Anal intraepithelial neoplasia in HIV+ men

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Chapter

The increasing incidence of anal cancer: can it be explained by trends in risk groups?

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Abstract

Background: Anal cancer incidence is gradually increasing. The cause of this increase is not exactly known. This systematic literature review aimed to investigate the trend in time of anal cancer incidence and to find an explanation for the supposed increase. Methods: The TRIP database and PubMed were searched for trends in time in incidence of anal cancer in the general population, for risk factors and risk groups for anal cancer, and for incidence trends in time in these risk groups.

Results: Age-adjusted incidence rates have increased in all Western countries during the last decades, up to 2,2% per year. Infection with the oncogenic human papilloma virus is the most important aetiological factor. Besides increasing age, other risk factors have been identified: smoking, sexual practices, in particular receptive anal intercourse, and being human immunodeficiency virus (hiv)- positive. The standardized incidence risk (SIR) is significantly increased in hiv-positive men who have sex with men (MSM) (SIR 77.8), organ transplant recipients (SIR approx. 6) and women with a history of cervical cancer (SIR 6) or cervical intraepithelial neoplasia (SIR 16). Absolute numbers of hiv-positive MSM and organ transplant recipients have increased significantly in the last decades. Conclusion: The increasing incidence of anal cancer can be partially explained by an increase of the incidence rate in and absolute number of the most important risk group: hiv-positive MSM. The increasing number of renal transplant recipients probably also contributes. Further studies should answer the question whether these risk groups would benefit from preventive screening for anal cancer.

Introduction

Anal cancer originates from or nearby the transition zone in the anal canal. The squamous cell carcinoma is the most common form of anal cancer. Other, more rare, tumours of the anal canal are adenocarcinomas, anal melanomas, anal sarcomas and anal neuroendocrine tumours. As with cervical cancer, anal squamous cell carcinoma is caused by a persistent infection with the sexually transmitted oncogenic human papillomavirus (HPV). [1,2,3,4] Several studies from different countries have reported an increase in anal cancer incidence during the last 20 years. [5,6,7,8,9,10] In the Netherlands, for example, the incidence of anal cancer has doubled during the last decennia. [3] Although anal cancer remains relatively rare in the general population, it accounts for a significant burden of disease in certain risk groups. [5,6,10] The cause of this reported increasing incidence of anal cancer is relatively unknown, but an important role is attributed to the increase in number of immunocompromised persons. Studies have shown that human immunodeficiency virus (hiv) positive persons and men who have sex with men (MSM) are at increased risk for anal cancer. Organ transplant recipients and women with a history of cervical cancer or cervical intraepithelial neoplasia are also known to have a greater risk for anal cancer. [1,4,10] This literature review aimed to investigate the trend in time of anal cancer incidence in Western countries and to find an explanation for the supposed increase. We therefore explored whether there is indeed a change in incidence of anal cancer since 1970. Next, we tried to explain the grounds of this change by identifying known risk factors and risk groups of anal cancer. Finally, we focussed on changes in anal cancer incidence among these risk groups, to see whether such changes, if present, could explain the overall increase in anal cancer incidence. The findings of this literature review might be of help in identifying risk groups who could benefit from adequate prevention measures, including screening for anal cancer by high-resolution anoscopy.

Methods

Two comprehensive literature searches were performed. For the first search, focussing on trends in the incidence of anal cancer, the TRIP database was searched in February 2012, using the term 'anal cancer' and the combination 'anal cancer'

and 'incidence'. The Medline/PubMed database was searched for data from 1970 onwards on the incidence of anal cancer. This search was restricted to the English and Dutch language. The exact search was: (("Anus Neoplasms"[Mesh]) OR (anal cancer[tiab]) OR (anal carcinoma[tiab]) OR (anal intraepithelial neoplasia[tiab])) AND (("Incidence"[Mesh]) OR (incidence[tiab])) Limits: English, Dutch, Publication Date from 1970/01/01 From both the TRIP and PubMed searches, relevant studies on trends in time in the incidence of anal cancer in the general population were identified, as well as specific studies on the trends in time among the risk groups hiv-positive persons, men who have sex with men, organ transplant recipients and women with a history of cervical cancer or cervical intraepithelial neoplasia.

For the second search, focussing on risk factors and risk groups, the TRIP database was searched in February 2012, using the terms 'anal cancer' and 'etiology', 'anal cancer' and 'risk factors' and 'anal cancer' and 'risk group'. The Medline/PubMed database was searched for reviews (from 2007 through June 2012) on risk factors and risk groups for anal cancer. This search was restricted to the English and Dutch language. Initially, this search included original studies from 1970 onwards. This yielded too many articles on risk factors and risk groups. Therefore, we restricted the search to reviews from 2007 onwards. We assumed that data published before this date will have been covered by these recent reviews.

The exact search was: (("Anus Neoplasms"[Mesh]) OR (anal cancer[tiab]) OR (anal carcinoma[tiab]) OR (anal intraepithelial neoplasia[tiab])) AND (("Epidemiologic Factors"[Mesh]) OR (Etiology[Subheading])

OR (Etiology[tiab]) OR (Risk factor[tiab]) OR (Risk group[tiab])) Filters: Publication date from 2007/01/01; Review; English; Dutch

Reference lists of the retrieved articles were reviewed to identify the original studies on risk factors and risk groups. These studies were also retrieved. Studies on the incidence of anal intraepithelial neoplasia (AIN) and HPV infections only, studies that did not report population-based incidence rates, and studies that did not distinguish between colorectal cancer and anal cancer were excluded. Studies on incidence rates of anal cancer from other than Western countries

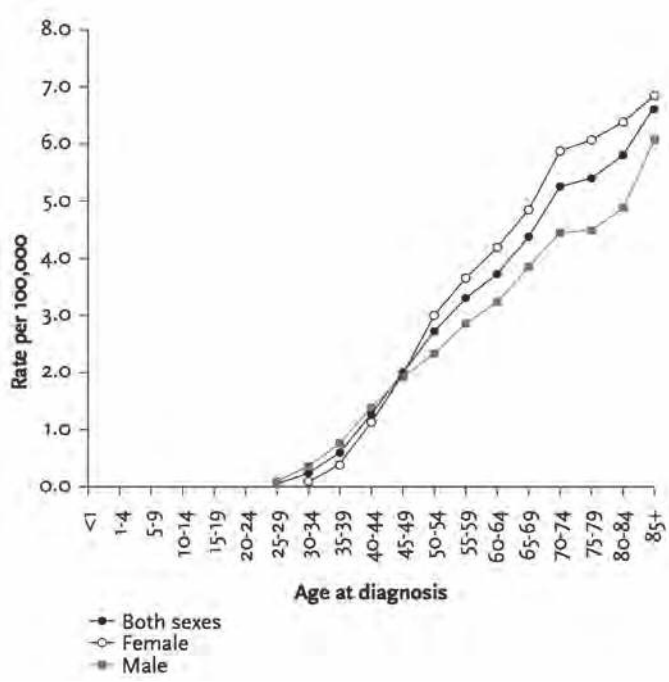
(i.e. Northern America, Western Europe and Australia) were also excluded, since most of these countries lack nationwide databases that go back in time for sufficient years to see trends.

Additional data on the incidence of anal cancer in The Netherlands were obtained from the Dutch Cancer Registry (NKR) database (http://cijfersoverkanker.nl/). Incidence data of anal cancer in the United States were obtained from the Surveillance, Epidemiology and End Results (SEER) Program database of the US National Cancer Institute (http://seer.cancer.gov/). We did not find other easily accessible national cancer registries. Additional data on the proportion of hiv-infected MSM in the total hiv-positive population in follow-up in The Netherlands were obtained from the 2007 and 2011 Monitoring Reports of the Dutch HIV Monitoring Foundation (http://www.hiv-monitoring.nl/).

Interpretation of data

Most commonly used to classify anal tumours is the International Classification of Diseases for Oncology, Third Revision, (ICD-O-3) codes C21.0–C21.8, which corresponds with International Classification of Diseases for Oncology, Tenth edition, (ICD-10) codes C21.0–C21.8. [11] All studies reported used this or similar histological and topographical classifications of anal cancer, unless otherwise specified. Age-adjustment of anal cancer rates is necessary, since cancer is more prevalent among the elderly (Figure 1). Countries or regions with an increasing number of elderly people would therefore get erroneously increasing incidence rates without age-adjustment. All studies used age-adjustment, unless otherwise specified. Differences in incidence rates over time were considered significant at P-value < 0.05. [12,13]

Figure 1. Age-specific SEER incidence rates by sex. Anus, anal canal and anorectum, all ages, all races 1992-2009. Derived from reference 13.

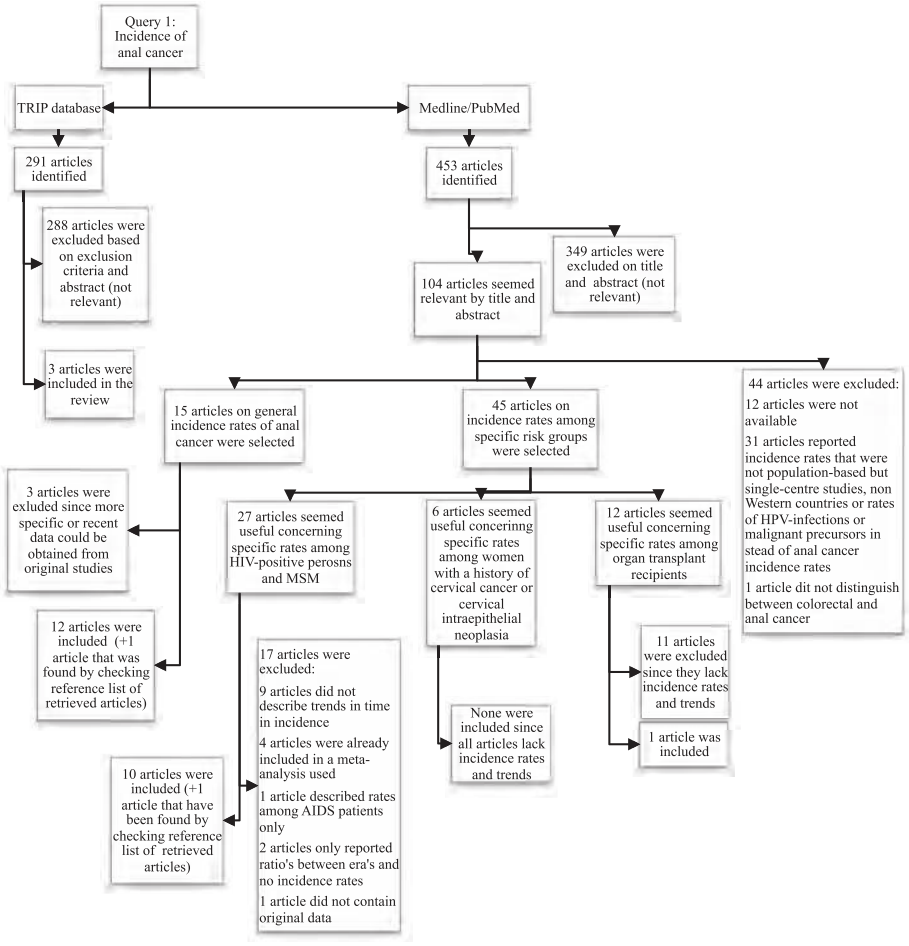


Results

Incidence of anal cancer and trends in time

The first search in the TRIP database, using the term 'anal cancer', yielded 291 articles of the level of secondary evidence, from which 3 studies seemed relevant after selection of the title and abstract, and they were used. The other search in the TRIP database, combining the terms 'anal cancer' and 'incidence', yielded 129 articles, none of which seemed relevant. The first Medline/PubMed search, focussing on the incidence of anal cancer, identified 453 articles, from which 104 articles seemed relevant by title and abstract. Eventually twelve articles were used for the general incidence rates of anal cancer (Figure 2). One additional article was found by checking the reference lists of retrieved articles

Figure 2. Results of systematic literature search on general incidence rates of anal cancer and incidence rates among specific risk groups for anal cancer



We found that recent age-adjusted incidence rates of anal cancer differ between Western countries, with rates ranging from 0.7 per 100,000/year in the United Kingdom [7], 0.83 in The Netherlands [14], 1.35 in Australia [10] to 1.7 per 100,000/year in the United States [13]. In most countries, incidence rates are higher for women. Incidence rates have increased in all Western countries during the last decades (Table 1). Except for Canada [15], incidence rates of anal cancer increased in both sexes for the studied countries.

Table 1. Age-adjusted incidence rates of anal cancer and changes over time in anal cancer incidence by country, gender and period.

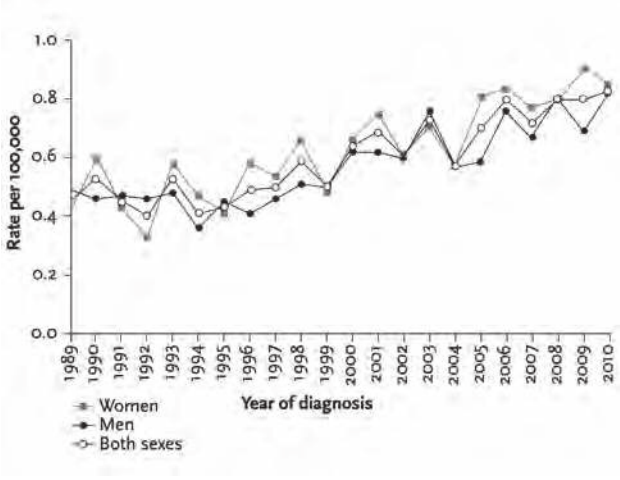
Country	Diagnose	Age-adjusted incidence rates per 100.000 per year/period			Annual percentage change per period (%)
USA [12, 13]	All histological types of cancer of the anus, anal canal and anorectum (except sarcomas) (ICD-10 C21.0-C21.8)		1975:	2005-2009:	1975-2009:
		Total	0.8	1.7	2.2 *
		Female	0.9	1.9	2.0 *
		Male	0.7	1.5	2.6 *
Canada (Quebec) [15]	Squamous cell carcinomas of the anus, anal canal and anorectum (except sarcomas) (ICD-10 C21.0-C21.8)		1984-1986:	1999-2001:	-
		Total	-	-	
		Female	0.4	0.7	
		Male	0.3	0.4	
Netherlands [14]	All histological types of cancer of the anus, anal canal and anorectum (except sarcomas) (ICD-10 C21.0-C21.8)		1989:	2010:	-
		Total	0.45	0.83	
		Female	0.42	0.85	
		Male	0.49	0.82	
Southeast England [7]	All histological types of cancer of the anus, anal canal and anorectum (except sarcomas) (ICD-10 C21.0-C21.8)		1960-1964:	2000-2004:	-
		Total	0.50	1.10	
		Female	0.45	1.18	
		Male	0.79	1.06	
Scotland [8]	Squamous cell carcinomas of the anus, anal canal and anorectum (except sarcomas) (ICD-10 C21.0-C21.8)		Late 1970s:	1998-2002:	-
		Total	-	-	
		Female	0.23-0.27	0.55	
		Male	0.14-0.17	0.37	
Denmark [9, 70]	All histological types of cancer of the anus, anal canal and anorectum (except sarcomas) (ICD-10 C21.0-C21.8)		1943:	1983-1987:	-
		Total	-	-	
		Female	0.25	0.74	
		Male	0.20	0.38	
			1978-1982:	2003-2008:	1978-2008:
		Total	-	-	-
		Female	0.68	1.48	2.9 (95% CI, 2.2-3.6) †
		Male	0.45	0.80	1.4 (95% CI, 0.6-2.2) †
Australia [10]	All histological types of cancer of the anus, anal canal and anorectum (except sarcomas) (ICD-10 C21.0-C21.8)		1982-1987:	2000-2005:	-
		Total	0.91	1.35	
		Female	1.01	1.40	
		Male	0.77	1.30	
	Squamous cell carcinomas of the anus, anal canal and anorectum (except sarcomas) (ICD-10 C21.0-C21.8)	Total	0.65	1.00	
		Female	0.78	1.10	1.88 (95% CI, 1.18–2.58) ‡
		Male	0.48	0.88	3.42 (95% CI, 2.49–4.35) ‡

* No confidence interval available; † $P < 0.05$; ‡ $P < 0.001$

Data for The Netherlands

Incidence data of anal cancer in The Netherlands was retrieved from the Dutch Cancer Registry (NKR) database. It includes all cancer diagnoses of the anal canal and anus and is age-adjusted using the European standard population. [14] The age-adjusted incidence rate of anal cancer in the Netherlands in 1989 for both sexes combined was 0.45 per 100,000 inhabitants and the gender-specific rate was higher for men than for women. The incidence has increased significantly (84%) between 1989 and 2010, with the increase being more prominent in women than in men (102% versus 67%) (Figure 3). In 2010 the overall incidence was 0.83 per 100.000, and it is slightly higher for women (0.85 per 100,000) than for men (0.82 per 100,000). In 2011, 40 persons died from anal cancer in The Netherlands. [14]

Figure 3: Age-adjusted incidence rates of cancer of the anus and anal canal in The Netherlands 1989-2010. Derived from reference 14.

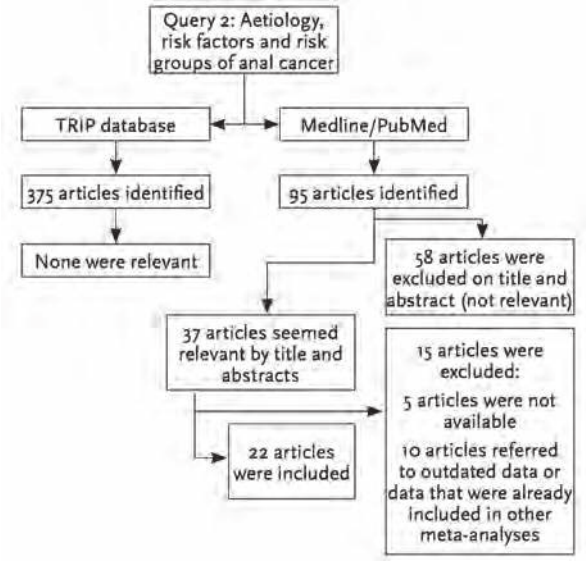


Aetiology, risk factors and risk groups

The searches in TRIP database, using the terms 'anal cancer' and 'etiology', 'anal cancer' and 'risk factors' and 'anal cancer' and 'risk group' yielded 60, 137 and 178 articles of the level of secondary evidence, respectively. None of these articles seemed relevant. The Medline/PubMed search, focussing on risk factors and risk groups, identified 95 reviews, from which 37 reviews seemed relevant by title and abstract. Eventually 22 reviews were used (Figure 4).

For a long time anal cancer was thought to develop as a result of chronic irritation from hemorrhoids, anal fissures, fistulae and inflammatory bowel disease. More recent studies have rejected these ideas and identified certain aetiological factors, risk factors and risk groups. [1,4]

Figure 4. Results of systematic literature search on aetiology, risk factors and risk groups of anal cancer



Smoking

Several studies have confirmed cigarette smoking to be a risk factor for the development of anal cancer. A study in 1992 estimated the Odds Ratio's (OR) for anal cancer among smokers versus non- smokers at 3.0 (95% CI, 1.9–5.0) for women and 5.0 (95% CI, 1.6–16.1) for men, with the risk decreasing after cessation of smoking. [16] More recently, a study confirmed the risk of smoking for anal cancer for men (adjusted OR = 3.9; 95% CI, 1.9–8.0) and women (adjusted OR = 3.8; 95% CI, 2.3–6.2), without variation in age. [17] A population-based case-control study from Denmark and Sweden found that the risk increased linearly by 6.7% per pack-year. [18] An earlier study already found a correlation between pack-years of smoking and anal cancer (RR = 1.9 for 20 pack-years, *P*-value < 0.001; RR = 5.2 for 50 pack-years, *P*-value < 0.001). [19,20,21]

HPV infection

Infection with human papillomavirus is the most prevalent sexually transmitted disease with approximately 75% of all sexually active people infected during lifetime. [22] Normally the virus is rapidly cleared and only in 1% of infected patients genital warts (caused by the non-oncogenic HPV types 6 and 11) will develop. [1,23] Infection with oncogenic HPV types (HPV-16 and HPV-18) is the most important aetiological factor for anal cancer. [2,24] A population-based case-control study in Denmark and Sweden tested 386 patients with anal cancer and found oncogenic HPV types in 90% of women and 64% of men. [25] A similar study in the United States detected oncogenic HPV in 87.9% of 262 anal cancers. No differences were reported between sexes. [17] Of the more than 120 subtypes of HPV, HPV-16 was shown to be the most frequently (70%) detected in patients with anal cancer. [1,17,18,26] A recent systematic review, combining worldwide data, found a prevalence of 65.6% of HPV-16 and 5.1% of HPV-18 in anal cancer. [27] Similar to cervical cancer, anal cancer seems to be preceded by a premalignant lesion, called anal intraepithelial neoplasia (AIN), which is also associated with HPV infection. [1,28] Anal condylomata are associated with anal cancer as well. [17,18,29] Because genital warts are caused by HPV-6 or HPV-11, which are not oncogenic, the association of genital warts with anal cancer is more likely to be a marker for high-risk sexual behaviour resulting in co-infection with oncogenic HPV-subtypes. [19,30]

Sexual practices

Several studies have investigated the relationship between sexual practices and the risk for anal cancer. Early population-based case-control studies in 1987 and 1989 have shown that men who were never married, who not have been exclusively heterosexual and men who have practiced receptive anal intercourse had higher risks for anal cancer. [19,29] Another population-based case-control study in 2004 confirmed these findings by showing that the risk of anal cancer was higher in men who were not exclusively heterosexual (OR = 17.3; 95% CI, 8.2–36.1). Among these men, practicing receptive anal intercourse was independently strongly related to the risk of anal cancer (OR = 6.8; 95% CI, 1.4–33.8). Men who have had more than 15 sexual partners were also at risk for anal cancer (for heterosexual men: OR = 3.9, for homosexual men: OR =6.6). [17] These findings suggest that men who have sex with men (MSM) can be considered a risk group for anal cancer. Women with anal cancer were more

likely to report a history of anal intercourse (16.9%) compared with women without anal cancer (11.0%). The risk for anal cancer was especially high in women who had more than 10 sexual partners. [17,31]

A history of sexually transmitted diseases is correlated with a higher risk for anal cancer. [17,19,29,31] This is prone to confounding, since it is hard to distinguish from the increasing risk that is already caused by receptive anal intercourse.

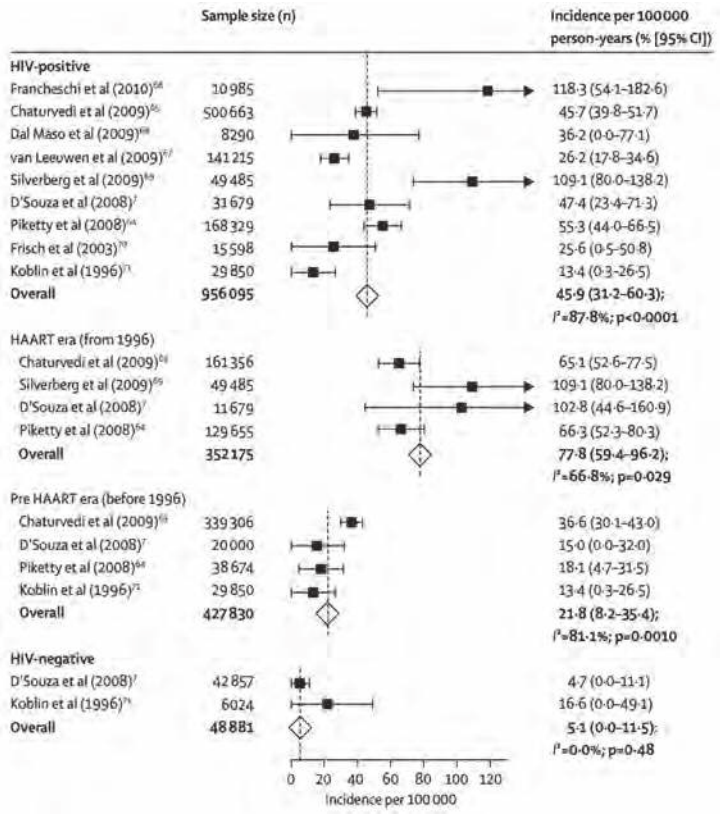
Hiv-positive persons

Immunosuppression is reported to be an important factor in the development of anal cancer. The association between anal cancer and hiv infection is difficult to confirm because of confounders. The relationship between anal cancer and receptive anal intercourse has been mentioned above. In addition, hiv-positive individuals are reported to be detected with an HPV infection more often than hiv-negative individuals and when infected, often with more than one subtype. [32,33,34,35] On the other hand, patients infected with HPV are seen to have higher rates of hiv infections. [36] Hiv-positive persons are more likely to be detected with AIN [32,33,37,38], and have a more rapid progress from AIN to anal cancer. It is suggested that the greater risk for anal cancer in hiv-positive as compared to hiv-negative persons is caused by differences between hiv-positive and hiv-negative persons in biology of anal HPV infection and anal cancer. [38,39] Immunosuppression probably plays a role: a negative correlation was found between CD4+ T cell-counts and the appearance of AIN [32,37,40] and anal cancer [41,42,43] in hiv-positive persons. There are also studies that suggest an independent correlation between anal cancer and hiv infection itself. [44] A decrease of incidence has not been seen during the last years and it has been suggested that the widespread use of cART makes hiv-positive individuals live longer and makes them prone to infection with HPV for a longer period, leaving more time for developing anal cancer. According to this explanation, anal cancer is more associated with a persistent HPV infection than with hiv. [1,32,45]

One study reported that even during an early stage of hiv infection the incidence of anal cancer was increased significantly. This finding also suggests that severe immunosuppression caused by the hiv infection is not the only explanation for the development of anal cancer. [46] Two recent meta-analyses, combining

data from 6 [47] and 8 [48] individual studies respectively, showed an increased risk for anal cancer in hiv-infected patients of approximately 30-fold compared with the general population ((SIR = 28.75; 95% CI, 21.6-38.3) [47], (SIR = 28; 95% CI, 21-35) [48]). Before the introduction of combination Antiretroviral Therapy (cART) in 1996, the incidence of anal cancer was 6.8-fold higher among hiv-positive women compared with the general population. [39] Hiv-infected MSM were reported to have the highest risk for anal cancer. [38,49,50,51] A recent meta-analysis, including 9 individual studies, revealed that the incidence of anal cancer among hiv- positive MSM was 46 per 100,000 person-years and therefore much higher (P = 0.011) than the incidence among hiv-negative MSM, which was 5 per 100,000 person-years (Figure 5). The incidence rate found in hiv-negative MSM is still higher than the incidence in the general population. [35]

Figure 5. Incidence of anal cancer in men who have sex with men, by HIV status and before and after the introduction of combination Antiretroviral Therapy (cART) (= HAART). Derived from reference 35.



Organ transplant recipients

Chronic immunosuppressive therapy, for example following solid organ transplantation, is known to be a risk factor for several types of squamous cell carcinomas. Since the most common type of anal cancer is squamous cell carcinoma, several studies have found a high risk for anal cancer for patients receiving immunosuppressive therapy. [52,53] It is thought that the increased risk is the result of persistent HPV infection, caused by chronic immunosuppression. [54,55,56,57,58] A recent meta-analysis in 2007 estimated the risk of anal cancer for solid organ transplant recipients at 6-times higher compared with the general population (SIR = 5.85; 95% CI, 1.36–17.3), based on two studies from Sweden and Australia/New Zealand. [47] A Danish nationwide cohort study published in 2010 revealed a 14-fold higher risk for anal squamous cell carcinoma compared with the general Danish population (SIR = 14.4; 95% CI, 7.0-26.4) [59], and a comprehensive cohort study (1987- 2008) in the United States reported a 6-fold higher risk compared with the US general population (SIR = 5.84; 95% CI, 4.7-7.18) (*P*-value <0.001). The incidence of anal cancer among organ transplant recipients was 11.6 per 100,000 person-years according to this study. [60]

Women with a history of cervical cancer or cervical intraepithelial neoplasia

As mentioned above, population-based studies have found a link between cervical cancer and anal cancer. [61] This link is explained by HPV infection. [3] Women with anal cancer are more likely of having had a history of vulvar/vaginal cancer (OR = 15.4; 95% CI 4.9-48.0) or cervical cancer (OR = 4.3; 95% CI 2.7-6.9) according to data from the Danish Cancer Registry for the period 1943-1989. [21] In a prospective population-based study of all Swedish women aged 18–50 years the incidence rate ratios of anal cancer in women with a history of cervical intraepithelial neoplasia (CIN) grade 3 was investigated for the period 1968-2004. Women with such history had a 5-fold higher risk for anal cancer. [62] A more recent study in the United States using data from the SEER program from the period 1973-2007, reported a 16-fold higher risk for anal cancer for women with a history of cervical intraepithelial neoplasia and a 6-fold higher risk for women with a history of cervical cancer. Women with histories of vulvar intraepithelial neoplasia and vulvar cancer had higher risks as well: SIR = 22.2 and SIR = 17.4, respectively. [63] The increased risks could not be explained by therapeutic interventions for cervical cancer, such as radiation, in any of the studies.

Incidence and trends in incidence of anal cancer among risk groups

The first literature search focussing on the incidence of anal cancer was used to identify articles on the specific incidence rates and trends in time of anal cancer among risk groups as well (Figure 2). From this search 10 articles were useful concerning the hiv-positive persons and men who have sex with men, one concerning the specific incidence rates and trends in time of anal cancer among organ transplant recipients, and no articles were useful for the risk group women with a history of cervical cancer or cervical intraepithelial neoplasia.

If significant changes can be seen in the incidence of anal cancer for these risk groups, this might (partly) explain the increasing incidence of anal cancer world-wide. Studies that describe trends in time in anal cancer incidence among these groups are rare. Therefore we also used an alternative way to determine whether a risk group contributes to the increase in anal cancer. The (increasing) incidence of anal cancer in a risk group can be estimated by a simple multiplication using the two factors increased risk for anal cancer (defined by standardized incidence ratios, for example) in that particular risk group and the increase in absolute number of persons in that risk group.

Hiv-positive persons

A meta-analysis combining incidence data from 4 studies of the pre-cART era (before 1996) and 5 studies of the cART era (from 1996 onwards), showed that the standardized incidence ratio increased from 37 (95% CI, 19-75) in the pre-cART era to 47 (95% CI, 22-100) in the cART era. [48] A prospective cohort study in England, not included in this meta-analysis, found similar data. [64] The standardized incidence rate of anal cancer compared with the general population in this cohort, including 8640 hiv-positive patients, has risen from 35 per 100,000 person-years in the period before the introduction of cART (1984–1995) to 92 per 100,000 in the cART era (1996–2003) (*P*-value > 0.05), which is significantly higher than the incidence in the general population (*P*-value < 0.001 for both). [64]

Hiv-positive MSM

As discussed above, hiv-positive MSM are the most prominent risk group for anal cancer. One meta- analysis, investigating the incidence of anal cancer among hiv-positive MSM before and after the introduction of cART, combines data from

nine individual studies (six hiv/AIDS and cancer registries linkage studies and three observational cohort studies). The incidence of anal cancer among hiv-positive MSM was higher from 1996 onwards (after introduction of cART) (78 per 100,000 person- years), than it was before 1996 (22 per 100,000) (*P*-value = 0.013) (Figure 5). The authors of this meta-analysis remark that incidence rates of the pre-cART era are not age-adjusted and some of the increase might be explained by aging of the hiv-positive population. [35]

One of the studies in above meta-analysis, based on combined incidence data of 13 cohorts in North America from 1996 and 2007, reports a plateau phase in the increase of incidence among hiv-positive MSM for recent years. Standardized incidence rates for hiv-positive MSM have developed from 90 per 100,000 in the period 1996-1999 to 159 per 100,000 in the period 2000-2003 and 131 per 100,000 in the period 2004-2007. [65] For the Netherlands, we also observed such a plateau in incidence, with approximately 20 cases of anal cancer diagnosed annually in hiv-positive MSM (Richel O, unpublished data).

Since hiv-positive MSM have a 80-fold higher risk for anal cancer, an increase in the proportion of hiv-positive MSM in the population will contribute to a higher incidence of anal cancer in the general population. If we look further into the MSM population in The Netherlands, by means of the Monitoring Reports of the Dutch HIV Monitoring Foundation, we see that the hiv-infected MSM population in follow-up has increased with 51.7% from 5619 in 2007 to 8523 in 2011. This means that the proportion of hiv-positive MSM in the population is increasing over time. Registration differed for the years before 2007. [66,67]

Organ transplant recipients

No studies on the trend in time in incidence of anal cancer among organ transplant recipients could be found. As already discussed, organ transplant recipients have a much higher risk for anal cancer compared with the general population. If the proportion of organ transplant recipients in the population increases, this is likely to increase the incidence of anal cancer. A recent Dutch population-based retrospective cohort-study, based on data from the Dutch Foundation for Renal Replacement Therapy Registration (Renine), showed that the number of renal transplant recipients has increased in the period 1995-2009, from 3,640 renal transplant recipients in 1995 to 8,400 recipients in 2009. [68]

Discussion

Incidence rates have increased in practically all Western countries during the last decades. Whereas infection with oncogenic HPV is the most important etiological factor, several risk factors and risk groups for anal cancer have been identified during the last decennia, in particular smoking (OR = 3.9 – 5 for men, OR = 3 – 3.8 for women), men who have sex with men (MSM) (OR = 17.3), MSM practising receptive anal intercourse (additional OR = 6.8), a history of sexually transmitted diseases, having had more than 15 sexual partners, human immunodeficiency virus (hiv)-positivity (OR = 28 - 28,75), hiv-positive MSM (SIR = 77.8), organ transplant recipients (SIR = 5.85) and women with a history of cervical cancer (SIR = 6.2) or cervical intraepithelial neoplasia (SIR = 16.4). We showed that incidence rates of anal cancer among hiv-positive persons have significantly increased over time in multiple countries. Such data are not available for other risk groups.

The increasing incidence of anal cancer could be caused by an increased risk for anal cancer in specific risk groups and in addition by increasing numbers of patients belonging to these risk groups. If the absolute number of these risk groups in the population increases, this is likely to contribute to the increasing incidence of anal cancer. We found that the number of hiv-positive MSM in the Dutch population has increased with 51.7% from 2007 to 2011. Since hiv-positive MSM have a significant risk for anal cancer, this supports our hypothesis that this risk group contributes to the overall increase in incidence. Hiv-positive MSM account for approximately 50% (20 deaths per year) of the total of 40 people dying annually from anal cancer in the Netherlands. The increased number of renal transplant recipients probably contributes to the increased incidence of anal cancer as well: in the Netherlands, the number of renal transplant recipients has increased from 3,640 in 1995 to 8,400 in 2009. This probably also applies to other countries. Other factors are also likely to influence the incidence of anal cancer. In The Netherlands, for example, the number of people smoking cigarettes has decreased with 20% from 2000 through 2007.

[69] Based on these figures one would expect the incidence of anal cancer to decrease, since smokers have an 3-5-fold increased risk for anal cancer.

Limitations of this review mostly result from limitations in the studies used in this review. One of the limitations is the difference in defining anal cancer between studies from individual countries. Most, but not all, studies used identical topographical codes from the International Classification of Diseases for Oncology (ICD) to classify cancer of the anus, anal canal, and anorectum (C21.1-C21.8). Another limitation is that distinction between histological types of anal cancer (e.g. squamous cell carcinoma or adenocarcinoma) is not always made in articles we used. Furthermore, the studies reported incidence data for different periods of time and used different standard populations for age-adjustment. Therefore a direct comparison of the results was sometimes difficult. One factor that should be considered is the use of more and/or better diagnostic methods for the detection of anal cancer over time. However, studies that support this suggestion have not been found.

In conclusion, we have shown that an increased risk for anal cancer in certain risk groups, in particular hiv-positive MSM and organ transplant recipients, and increasing numbers of people belonging to these risk groups contributes to the overall increase in anal cancer incidence. Further studies should answer the question to what exact extent these risk groups contribute to the overall anal cancer incidence, and whether these risk groups would benefit from preventive screening for anal cancer.

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