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National epidemiology of digital papillary adenocarcinoma in England 2013-2020: a population-based registry study

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Data availability: Data available within the article or its supplementary materials and further data are available on request from the authors. Raw data is available on request to approved researchers via Data Access Request Service from NHS England.

Ethics statement: Ethical approval was not required. Informed consent: The National Disease Registries Directions 2021, Sections 254(1) and 254(6) of the 2012 Health and Social Care Act (the 2012 Act) allows the collection and processing of data on patients with cancer in England by NHS England and NDRS. Patients may opt out of having their confidential patient information being used for research and planning.

What is already known about this topic?

- Digital papillary adenocarcinoma (DPA) is a rare skin sweat gland cancer with a risk of metastasis.
- One U.S.-based DPA epidemiology study reported an incidence rate of 0.08 cases per 1,000,000 population.

What does this study add?

- DPA has an incidence of 0.10 [95% confidence interval (CI) 0.07-0.14] per 1,000,000 person-years in England which broadly matches that of the U.S.-based data with a predilection for males and the upper limbs.
- We provide additional data on recurrence, metastatic potential, chosen treatment options and patient outcomes from our English cohort of patients.

Abstract

Background: Digital papillary adenocarcinoma (DPA), formerly known as aggressive DPA, is a rare adnexal cancer of sweat gland differentiation with metastatic potential. DPA epidemiology and patient outcome data are a prerequisite to develop diagnostic and therapeutic guidance, which is lacking for this rare cancer.

Objectives: To report the incidence, patient demographics and treatment of patients with DPA in England from 1 January 2013 to 31 December 2020 using national cancer registry data.

Methods: DPA diagnoses in England during 2013–2020 were identified from the National Cancer Registration Dataset using morphology and behaviour codes. These were registered from routinely collected pathology reports and cancer outcomes and services datasets. The 2013 European age-standardised incidence rates (EASRs) were calculated.

Results: In total, 36 DPA (7 in females and 29 in males) were diagnosed. The median age at diagnosis for the cohort was 54 years (interquartile range 46 – 64). The most frequently affected sites were upper limbs (81%). All patients in the cohort received surgical excisions. The European age-standardised incidence rate (EASRs) was 0.10 [95% confidence interval (CI) 0.07–0.14] per 1,000,000 person-years (PY)].

Conclusion: This study reports the incidence and variation of DPA in England between 2013 and 2020. DPA was more common in older men and predominantly affected the upper limbs. This supports the need to develop a national policy for the reporting and management of DPA as well as clinical guideline development.

1 Introduction

2 Digital papillary adenocarcinoma (DPA), formerly known as aggressive digital papillary
3 adenocarcinoma, is a rare underreported cutaneous adnexal cancer of sweat gland origin with
4 metastatic potential, typically presenting on the digits. DPA was initially described by Helwig in
5 1979.¹ Historically, DPA has also been known as digital papillary carcinoma and papillary
6 adenoma. DPA typically presents as a solitary, slow-growing, cystic nodule, typically on acral
7 sites, most commonly on the fingers. However, it has also been reported on genital skin (such as
8 perineal and peri-anal skin).^{1,2} DPA is associated with a high recurrence rate and a risk for lymph
9 node and distant metastases.^{3,4} A U.S. registry-based study estimated the incidence of DPA as
10 0.08 per million person-years with a male preponderance, mainly between the ages of 50 and 70
11 years.⁵ Recently, genetic sequencing studies demonstrated human papillomavirus 42 (HPV-42) as
12 a key causative factor of DPA, and potentially targetable future HPV vaccines.^{6,7} These and other
13 studies have shown the almost universal presence of HPV-42 in DPA, and recently there has been
14 a proposal that DPA be renamed “HPV-42-associated sweat gland carcinoma”.⁷ Diagnosis of
15 DPA requires histopathological confirmation. DPA can be clinically and histologically
16 misdiagnosed as a benign lesion, and be difficult to discriminate from other adnexal tumours
17 such as hidradenoma (although additional tests such as expression of NUT1
18 immunohistochemistry^{8,9,10} may aid diagnosis). However, strict adherence to histological criteria
19 still remains the basis for diagnosis especially by specialist dermatopathologists with experience
20 in skin adnexal tumours.^{11,12} Prior to the discovery of HPV-42’s role in DPA,
21 immunohistochemical tests were non-specific but supportive in making a diagnosis of DPA; the
22 epithelial component is positive for pancytokeratins and cytokeratin 7 with CEA and EMA
23 showing luminal expression in glands and papillae, with variable S100 staining in this and the
24 myoepithelial component, the latter which is positive for p63, SMA and calponin.¹² The tumour

1 is mostly confined within the dermis and sometimes fat without connection to the overlying
2 epidermis, with a lobular or infiltrative architecture with a variable mixture of cystic, papillary
3 and solid areas. Fused back-to-back glands are common as well as true papillae and
4 pseudopapillae with cuboidal to low columnar cells most commonly with mild to moderate
5 cytological atypia although the tumour may demonstrate more severe cytological atypia,
6 necrosis, and invasion of soft tissue and blood vessels.^{4,11,12} Mitotic activity is very variable.¹²

7
8 There is a lack of consensus of treatment pathways for DPA internationally. First-line treatment
9 is wide local excision of DPA with clear margins with a case series from 1987 suggesting a high
10 local recurrence rate of up to 50% after excision.³ However, it remain uncertain (and not possible
11 to validate) whether the diagnosis of DPA from historical studies conform to the diagnostic
12 criteria of DPA outlined in the latest World Health Organisation Classification of tumours 5th
13 edition,¹² hence, potentially impacting on the validity and reliability of historical studies'
14 findings. There is no guidance on excision margin recommendations nor systematic data for the
15 use of radiotherapy or chemotherapy.^{1,4,13} Unlike other skin cancers where sentinel lymph node
16 biopsy (SLNB) has a role in detecting metastatic disease or clinical staging, the role of SLNB in
17 DPA has not been widely reported in the literature due to the rare nature of DPA.¹⁴ In one study,
18 regional disease spread or metastases was present in 22.3% of the patient cohort (n = 94); and the
19 associated disease specific mortality rate was 2.1%.⁵ The metastatic rate of DPA from
20 international case series ranges widely between 0 to 41.2% depending on the sample size,
21 inclusion criteria and length of follow up.^{3,15,16,17} This study aimed to report the incidence,
22 patient demographics and treatment of DPA in England between 2013 and 2020.

Materials and methods

Study design, settings, and participants

This is a retrospective national population-based cancer registry cohort study using a well-established study methodology used to report rare cancers in England.^{18,19,20} Patients diagnosed with DPA from 1 January 2013 to 31 December 2020 in England were identified from the National Cancer Registration Dataset.²¹ International Classification of Diseases (ICD)-O3 morphology code (8408) and ICD-10 C44 site code (non-melanoma skin cancer) as well as an expanded skin site definition which included male genital skin, female genital skin, and lips were used to identify tumours.²²

Cancer pathology reports must be sent to the National Disease Registration Service (NDRS) by all National Health Service (NHS) pathology laboratories. To create a cancer registration record, the patient administration system and pathology reports or cancer outcomes and services dataset data from multidisciplinary team (MDT) meetings are merged.²¹

Thirty days prior to and 183 days following the date of diagnosis, tumour registration data were linked to pertinent surgical codes in Hospital Episode Statistics (HES) Admitted Patient Care and HES Outpatient Care (Table S1; refer to Supporting Information). The Office of Population Censuses and Surveys Classification of Interventions and Procedures, version 4, served as the source of these codes. Punch or incisional biopsy, curettage or shave biopsy, lymph node biopsy, and biopsy not otherwise specified were among the diagnostic techniques performed. Treatment with surgery included excision, flap/graft repair, amputation, dissection and/or excision of lymph

nodes, Mohs micrographic surgery (MMS), and re-excision. Tumour registration data was also linked to Office for National Statistics mortality data. The follow-up period ended on 2 September 2021, and the event of interest was death. Through Systemic Anti-Cancer Therapy data set²³ and Radiotherapy Data Set²⁴ linkage, information about chemotherapy or radiation treatment for DPA was found, and associated data was found using the timeframe from the date of diagnosis.²⁵ The stage of DPA at diagnosis was also extracted. The total number of deaths in the cohort within the follow-up period was used to calculate the all-cause mortality rate.

Variables

Variables extracted included diagnosis year, body site location, age, gender, clinical stage and self-reported ethnicity (Table S2; see Supporting Information). Deprivation quintiles data were extracted based on DPA diagnosis year and postcode at diagnosis, and were calculated using Indices of Multiple Deprivation (IMD) 2015 for diagnoses made in 2013 and IMD 2019 for diagnoses made during 2014-2020.^{26,27} This relative measure of deprivation, calculated at small geographical areas, used domains such as income, employment, education and crime. Postcode at diagnosis was used to group patients into seven regions based on grouped NHS regions in England.²⁸ Charlson comorbidity index predicts a patient's risk of death within a year of hospitalisation based on specific comorbidities (ICD codes) that were recorded as an inpatient (outpatient diagnosis were excluded).²⁹ Population by 5-year age bands, population at risk and DPA crude counts were used to calculate European age-standardised incidence rate (EASR) per 1,000,000 people using European Standard Population 2013.³⁰ All histopathology reports with ICD-O3 8404 morphology code during the study period were reviewed by a dermatologist

(ZCV) to confirm DPA diagnosis (with 2 cases reallocated after review) and to identify the occurrence of DPA metastasis.

Statistical analysis

Data were extracted and analysed using SQL developer (Oracle), R (4.3.2) and RStudio (2023.06.0).

Results

Cohort demographics

A total of 36 patients (7 women and 29 men) were diagnosed with DPA in England between 2013 and 2020. The median age at diagnosis for the whole cohort was 54 years [Interquartile range (IQR) 46 - 64]. The male-to-female ratio was 4:1. Median age was 47 years (IQR 30 -58) in females and 57 years (IQR 48 - 65) in males. The ethnicity of 6 of 36 patients were not defined in the data and 30 patients self-reported as white ethnicity. DPA was approximately evenly distributed amongst IMD quintiles. The Midlands (22%, n = 8) NHS regions had the highest number of cases while the South-west and South-east NHS regions had the lowest number of cases with 5.6% (n=2) each. Most of the patients have a Charlson comorbidity index score of 0 (92%, n = 33) and the remainder has a score of 1 (8.3%, n = 3).

Digital papillary adenocarcinoma age-specific and annual incidence

DPA has an overall incidence (EASR) of 0.10 [95% confidence interval (CI) 0.07-0.14] per 1,000,000 person-years (PY). The incidence in males is 0.16 [CI 0.10-0.23] per 1,000,000 PY

which is four times higher than the incidence in females 0.04 [CI 0.02-0.08] per 1,000,000 PY. Age-specific standardised incidence rates peaks between the 55-79 age groups in the cohort across 2013-2020 (Figure 1).

Digital papillary adenocarcinoma body site distribution

The most common affected sites were the upper limb in 81% (29 patients) of cases followed by the lower limbs 17% (6 patients). In one case the affected site was unknown. (Table 1).

Digital papillary adenocarcinoma clinical stage

The clinical stage of the disease at diagnosis was captured in 5 DPA cases (13.9%), It was unknown in the rest of the patient cohort (Table 1).

Treatment of Digital Papillary Adenocarcinoma

The most common surgical treatments for DPA were excision (42 treatments) or amputation of the affected digit (27 treatments) (Table 2). MMS was performed in one patient. There were six re-excision treatments performed. One patient had chemotherapy while another patient had radiotherapy.

Digital papillary adenocarcinoma all cause mortality

At the time of data collection, 89 % (32 patients) of all individuals with a diagnosis of DPA were alive and 5.6 % (2 patients) were noted to have died within the study period of 2013-2020 (the time between DPA diagnosis and deceased status was unknown). All deaths were due to non-DPA causes. Two patients were lost to follow up and their status unknown at time of analysis (Table 1). Median follow-up was not calculated due to the small number in the cohort. 4/36 DPA (11.11%) were metastatic at the time of registration. The time interval between diagnosis and metastases of DPA was known in 4 patients with a median of 483 days (IQR 84.5 - 912 days) (Table 3).

Other cancers

During the study period, one patient was recorded to have malignant melanoma and two patients were recorded to have prostate cancer.

Discussion

There is a paucity of literature on the epidemiology of DPA internationally. A search of the literature revealed one North American study consisting of data from 18 registries with a total of 94 cases of DPA.⁵ The data we present here represent the largest registry of cases of DPA reported in Europe to date with 36 cases. This study shows that DPA has an overall incidence of 0.10 [CI 0.07-0.14] per 1,000,000 PY, with a male-to-female ratio of 4:1 and it was more likely to occur in individuals between the ages of 55 years and 79 years. This is similar to the sex ratio and the incidence of 0.08 per 1,000,000 PY reported in the North American cohort.⁵ The age-specific standardised incidence rates (ASIR) for men increased sharply from the age band of 40 -

1 44 years, and peaked at the 55 - 59 years and the 75 - 79 year age bands, before dropping sharply
2 at the age band 80 - 84 years (Figure 1). In contrast, the ASIR for females was relatively stable
3 across the age bands. This gender difference may stem from the hormonal and genetic
4 constitution of the different genders.

5
6 The data also showed that the most common site affected was the upper limbs. This finding is
7 similar to the reports from cancer registries in the US and many case reports.^{5,13,14,15,31} Most of
8 the patients in this cohort did not have multiple comorbidities as the data showed that a Charlson
9 comorbidity index of 0 was recorded in 92% of the reported DPA cases. This implies that co-
10 morbidities may not have contributed to the development of the disease in this cohort. However,
11 the Charlson comorbidity index has limitations as the index does not consider comorbidities
12 recorded in outpatient or community settings. The Index of Multiple Deprivation, IMD Quintiles,
13 is the official grouping of small areas into five categories by relative deprivation. These data do
14 not show any correlation between the incidence of DPA with the degree of economic deprivation
15 as there was no variation in the incidence across IMD Quintiles in England. Our study findings
16 contrasted with UV-dependent skin cancers such as melanoma, cutaneous squamous cell
17 carcinoma, and basal cell carcinoma which have a higher incidence in the least deprived
18 quintiles.³² However, such variations may not be pronounced due to our small cohort.

19
20 We noted that England's Midlands NHS regions had the highest number of DPA while the
21 southwest and southeast NHS regions had the lowest number. However, data on the age-
22 standardised incidence rate in each region is not known. This variation in number of DPA cases

1 across regions could be due to factors including variation in regional population, reporting bias
2 given the lack of DPA-specific immunohistochemical markers during the study period rather than
3 a true geographical variation in incidence. All deaths were due to non-DPA causes. Our data
4 suggested the rate of DPA metastases in England was 11.1% as metastasis was identified in 4
5 patients from the cohort (n = 36). This contrasts with US registry data that reported a metastasis
6 in 22.3% of patients, which could be attributed to the larger number of cases and a longer follow-
7 up period of 19 years in their cohort.⁵ It should be noted that there is variability in time course to
8 metastasis in skin cancer with literature reporting ultra-late metastasis from cutaneous malignant
9 melanoma of more than 20 years from initial diagnosis.³³ Given the risk of metastatic DPA and
10 the wide variation in the timeline of metastases in our cohort, a robust follow-up period should
11 be considered when developing clinical management guidelines for DPA.

12
13 The clinical stage of DPA was only captured in 13.9% of cases; 3 patients presented with stage 1
14 disease, while 2 patients had stage 4 disease. The rest of the reported cases had no known clinical
15 stage and may reflect that it is not mandatory to report staging to the NDRS. This also highlights
16 the need to have a national policy for reporting pathological and clinical parameters of DPA
17 cases to ensure uniformity of the data collected by the NDRS.

18
19 Surgical management of DPA was most frequently chosen, with excisions and/or digital
20 amputations selected in this cohort. Subsequent treatments following biopsy or excision included
21 re-excisions and primary MMS to ensure complete clearance and reduce the risk of recurrence
22 and distant metastasis. This is very similar to treatments reported by clinicians in cohort reports

1 and case reports where wider excisions and digital amputations are offered to minimise the risk
2 of recurrence and metastasis due to the risk of metastasis.^{3,31,34,35}

3
4 Chemotherapy and radiotherapy are also rarely offered in cases of completely excised DPA with
5 clear margins. In this cohort one patient received chemotherapy while another patient had
6 radiotherapy, however, the comorbidities, vital status and clinical outcome in both cases could
7 not be determined. Chemotherapy was offered to patients with metastatic DPA in case reports
8 and case series but failed to alter the clinical outcome of the disease, this may be due to high
9 tumour burden^{34,35} or a lack of understanding of the biology and potential therapeutic targets of
10 DPA. Radiotherapy may be reserved for locally aggressive DPA not amenable to surgical
11 excision or metastatic DPA for palliative treatment, however, there is a lack of literature to
12 support its use in DPA.³⁵

13
14 These data have limitations. NDRS data may be incomplete for some patients, for example, if
15 they do not undergo histological confirmation of DPA or MDT discussion. This is because NDRS
16 data depend on accurate histological reporting or MDT discussion. The coverage and quality of
17 registry data could also be limited as the registry applies the NHS opt-out scheme, where patients
18 could opt out of having their confidential patient information being used for research. Registry
19 data could not capture radiological reports, or patient outcome data for patients who relocated or
20 accessed treatment overseas. Our study findings showed DPA predominantly affects the upper
21 limbs and lower limbs but there is a lack of site specificity from the data (international coding
22 restricted our interpretation but it would be reasonable to assume DPA affects the digits).

Conclusion

Over 250,000 skin cancers are diagnosed yearly in the UK and DPA makes up less than 0.1% of the cases. There is no national consensus on the clinical management of this aggressive skin cancer despite its aggressive biology. This is the first registry study in England reporting the incidence rate of DPA between 2013 and 2020. DPA was more common in older men and affected the upper limbs predominantly. This supports the need to develop a national policy for improving the understanding of DPA pathogenesis, standardised reporting, diagnostic criteria, management of DPA as well as clinical guideline development.

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Figure legend

Figure 1. Age-specific incidence rate per 1,000,000 person-years in individuals diagnosed with digital papillary adenocarcinoma in England from 2013 to 2020.

Table 1. Patient demographics and distribution of body sites affected of those diagnosed with digital papillary adenocarcinoma in England 2013–2018.

Characteristic	All	By gender	
	N = 36	Female, N = 7	Male, N = 29
Age			
Mean (SD)	52 (18)	46 (20)	54 (17)
Median (IQR)	54 (46 - 64)	47 (30 - 58)	57 (48 - 65)
Range	14 - 80	22 - 76	14 - 80
Age			
Under 25	4 (11%)	1 (14%)	3 (10%)
25-39	3 (8.3%)	2 (29%)	1 (3.4%)
40-49	6 (17%)	1 (14%)	5 (17%)
50-59	10 (28%)	1 (14%)	9 (31%)
60-69	7 (19%)	1 (14%)	6 (21%)
70-79	5 (14%)	1 (14%)	4 (14%)
80-89	1 (2.8%)	0 (0%)	1 (3.4%)
90+	0 (0%)	0 (0%)	0 (0%)
IMD Quintile			
1 - most deprived	9 (25%)	3 (43%)	6 (21%)
2	5 (14%)	1 (14%)	4 (14%)
3	3 (8.3%)	0 (0%)	3 (10%)
4	8 (22%)	2 (29%)	6 (21%)
5 - least deprived	11 (31%)	1 (14%)	10 (34%)
NHS Region			
East of England	7 (19%)	2 (29%)	5 (17%)
London	5 (14%)	1 (14%)	4 (14%)

Characteristic	All	By gender	
	N = 36	Female, N = 7	Male, N = 29
Midlands	8 (22%)	2 (29%)	6 (21%)
North East and Yorkshire	5 (14%)	0 (0%)	5 (17%)
North West	7 (19%)	2 (29%)	5 (17%)
South East	2 (5.6%)	0 (0%)	2 (6.9%)
South West	2 (5.6%)	0 (0%)	2 (6.9%)
Tumour location			
Lower limb	6 (17%)	1 (14%)	5 (17%)
Unknown	1 (2.8%)	1 (14%)	0 (0%)
Upper limb	29 (81%)	5 (71%)	24 (83%)
Charlson comorbidity index			
None	33 (92%)	6 (86%)	27 (93%)
1	3 (8.3%)	1 (14%)	2 (6.9%)
2	0 (0%)	0 (0%)	0 (0%)
3	0 (0%)	0 (0%)	0 (0%)
4 or more	0 (0%)	0 (0%)	0 (0%)
Unknown	0 (0%)	0 (0%)	0 (0%)
Stage at diagnosis			
Stage 1	3 (8.3%)	1 (14%)	2 (6.9%)
Stage 4	2 (5.6%)	0 (0%)	2 (6.9%)
Stage unknown	31 (86%)	6 (86%)	25 (86%)
Vital status			
Alive	32 (89%)	6 (86%)	26 (90%)
Death	2 (5.6%)	0 (0%)	2 (6.9%)
Unknown	2 (5.6%)	1 (14%)	1 (3.4%)

Data are n (%) unless specified otherwise. IMD, Indices of Multiple Deprivation; IQR, interquartile range; SD, standard deviation.

Table 2. Surgical treatments received by individuals diagnosed with digital papillary adenocarcinoma in England from 2013 to 2020.

Type of Surgery	n
Amputation	27
Definitive lymph node excisions/dissections	1
Excision	42
Flap	2
Graft and autograft	4
Harvest of graft/flap	1
Moh's micrographic surgery	1
Re-excision	6

Note: Individuals may have received more than one type of surgery and/or received the same type of surgery more than once.

Table 3. Time interval between diagnosis and metastases of digital papillary adenocarcinoma (DPA) in 4 individuals diagnosed with histologically confirmed metastatic DPA from the cohort of DPA in England from 2013 to 2020.

Patient	Time between primary and metastatic diagnoses (days)
M1	853
M2	971
M3	56
M4	113

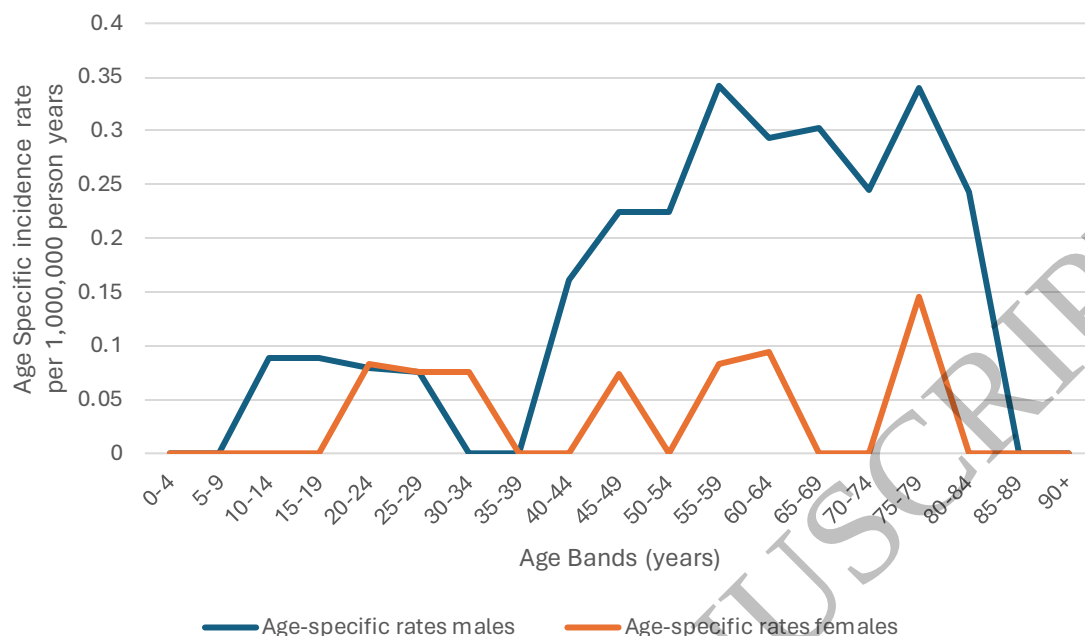


Figure 1. Age-specific incidence rate per 1,000,000 person-years in individuals diagnosed with digital papillary adenocarcinoma in England from 2013 to 2020.