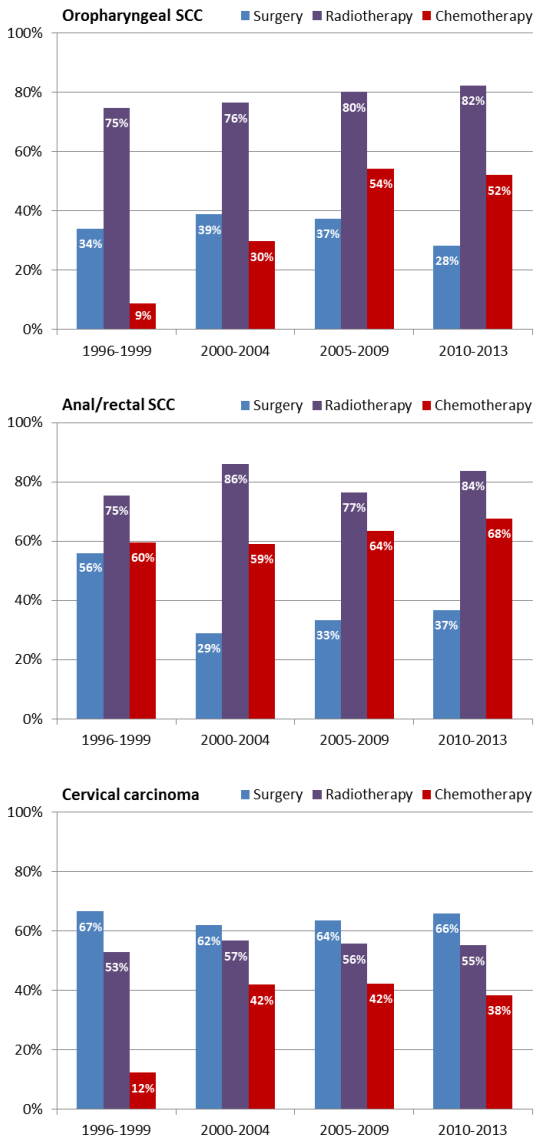
Radiotherapy and surgery were the most frequent treatment modalities overall for HPV-associated cancers: 60% of patients diagnosed during 2010-2013 had radiotherapy and 57% surgery as part of their initial treatment (*Figure 3*). Chemotherapy use was also substantial (40% for 2010-2013).

Treatment varied substantially by cancer site. Surgery was the most frequent treatment for vulvar and penile SCC and, to a lesser extent, cervical carcinoma; radiotherapy for oropharyngeal, anal/rectal and vaginal SCC. Chemotherapy use was highest for anal/rectal and oropharyngeal SCC and also substantial for cervical cancer.

Use of chemotherapy increased markedly over time for most sites, notably oropharyngeal SCC and cervical carcinoma. Time-trends for surgery and radiotherapy were less clear, but there was a reduction in use of surgery for some sites (notably anal/rectal and vaginal SCC) and an increase in radiotherapy for others (vulvar and to a lesser extent oropharyngeal SCC).

Approximately equal numbers of patients had single-modality (most commonly surgical) and multi-modality treatments (most commonly radiotherapy and chemotherapy) (*Figure 4*).

Figure 3. Proportions of patients having tumour-directed treatment within 12 months after diagnosis, by cancer type and diagnosis period.



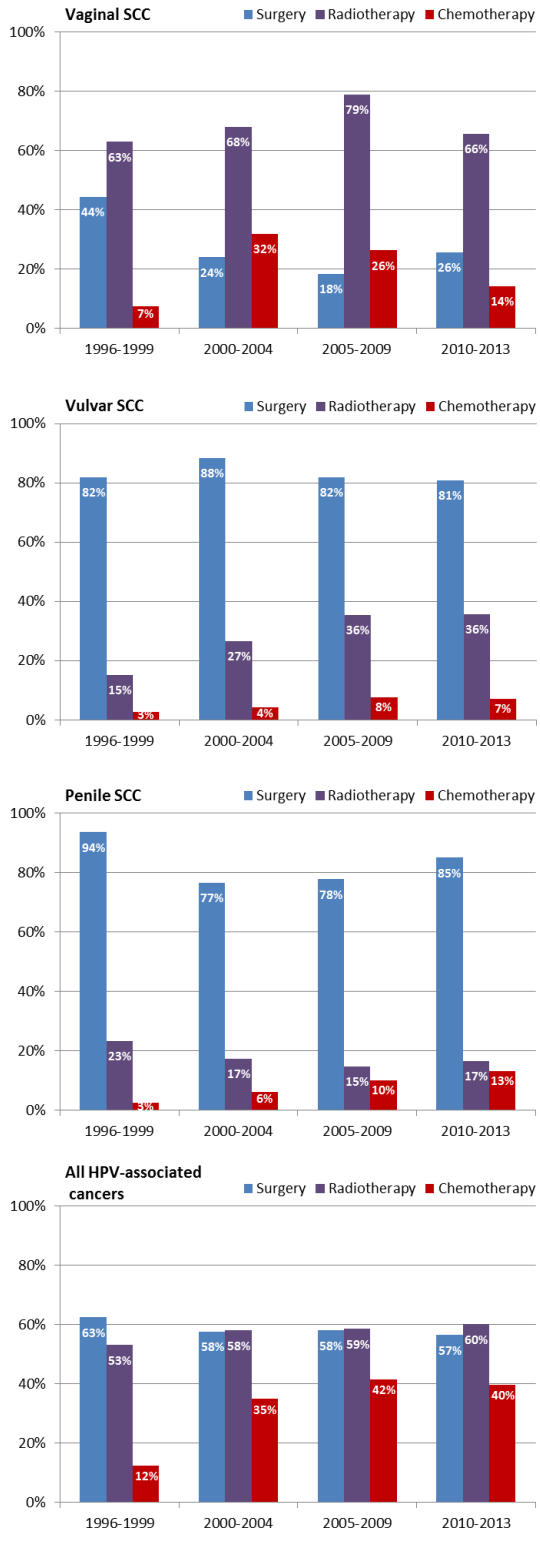
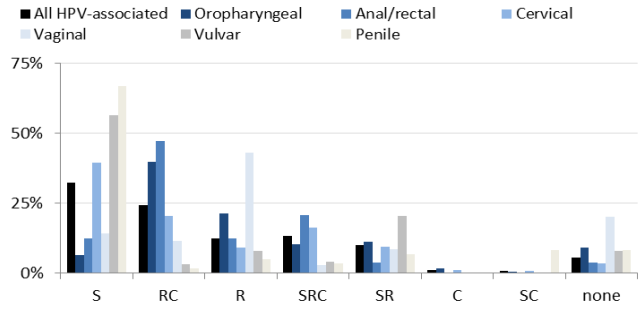


Figure 4. Single- and multi-modality treatments used for patients diagnosed 2010-2013. S = surgery, R = radiotherapy, C = chemotherapy.

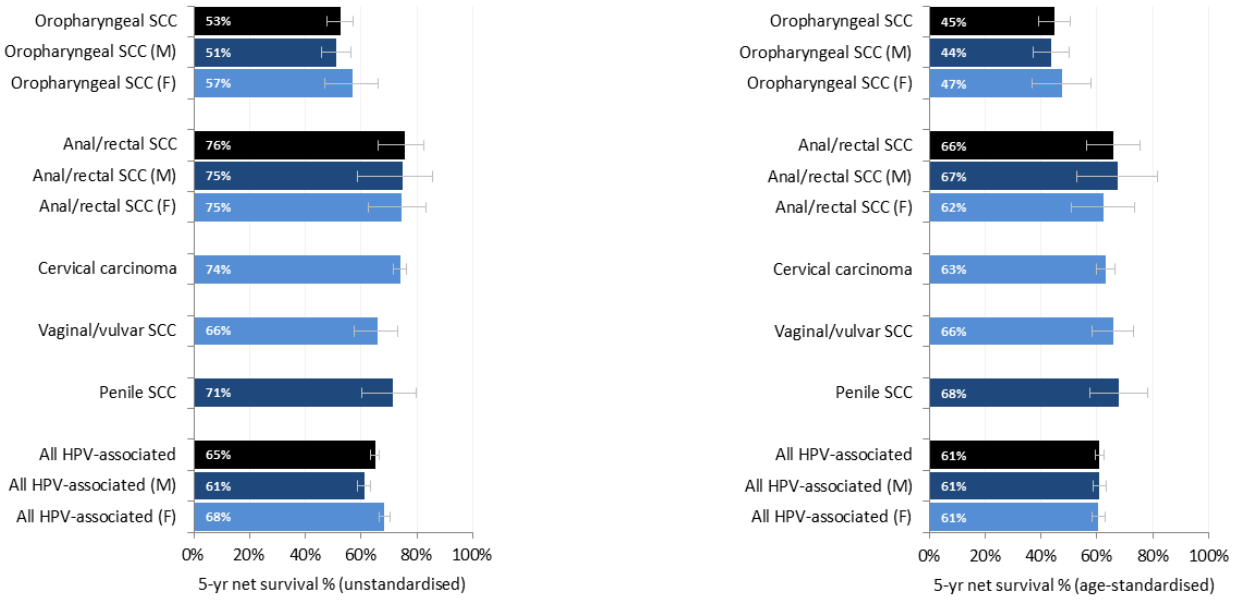


Survival

The most recent estimates of five-year net survival (i.e. survival relative to that expected in the general population) range from 53% for patients with oropharyngeal SCC to 76% for patients with anal or rectal SCC, before standardising for age (*Figure* 5). These figures reflect the survival of Irish patients followed up during 2010-2014. (Survival estimates age-standardised to the standard patient populations proposed by Corrazziari et al. 2004[20] are also presented, but for cervical cancer the estimates give greater weight to younger patients thus are not directly comparable with those for other cancers.)

Five-year survival of patients with HPV-associated cancers averaged 65% overall, 61% for men and 68% for women, reflecting older average age at diagnosis in males. However, age-standardised survival averaged 61% for both sexes, i.e. no significant difference. Likewise, there was no significant difference in age-standardised survival between males and females for oropharyngeal SCC or for anal/rectal SCC.

Figure 5. Five-year net survival estimates for HPV-associated cancers, based on all patients followed up during the period 2010-2014. Both age-standardised[18] and unstandardised estimates are presented (age-standardised cervical estimates use different population weights). 95% confidence intervals are shown.

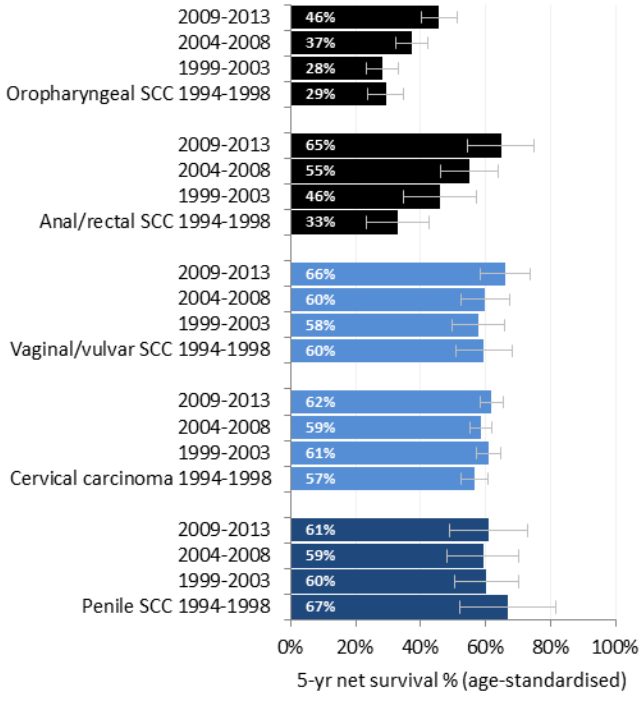


Age-standardised net survival improved significantly between diagnosis periods 1994-1998 and 2009-2013 for oropharyngeal SCC, from 29% to 46%, and for anal/rectal SCC, from 33% to 65% (*Figure* 6). However, there was only limited evidence of any improvement for cervical carcinoma or vaginal/vulvar SCC and none for penile SCC.

It is not straightforward to relate these survival changes to possible changes in treatment, early detection or other factors. Improvements in survival from oropharyngeal SCC seem consistent with increases in use of chemotherapy (see Figure 3). But survival improvements for anal/rectal SCC seem more marked, and for cervical carcinoma less marked, than chemotherapy trends might imply.

There is evidence from a range of studies that prognosis of oropharyngeal cancer patients is better for cases with HPV involvement.[21-22] Possible trends in the HPV status of Irish cases that might contribute to improving survival are unknown at present. However, in the UK the proportion of HPV-positive oropharyngeal SCCs showed no change between 2002 and 2011.[12]

Figure 6. Five-year net survival estimates (age-standardised) for HPV-associated cancers, by diagnosis period.



Mortality

Mortality from cancers of specific cell-types is not well captured by death certificates, thus it is not straightforward to assess time-trends in mortality for HPV-associated cancers using typical mortality data. However, *Table 2* uses an 'incidence-based mortality' approach and summarises the annual average numbers of cause-specific cancer deaths during 2010-2014 among patients diagnosed with HPV-associated cancers from 1994 onwards. (This covers the period for which incidence data by cell-type are available). This may miss a small number of deaths from cancers diagnosed pre-1994, but most 2010-2014 deaths will be from recently-diagnosed cases.

There were, on average, about 180 deaths per year from HPV-associated cancers during 2010-2014, with approximately twice as many in women as in men. Using the proportions of cases recently attributed to HPV in the US[1,2] for anogenital cancers and in the UK[11] for oropharyngeal SCC would suggest that up to 130 cancer deaths per year (c100 in women and c30 in men) in Ireland might be attributed to HPV. This would be equivalent to 1.5% of all cancer deaths in Ireland, or 2.5% of female cancer deaths and 0.7% of male cancer deaths. Of these, up to 100 deaths per year (c75 in women and c25 in men) might be attributable to HPV types 16 and 18 included in the current 4-valent HPV vaccine in Ireland, or up to 120 deaths per year (c90 in women and c30 in men) to HPV types included in the 9-valent vaccine now used in the US. These figures may be slightly overestimated because HPV-positive oropharyngeal cases have higher average survival.[21-22]

Table 2. Numbers of deaths per year from HPV-associated cancers, Ireland, 2010-2014.[a]

	#Ireland 2010-2014		
	female	male	total
Oropharyngeal SCC			
deaths/year	13	44	57
Anal/rectal SCC			
deaths/year	4	3	8
Cervical carcinoma			
deaths/year	86	-	86
Vaginal SCC			
deaths/year	5	-	5
Vulvar SCC			
deaths/year	13	-	13
Penile SCC			
deaths/year	-	10	10
All HPV-associated cancers			-
deaths/year	121	57	178

[a] Incidence-based mortality estimates based on cause-specific cancer deaths during 2010-2014 among patients diagnosed 1994-2014 with the site/morphology combinations specified in Table 1 (incidence), including adjustment for non-specific morphology types.

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