



Cancer

International trends in anal cancer incidence rates

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Abstract

Background: Previous studies have reported rapid increases in anal cancer incidence rates in seven high-income countries in North America, Europe and Oceania. There is very limited information on whether this pattern is replicated in other parts of the world. In this study, we examine recent trends in anal cancer incidence in 18 countries worldwide.

Methods: We calculated age-standardized incidence rates for anal squamous cell carcinoma (ASCC) and anal adenocarcinoma (AAC) for a minimum of 13 years through to 2007, using data from the International Agency for Research on Cancer's *Cancer Incidence in Five Continents* series, and applied joinpoint regression models to assess changes in incidence rates. We also conducted an extended analysis of the data from the USA through to 2012.

Results: ASCC was the main histological subtype in most of the countries considered in this analysis. The incidence of ASCC increased in both men and women in several high-income countries, including Australia, Canada, Denmark, France, Italy, Netherlands, the UK and the USA, whereas it increased only in women in Colombia, Estonia, the Russian Federation, Slovakia and Switzerland. Conversely, there was little change in the incidence of ASCC in either men or women in India, Israel, Japan, Singapore and Spain. The incidence rates of AAC decreased or were stable in most populations.

Conclusions: The ASCC incidence rates increased in both men and women or in women in all countries included in this study, except Asian countries and Spain, where the rates remained unchanged. Population-based preventive measures, including human papillomavirus vaccination and advocacy for safe sexual behaviours, may contribute to curbing the surging burden of the disease.

Key words: Anal cancer, epidemiology, cancer registry

Key Messages

- The incidence of anal cancer has been increasing in most populations included in this study.
- In these countries, anal squamous cell carcinoma (ASCC) is the most common histological subtype of anal cancer.
- Reasons for the increase in ASCC incidence are unknown but likely include a rise in prevalence of the factors that may increase the incidence and persistence of anal HPV infection, such as cervical HPV infection in women.
- Factors that mediate the risk are linked to sexual behaviour and HIV infection, but further studies on contributing factors are needed.
- Certain preventive measures if implemented, including HPV vaccination and campaigns for safer sexual behaviours, would serve to prevent a substantial number of anal cancer cases in the future.

Introduction

Anal cancer is often neglected because it is a relatively rare cancer. It has been estimated that approximately 14 500 cases of anal cancer in women and 12 500 in men occurred in 2008 worldwide.^{1,2} Previous studies have reported a relatively rapid increase in the incidence rate in some very high-income countries, including Australia,^{3,4} Canada,^{5,6} Denmark,⁷ France,⁸ The Netherlands,^{9,10} the UK^{11–13} and the USA.^{14, 15} However, the direction and magnitude of anal cancer trends elsewhere is largely unknown. Understanding the epidemiology of a cancer is the first step in recognizing and reducing the burden of that cancer.

In this paper, we present contemporary variations in the incidence of anal cancer across 18 countries in four continents (excluding Africa), including several countries that are economically less developed than the above-mentioned countries, using the most up-to-date data. We use a systematic approach to address a limitation of previous reports, that of ensuring comparability of the different datasets. We report these results by histological subtype, as the descriptive epidemiology and aetiology of anal squamous cell carcinoma (ASCC) and anal adenocarcinoma (AAC) are somewhat heterogeneous due to differences in cellular origin.¹⁶

Methods

In this analysis, anal cancer is defined as malignant neoplasm of the anus and anal canal (ICD-10 C21). Using data from population-based cancer registries, we extracted the number of new cases of anal cancer by year, sex and age group and the corresponding population at risk from the *Cancer Incidence in Five Continents* (CI5), *CI5plus* database held at the International Agency for Research on Cancer.¹⁷ Data on anal cancer by histological subtype were available from 28 countries. To examine temporal trends in anal cancer incidence worldwide, while ensuring that the inherent random variation in individual datasets

was sufficiently limited to enable interpretation, we restricted the analysis to countries with at least 200 cases in men and/or 200 cases in women in the entire period of observation, and countries in which the proportion of anal cancers with an unspecified histology (unspecified carcinomas or unspecified morphology) was less than 20%. Finally, 19 populations from 18 countries were included in this study, as we considered data from US Whites and Blacks separately. Incidence data were based on national registries in six countries: Denmark, Estonia, Israel, The Netherlands, Singapore and Slovakia. In nine countries, including Australia, Canada, France, Italy, Japan, Spain, Switzerland, the UK and the USA, aggregated data from at least three local cancer registries were available. When the starting date of cancer registries in a given country was not the same, we selected a starting date to maximize population coverage while ensuring a sufficient span of registration years. In Colombia, India and the Russian Federation, incidence data were based on a single local cancer registry.

To calculate age-standardized rates (ASR), we stratified the cases by the traditional 5-year age groups by sex, and used the 1960 Segi world standard population.¹⁸ ASRs and associated 95% confidence intervals (CIs) were calculated for: all anal cancers combined; ASCC; AAC; a combined group of anal cancers with other specified histologies; and a combined group of unspecified carcinomas and anal cancers with an unspecified morphology. We did not adjust ASCC and AAC categories for the latter category, as the proportion of anal cancers with an unspecified histology in both men and women was < 20% in all and ≤ 5% in half of the included populations. In the CI5 series, and consequently in this analysis, the following ICD-O-2 (M) codes were used to identify ASCC (8050–8076, 8123–8124) and AAC (8140–8145, 8190–8231, 8260–8263, 8310, 8480–8490, 8560, 8570).¹⁹

We report mean incidence rates over a 2-year period (2006–07) to increase the stability of the results. Trends in incidence by sex are shown with smoothed lines on fitting locally weighted regression (LOWESS) curves, in which

30% of the data were used in the smoothing. Using the same methodology as above, we extended the analysis for the USA through to 2012, as more up-to-date data stratified by histology were available for the country.²⁰ We performed similar analyses stratified by broad age groups (20–44, 45–64, ≥ 65 years) for selected populations with at least 400 anal cancer cases in each sex. Stata software (Stata Corp LP, version 13) was used for all calculations. We also show average incidence rates for overlapping tumours of the rectum and anus (ICD 10 code C21.8) in 1993–97, 1998–2002, and 2003–07, available from three latest editions of CI5 (editions VIII through to X), for select registries.

In addition, we applied joinpoint regression models, in which a series of joined straight lines were fitted to ASR trends, using Joinpoint Regression Program, version 4.1.1.5.²¹ This analysis was performed only when there were at least 100 cancer cases in the respective group (by population, sex and histological subtype) during the study period. We specified a logarithmic transformation of ASRs and a maximum number of three joinpoints in order to avoid capturing unstable trends due to relatively small numbers of cases. We present the annual percentage changes (APC) and the corresponding 95% CIs to quantify the magnitude of changes in anal cancer incidence over time.

Results

Table 1 shows the registries, time periods, corresponding population counts and cancer cases in 19 populations from 18 countries included in this analysis, by sex and histological subtype. The earliest starting year in this analysis was for Estonia (1968) and the latest was for the Russian Federation (1994). The number of anal cancer cases ranged from 80 in the Russian Federation to 3114 in the UK in men, and from 195 in Singapore to 4639 in White women in the USA.

Incidence rates in 2006–07

The ASRs for anal cancer (per 100 000) ranged from 0.2 in the Russian Federation to 1.6 in Blacks in the USA among men, and from 0.2 in Spain and Japan to 2.1 in Colombia among women (Supplementary Table S1, available as Supplementary data at *IJE* online). The point estimate of ASR for ASCC was greater in women than in men in all populations except for US Blacks, Spain, Israel and Japan. The incidence rates of ASCC in both men and women in Australia and populations in the Americas and Northern and Western Europe, except for men in Estonia, were generally higher than in other studied populations (Figure 1,

Supplementary Table S1). The highest ASR (per 100 000) for ASCC was found for US Blacks (1.3) and US Whites (0.8) among men and for Switzerland (1.7), Denmark (1.5) and US Whites (1.3) among women. The ASR for ASCC in both men and women was < 0.5 per 100 000 in Asian and Central/Eastern European populations.

In both men and women, the incidence of AAC was generally lower than ASCC, except for Japan, Singapore and Slovakia, where at least half of anal cancers in 2006–07 were AACs. However, the latter pattern was based on modest numbers of anal cancer cases. Also, substantial proportions of anal cancers in Japan and Singapore were overlapping tumours of the rectum and anus, some of which could actually be misreported cases of rectal cancer (Supplementary Table S2, available as Supplementary data at *IJE* online). Overall, AAC was more common in men than in women in most populations.

Trends in incidence

Incidence trends by population and sex for all anal cancers combined are shown in Supplementary Figure S1 and Supplementary Table S3 (available as Supplementary data at *IJE* online), but we focus on trends for ASCC and AAC because rates and the direction and relative magnitude of the trends of the two main subtypes varied substantially by population and sex. Incidence for ASCC in both men and women has been increasing in Australia, Canada, Denmark, France, Italy, The Netherlands, the UK and Blacks and Whites in the USA (Table 2, Figure 2). Uniform increases were apparent, except for women in Australia and in US Whites where a steeper increase beginning in the mid 1990s was observed. In all above-mentioned populations, incidence for ASCC was higher in women than in men in all years of observation, except for US Blacks in whom male incidence surpassed female incidence in 1996 (Figure 2). In Colombia, the Russian Federation, Slovakia and Switzerland, the increase was confined to women. In Estonia, incidence for ASCC also appears to be increasing in women, although a joinpoint analysis for ASCC was not feasible: in this group, anal cancer incidence has been increasing, ASCC constitutes two-thirds of all anal cancers and there has been little change in incidence of other histological subtypes. Incidence for ASCC was stable over time in India, Israel, Japan, Singapore and Spain. When we limited the joinpoint analysis to 1989–2007 to examine the trends in the same time period, the overall patterns did not change substantially (Table 3).

Incidence trends for AAC have been decreasing in men and women in The Netherlands, in men in Australia (following an earlier increase), France and Israel, and in women in Denmark (Table 2, Figure 3). In contrast, the

Table 1. Countries, cancer registries, population counts, and number of anal cancer cases (%) included in this analysis

Country (period)	HDI ^a	Registries	Males					Females						
			Population	All	ASCC	AAC	Uns.	Other	Population	All	ASCC	AAC	Uns.	Other
Australia (1983–2007)	Very high	6 registries: New South Wales, Queensland, South Australia, Tasmania, Victoria, Western Australia	10176924	2112	1237 (58.6)	704 (33.3)	67 (3.2)	104 (4.9)	10310537	2726	1904 (69.8)	579 (21.2)	87 (3.2)	156 (5.7)
Canada (1983–2007)	Very high	3 registries: Manitoba, Nova Scotia, Saskatchewan	1538969	298	154 (51.7)	127 (42.6)	10 (3.4)	17 (2.3)	1588210	454	319 (70.3)	107 (23.6)	11 (2.4)	17 (3.7)
Colombia (1987–2007)	High	1 registry: Cali	1000036	86	42 (48.8)	28 (32.6)	10 (11.6)	6 (7.0)	1124648	235	159 (67.7)	41 (17.4)	21 (8.9)	14 (6.0)
Denmark (1978–2007)	Very high	National	2704655	723	472 (65.3)	185 (25.6)	32 (4.4)	34 (4.7)	2756660	1383	1070 (77.4)	190 (13.7)	70 (5.1)	53 (3.8)
Estonia (1968–2007)	Very high	National	617828	109	29 (26.6)	53 (48.6)	19 (17.4)	8 (7.3)	723844	250	125 (50.0)	73 (29.2)	40 (16.0)	12 (4.8)
France (1983–2007)	Very high	6 registries: Bas-Rhin, Calvados, Doubs, Isere, Somme, Tarn	2150199	411	224 (54.5)	163 (39.6)	13 (3.2)	11 (2.7)	2245640	975	770 (79.0)	141 (14.5)	36 (3.7)	28 (2.9)
India (1983–2007)	Medium	1 registry: Mumbai (Bombay)	9785806	641	278 (43.4)	221 (34.5)	106 (16.5)	36 (5.6)	8229679	456	232 (50.9)	135 (29.6)	78 (17.1)	11 (2.4)
Israel (1971–2007)	Very high	National (Jews only)	2674800	450	159 (35.3)	225 (50.0)	17 (3.8)	49 (10.9)	2760400	537	231 (43.0)	209 (38.9)	23 (4.3)	74 (13.8)
Italy (1988–2007)	Very high	6 registries: Varese province, Parma, Ragusa Province, Romagna, Torino, Modena	2119463	474	220 (46.4)	210 (44.3)	30 (6.3)	14 (3.0)	2239953	772	538 (69.7)	149 (19.3)	54 (7.0)	31 (4.0)
Japan (1988–2007)	Very high	3 registries: Miyagi Prefecture, Nagasaki Prefecture, Osaka Prefecture	6185009	589	66 (11.2)	424 (72.0)	82 (13.9)	17 (2.9)	6627571	571	188 (32.9)	268 (46.9)	89 (15.6)	26 (4.6)
The Netherlands (1989–2007)	Very high	Nationwide	8100293	809	556 (68.7)	194 (24.0)	20 (2.5)	39 (4.8)	8281402	1090	783 (71.8)	237 (21.7)	24 (2.2)	46 (4.2)
Russian Federation (1994–2007)	High	1 registry: Saint Petersburg	2047455	80	34 (42.5)	32 (40.0)	12 (15.0)	2 (2.5)	2523729	259	159 (61.4)	51 (19.7)	36 (13.9)	13 (5.0)
Singapore (1968–2007)	Very high	National	1775700	206	52 (25.2)	126 (61.2)	6 (2.9)	22 (10.7)	1806600	195	78 (40.0)	94 (48.2)	6 (3.1)	17 (8.7)
Slovakia (1980–2007)	Very high	National	2621095	394	46 (11.7)	271 (68.8)	65 (16.5)	12 (3.0)	2776671	418	119 (28.5)	216 (51.7)	65 (15.6)	18 (4.3)
Spain (1993–2007)	Very high	7 registries: Albacete, Cuenca, Granada, Murcia, Navarra, Tarragona, Girona	2492448	250	97 (38.8)	125 (50.0)	9 (3.6)	19 (7.6)	2463564	212	72 (34.0)	96 (45.3)	15 (7.1)	29 (13.7)
Switzerland (1989–2007)	Very high	5 registries: Geneva, Neuchatel, St Gall-Appenzell, Valais, Vaud	1024112	224	147 (65.6)	56 (25.0)	6 (2.7)	15 (6.7)	1076514	612	480 (78.4)	90 (14.7)	31 (5.1)	11 (1.8)
(continued)														

(continued)

Table 1 Continued

Country (period)	HDI ^a	Registries	Males					Females						
			Population	All	ASCC	AAC	Uns.	Other	Population	All	ASCC	AAC	Uns.	Other
UK (1979–2007)	Very high	5 registries: Scotland and 4 registries in England (Birmingham and West Midlands Region, North Western, South and Western Regions, Merseyside, and Cheshire)	12938176	3114	1819 (58.4)	825 (26.5)	379 (12.2)	91 (2.9)	13533569	4589	3098 (67.5)	835 (18.2)	512 (11.2)	144 (3.1)
USA (1975–2007)	Very high	Surveillance, Epidemiology, and End Results (SEER), 9 registries: Atlanta, Connecticut, Detroit, Hawaii, Iowa, New Mexico, San Francisco-Oakland, Seattle-Puget Sound, Utah	Blacks: 1724091 Whites: 10682176	443 2927	328 (74.0) 2161 (73.8)	92 (20.8) 610 (20.8)	4 (0.9) 63 (2.2)	19 (4.3) 93 (3.2)	1897699 10736380	489 4639	369 (75.4) 3789 (81.7)	89 (18.2) 605 (13.0)	15 (3.1) 77 (1.7)	16 (3.3) 168 (3.6)

Uns., unspecified carcinoma or unspecified morphology; Population, the population covered by the registries in 2007; Other, specified carcinomas other than ASCC or AAC, melanoma, and other morphology, excluding unspecified carcinoma or unspecified morphology.

^aThe Human Development Index, defined by the United Nations Development Program, obtained from [http://hdr.undp.org/en/content/table-1-human-development-index-and-its-components] (30 October 2015, date last accessed). This index is a summary measure of life expectancy at birth, years of schooling for adults, expected years of schooling for children, and gross national income (GNI) per capita.

incidence of AAC has been increasing in men and women in Japan and in women in the UK. In the joinpoint analysis limited to 1989–2007, however, the increasing trend of AAC in women in the UK disappeared. An examination of average incidence rates of overlapping tumours of the rectum and anus in the past three editions of CI5 suggested an increasing trend for these tumours in Japan, which could be responsible for the increase in AAC incidence rates in that country (Supplementary Table S2). In other populations, there has been little change or too few cases to perform a joinpoint analysis. There has been little change in incidence of anal cancers with a specified histology other than ASCC or AAC (Supplementary Figure S2, available as Supplementary data at *IJE* online) or with an unspecified histology (Supplementary Figure S3, available as Supplementary data at *IJE* online).

The extended analysis of the data from the USA conveys a continuation of the increasing trends in ASCC incidence rates in both men and women (Supplementary Figure S4, available as Supplementary data at *IJE* online). Based on a small number of cases, the increase halted in Black men in 2010. Similar patterns were observed when the incidence rates were standardized to the WHO Standard Population (World Health Organization 2000–25), rather than the 1960 Segi World Standard Population (Supplementary Figure S5, available as Supplementary data at *IJE* online). In a supplementary analysis, using the only source of that information available to us at such level of detail globally, we examined trend in incidence of rectal cancers (ICD code C20) that had a morphology code for SCC (ICD-O-3 M of 8050–8085 and 8120–8131) in the USA. The incidence rates for this group of cancers were low (0.2 per 100 000, or less in 2011–12) in each sex/race (Black or White) stratum, with little change over time (data not shown), indicating little impact of the SCCs categorized as rectal cancer on the observed trends of ASCC in the USA.

In stratified analysis by age groups, in all populations included in this analysis except in Japan, the incidence of ASCC was the highest in ages 45–64 years with a sharp increase starting in the 1990s, followed by rates for ages ≥ 65 years (Supplementary Figure S6, available as Supplementary data at *IJE* online). Among US Blacks, the incidence at ages 20–44 years has been higher than among ages ≥ 65 years since the 1990s. Incidence of AAC was generally higher in older age groups (Supplementary Figure S7, available as Supplementary data at *IJE* online).

Discussion

We found that incidence of anal cancer has been increasing—either in both sexes or in women—in many populations, especially in the Americas, Northern and Western

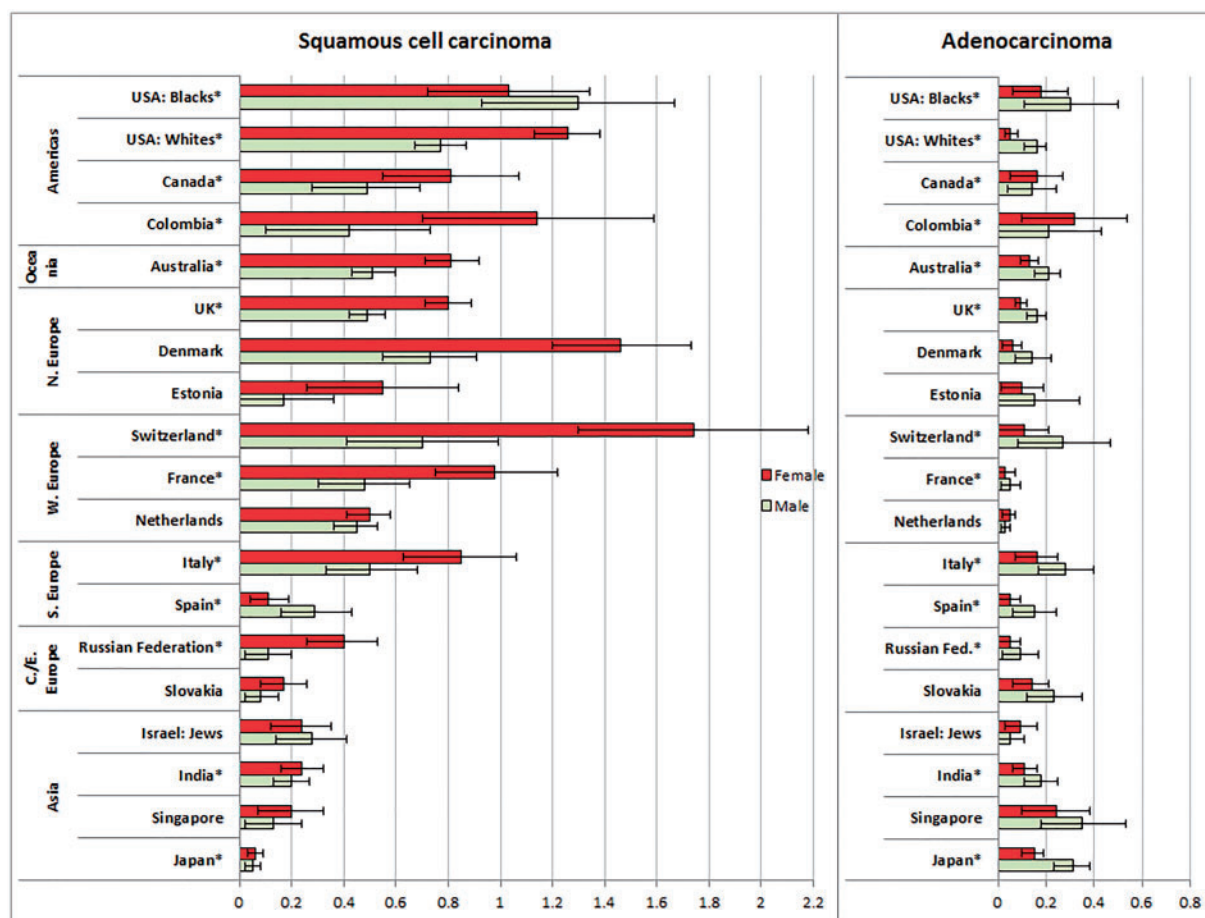


Figure 1. Age-standardized incidence rates for all ages combined (95% confidence intervals) of anal squamous cell carcinoma and adenocarcinoma by sex in 2006–2007

C./E., Central and Eastern; N., Northern; S., Southern; W., Western. Incidence rates are per 100,000 and standardized to the 1960 World standard population. * Regional data.

Europe, and Australia. In these populations, ASCC was substantially more common than other histological subtypes and was the main contributor to the increase in anal cancer incidence. The incidence of ASCC is lower in Asia, Central/Eastern Europe, and Spain, and Spanish and Asian populations have seen little change. In contrast to ASCC, incidence for AAC has been stable or decreasing in most populations.

The reason for the increasing ASCC incidence rates in many populations is unclear, but is likely to reflect changes in prevalence of environmental risk factors. Infection with human papilloma virus (HPV), in particular HPV16,^{22–24} is an established risk factor for anal cancer.^{24,25} Almost all cases of ASCC are positive for HPV.^{2,22,23,26} Despite this strong correlation between HPV and ASCC, there is limited longitudinal information on the prevalence of anal HPV infection in the general population. Current evidence suggests that anal HPV infection in those with HPV-related anogenital diseases or cervical HPV infection is common,^{2,27} but in the majority of infected cases, HPV

clearance occurs in a relatively short time.^{2,28,29} Factors that lead to persistent anal HPV infection may thus be of great importance in the risk of developing anal cancer. These factors include concurrent cervical HPV infection and other HPV-related anogenital diseases, receptive anal intercourse and probably tobacco smoking.^{26–29} Furthermore, concomitant infection with human immunodeficiency virus (HIV) indirectly increases the risk of anal cancer by immunosuppression and increased replication of HPV.³⁰ Consistent condom use during intercourse may reduce the risk of genital HPV infection, although it does not provide complete protection.^{31,32}

Anal cancer is linked to current and past sexual practices that increase the risk of HPV infection or its persistence, including lower age at first intercourse, higher number of male sexual partners, and receptive anal intercourse.^{26,28,29,33,34} Sexual behaviour has been changing towards lower mean age at first intercourse and a higher number of sexual partners, notably in higher-income countries.^{35–37} Little information is available on the prevalence

Table 2. Annual percentage of change in the incidence of anal SCC and adenocarcinoma by sex^a

Population	Period	Males		Females	
		ASCC APC (95% CI)	AAC APC (95% CI)	ASCC APC (95% CI)	AAC APC (95% CI)
Australia	1983–2007	3.3 (2.4, 4.3)	See below	See below	1.8 (-0.2, 1.8)
	1983–95		7.7 (3.0, 12.6)		
	1995–2007		-3.8 (-7.1, -0.4)		
	1983–97			1.1 (-0.5, 2.8)	
	1997–2007			5.9 (3.3, 8.7)	
Canada	1983–2007	4.5 (2.3, 6.7)	NC	4.9 (3.2, 6.6)	-0.5 (-2.9, 2.1)
Colombia	1987–2007	< 100 cases	< 100 cases	2.9 (0.002, 5.9)	< 100 cases
Denmark	1978–2007	4.3 (3.2, 5.4)	NC	4.7 (3.8, 5.6)	-2.7 (-4.2, -1.3)
Estonia	1968–2007	< 100 cases	< 100 cases	NC	< 100 cases
France	1983–2007	2.8 (1.1, 4.4)	-7.6 (-10.6, -4.5)	1.5 (0.2, 2.8)	NC
India	1983–2007	-1.1 (-3.0, 0.9)	0.9 (-1.3, 3.2)	0.5 (-1.8, 2.8)	-0.8 (-2.8, 1.2)
Israel, Jews	1971–2007	-0.4 (-2.0, 1.2)	See below	1.0 (-0.4, 2.5)	NC
	1971–98		0.3 (-1.7, 2.3)		
	1998–2007		-20.7 (-30.3, -9.7)		
Italy	1988–2007	5.1 (2.8, 7.5)	1.5 (-1.5, 4.7)	5.8 (3.3, 8.4)	0.2 (-2.9, 3.3)
Japan	1988–2007	< 100 cases	7.1 (4.3, 9.9)	See below	5.5 (2.4, 8.7)
	1988–2000			3.6 (-2.7, 10.4)	
	2000–2004			-28.1 (-60.3, 30.1)	
	2004–2007			42.8 (-15.0, 140.0)	
The Netherlands	1989–2007	6.3 (4.4, 8.2)	-5.0 (-7.6, -2.3)	6.1 (4.3, 7.9)	-5.2 (-8.0, -2.3)
Russian Federation	1994–2007	< 100 cases	< 100 cases	10.7 (5.4, 16.3)	< 100 cases
Singapore	1968–2007	< 100 cases	NC	< 100 cases	< 100 cases
Slovakia	1980–2007	< 100 cases	See below	6.5 (3.7, 9.5)	0.7 (-1.5, 2.9)
	1980–2000		4.7 (1.4, 8.0)		
	2000–07		-13.2 (-24.8, 0.2)		
Spain	1993–2007	< 100 cases	-2.2 (-6.3, 2.1)	< 100 cases	< 100 cases
Switzerland	1983–2007	1.6 (-2.1, 5.3)	< 100 cases	2.7 (0.3, 5.1)	< 100 cases
UK	1979–2007	3.3 (2.7, 3.8)	0.1 (-0.7, 0.9)	4.5 (3.9, 5.1)	1.2 (0.2, 2.3)
	1979–88				
	1988–2007				
USA, Blacks	1975–2007	4.2 (2.9, 5.4)	< 100 cases	1.4 (0.5, 2.4)	< 100 cases
USA, Whites	1975–2007	3.3 (2.7, 4.0)	0.1 (-1.0, 1.3)	See below	See below
	1975–96			2.0 (1.1, 2.9)	
	1996–2007			4.6 (2.8, 6.4)	
	1975–89				4.9 (2.6, 7.3)
	1989–2005				-0.8 (-2.4, 0.8)
	2005–07				-61.9 (5.4, -1.8)

APC, annual percentage of change; NC, non-calculable due to zero cases in one or more years.

^aResults are shown when there were at least 100 cancer cases in each category (by population, sex and histological subtype). When our models suggested a joint point (point of change) in APC, the APCs were shown in the periods before and after that point. Trends with 95% CIs that do not include zero are shown in bold.

of anal intercourse from nationally representative and comparable surveys. However, a few cross-sectional national surveys in the USA conducted in the early 1990s and late 2000s suggest that prevalence of receptive anal intercourse has increased in both men and women in that country.^{38–40} It should be noted however that in many cases, in particular in women, anal cancer occurs with no history of receptive anal intercourse.²⁷ The association between receptive anal intercourse and anal cancer appears to be

weaker in women than in men,^{26,33} probably because cervical HPV infection is the most important factor for the persistence of anal HPV infection in women.²⁹ An increase in the prevalence of cervical HPV infection may be the most plausible explanation for the increase in ACSS incidence rates only in women in several countries that have seen substantial changes in sexual behaviour in recent decades.^{35–37} The increase in cervical cancer incidence rates in some of these countries (such as the Russian Federation)

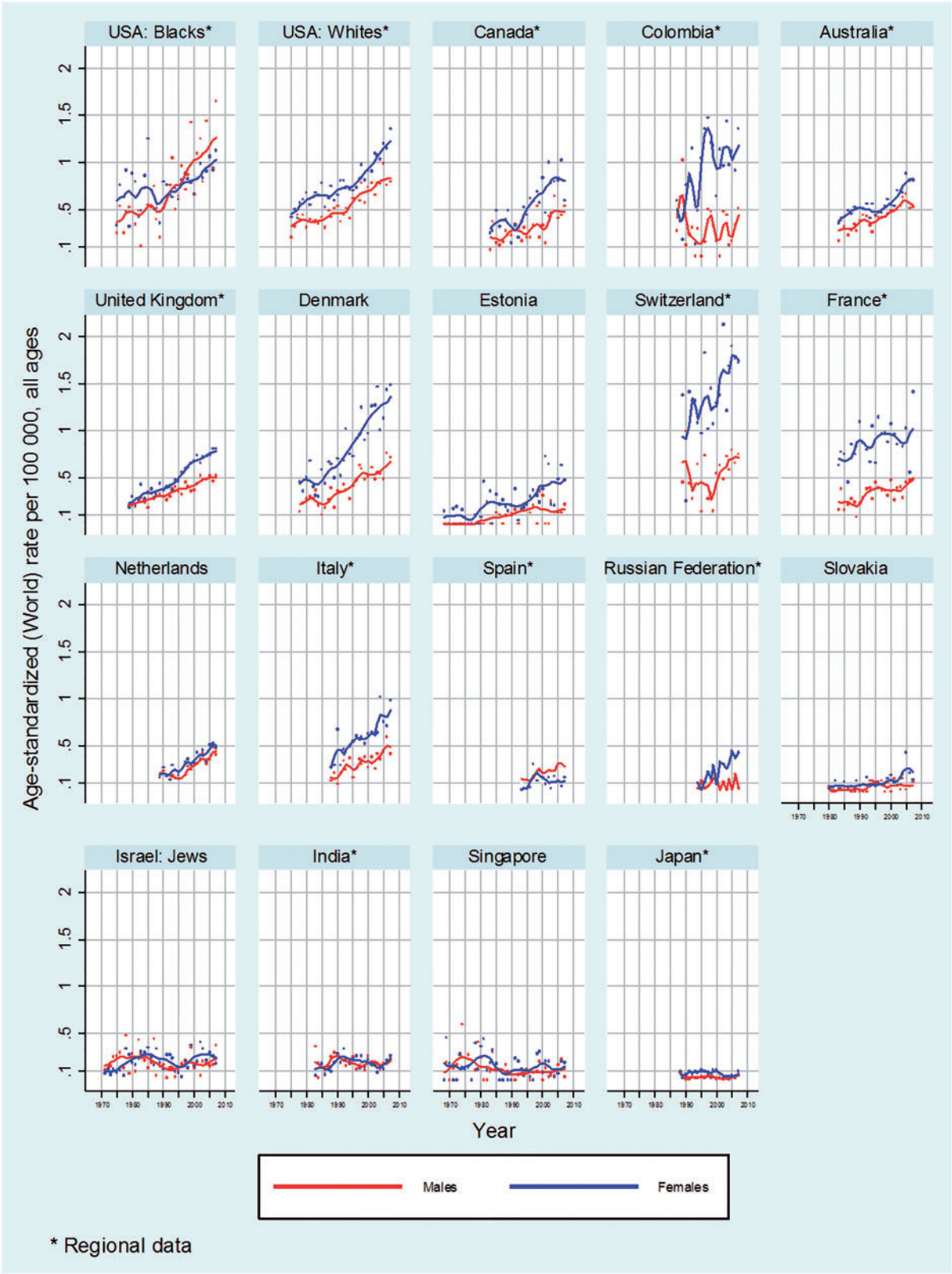


Figure 2. Age-standardized incidence rates of anal squamous cell carcinoma by sex.

Table 3. Annual percentage of change in the incidence of anal SCC and adenocarcinoma by sex, 1989–2007^a

Population	Period	Males				Females			
		ASCC		AAC		ASCC		AAC	
		N	APC (95% CI)	N	APC (95% CI)	N	APC (95% CI)	N	APC (95% CI)
Australia	1989–2007	1079	3.3 (2.0, 4.6)	605	–0.9 (–3.4, 1.6)	1609	See below	501	1.0 (–1.7, 3.7)
	1989–96						–1.8 (–6.3, 2.9)		
	1996–2007						5.9 (3.9, 7.9)		
Canada	1989–2007	133	4.5 (1.6, 7.4)	97	–	279	5.5 (2.8, 8.3)	87	–
Colombia	1989–2007	38	–	25	–	154	2.2 (–1.0, 5.6)	36	–
Denmark	1989–2007	375	4.3 (2.5, 6.1)	112	NC	849	4.9 (3.3, 6.4)	115	–4.5 (–7.1, –1.7)
Estonia	1989–2007	24	–	33	–	60	NC	40	–
France	1989–2007	190	2.5 (0.1, 4.9)	104	–9.6 (–13.9, –5.0)	639	0.9 (–1.1, 2.9)	93	–
India	1989–2007	233	–1.8 (–3.8, 0.3)	185	0.2 (–3.1, 3.5)	205	–1.6 (–4.1, 1.0)	112	–1.3 (–4.4, 1.9)
Israel, Jews	1989–2007	89	–	127	See below	152	2.2 (–1.6, 6.1)	139	–7.2 (–11.0, –3.4)
	1989–98				4.5 (–2.8, 12.3)				
	1998–2007				–22.9 (–30.6, –14.4)				
Italy	1989–2007	216	4.7 (2.3, 7.2)	207	1.1 (–2.0, 4.3)	527	4.3 (2.4, 6.2)	143	0.6 (–2.8, 4.1)
Japan	1989–2007	59	–	414	7.3 (4.3, 10.4)	179	See below	267	5.2 (2.1, 8.3)
	1989–2000						4.3 (–3.4, 12.7)		
	2000–04						–28.6 (–61.5, 32.6)		
	2004–07						43.1 (–16.7, 145.8)		
The Netherlands	1989–2007	556	6.3 (4.4, 8.2)	194	–5.0 (–7.6, –2.3)	783	6.1 (4.3, 7.9)	237	–5.2 (–8.0, –2.3)
Singapore	1989–2007	28	–	91	–	49	–	70	–
Slovakia	1989–2007	40	–	211	–1.7 (–5.5, 2.3)	102	8.4 (3.3, 13.8)	162	–0.3 (–4.0, 3.5)
Switzerland	1989–2007	147	1.6 (–2.1, 5.3)	56	–	480	2.7 (0.3, 5.1)	90	–
UK	1989–2007	1416	3.2 (2.2, 4.1)	571	0.1 (–1.6, 1.8)	2485	See below	606	1.0 (–1.2, 3.4)
	1989–93						–0.9 (–7.4, 6.0)		
	1993–97						11.4 (1.3, 22.5)		
	1997–2007						2.8 (1.5, 4.1)		
USA, Blacks	1989–2007	270	5.0 (2.2, 7.9)	66	–	269	3.1 (1.7, 4.4)	57	–
USA, Whites	1989–2007	1620	3.7 (2.3, 5.1)	398	–1.5 (–3.8, 0.8)	2694	3.9 (3.2, 4.7)	405	See below
	1989–2005								0.8 (–2.3, 0.7)
	2005–07								–3.6.6 (–62.8, 8.3)

APC, annual percentage of change; NC, non-calculable due to zero cases in one or more years.

^aResults are shown when there were at least 100 cancer cases in each category (by population, sex and histological subtype). Registries in the Russian Federation and Spain were excluded from this analysis, as the starting point for the included data was after 1989. Trends with 95% CIs that do not include zero are shown in bold.

supports this assumption.⁴¹ A decrease in incidence rates of cervical cancer in many other countries, however, may reflect the role of cervical cancer screening which reduces cervical cancer incidence rates as a result of treatment of precancerous lesions.^{42,43} We observed little change in the incidence of female ASCC in the Asian countries included in this analysis, where the number of women's sexual partners and prevalence of cervical HPV infection have usually been lower than in Europe or Americas,^{37,44} supporting the importance of cervical HPV infection prevalence in trends in incidence of anal cancer in women.

In both sexes, anal HPV infection and anal cancer are more common in HIV-infected individuals, in particular HIV-infected men who have sex with men.^{16,45,46} The risk of anal cancer increases with duration of HIV infection.⁴⁷ Current evidence suggests that the introduction of effective

therapies to control HIV infection, which has resulted in a substantial increase in survival of HIV-positive individuals, has been associated with an increase (or at least no decrease) in the incidence of anal cancer.^{47–51} The global epidemic of HIV infection started in the early 1980s; after an increase, the average global prevalence of the infection in ages 15–49 years has been stable at ~ 1% since the early 2000s.^{52–54} The highest increase in prevalence of HIV infection occurred in sub-Saharan Africa (average prevalence of ~ 6% since 2000), but for the present analysis we did not have data on anal cancer occurrence from this region. A much more modest increase in prevalence, followed by stabilization, has been reported from most high-income countries included in this analysis.⁵³ Among the other included countries, the Russian Federation has had the highest increase in the number of HIV cases in Europe, and

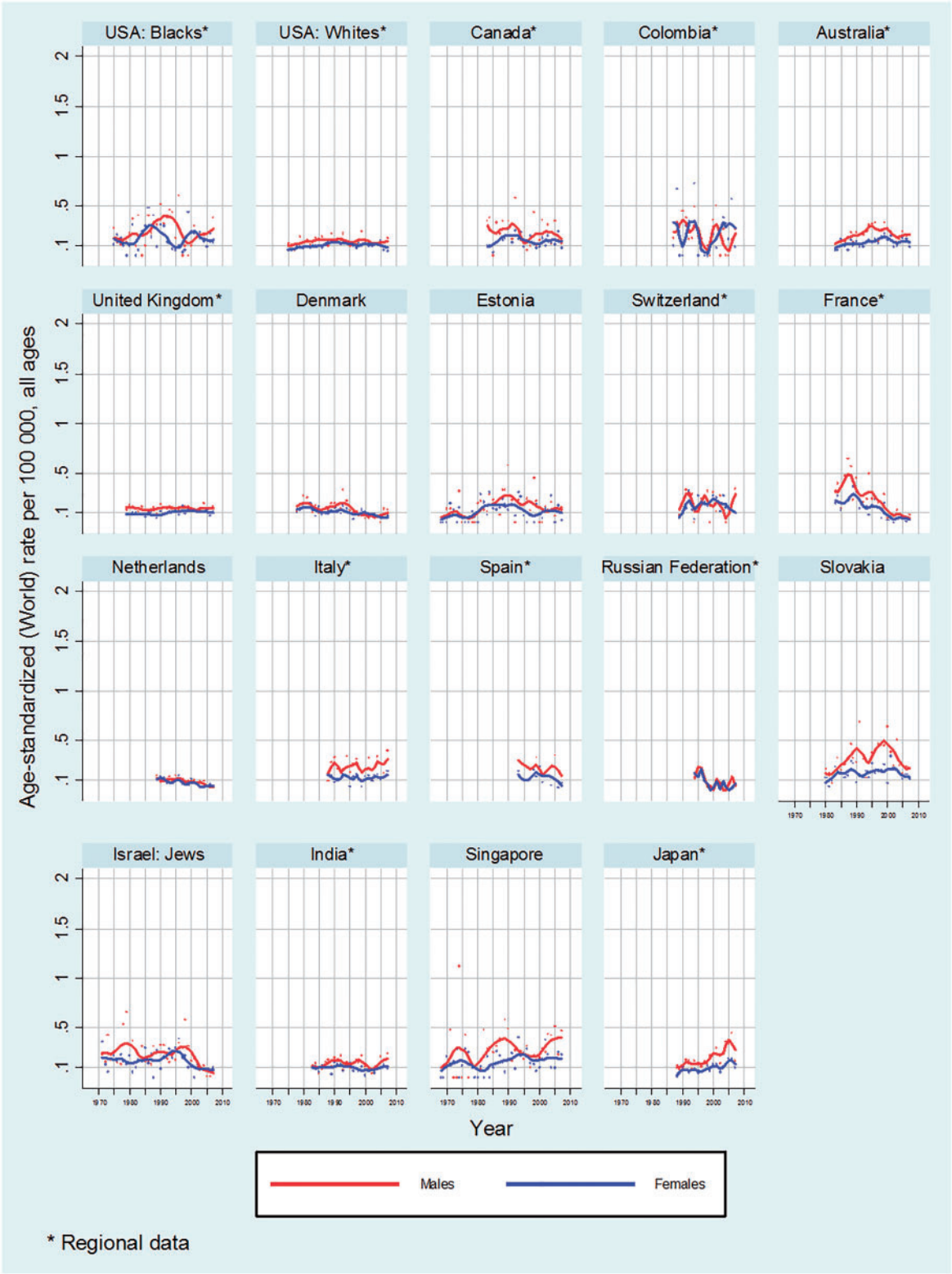


Figure 3. Age-standardized incidence rates of anal adenocarcinoma by sex.

Estonia has the highest prevalence among the Baltic states.⁵³ Our analysis suggests that in view of rapid increases in ASCC incidence rates among Black men in the USA, HIV infection may have a more significant role in anal cancer incidence in this group, given that they are disproportionately affected by HIV.⁵⁵ However, although HIV infection appears to be one of the reasons for an increase in anal cancer incidence rates, it cannot totally explain the temporal pattern. In the USA, for example, HIV does not seem to be a major determinant of anal cancer trends in women, and only 1% of female anal cancers occur in women with HIV infection.⁵⁶ In fact, whereas the increase in anal cancer incidence in our analysis is generally greater in women, in most countries (outside sub-Saharan Africa) the number of men infected with HIV has been higher than infected women.⁵³

A number of studies have reported an association between tobacco smoking and anal cancer.^{13,26,33,46,57,58} Given a typical lag period between the peak of smoking and cancer incidence rates in a population (although as yet unknown for anal cancer), trends in anal cancer rates among women in many European countries are in line with an increase in smoking prevalence until recently.^{59,60} Conversely, smoking prevalence in both men and women in the USA, Australia and several countries in Northern Europe has been decreasing for more than four decades,^{59,60} whereas anal cancer incidence rates are still increasing in those countries. Nevertheless, HPV infection may confound the correlation between smoking and anal cancer trends, because smoking may primarily increase the risk of anal cancer by delaying the clearance of anal HPV.²⁸ A higher incidence of ASCC among the middle-aged (45–64 years) than in older age groups may reflect differences in sexual behaviour and prevalence and duration of HIV infection and smoking⁶¹ across age groups, although the contribution of these factors may vary by sex. The association between smoking and anal cancer needs further research.

Immunosuppression following transplantation, and with some diseases, are associated with an increased risk of anal cancer.⁶² Due to the low prevalence of these risk factors, however, they are unlikely to play a major role in the overall increase in anal cancer incidence rates. An association between some other factors—such as longer duration of oral contraceptive use and nulliparity among women¹³ and physical inactivity³³—and anal cancer risk has been reported in a few studies, but more research on the causality of these associations is required before coming to any conclusions about the possible impact of these factors in the observed incidence trends of anal cancer.

Little is known about risk factors of AAC, but anal fistula, chronic local inflammation and Crohn's disease may

contribute to the development of this subtype of anal cancer.⁶³ The information available from the 1980s to early 2000s indicates a steady increase in the incidence of Crohn's disease in Japan,⁶⁴ but in the UK, which has among the highest incidence and prevalence rates for Crohn's disease worldwide and has seen an increase in admission rates for the disease, the incidence of Crohn's disease has not shown a clear trend in recent decades.^{65,66} Nevertheless, the increase in AAC incidence rates in Japan may be mostly related to an increase in overlapping tumours of the rectum and anus; given the very low incidence rate of AAC in Japan, even inclusion of a modest number of rectal cancer cases as anal cancer might explain this trend. Another analysis using CI5 data showed an increase in the incidence of colorectal cancer in many countries included in our analysis (Canada, Colombia, Denmark, Estonia, Italy, The Netherlands, the Russian Federation, Singapore, Slovakia, Spain, Switzerland and the UK) in relatively comparable time periods (up to 2007), but a decrease in the incidence in Australia, France, Israel, Japan, US Blacks and US Whites.⁶⁷ Part of the decrease in the latter group may be related to colorectal cancer screening, which may help to reduce colorectal cancer incidence by removing precancerous lesions. In any case, these and our results show that anal and colorectal cancers do not share the same global trends in incidence, probably due to differences in their aetiological factors.

A few studies have projected trends in incidence of anal cancer in the future. One study projected an increase in the incidence of ASCC in both sexes combined in New South Wales, Australia, in 2010–32.⁴ On the other hand, the incidence of AAC, which was much lower compared with ASCC, was projected to decrease or remain stable.⁴ Another analysis predicted little change in age-standardized rates (ASRs) for anal cancer mortality in either sex in Spain.⁶⁸ These results are consistent with contemporary trends in the above countries in our analysis. Another analysis predicted little change in the ASRs for anal cancer mortality from 2006–10 to 2021–25 in either men (from 0.10 to 0.11 per 100 000) or women (from 0.16 to 0.13) in Brazil.⁶⁹ It should be noted, however, that anal cancer mortality rates examined in the latter two studies may also be influenced by stage at diagnosis and access to treatment, and may not be directly comparable with anal cancer incidence rates.

Future perspectives

HPV vaccination can provide protection against anal HPV infection.⁷⁰ As it was first made available in 2006, it is probably too early to see preventive effects of vaccination of young adults on anal cancer incidence rates in the

general population, but HPV vaccination has been shown to prevent anal intraepithelial neoplasia⁷¹ and anal cancer⁷² in high-risk groups. Despite benefits of HPV vaccination in preventing several HPV-related cancers,⁷³ it is yet to be routinely administered in most low- and middle-income countries (LMICs), or at present the uptake is not optimal.⁷⁴ Raising awareness about safer sex is also important. Without these preventive measures, even populations with a stable trend for ASCC in this analysis could see a future increase in the burden of HPV-related diseases, including anal cancer, as a result of changes in sexual behaviour.

Currently, mass screening for anal cancer is not recommended because anal cancer is a rare disease, and there is no evidence that screening for anal cancer improves the outcome of the disease.⁷⁵ Some cost-effectiveness analyses have shown mixed results or no benefit from screening of high-risk individuals.^{76,77} However, due to paucity of data, screening in high-risk groups is a subject for debate. Based on expert opinion, a few guidelines recommend regular digital anorectal examination in high-risk individuals.^{75,78} Some experts suggest annual anal Pap screening of HIV-infected men who have sex with men, with referral for high-resolution anoscopy for any abnormal cytology.⁷⁹ Nevertheless, few national authorities worldwide recommend routine Pap screening at present, even for high-risk individuals.⁸⁰ In the USA, the Centers for Disease Control and Prevention (CDC) does not recommend any systematic screening for anal cancer, but a few state-level authorities in New York and professional organizations recommend annual screening in certain high-risk groups.^{78,81,82}

Strength and limitations

The main strengths of this study are the use of longitudinal data from the cancer registries of high quality (passing CI5's inclusion criteria), and the uniform approach applied in our analysis, allowing comparisons across countries. This reduces potential problems associated with heterogeneity in the definition of the morphological group codes across a country or between countries. The CI5 series selects only registries that comply with the International Agency for Research on Cancer (IARC)'s standards for quality of data, and after selection of registries, every effort is made to standardize the data presented.⁸³ In our analysis, moreover, we used data from the same registry/registries from any given country throughout the study period, to reduce the possibility of any residual heterogeneity in quality of data that could have been introduced by adding new registries over time. Therefore, a substantial change in the observed trends only because of heterogeneity in the data collection method is unlikely. However, the analysis

of data from several countries was based on small numbers, given the rarity of the disease and the size of the underlying catchment populations. Nevertheless, consistent trends in neighbouring countries within a region imply that the local data are at least partially representative of national trends. Although the inclusion of a relatively small group of anal cancers with an unspecified histology would lead to underestimation of incidence rates for ASCC and AAC to some degree, it would have a minimal effect on temporal trends in our analysis, as the incidence rates for this group showed little change over time in the populations considered in this study.

Conclusions

The incidence of anal cancer has been increasing in most populations included in this study. Reasons for this increase are unknown, but may include a rise in prevalence of factors that increase the incidence and persistence of anal HPV infection. Certain preventive measures if implemented, including HPV vaccination and campaigns for safer sexual behaviours, would serve to prevent a substantial number of anal cancer cases in the future.

Supplementary Data

Supplementary data are available at *IJE* online.

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Author Contributions

All authors contributed to study concept and design, data interpretation and manuscript writing, and approved the final version of the manuscript. J.F. and F.B. assembled the data. F.I. analysed the data and drafted the manuscript.

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