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Anal Intraepithelial Neoplasia

ANAL INTRAEPITHELIAL NEOPLASIA (AIN) may be defined as the presence of nuclear abnormalities in the anal epithelium in the absence of inflammation without breach of the basement membrane. It was first described by Fenger and Nielsen [1] who reviewed all the anal surgical pathology specimens in the whole of Denmark over a 2-year period [2] and found 19 cases of AIN and graded them according to the cervical intraepithelial neoplasia (CIN) system. In AIN 1, nuclear abnormalities are restricted to the lower third of the epithelium, in AIN II the lower two-thirds are affected, and in AIN III nuclear abnormalities are present throughout the full thickness of the epithelium.

The most frequent site of AIN would appear to be the anal transitional zone. This is an area of transitional epithelium that lies between columnar epithelium above and squamous epithelium below, similarly to the cervical transitional zone. AIN lesions have also been identified in the squamous epithelium of the perianal skin and in certain patients both sites may be affected.

The prevalence of AIN, its clinical significance, whether it is analogous to CIN where a proportion may progress to invasive cancer and whether lesions associated with certain human papillomavirus (HPV) types have a more aggressive course remains unknown.

Although its exact role is unclear, HPV seems to be associated with cervical intraepithelial neoplasia, with certain types, notably 16 and 18, appearing to be associated with more severe grades of CIN and invasive carcinoma of the cervix [3]. HPV type 16 is increasingly frequently being identified in squamous cell carcinoma of the anus [4] and has also been identified in AIN lesions [5]. Although the number of patients with AIN in most reports is small, AIN III lesions do appear to contain HPV 16 more frequently than lesser grades of AIN [6].

Fenger and Nielsen [2] originally felt that AIN was a rare condition; however subsequently several groups have been identified in whom there is a high prevalence of AIN, in particular homosexual men with anal condylomata and to a lesser extent heterosexual men and women with anogenital warts [5–7].

Homosexual men commonly develop anal condylomata and appear to be at an increased risk of developing anal cancer, a malignancy which is becoming increasingly prevalent in this group [8,9]. Studies from the USA have demonstrated a high prevalence of AIN in HIV-positive homosexual and bisexual patients, particularly in those with advanced HIV infection and anal condylomata [10,11]. An examination of cancer registration in New York looked at the incidence of various types of cancer in men deemed to be at risk of AIDS and compared the period 1977–1985 with a pre-AIDS period of 1973–1976 [12]. Predictably, the greatest increase was in the incidence of Kaposi's sarcoma followed by non-Hodgkin lymphoma; however, the only other cancer that showed a significant increase was anal cancer. At present Kaposi's sarcoma and non-Hodgkin lymphoma are the only two tumours recognised as being definitely associated with HIV. However, it is possible that as our ability to look after HIV-positive patients improves and these patients continue to live longer in an immunosuppressed state, other tumours including anal cancer may become more common. Should that be the case, the identification of possible precursor lesions in the form of AIN may be increasingly important.

The association between anal cancer and immunosuppression was well established before the recognition of the HIV epidemic. Studies primarily of renal transplant recipients have demonstrated that immunosuppressed patients are at an increased risk of developing several malignancies including cancer of the

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cervix, vulva, perineum and anus [13]. AIN has also been identified in these patients, either in isolation or together with multiple foci of genital intraepithelial neoplasia demonstrating a so called field effect [14].

Immunosuppression is not a prerequisite for multifocal neoplasia. In one study, 11 out of 64 women with anal carcinoma had evidence of multiple primaries in the anogenital tract [15]. Multifocal intraepithelial neoplasia including AIN has also been described. Of 28 women with anal condylomata examined by Scholefield *et al.* [6], 10 had evidence of CIN on cytology and 5 of these had histological evidence of AIN. None of these women had AIN without also having CIN, demonstrating the possible importance of examining the entire anogenital region for intraepithelial neoplasia.

The optimum method for diagnosing AIN remains to be established. Several studies have used the anal smear for cytological diagnosis of HPV and AIN by sampling the anal transitional zone. This poses two potential problems. The first is that taking a smear from the transitional zone alone may miss perianal AIN lesions. The second concerns the fact that the sensitivity and specificity of this technique for the detection of AIN have not been fully established.

Microanoscopy (involving proctoscopy with an operating microscope or colposcope) has been used in several studies. Using criteria that have been suggested for the colposcopic diagnosis of CIN by assessing the colour, the vascular pattern and the appearance of the surface of the lesion with and without 5% acetic acid, it is possible to make some assessment of the likelihood of the presence of HPV and/or AIN. However, although increasing expertise is being gained in microanoscopy of the anal canal and perianal area, at present the gold standard for diagnosing AIN remains that of biopsy and histology. This poses a problem for studies wishing to determine the natural history of AIN as a biopsy may alter the natural history of a lesion or indeed remove it altogether. It has been well documented that natural history studies of CIN using biopsy result in a higher rate of regression and a lower rate of progression compared with studies using cytology as the diagnostic method [16].

There have been no studies published regarding the natural history of AIN. Looking at Fenger and Nielsen's original 19 patients [2], 2 died from colorectal carcinoma and 17 were alive 5 years later. 9 cases of AIN were controlled by biopsy and in 4 of those 9 cases, all originally AIN III, there was some evidence of recurrence of AIN in the follow-up period. Not one patient developed invasive anal cancer during the 5 years of follow-up. A further study from Fenger and Nielsen [17] examined 139 abdominoperineal resection specimens and found AIN III in 13 out of 16 cases of squamous carcinoma. The lesions were found at the border of the tumours as well as in areas separated from the tumour by normal mucosa.

Several issues should be carefully considered regarding the possible treatment of AIN. Firstly, anal cancer is a rare malignancy representing 1–2% of all large bowel tumours. Although relatively few studies have looked at the prevalence of AIN, it would appear to be fairly common in certain risk groups, leading one to assume that the majority of AIN lesions will either regress or remain static. Treating all AIN lesions would therefore result in the overtreatment of a large number of patients. Secondly, if it is decided to treat these lesions, then how should this be done? As well as the possibility that AIN can occur at both the transitional zone and the perianal area, there may be several foci of AIN at the transitional zone. The anal transitional zone is considerably larger than that of the cervix and ablating or resecting the mucosa of the entire transitional zone could result in significant morbidity. In addition, as lesions can occur in the perianal area, should this area also be resected? Thirdly, it is recognised that HIV-positive patients, in particular those with symptomatic disease, may have a high morbidity following anorectal surgical procedures [18]. If these patients are subjected to a procedure which may involve resecting large areas of mucosa, this may be associated with defective healing and chronic perianal sepsis with possible anal incontinence for a period of time before they succumb to their HIV infection. Such a procedure would therefore not be in the patients' best interests. On the other hand, one has to consider the possibility that a small number of patients with untreated AIN may progress and develop invasive cancer, a condition which, even with treatment, is still associated with significant mortality.

At present there is no evidence to support widespread screening for AIN or treatment of patients with the condition. However, as AIN is increasingly recognised in certain risk groups, there is an urgent need for well-designed prospective studies to determine the natural history of this lesion in HIV-positive and -negative patients.

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Black Tobacco and Cancer: Introducing an Epidemiological Review

MANY EPIDEMIOLOGICAL studies have been carried out since the 1950s on the carcinogenic effect of tobacco smoking. Most of these have shown a strong association between smoking cigarettes and the risk of developing cancer of the lung, larynx, oral cavity and pharynx, oesophagus, pancreas, renal pelvis and bladder; some evidence also exists for cancer of the cervix uteri and perhaps for cancer of the liver [1].

Several studies have allowed the quantitative and qualitative evaluation of the risk as a function of the characteristics of smoking history (such as age at start of smoking, duration of exposure and smoking cessation). Substantial information also exists on the increased risk linked to specific smoking practices such as smoke inhalation and use of smokeless tobacco, and evidence is accumulating on the effects of changes introduced in marketed tobacco products (use of filters and changes in the composition of cigarettes, in particular the availability of low tar, low nicotine cigarettes).

The majority of epidemiological studies have been conducted in countries where the predominant or even the sole type of tobacco consumed in past decades is blond (flue-cured), and it has been estimated that in these countries, 30–40% of all cancers are attributable to smoking. In contrast, relatively little information is available on the public health impact of black (air-cured) tobacco in spite of growing epidemiological evidence suggesting that the carcinogenic potency of black tobacco products is two to three fold greater.

Black tobacco has traditionally been used in Latin America and in parts of Europe including most of the Mediterranean countries, although the relative proportion of smokers of black and blond tobacco varies from country to country (Table 1). Analyses of recent trends in tobacco consumption in southern Europe indicate that blond tobacco consumption is increasing in these countries relative to black tobacco, but that the rate and magnitude of this change is also country dependent [2]. A

Table 1. Proportion of smokers in samples of the general population and of types of tobacco currently used

Country (city)	Ref.	% of current smokers	Type of tobacco: Black (%)	Type of tobacco: Blond (%)
Colombia (Bogota)	PAHO, 1977* [32]	52	59	30
Venezuela (Caracas)	PAHO, 1977* [32]	49	4	93
Guatemala (Guatemala City)	PAHO, 1977* [32]	36	13	74
Argentina (La Plata)	PAHO, 1977* [32]	58	26	65
Peru (Lima)	PAHO, 1977* [32]	34	17	76
Mexico (Mexico City)	PAHO, 1977* [32]	45	14	75
Chile (Santiago)	PAHO, 1977* [32]	47	34	59
Brazil (Sao Paulo)	PAHO, 1977* [32]	54	2	96
Uruguay (Montevideo)	de Stefani, 1990† [20]	64	45	25
Spain (Navarra)	Berrino *et al.*, 1988† [2]	41 (73)‡	88	—
Spain (Zaragoza)	Berrino *et al.*, 1988† [2]	25 (60)	82	—
Italy (Varese)	Berrino *et al.*, 1988† [2]	50 (95)	28	—
Italy (Torino)	Berrino *et al.*, 1988† [2]	24 (87)	35	—
France (Calvados)	Berrino *et al.*, 1988† [2]	46 (79)	93	—
Switzerland (Geneva)	Berrino *et al.*, 1988† [2]	33 (74)	74	—

*Men 15–74 years of age; tobacco survey.
†Men; hospital controls in Uruguay; population controls aged 25–85 in Europe.
‡Proportion of ever smoked cigarettes.
— = Not reported.

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