Demographics and incidence of anal squamous cell carcinoma in people living in high HIV prevalence geographical areas

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ABSTRACT

Objectives Anal squamous cell carcinoma (ASCC) is an uncommon cancer that is rapidly increasing in incidence. HIV is a risk factor in the development of ASCC, and it is thought that the rapidly increasing incidence in men is related to increasing numbers of people living with HIV (PLWH). We undertook a population-based study comparing the demographics and incidence of ASCC in patients residing high HIV prevalence areas in England compared with average HIV prevalence areas in England.

Methods This is a cross-sectional study following the ‘Strengthening the Reporting of Observational Studies in Epidemiology’ (STROBE) statement. Demographic data and incidence rates of ASCC within Clinical Commissioning Groups (CCGs) between 2013 and 2018 were extracted from the Cancer Outcomes and Services Dataset. CCGs were stratified by HIV prevalence from data given by Public Health England, and high HIV prevalence geographical areas were compared with average HIV geographical areas.

Results Patients in high HIV areas were more likely to be young and male with higher levels of social deprivation. Incidence rates in men between 2013 and 2017 were higher in high HIV areas than average HIV areas with a rapidly increasing incidence rates in early-stage disease and a 79.1% reduction in incidence of metastatic stage 4 disease. Whereas women in high HIV areas had lower ASCC incidence than the national average and a low incidence of early-stage disease; however, metastatic disease in women had quintupled in incidence in high HIV areas since 2013.

Conclusions Patients presenting with ASCC in high geographical areas have different demographics to patients presenting in average HIV geographical areas. This may be related to screening programmes for PLWH in high HIV areas.

INTRODUCTION

Anal squamous cell carcinoma (ASCC) is an uncommon cancer associated with human papillomavirus infections. Its incidence rate is frequently quoted as between one and two cases per 100 000 people.1 It has a dysplastic precursor anal intraepithelial neoplasia (AIN) that can progress to ASCC.

The incidence rate of ASCC is rapidly increasing in economically developed countries, where the percentage incidence change has increased annually between 2.5%–6.3% per year in men and 2.7%–11.4% per year in women between 1989 and 2007.2 In England, the incidence rate in 2017 was 1.9 cases per 100 000 people; however, this was associated with a rapid increase in incidence over 5 years (23.4%).3 ASCC is associated with persistent infections of high-risk HPV genotypes,4,5 and HIV is a significant risk factor for ASCC. People who live with HIV (PLWH) have a high prevalence of AIN6 especially if they also are men who have sex with men (MSM).7 Up to a third of MSM PLWH have high-grade intraepithelial lesions on high resolution anoscopy (HRA).7,9–11 and 16% of female PLWH have AIN.10 A recent meta-analysis estimating risk of ASCC in MSM PLWH describes the incidence rate in this patient group to be 85 per 100 000 cases per person years.12 As HIV is a protected characteristic and there are relatively low numbers of ASCC within a population, it is difficult to undertake linked population analyses of ASCC in PLWH.

In the UK, there are an estimated 105 200 PLWH.13,14 London has the highest rates of HIV, 39% of new diagnoses of HIV in 2019 were in London15 and 41.8% of PLWH in England in 2019 accessed HIV services in London.13 As there is significant geographical variation in HIV prevalence, we undertook an analysis of ASCC outcomes in England between 2013 and 2018 comparing between areas of high HIV prevalence and average HIV prevalence in England with emphasis on differences in ASCC disease patterns seen in areas with high and low HIV prevalence.

METHOD

This is a cross-sectional study following the ‘Strengthening the Reporting of Observational Studies in Epidemiology’ (STROBE) statement.16 Patients diagnosed with ASCC between January 2013 and June 2018 were identified from the Cancer Outcomes and Services Dataset (COSD). COSD is an anonymised dataset maintained by Public Health England (PHE) that includes demographic data stratified by geographical health service area. In particular, COSD stratifies by Clinical Commissioning Group (CCG), a National Health Services organisation responsible for the commissioning of clinical services within one geographical area. Currently, there are 135 CCGs in England.

COSD reports data on gender of patient, year of diagnosis, age at diagnosis, staging, ethnicity,
treatment and deprivation score for all patients diagnosed with 

ASCC.

HIV prevalence data were collated from PHE; this was strati-

fied by CCG and year per 100 000 people. The number of people 

residing in each CCG each year between 2013 and 2018 and the 

CCG’s demographic characteristics (gender, age and ethnicity) 

was also retrieved from the Office of National Statistics.

Data categories and definitions

Gender was expressed as male or female, ethnicity as Cauca-

sian, black African and black Caribbean, Indian subcontinent, 

other Asian, Chinese, mixed race, other ethnicity and unknown 

ethnicity.

Age at diagnosis was stratified into 5-year intervals from 20 

years to over 90 years. Staging was classified into four stages 

as described by the American Joint Committee Cancer Staging 

TMN system. Socioeconomic status (SES) was described by the 

UK Government English Indices of Deprivation into five equal 

quintiles or ‘deprivation score’ containing 20% of the population 

where ‘deprivation score 1’ represents 20% of the population 

with the highest SES and ‘deprivation score 5’ represents 20% 

of the population with the lowest SES. SES is based on levels 

of education attainment, income levels, employment levels, risk 

of crime, barriers to housing and services, acceptability of living 

environment and the risk of poor health and quality of life.

Treatment received by each patient was described in the COSD 

dataset using categorical data (yes/no).

Study outcomes

The primary end outcome of this study was to identify if there 

were any differences in ASCC incidence in men and women 

between CCGs with high HIV prevalence and CCGs with 

average HIV prevalence. In particular to assess whether the 

rapid increase in incidence in men with early staging previ-

ously reported is associated with high HIV prevalence areas. 

Secondary end outcomes included whether there was any 

difference in age, gender, ethnicity, staging, SES and treatment 

received between high HIV prevalence and average prevalence 

CCGs.

Inclusion and exclusion criteria

All adult patients reported to have been diagnosed with ASCC 

between January 2013 and June 2018 in the COSD. Patients 

under the age of 18 years and patients with histopathology other 

than ASCC were excluded.

Identification of geographical areas with HIV prevalence

PHE reported the numbers of PLWH registered within each 

CCG between 2013 and 2017. This was expressed in number of 

PLWH per 100 000 people. Funnel plots were constructed for 

HIV prevalence per year. Statistical CCG outliers on the funnel 

plots were identified (online supplemental figures A–E). If the 

HIV prevalence within a CCG was plotted outside the 99% CI 

of the funnel plot for every year between 2013 and 2017, the 

CCG was classified as a ‘high HIV areas’. These CCGs were then 

compared with CCGs with average HIV prevalence who were 

classified as ‘average HIV areas’.

Data collection and statistical analysis

Data were extracted by DRLB and then double-checked for 

accuracy to limit the possibility of duplication of entries.

Data were analysed using IBM SPSS Statistics V.25 software. 

Funnel plots were used to identify CCGs with statistically higher 

prevalence of HIV in their population compared with national 

averages. χ² or Fisher’s exact tests were used for categorical data 

extracted from COSD, and ASCC incidence was calculated per 

100 000 people in England per year.

RESULTS

There was significant geographical variation in HIV prevalence 

in England between 2013 and 2017 (see online supplemental 

figures A–E and figure 1). Thirteen CCGs were identified as 

having a significantly higher than average HIV prevalence in 

every year between 2013 and 2017. All but one CCG were 

located in London (box 1).

Patient demographics

Between January 2013 and June 2018, 5457 patients were diag-

nosed with ASCC (table 1). In high HIV areas, 325 patients were 

diagnosed; 6% of the total ASCC burden in England. Patients 

within a high HIV areas were more likely to be male (p<0.001, 

χ² test) be another ethnicity apart from Caucasian, in particular 

black African or black Caribbean (p<0.001, χ² test) and were 

associated with higher levels of social deprivation (p<0.001, 

χ² test). There was no statistical difference in staging between 

groups.

Male patients in high HIV areas were more likely to be 

younger when compared with average HIV areas (19.4% <55 

years vs 7.7% <55 years, p=0.002, χ² test). Gender of patient 

was not a contributing factor to the differences in ethnicity and 

depression between HIV prevalence groups; however, male 

gender was associated with a trend to earlier staging in the High 

HIV areas (p=0.006, χ² for trend test).
Box 1  List of Clinical Commissioning Groups categorised with high HIV prevalence between 2013 and 2017 (created by the authors)

Clinical Commissioning Groups with High HIV prevalence
National Health Service (NHS) Brighton and Hove CCG.
NHS Camden CCG.
NHS Central London (Westminster) CCG.
NHS City and Hackney CCG.
NHS Hammersmith and Fulham CCG.
NHS Haringey CCG.
NHS Islington CCG.
NHS Lambeth CCG.
NHS Lewisham CCG.
NHS Newham CCG.
NHS Southwark CCG.
NHS Tower Hamlets CCG.
NHS West London CCG.

Ethnicity
Within high HIV areas 19.7% of patients were not Caucasian. Whereas, in average HIV areas 94% of patients were Caucasian. Nevertheless, ethnicity had no effect on tumour staging or age of patient. In high HIV areas male patients were more likely to be Caucasian (p<0.001, Fisher’s exact test).

In average HIV areas, there was a trend for Caucasian patients to have lower levels of deprivation compared with high HIV areas (p<0.001, χ² test).

Table 1  Comparing patient demographics between high HIV areas and average HIV areas (created by the authors)

|                      | All CCGs   | Average HIV areas | High HIV areas | Statistical significance |
|----------------------|------------|-------------------|----------------|--------------------------|
|                      | (n=5457)   | (n=5132)          | (n=325)        |                          |
| Gender, n (%)        |            |                   |                |                          |
| Female               | 3692 (67.7)| 3527 (68.7)       | 165 (50.8)     | p<0.001                  |
| Male                 | 1765 (32.3)| 1605 (31.3)       | 160 (49.2)     |                          |
| Age                  | Median=60–64 years | Median=60–64 years | Median=60–64 years | p=0.156                 |
| Staging, n (%)       |            |                   |                |                          |
| Stage 1              | 684 (12.5) | 632 (15.3)        | 52 (19.5)      | p=0.156                  |
| Stage 2              | 1354 (24.8)| 1284 (31.0)       | 70 (26.2)      |                          |
| Stage 3              | 1963 (36.0)| 1840 (44.4)       | 123 (46.1)     |                          |
| Stage 4              | 409 (7.5)  | 387 (9.3)         | 22 (8.2)       |                          |
| Ethnicity, n (%)     |            |                   |                |                          |
| Black African or black Caribbean | 64 (1.2) | 41 (0.8) | 23 (7.1) | p<0.001 |
| Chinese              | 4 (0.1)    | 2 (0.0)           | 2 (0.6)        |                          |
| Indian subcontinent  | 36 (0.7)   | 28 (0.5)          | 8 (2.5)        |                          |
| Other Asian          | 8 (0.1)    | 7 (0.1)           | 1 (0.3)        |                          |
| Other ethnicity      | 53 (1.0)   | 42 (0.8)          | 11 (3.4)       |                          |
| Unknown ethnicity    | 188 (3.4)  | 173 (3.4)         | 15 (4.6)       |                          |
| Caucasian            | 5083 (93.1)| 4822 (94.0)       | 261 (80.3)     |                          |
| Deprivation score    |            |                   |                |                          |
| Score 1              | 865 (15.9) | 846 (17.0)        | 19 (6.1)       | p<0.001                  |
| Score 2              | 1059 (19.4)| 1037 (20.8)       | 22 (7.1)       |                          |
| Score 3              | 1083 (19.8)| 1031 (20.7)       | 52 (16.7)      |                          |
| Score 4              | 1147 (21.0)| 1066 (21.4)       | 81 (26.0)      |                          |
| Score 5              | 1142 (20.9)| 1005 (20.2)       | 137 (44.1)     |                          |

CCGs, Clinical Commissioning Groups.

Socioeconomic status
Patients with ASCC living in high HIV areas were more likely to have higher levels of deprivation. Patients with high deprivation within high HIV areas were more likely to be diagnosed under 55 years of age when compared with average HIV areas (26.3% vs 21.7%, p=0.002, χ² test). The male gender was associated with higher levels of social deprivation (p<0.001, Fisher’s exact test), and this trend was associated with being Caucasian (p<0.001, Fisher’s exact test). There was no difference when stratifying SES with tumour staging in either subgroup.

Tumour staging
There was no difference in age of patient and staging between subgroups; however, in high HIV areas, men had earlier staging (p<0.001, Fisher’s exact test). The trends of increasing deprivation and ethnicity other than Caucasian in high HIV areas remained despite controlling for staging.

ASCC treatment
Treatments received within each HIV subgroup are described in table 2. Patients in high HIV areas were less likely to have chemoradiotherapy (29.8% vs 37.5%, p=0.005, Fisher’s exact test) and more likely to receive no treatment at all (24.6% vs 15.2%, p<0.001, Fisher’s exact test).

Female patients in high HIV areas were less likely to have radiotherapy only (p=0.032, Fisher’s exact test) and more likely to receive no treatment (p<0.001, Fisher’s exact test). Patients who identified as black African or black Caribbean as well as patients who were Caucasian were more likely receive no treatment for ASCC when compared with other ethnicities in the high HIV areas (p=0.049 and p=0.002, respectively, Fisher’s...
The rapidly increasing rate of incidence of ASCC has been noted since 2013 (0.06 cases vs 0.3 cases per 100,000 women). This increase was driven by stage four disease, which was associated with a 104.7% incidence increase compared with average HIV areas, but overall had a lower incidence rate compared with average HIV areas since 2013 (7.2%); however, late-stage disease had a 203.8% increase in incidence in high HIV areas, compared with average HIV areas. Women in high HIV areas also had a similar increase in incidence since 2013 to both genders compared with average HIV areas (44.3% vs 23.4%).

In females, high HIV areas have a lower incidence rate compared with average HIV areas. Women in high HIV areas had a similar increase in incidence since 2013 to both genders in high HIV areas but remains higher than the overall female incidence increase (42.3% vs 28.6%).

The incidence rates of ASCC in men in high HIV areas are significantly higher than the rates for average HIV areas, and there was an 88.9% incidence increase within high HIV areas since 2013 compared with a 13.5% increase in average HIV areas.

When stratified by stage and gender, men with stage 1 and 2 tumours had a 90.6% increase in incidence in high HIV areas, but they also had a 203.8% increase in incidence in late-stage ASCC. This increase was driven by the high incidences of stage 3 disease as there was a reduction in incidence in stage 4 disease since 2013 in men in high HIV areas.

In women in high HIV areas, the early staging incidence increases had largely been stable since 2013 (7.2%); however, late-stage disease had a lower incidence rate compared with average HIV areas, and there was a 104.7% incidence rate between 2013 and 2017, which was driven by stage four cancers in women living in high HIV areas quintupling incidence since 2013 (0.06 cases vs 0.3 cases per 100,000 women).

DISCUSSION

We undertook an analysis of the ASCC patient demographics and outcomes in England between 2013 and 2018 in particular to examine whether the rapidly increasing rate of incidence of early disease in men described in a previous analysis of this dataset originated from areas of high HIV prevalence. This effect could be as a result of several reasons. First, simply that there are now greater numbers of PLWH on highly active antiretroviral therapy (HAART) and who have a near normal life expectancy. Despite the effect on life expectancy and quality of life that HAART provides, it is unclear whether the use of HAART does prevent ASCC or AIN. Studies comparing incidence rates of ASCC between pre-HAART and HAART eras of HIV treatment did not show any difference, and Fox et al demonstrated that the use of HAART did not significantly prevent the progression of established AIN from developing ASCC. However, D’Souza et al identified an increased risk of ASCC in patients treated for HIV in the HAART era compared with pre-HAART era (137 vs 30 per 100,000 person years), and there is evidence to suggest that the use of HAART makes the time to progression from AIN to ASCC significantly longer. Regardless, it is fair to say that as more PLWH live longer, the increasing likelihood that ASCC incidence in this population will increase.

Another reason for the increasing rate of early disease in PLWH is the availability of HRA screening programmes. HRA is the gold standard for the detection of anal dysplasias which, in theory, can permit the treatment of high-grade AIN and prevent its progression to ASCC. The theory is based on the successful screening programmes for cervical cancer that have shown a significant survival benefit. Unfortunately, the evidence recommending screening for AIN is not as clear-cut as gynaecological dysplasias. Indeed, most clinical guidelines, although they agree that screening for AIN is likely to be beneficial for high-risk populations, the evidence is inconclusive that screening for AIN prevents ASCC. Neither is there any evidence that treating high-grade AIN can prevent ASCC, and studies undertaken have high recurrence rates and are limited by small study numbers and short follow-up times. National screening programmes are therefore not in place, and when HRA is recommended, there is often a caveat that it should be undertaken by expert practitioners only. Although HRA remains controversial, many HIV clinical centres are offering this service 'off label' to their high-risk patients. The increasing numbers of early-stage ASCC in men in PLWH areas could therefore be as a result of successful screening programmes in this population.

This analysis identified that for male patients in high HIV prevalence CCGs, there were large increases in the incidence of stage 1, 2 and 3 disease since 2013 and a relative decrease in metastatic disease since 2015. Whereas in women, ASCC incidences overall were lower in high HIV geographical areas, but metastatic disease was associated with massive increases in incidence since 2013, although early-stage disease incidences remained largely stable.

### Table 2

| Treatment received | All CCGs (n=5457) (n (%)) | Average HIV areas (n=5133) (n (%)) | High HIV areas (n=325) (n (%)) | Statistical significance (Fisher’s exact test) |
|--------------------|--------------------------|-----------------------------------|-------------------------------|-----------------------------------------------|
| Chemotherapy only  | 131 (2.4)                | 123 (2.4)                         | 8 (2.5)                       | p=0.852                                       |
| Surgery only       | 807 (14.8)               | 752 (14.7)                        | 55 (16.9)                     | p=0.260                                       |
| Radiotherapy only  | 503 (9.2)                | 475 (9.3)                         | 28 (8.6)                      | p=0.767                                       |
| Surgery and radiotherapy | 228 (4.2)          | 216 (4.2)                         | 12 (3.7)                      | p=0.775                                       |
| Surgery and chemotherapy | 78 (1.4)        | 75 (1.5)                          | 3 (0.9)                       | p=0.628                                       |
| Chemoradiotherapy  | 2023 (37.1)              | 1926 (37.5)                       | 97 (29.8)                     | p=0.005                                       |
| Surgery, chemotherapy and radiotherapy | 826 (15.1)    | 784 (15.3)                        | 42 (12.9)                     | p=0.265                                       |
| No treatment received | 861 (15.8)           | 781 (15.2)                        | 80 (24.6)                     | p<0.001                                       |

ASCC, anal squamous cell carcinoma.
This is interesting, as it not only demonstrates the male PLWH effect that we were investigating, it reiterates the findings of the previous analysis that, as areas of high HIV prevalence, are also areas with higher ethnic diversity and social deprivation than average HIV prevalence areas, both social deprivation and ethnicity factors that can result in a poorer prognosis of patients with ASCC.

**Strengths and limitations**

This study involves the analysis of a national dataset for a rare cancer where data involving this number of ASCC patients with demographics and HIV outcomes is scarce. We modelled geographical areas based on HIV prevalence; this appeared to be a good model as there was significant disparity in HIV prevalence. Nevertheless, without personalised data, it would be impossible to prove causality, but we can observe relationships within the population. There are PLWH outside high HIV prevalence areas who will develop ASCC; what is unclear without personalised data is whether these patients travel to HIV clinical centres for expert care and AIN screening.

The study is limited by the data we have access to within COSD. COSD produces anonymised data that are collated by local hospital trusts and CCGs, and we expect there to be some variance in the local methods of doing so that may or may not introduce bias into the data. Duplication of entries, although the study investigators did their upmost to identify, is also impossible to rule out completely.

COSD does not include end outcomes such as recurrence or survival statistics; therefore, we are unable to comment about the prognosis of patients included in this study; also, COSD does not detail what specific treatments patients had or the order in which the treatments took place.

Without reliable large datasets with HIV outcomes combined with ASCC outcomes, it is impossible to be able to describe for certain the differences in demographics, staging, treatment and end outcomes between PLWH and HIV negative subgroups presenting with ASCC. The mASCARA (Multinational Anal Squamous Cell cArcinoma Registry and Audit) registry is a collaborative approach to combining HIV outcomes with ASCC outcomes and demographics; launched in at the end of 2019, it is the first international research registry for ASCC and high-grade AIN. As well as including HIV outcomes, it also combines AIN screening data, sexual health outcomes, survival and recurrence statistics and other HPV related dysplasia treatments into one dataset. It is hoped that mASCARA will be able to describe conclusively the differences in demographics and outcomes between PLWH and HIV negative patients with ASCC once results are available.

**CONCLUSION**

Patients diagnosed with ASCC within high HIV areas have different demographics compared with patients with ASCC diagnosed in areas of low HIV prevalence. Overall, two subgroups with distinct differences in clinical presentation and demographic patterns exist in high HIV prevalence areas. First, a subgroup of socially deprived, male Caucasian patients with early node negative disease with rapidly increasing incidence consistent with PLWH living longer on HAART and receiving expert care from HIV centres. Second, a rapidly increasing incidence of socially deprived, ethnically diverse women presenting with late stage or metastatic disease. Larger scale clinical datasets with linked HIV and ASCC outcomes are required to fully understand the differences in clinical ASCC presentation for patients with and without HIV.

**Key messages**

- Two subgroups with distinct differences in clinical presentation and demographic patterns exist in high HIV prevalence Clinical Commissioning Groups.
- First, a subgroup of socially deprived, male Caucasian patients with early node negative disease with rapidly increasing incidence consistent with people living with HIV living longer on highly active antiretroviral therapy and receiving expert care from HIV centres.
- Second, a rapidly increasing incidence of socially deprived, ethnically diverse women presenting with late stage or metastatic disease.

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