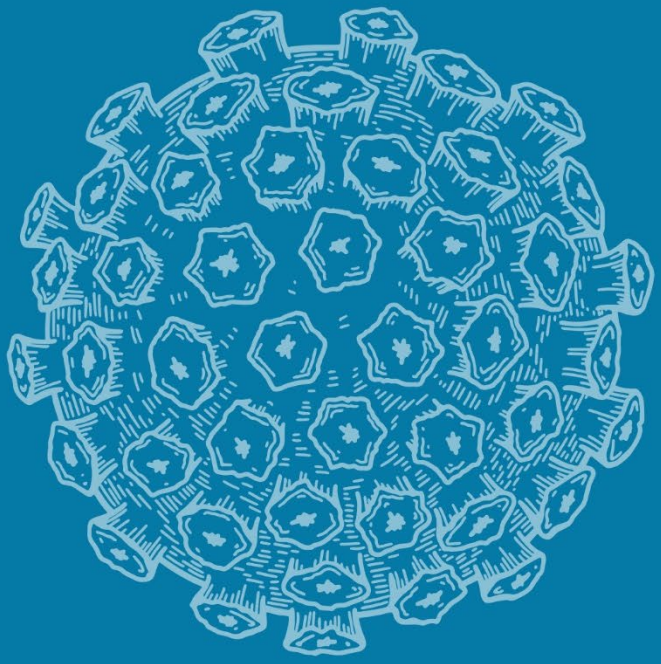
National Cancer Registry Ireland

HPV-ASSOCIATED CANCERS

Cancer Trends Report



THE NATIONAL CANCER REGISTRY

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HPV-associated cancers

Key points

HPV-associated cancers accounted for 2.7% of all invasive cancers excluding non-melanoma skin cancer (NMSC) in Ireland in 2017-2021.

The age-standardised incidence rate for cervical carcinoma has been decreasing since 2010, following the introduction of a population based screening programme in 2008.

The age standardised incidence rate for most other HPV-associated cancers is increasing.

The stage at diagnosis varies by cancer site, with the majority of cervical carcinoma, vulval squamous cell carcinoma (SCC), and penile SCC being diagnosed early (at stage I or II), whereas the majority of oropharyngeal SCC were diagnosed late (at stage III or IV). Survival for most HPV-associated cancers has increased from 1994-1998 to 2014-2018.

Introduction

Human papilloma virus (HPV) is a group of viruses known to infect the genital area, as well as the mouth and the throat. There are 13 HPV subtypes which are considered high-risk, as these are more likely to cause cell changes that over time can develop into cancers. The most common subtypes are subtypes 16 and 18 (1). Almost all sexually active people develop HPV infection within a few years of becoming sexually active and about half of these infections are with a high risk HPV-type virus. These high risk HPV infections are estimated to cause about 5% of all cancers worldwide (2).

The most common HPV-associated cancer is cervical cancer and almost all cervical cancer is caused by chronic HPV infection (2–4). Only 2% of cervical cancers diagnosed in Ireland during 2017-2021 were cancer subtypes not associated with HPV infection. In addition, HPV infection is associated with squamous cell carcinomas (SCC) of the vulva, vagina, penis, anus, oral cavity, and oropharynx (5). Vaccination and regular screening play crucial roles in preventing and detecting HPV-associated cancers early.

Population screening for cervical cancer was rolled out in Ireland in 2008, with the positive impact of screening on cancer incidence being seen almost immediately (6,7). HPV vaccination was introduced for girls in first year of secondary school from 2010. In 2019, the vaccination was extended to boys, and the vaccine offered was changed to one which offered wider protection (1). However, the time lag between HPV infection and development of cervical cancer means that the full impact of the introduction of HPV vaccination in Ireland is yet to be seen. It is expected that HPV vaccination will reduce the incidence of HPV-associated cancers in the long term.

Incidence

An estimated average of 641 cases of HPV-associated cancers were diagnosed per year in the period 2017-2021, 65% of cases were in females and 35% in males.

In total, these cancers accounted for 2.7% of all invasive cancers (excluding NMSC) diagnosed in Ireland during 2017-2021, or 3.7% for females, 1.7% for males.

Cervical carcinomas were the most frequently diagnosed of all the HPV associated tumours (41%), followed by oropharyngeal SCC (31%). The estimated annual numbers and age-standardised incidence rates of oropharyngeal SCC, anorectal SCC, vulval SCC, vaginal SCC and penile SCC for the period 2017-2021 are shown in Table 1. These estimates are adjusted to include allowance for non-specific cancers. The unadjusted case counts are available in Appendix 1.

Table 1. Average annual estimated number of cases of invasive HPV-associated cancers and age-standardised rates 2017-2021

	Females		Males		Total	
	Cases/yr[#]	EASR† (95% CI)	Cases/yr[#]	EASR† (95% CI)	Cases/yr[#]	EASR† (95% CI)
Oropharyngeal SCC[ab]	46	2.2 (1.9-2.4)	154	7.7 (7.1-8.2)	200	4.8 (4.5-5.1)
Anorectal SCC[bc]	44	2.1 (1.8-2.4)	24	1.1 (0.9-1.3)	68	1.6 (1.5-1.8)
Cervical carcinoma[cd]	265	11 (10.4-11.6)			265	
Vulval SCC[ac]	55	2.7 (2.4-3)			55	
Vaginal SCC[ac]	9	0.4 (0.3-0.6)			9	
Penile SCC[ac]			45	2.4 (2.1-2.7)	45	
Total	419	18.3 (17.5-19.1)	222	11.2 (10.5-11.9)	641	

Cancer definitions (8,9)**:**

[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.

#Estimated numbers 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 (2013 European standard).

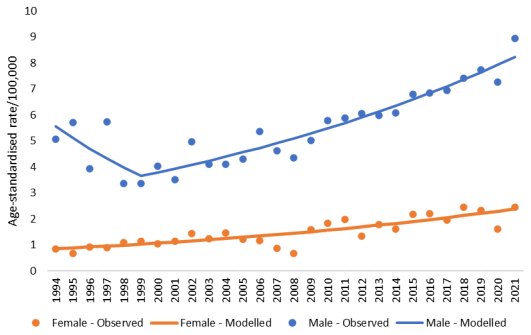
Trends over time

There have been significant changes in the incidence trends of HPV-associated cancers over time, with substantial differences between cancer types. The age standardised incidence rates of female and male oropharyngeal SCC (Figure 1A), female and male anorectal SCC (Figure 1B), vulval SCC (Figure 1D), and penile SCC (Figure 1F) have been increasing since the 1990s. The trend in incidence of vaginal SCC has been stable since 1994 (Figure 1E). The incidence of cervical carcinoma has decreased significantly, by 3.3% per year between 2010 and 2021, largely influenced by the introduction of a population screening programme in 2008 (Figure 1C).

When all HPV-associated cancers are combined, there has been a significant increasing trend in the age standardised incidence rate in females since 1994 (annual percentage change (APC) 0.8% per year), and in males since 2004 (APC 3.6% per year), Figure 1G.

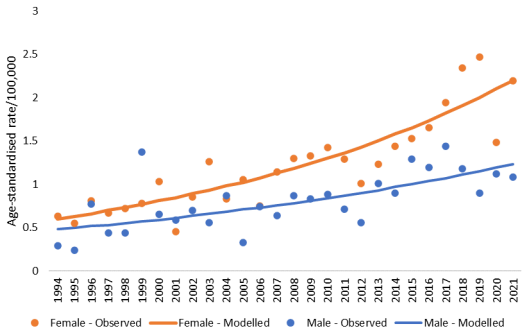
Figure 1. Observed and modelled trends in EASR by cancer site and sex, 1994-2021. All HPV-associated cancers include the five sites shown plus cervical carcinoma.

A. Oropharyngeal SCC



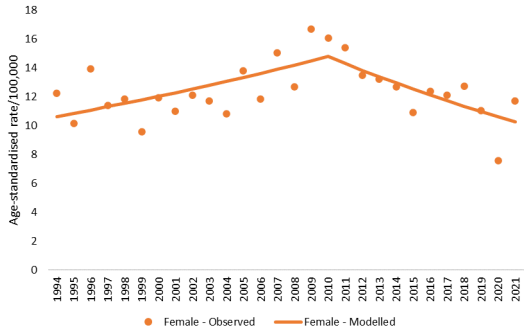
Sex	Years	APC (95% CI)	Trend
M	1994-1999	-8.1 (-15.3, -0.3)	↓
M	1999-2021	3.8 (3.1, 4.4)	↑
F	1994-2021	3.9 (2.9, 4.9)	↑

B. Anorectal SCC



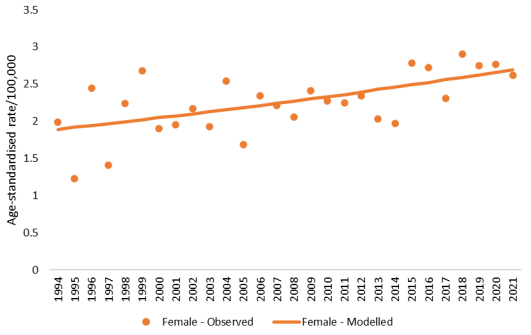
Sex	Years	APC (95% CI)	Trend
M	1994-2021	3.5 (2.1, 5)	↑
F	1994-2021	4.9 (3.9, 6)	↑

C. Cervical carcinoma



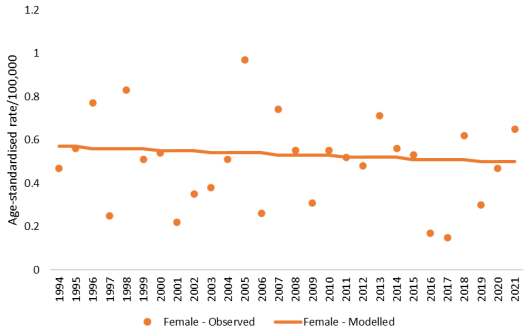
Sex	Years	APC (95% CI)	Trend
F	1994-2010	2.1 (0.6, 3.6)	↑
F	2010-2021	-3.3 (-5.4, -1)	↓

D. Vulval SCC



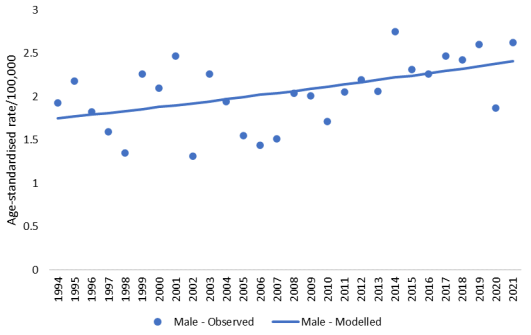
Sex	Years	APC (95% CI)	Trend
F	1994-2021	1.3 (0.6, 2)	↑

E. Vaginal SCC



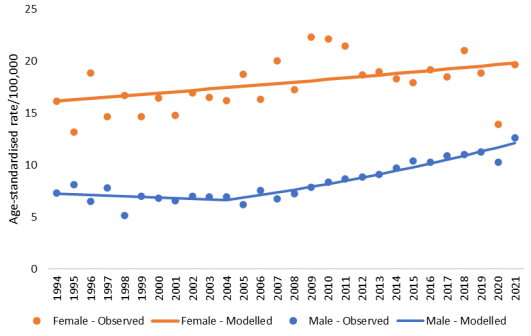
Sex	Years	APC (95% CI)	Trend
F	1994-2021	-0.5 (-2.3, 1.4)	↔

F. Penile SCC



Sex	Years	APC (95% CI)	Trend
M	1994-2021	1.2 (0.4, 2)	↑

G. All HPV-associated cancers



Sex	Years	APC (95% CI)	Trend
M	1994-2004	-0.9 (-3, 1.3)	↔
M	2004-2021	3.6 (2.9, 4.4)	↑
F	1994-2021	0.8 (0.1, 1.4)	↑

Years=range of years; apc =annual percentage change over range (%); ci =95% confidence intervals of apc for each distinct range;
trend: ↑=significant increase, ↓=significant decrease, ↔ =no change, at the 95% level

Age breakdown/age specific rates

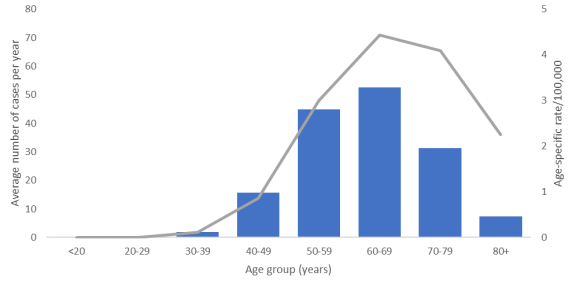
Average annual age specific counts and rates for the period 2017-2021 are shown in Figure 2. The age profile of those diagnosed with HPV-associated cancers other than cervical cancer tends to be older than women diagnosed with cervical carcinoma. Approximately 50% of women diagnosed with cervical carcinoma were aged between 30 and 49 years at diagnosis (Figure 2F). Age-specific rates of oropharyngeal SCC were highest in the 60-69 year age group in both males and females (Figure 2A and 2B). Age-specific rates of anorectal cancers also peaked in the 60-69 year old males (Figure 2C). For all other cancers (anorectal female, penile and vulval/vaginal), the age-specific rates continued to increase with age (Figure 2D, 2E and 2G).

Overall HPV-associated cancers accounted for 7.1% of all invasive cancers (excluding NMSC) in young adults aged 20-49 years (9.6% in females and 2.8% in males) but only 2.0% of invasive cancers (excluding NMSC) in adults 50 years of age and over (2.5% in females and 1.6% in males).

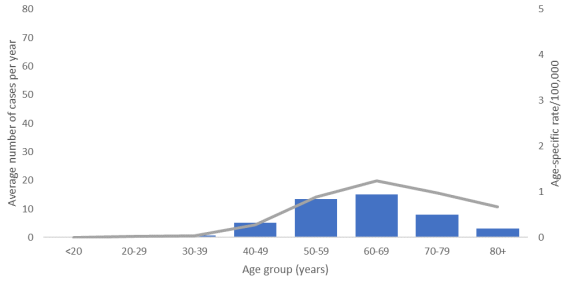
The mean age at diagnosis of cervical carcinoma, female oropharyngeal SCC and vulval SCC all decreased significantly between 1994-1998 and 2014-2018 (Table 2). No significant decreases were seen in age at diagnosis of male oropharyngeal SCC, male or female anorectal SCC penile SCC or vaginal SCC.

Figure 2. Age distribution, average annual case counts and age-specific rates, by cancer site and sex, 2017-2021.

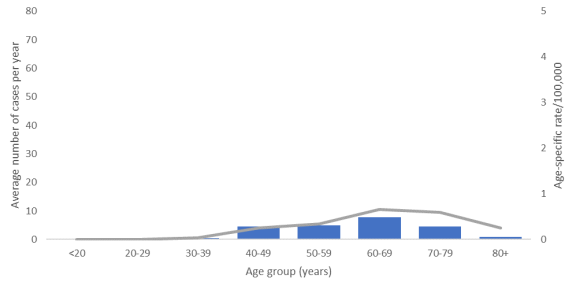
A. Oropharyngeal SCC, male



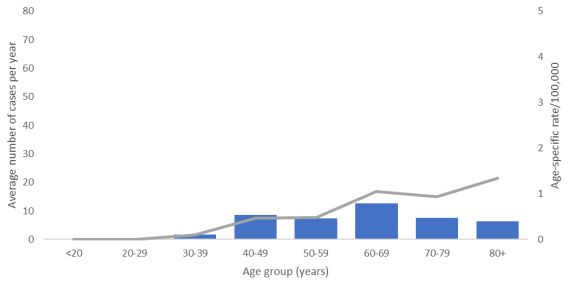
B. Oropharyngeal SCC, female



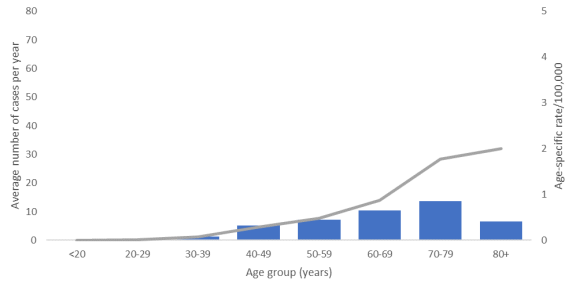
C. Anorectal SCC, male



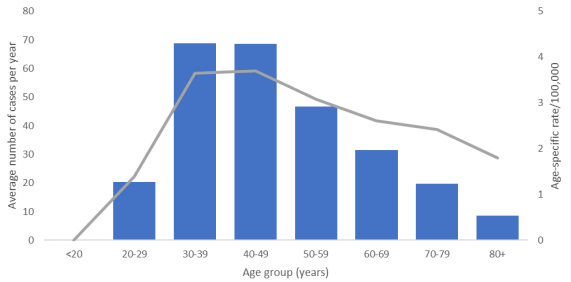
D. Anorectal SCC, female



E. Penile SCC, male



F. Cervical carcinoma, females



G. Vulval & vaginal SCC, female

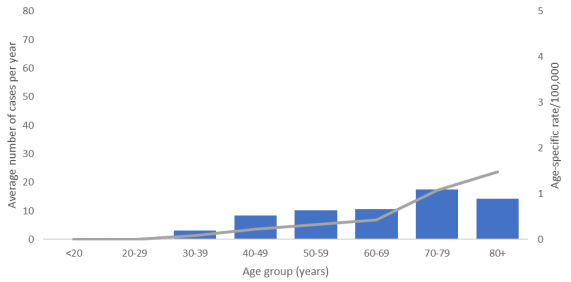


Table 2. Mean age at diagnosis (in years0, by diagnosis period, cancer site and sex

	1994-1998 (baseline)	1999-2003	2004-2008	2009-2013	2014-2018
Oropharyngeal SCC					
Female	65.9	60.1**	58.0**	60.5**	60.3**
Male	61.6	61.2	60.7	60.1	60.8
Anorectal SCC					
Female	63.3	63.1	65.1	61.1	61.9
Male	68.2	58.0*	62.0	62.1	62.0
Cervical carcinoma					
Female	48.7	48.7	47.2*	47.1*	47.1*
Vulval SCC					
Female	69.0	68.1	65.9	64.7*	64.9*
Vaginal SCC					
Female	63.3	70.7	68.0	68.4	63.3
Penile SCC					
Male	63.4	66.5	65.0	64.7	66.6

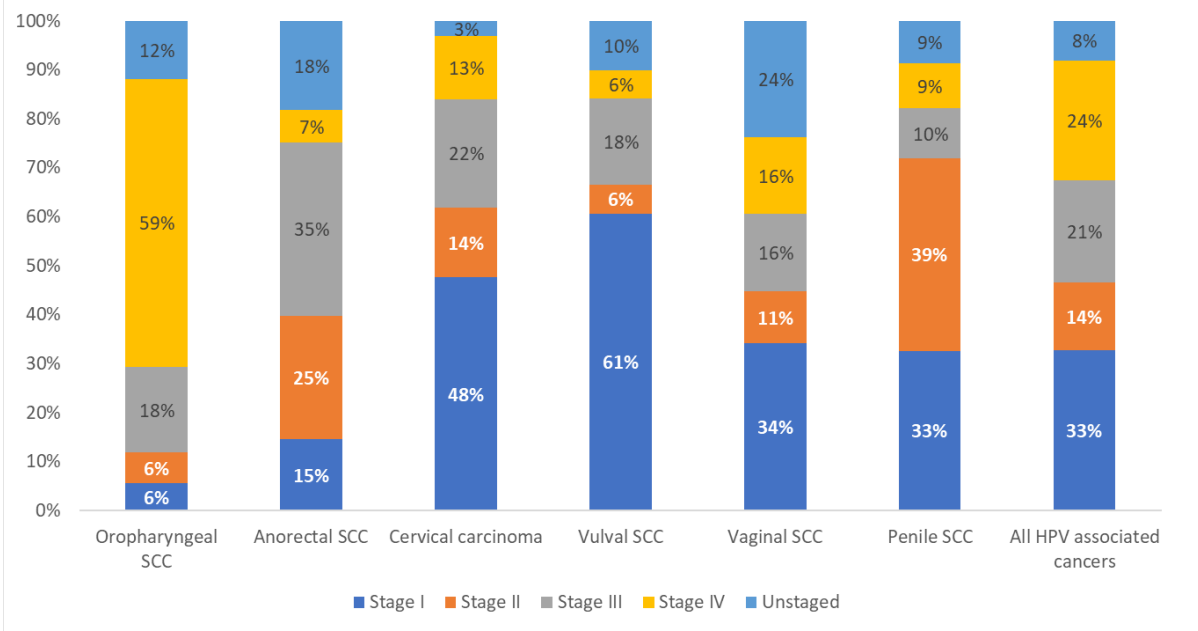
*p<0.05 for comparison with 1994-1998 period (ANOVA); ** p≤0.005 for comparison with 1994-1998 period (ANOVA)

Stage

There is wide variation in the stage at diagnosis across cancer sites (Figure 3), with the majority of cervical carcinoma (62%), vulval SCC (67%) and penile SCC (72%) being diagnosed early (at stage I or II), whereas the majority (76%) of oropharyngeal SCC were diagnosed late (at stage III or IV).

While currently a large proportion of oropharyngeal SCC cases are diagnosed late, at stage III or IV, these tumours were staged using TNM 7th edition (10). There are significant changes, including the incorporation of the prognostic marker p16, in the staging of oropharyngeal tumours recommended in TNM 8th edition (11). From 2024 the NCRI will be using TNM 8th edition to stage tumours, which will likely result in a smaller proportion of cases being diagnosed at stage III or IV in the future.

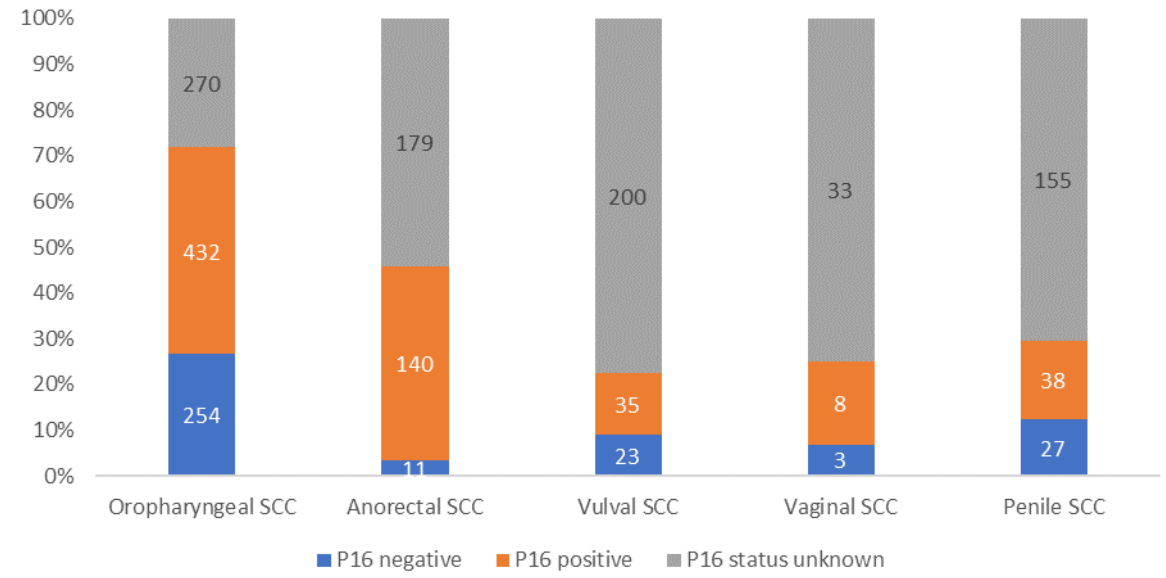
Figure 3. Stage distribution of cases diagnosed 2014-2018, by cancer site



Markers – p16

P16 is a prognostic marker of HPV infection. Patients with p16 positive oropharyngeal tumours have been shown to have better outcomes than those with p16 negative tumours and as a consequence routine testing of oropharyngeal SCC for p16 is recommended by the College of American Pathologists and has been incorporated into the 8th edition of TNM staging classification (11,12). The prognostic value of p16 for other cancer sites is less certain although generally p16 positivity appears to be associated with improved outcomes (13–16). The number of tumours with an available p16 result and of those, the proportion of tumours who tested positive for p16 are shown in Figure 4.

Figure 4. P16 availability and result by cancer site 2017-2021



Treatment

The proportion of cases receiving surgery, chemotherapy and radiotherapy within 1 year of diagnosis are shown in Figure 5. Treatment modality varied by site, with surgery the most common modality for penile and vulval SCC and cervical carcinoma, whereas radiotherapy was the most common modality for oropharyngeal, anorectal and vaginal SCC. Combinations of treatments are shown in Table 3. For both oropharyngeal SCC and anorectal SCC, the combination of chemotherapy and radiotherapy was the most common treatment modality received, whereas surgery alone was the most common treatment modality for cervical carcinoma, vulval SCC and penile SCC.

Figure 5. Proportion of cases receiving treatment within 1 year of diagnosis, 2014-2018

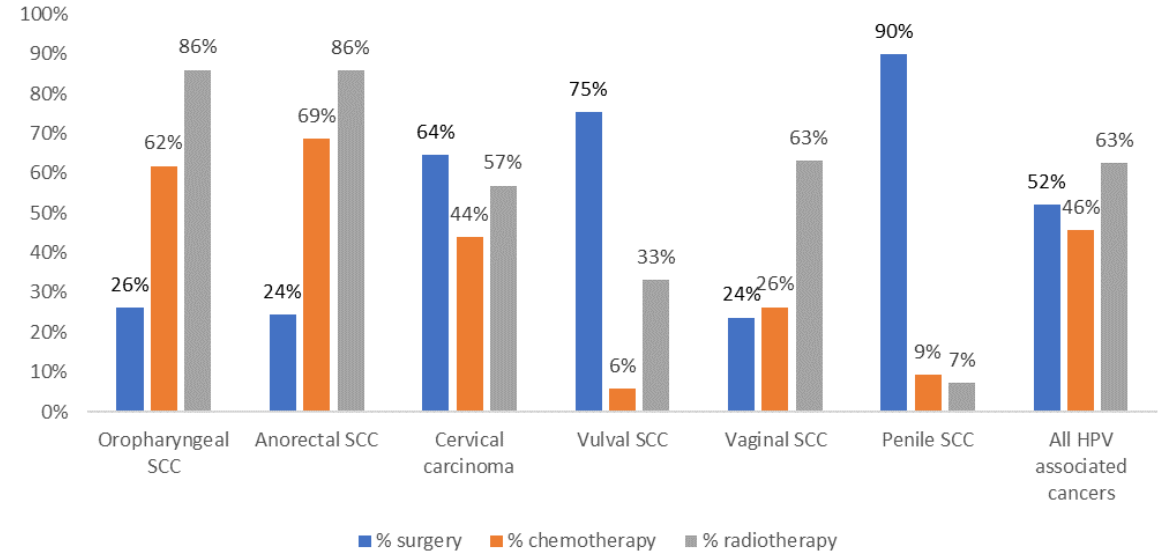


Table 3. Proportion of cases receiving treatment combinations within 1 year of diagnosis, 2014-2018

Treatment	Oropharyngeal SCC	Anorectal SCC	Cervical carcinoma	Vulval SCC	Vaginal SCC	Penile SCC	All HPV-associated cancers
Surgery	5%	7%	39%	55%	21%	81%	30%
Chemotherapy + Radiotherapy	47%	57%	24%	3%	24%	1%	30%
Surgery + Chemotherapy + Radiotherapy	14%	11%	17%	3%	3%	3%	14%
Radiotherapy	18%	12%	8%	10%	37%	2%	11%
Surgery + Radiotherapy	7%	6%	7%	17%	0%	2%	7%
Chemotherapy	1%	1%	1%	0%	0%	1%	1%
Surgery + Chemotherapy	0%	0%	1%	0%	0%	5%	1%
No treatment	8%	6%	2%	12%	16%	7%	5%

Mortality

Mortality data are not available for specific sub-types of cancer, so it is not possible to report time-trends in mortality using typical mortality data. Incidence-based mortality estimates have been previously reported[1] (8) and Table 3 reports similar estimates (although unadjusted for non-specific morphology types) for deaths occurring 2015-2019.

The average number of deaths due to HPV-associated cancers is estimated to be 196 per year during the period 2015-2019, with twice as many deaths occurring in females compared to males.

Table 4. Average number of deaths per year, and median age at death from HPV-associated cancers, 2015-2019[1]

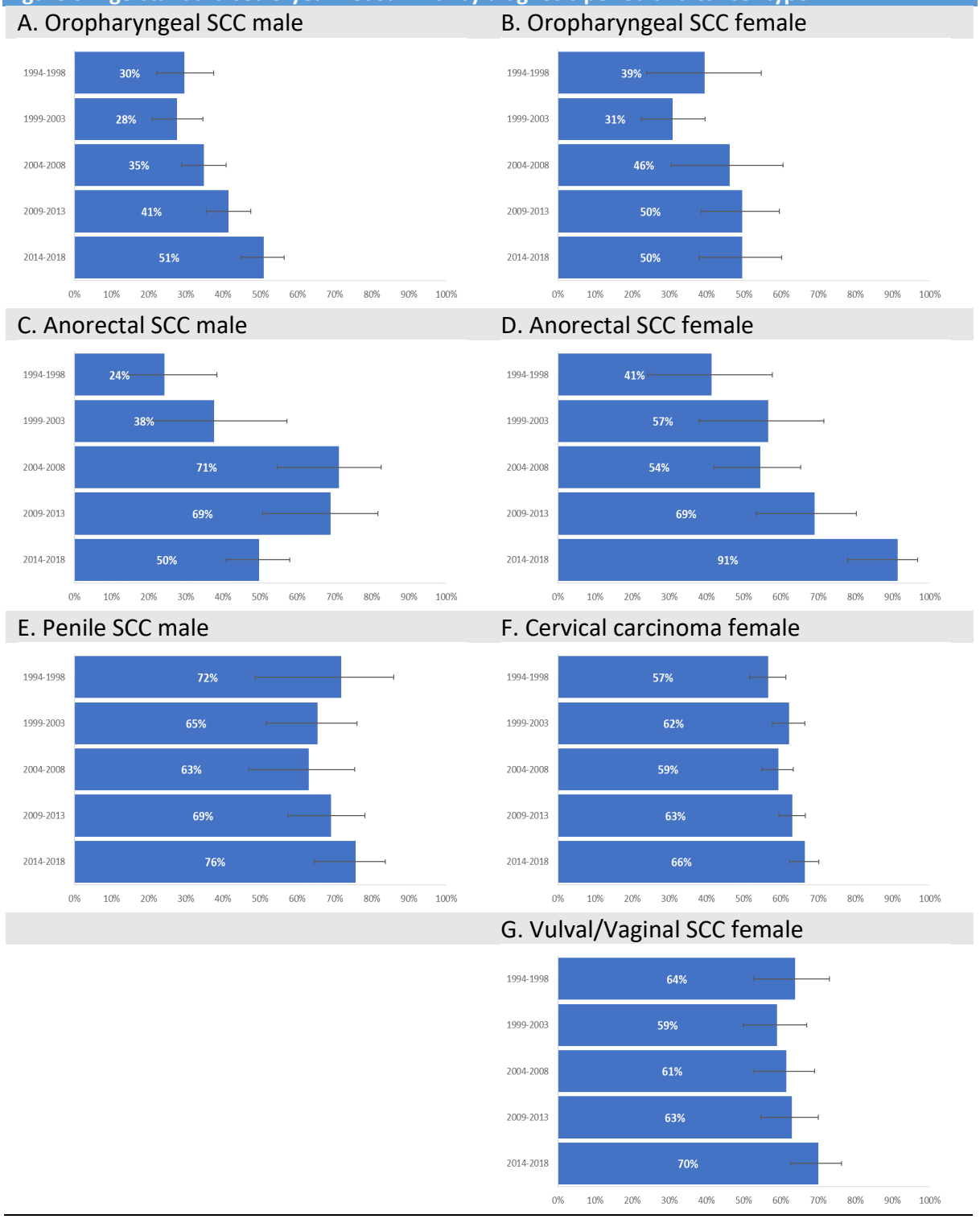
	Female		Male		Total	
	Number (%)	**Median age**	**Number (%)**	**Median age**	**Number (%)**	**Median age**
Oropharyngeal SCC	16 (12.6%)	67 years	54 (78.3%)	64 years	70 (35.7%)	65 years
Anorectal SCC	5 (3.9%)	70 years	6 (8.7%)	70 years	11 (5.6%)	70 years
Cervical carcinoma	85 (66.9%)	56 years			85 (43.4%)	
Vulval SCC	16 (12.6%)	78 years			16 (8.2%)	
Vaginal SCC	5 (3.9%)	78 years			5 (2.6%)	
Penile SCC			9 (13%)	72 years	9 (4.6%)	
All HPV-associated cancers	***127 (100%)***	***61 years***	***69 (100%)***	***66 years***	***196 (100%)***	***63 years***

Survival

5-year net survival estimates by site are shown in Figure 6. Given the relatively wide confidence intervals for some cancer sites (due to the small numbers on which these estimates are based), changes in survival over time should be interpreted with caution. For some cancers, it appears that there have been steady increases in survival over time (e.g. male oropharyngeal SCC and female anorectal SCC), but for other cancers, it appears there has been little improvement in survival over time (e.g. female oropharyngeal SCC, penile SCC and vulval/vaginal SCC). While the graph appears to show that survival for male anorectal cancer has disimproved in the most recent period, it should be noted that the number of cases these estimates are based on are relatively small numbers of cases and that there is no statistically significant difference between the 5-year net survival estimate in 2014-2018 compared to the survival estimate for the previous period 2009-2013. In other words, the observed difference could likely be explained by chance alone.

[1] Incidence-based mortality estimates based on cause-specific cancer deaths during 2015-2019 among patients diagnosed 1994-2019 with the site/morphology combinations specified in Table 1 (incidence), not including adjustment for non-specific morphology types. Due to completeness issues with cause of death data for 2020 and 2021 estimated number of deaths is limited to cases diagnosed 1994-2019 who died up to the end of 2019.

Figure 6. Age-standardised 5-year net survival by diagnosis period and cancer type.



Conclusion

Between 2017 and 2021, HPV-associated cancers accounted for 2.7% of invasive cancers (excluding NMSC). The incidence rates of most HPV-associated cancers, with the exception of cervical carcinoma, are increasing (Figure 1). The significant decrease in cervical carcinoma incidence is attributable to the national cervical screening programme. Routine cervical screening can reduce the incidence of cervical cancer through the identification and removal of abnormal cells before they

develop into cervical cancer. It has been estimated that cervical screening, in combination with HPV vaccination and cervical cancer treatment will result in the elimination of cervical cancer as a public health problem in Ireland by 2040 (17).

Countering the rise in other HPV-associated cancers requires a multi-faceted population health approach. Continuously improving vaccine uptake and coverage, enhancing awareness of HPV, its transmission and associated cancers, promoting safer sexual practices, along with access to early detection and treatment, while addressing health inequalities are all key to success. The national HPV vaccination programme is expected to prevent HPV infection and reduce the incidence of all HPV-associated cancers in the longer term. Continuous surveillance is essential for monitoring progress and adapting strategies as required.

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Appendix 1. Observed vs Estimates case counts (annual average 2019-2021)

	Females		Males		Total	
	Observed	Adjusted	Observed	Adjusted	Observed	Adjusted
Oropharyngeal SCC	44	46	147	154	191	200
Anorectal SCC	43	44	23	24	66	68
Cervical carcinoma	263	265			263	265
Vulval SCC	52	55			52	55
Vaginal SCC	9	9			9	9
Penile SCC			44	45	44	45
Total	**410**	**419**	**214**	**222**	**624**	**641**