



Sebaceous carcinoma epidemiology, associated malignancies and Lynch/Muir-Torre syndrome screening in England from 2008 to 2018

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Background: Sebaceous carcinomas (SC) may be associated with the cancer predisposition syndrome Muir-Torre/Lynch syndrome (MTS/LS), identifiable by SC mismatch repair (MMR) screening; however, there is limited data on MMR status of SC.

Objective: To describe the epidemiology of SC, copresentation of other cancers, and population level frequency of MMR screening in SC.

Methods: A population-based retrospective cohort study of SC patients in the National Cancer Registration and Analysis Service in England.

Results: This study included 1077 SC cases (739 extraocular, 338 periocular). Age-standardized incidence rates (ASIR) were higher in men compared with women, 2.74 (95% CI, 2.52-9.69) per 1,000,000 person-years for men versus 1.47 person-years (95% CI, 1.4-1.62) for women. Of the patients, 19% (210/1077) developed at least one MTS/LS-associated malignancy. MMR immunohistochemical screening was performed in only 20% (220/1077) of SC tumors; of these, 32% (70/219) of tumors were MMR deficient.

Limitations: Retrospective design.

Conclusions: Incorporation of MMR screening into clinical practice guidelines for the management of SC will increase the opportunity for MTS/LS diagnoses, with implications for cancer surveillance,

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Funding sources: NR's research is supported by the Newcastle NIHR Biomedical Research Centre (BRC).

IRB approval status: Project proposal was approved by the NDRS project development steering committee. Ethical approval was

not required; Section 251 of the National Health Service Act 2006 allows collection of data of cancer patients in England with the option to opt out. Data was shared following information standards board (ISB) K3 anonymity. Published data was required to meet the anonymization standard for publishing health and social care data (2013, version 1.0), including satisfying k-anonymity requirements and approval from the Caldicott Guardian.

Accepted for publication March 19, 2023.

Reprints not available from the authors.

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Published online April 7, 2023.

0190-9622

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<https://doi.org/10.1016/j.jaad.2023.03.046>

chemoprevention with aspirin, and immunotherapy treatment targeted to MTS/LS cancers. (J Am Acad Dermatol 2023;89:1129-35.)

Key words: dermatopathology; epidemiology; genetics; Lynch syndrome; mismatch repair deficiency; Muir-Torre syndrome; sebaceous carcinoma.

INTRODUCTION

Sebaceous carcinoma (SC) is a malignant skin adnexal tumor which can be locally invasive and metastasize.¹⁻³ SC presents most frequently in the seventh decade and patients have a 5-year survival rate of 78.2% (95% CI, 64.7-91.7) in England.⁴ SCs are considered in 2 categories by site by the World Health Organization, (1) periocular/eyelid and (2) extraocular (ie, all body locations except periocular/eyelid),⁵ with the former having greater metastatic potential.⁶ SC development has been associated with UV exposure^{7,8} and immunosuppression associated with organ transplantation.⁹ SC can occur in the genetic cancer predisposition syndrome, Muir-Torre syndrome (MTS), an allelic variant of Lynch syndrome (LS) defined by the presence of SC in LS. Sebaceous tumors are the most strongly associated marker of all LS-associated cancers, with 18.8% to 33.3% of patients with sebaceous tumors having LS.^{10,11} MTS/LS is caused by germline pathogenic variants in 1 of 4 mismatch repair (MMR) genes and results in increased risk of gastrointestinal (particularly colorectal), endometrial,¹² genitourinary,^{13,14} and other primary cancers (Supplementary Table I, available via Mendeley at <https://data.mendeley.com/datasets/f3hhxyyh8/1>). Screening for MMR deficiency in sporadic cancers linked to LS can be used to identify new patients with LS and is recommended for all colorectal and endometrial cancer in England.¹⁵ Early diagnosis of LS is clinically important as it could provide the opportunity for preventative interventions including (1) aspirin therapy for primary prevention of colorectal carcinoma and (2) regular cancer screening.¹⁶

MMR screening of SC samples to aid detection of LS is currently not standard practice in England and may represent a missed opportunity for LS detection for both patients with SC and their families.¹⁷ Clinical practice guidelines for the management of SC

CAPSULE SUMMARY

- Population-based cohort study of 1077 cases of patients with sebaceous carcinoma demonstrating a significantly higher risk of copresentation of Lynch syndrome-associated cancers and low rates of mismatch repair deficiency screening.
- Incorporation of mismatch repair screening into clinical practice guidelines has potential benefits in cancer surveillance, prevention, and treatment.

recommend germline testing for MTS/LS in patients with extraocular SC and a Mayo MTS risk score ≥ 2 or patients with MMR deficient (dMMR) SC arising before age of 50. Universal SC tumor testing for MMR deficiency using immunohistochemical tests was not recommended in a recent review due to the much lower sensitivity (81%-85%) and specificity (48%) of this strategy for detecting LS in sebaceous tumors compared with colorectal cancers, 92% to 94%

and 88% to 100%, respectively.⁶ Due to the rarity of SC, however, there are limitations to the data supporting these guidelines. First, the clinical practice guidelines were focused on studies with small case numbers. Second, sensitivity/specificity values were derived from studies relying on data from Surveillance, Epidemiology, and End Results registries, which are incomplete (Supplementary Table II, available via Mendeley at <https://data.mendeley.com/datasets/f3hhxyyh8/1>). Furthermore, the thresholds for testing SC and the assay methodology for dMMR detection are changing, with increasingly sensitive next generation sequencing assays that can detect microsatellite instability.^{18,19}

Here, we examine the epidemiology of SC and LS-associated cancers arising in the same individuals across England from 2008-2018 using high quality comprehensive national cancer registry data.²⁰ We aimed to identify the proportion of SC screened for MMR and the proportion found to be dMMR to inform clinical guidelines on the need for systematic MMR screening of all SC as part of an ongoing drive toward comprehensive LS detection in patients presenting with LS-associated cancer.

METHODS

Study design, setting, and participants

This study included all patients with histologically confirmed cutaneous SC (defined by International

Abbreviations used:

ASIR:	age-standardized incidence rate
LS:	Lynch syndrome
MTS:	Muir-Torre/Lynch syndrome
NCRAS:	National Cancer Registration and Analysis Service
SC:	sebaceous carcinoma
SIR:	standardized incidence ratio

Classification of Diseases for Oncology volume 2 morphology code 8410/3) in England between January 2008 and December 2018. Supplementary Fig 1, available via Mendeley at <https://data.mendeley.com/datasets/f3hhxyyh8/1>, indicates the inclusion criteria. Data was obtained from the National Cancer Registration and Analysis Service (NCRAS), an event-based cancer registry, where tumors are registered as they present and patient level data sets including pathology reports, Cancer Outcomes and Services Data sets, and Patient Administration Services data sets are recorded. Nationwide coverage of cancer events is estimated at 98% to 99% for a population of 55 million people. SC pathology reports for the study period were manually reviewed to confirm the diagnosis and site and extract MMR immunohistochemical data (see Supplementary Information, available via Mendeley at <https://data.mendeley.com/datasets/f3hhxyyh8/1>). Verified cases were then linked to registry data on patient characteristics and germline MMR status. Ethical approval and informed consent were not required for collection of data from NCRAS as per section 251 of the NHS Act 2006.²¹ Patients were assigned a deprivation quintile based on the income domain of the Index of Multiple Deprivation by Lower Layer Super Output Area using the patient's postcode at diagnosis. Date and cause of death were obtained from linked Office of National Statistics data. Statistical analyses are described in the Supplementary Information.

RESULTS

Incidence and population demographics of SC

In total, 1077 patients were confirmed as being diagnosed with SC in England between 2008 and 2018. The median age was 76 with an interquartile range (IQR) of 17 years (Table I). The European age-standardized incidence rate (ASIR) was 2.11 per 1,000,000 person-years (Table II and Supplementary Table III, available via Mendeley at <https://data.mendeley.com/datasets/f3hhxyyh8/1>). ASIRs were higher in men compared with women, 2.74 per 1,000,000 person-years for men versus 1.47 for women. The sex ratio was 1.4:1 male: female

Table I. Patient demographics of sebaceous carcinomas

Patient demographics	Overall (n = 1077)	Extraocular (n = 739)	Periocular (n = 338)
Age at diagnosis, median (IQR), y	76 (17)	77 (16)	75 (17.75)
Age ranges, No. (%)			
0-19	0	0	0
20-39	5	2	3
40-59	133	84	49
60-79	520	352	168
≥80	419	301	118
Sex			
Male	632	463	169
Female	445	276	169
Ratio, M:F	1.4:1	1.7:1	1:1

F, Female; IQR, interquartile range; M, male.

(632:445). Incidence rates were higher for extraocular SCs, 1.46 per 1,000,000, compared with periocular SCs, 0.64 per 1,000,000. Extraocular SCs accounted for 69% (739/1077) of the cases compared with 31% (338/1077) for periocular SCs (Table III). Of the extraocular tumors, the majority were located in the head and neck region, 68% (501/739), in particular on the face, 51% (374/739).

Supplementary Figure 2, available via Mendeley at <https://data.mendeley.com/datasets/f3hhxyyh8/1>, shows the ASIR by year; while suggesting increasing incidence of SC, with an estimated annual percentage change of 4.6, this did not reach significance ($P = .051$). Ethnicity data was available for 1013/1077 cases; this demonstrated that 94% (950/1013) of patients in this study were of White ethnicity. In 72% of cases (772/1077), the size of the SC in conjunction with reported high-risk factors (such as depth of invasion >6 mm) was available in pathology reports and used to calculate the pathological stage according to respective periocular and extraocular Union for International Cancer Control (UICC) tumor, node, metastasis (TNM) 8 staging (equivalent to American Joint Committee on Cancer [AJCC] staging) (Supplementary Table IV, available via Mendeley at <https://data.mendeley.com/datasets/f3hhxyyh8/1>). The majority of tumors were low stage, and 49% (529/1077) of all tumors were pT1. Similar proportions of periocular (62%, 117/189) and extraocular (71%, 412/583) were pT1.

Of the patients with known vital status, 42% (446/1069) were deceased at last follow-up; these patients had a mean survival of 3.04 years (SD, 2.28) after SC diagnosis. The mean follow-up period was 4.15 years (SD 2.82). Kaplan–Meier curves were generated for

Table II. Age-standardized incidence rates (ESP 2013) of sebaceous carcinomas in England per 1,000,000 person-years

	Overall			Extraocular			Periocular		
	<i>n</i>	Crude rate	ASIR	<i>n</i>	Crude rate	ASIR	<i>n</i>	Crude rate	ASIR
	1077	1.8	2.1	739	1.3	1.5	338	0.6	0.6
Sex									
Male	632	2.2	2.7	463	1.6	2.0	169	0.6	0.7
Female	445	1.5	1.5	276	0.9	0.9	169	0.6	0.6

ASIR, Age-standardized incidence rate.

Table III. Demographics of patients with SC stratified by MMR status

Patient demographics	Overall (<i>N</i> = 1077)	MMR deficient (<i>n</i> = 70)	MMR proficient (<i>n</i> = 150)	MMR not tested (<i>n</i> = 857)
Age at diagnosis, median (IQR), y	76 (17)	67 (19)	78 (14)	77 (17)
Age, No. (%)				
0-19	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
20-39	5 (0.5%)	1 (1.4%)	1 (0.7%)	3 (0.4%)
40-59	133 (12.3%)	17 (24.3%)	15 (10.0%)	101 (11.8%)
60-79	520 (48.3%)	35 (50.0%)	69 (46.0%)	416 (48.5%)
≥80	419 (38.9%)	17 (24.3%)	65 (43.3%)	337 (39.3%)
Sex, No. (%)				
Male	632 (58.7%)	51 (72.9%)	90 (60.0%)	491 (57.3%)
Female	445 (41.3%)	19 (27.1%)	60 (40.0%)	366 (42.7%)
Ratio, M:F	1.4:1	2.7:1	1.5:1	1.3:1
Ethnicity, No (%)				
White	950 (88.2%)	59 (84.3%)	134 (89.3%)	757 (88.3%)
Black	9 (0.8%)	0 (0.0%)	3 (2.0%)	6 (0.7%)
Asian	40 (3.7%)	5 (7.1%)	3 (2.0%)	32 (3.7%)
Mixed	3 (0.3%)	1 (1.4%)	0 (0.0%)	2 (0.2%)
Other	11 (1.0%)	1 (1.4%)	2 (1.3%)	8 (0.9%)
Unknown	64 (5.9%)	4 (5.7%)	8 (5.3%)	52 (6.1%)
Deprivation quintile, No (%)				
1	219 (20.3%)	12 (17.1%)	36 (24.0%)	171 (20.0%)
2	249 (23.1%)	15 (21.4%)	31 (20.7%)	203 (23.7%)
3	245 (22.7%)	19 (27.1%)	29 (19.3%)	197 (23.0%)
4	201 (18.7%)	14 (20.0%)	33 (22.0%)	154 (18.0%)
5	150 (13.9%)	9 (12.9%)	20 (13.3%)	121 (14.1%)
Unknown	13 (1.2%)	1 (1.4%)	1 (0.7%)	11 (1.3%)
Tumor location, No. (%)				
Periocular	338 (31.4%)	6 (8.6%)	50 (33.3%)	282 (32.9%)
Extraocular	739 (68.9%)	64 (91.4%)	100 (66.7%)	575 (67.1%)
Face	374 (51%)	12 (19%)	60 (60%)	302 (53%)
Scalp and neck	127 (17%)	12 (22%)	20 (20%)	93 (16%)
Trunk	140 (19%)	29 (45%)	6 (6%)	105 (18%)
Upper limb	35 (5%)	3 (5%)	3 (3%)	29 (5%)
Lower limb	39 (5%)	2 (3%)	6 (6%)	31 (5%)
Genitalia	7 (1%)	2 (3%)	2 (2%)	3 (1%)
Skin, NOS	17 (2%)	2 (3%)	3 (3%)	12 (2%)

F, Female; IQR, interquartile range; M, male; MMR, mismatch repair; NOS, not otherwise specified.

overall (all-cause) survival and demonstrated median survival of 6.8 years for men and 7.4 years for women (Fig 1). This is reduced compared to the median expected survival for a 75-year-old man and 79-year-old woman in England (2014-2016), which

was 11.4 and 10.4 years, respectively. Cause of death was available for 435 of these patients and was related to SC in 3% of patients (13/435). Furthermore, 32%(138/435) recorded other types of cancer as the cause of death.

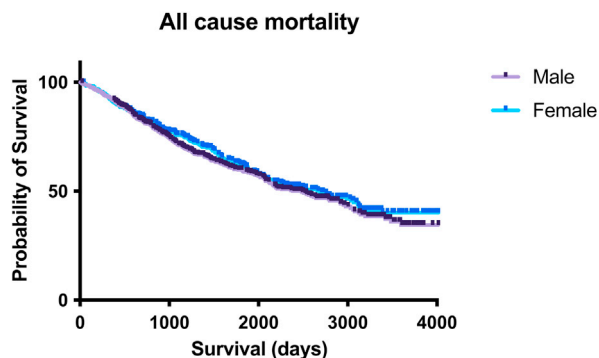


Fig 1. Kaplan–Meier survival analysis for all-cause mortality after a diagnosis of sebaceous carcinoma for all participants stratified by sex.

Multiple primary cancers in patients with SC

Of the patients, 19% (210/1077) developed at least one other recognized LS-associated cancer (Table IV). In total, 274 LS-associated cancers were diagnosed across 210 patients. Several cancers were found to occur at significantly higher rates in this cohort compared with the background population. Overall, these were colorectal cancers (standardized incidence ratio [SIR], 182; 95% CI, 148-216), uterine cancers (SIR, 179; 95% CI, 104-286), and salivary gland cancers (SIR, 387; 95% CI, 105-991), with increased SIR for upper urinary tract cancers, although this was nonsignificant (SIR, 264; 95% CI, 97-574). These significantly higher rates were seen in women for colorectal and uterine cancers, whereas in men, they were seen in colorectal cancers only. Breast and prostate cancers have been suggested to be part of the LS cancer spectrum; in this cohort of SC patients, significantly lower rates were observed, SIR 69 (95% CI, 49-94) and SIR 57 (95% CI, 42-75), for breast cancer in women and prostate cancer in men, respectively.

Rates of MTS/LS-associated cancers were analyzed separately for extraocular and periocular SC. Significantly increased rates were not observed in the periocular group. Extraocular SC tumors were associated with significantly increased rates of colorectal (SIR, 221; 95% CI, 179-270) and upper urinary tract (SIR, 376; 95% CI, 138-817) cancers. Men with extraocular SC tumors showed significantly increased rates of colorectal and upper urinary tract cancers, whereas women showed significant increases in only colorectal cancers, with uterine cancers not reaching statistical significance (SIR, 181; 95% CI, 94-316).

Cancers presenting after first diagnosis of SC

Of the LS-associated cancers, 29% (79/274) occurred after the diagnosis of SC. In 27.1% (57/210) patients, the median latency of presentation of a subsequent LS-associated cancer after SC was

2.3 years (IQR, 3.3). Several cancers were found to have significantly higher rates following a SC diagnosis; these included colorectal (SIR, 226; 95% CI, 151-324), small bowel (SIR, 794; 95% CI, 164-2320), upper urinary tract (SIR, 579; 95% CI, 120-1733), and salivary gland cancers (SIR, 2255; 95% CI, 614-5772). These significant rates were maintained in men for colorectal and salivary gland cancers only and in women for colorectal and gastric cancers (SIR, 525; 95% CI, 108-1534), which had shown only a trend toward significance overall.

Low rates of MMR immunohistochemistry (IHC) screening of SC and germline MMR gene testing

MMR IHC screening was reported in 20% (220/1077) of cases, with an annual increase in testing over the study period. There was an increase in MMR IHC testing during the period of the study, from a low of 4% (2/53) of cases in 2008 to a high of 34% (44/128) of cases in 2018. In cases where MMR IHC was performed, 32% (70/220) of SC were found to be dMMR. Patients with dMMR SC were younger, with a median age of 67 years (IQR, 19) compared with 78 years (IQR, 14) in MMR proficient SC. Extraocular SC had a higher frequency of being dMMR than periocular SC, 39% (64/164) compared with 11% (6/56) (Table III). Of extraocular dMMR SC, 45% (29/64) occurred on the trunk, compared with only 6% (6/100) of extraocular MMR proficient SC. The most common dMMR patterns detected by immunohistochemical screening were loss of MSH2 and MSH6 (74.3%, 52/70), followed by MLH1 and PMS2 (21.4%, 15/70), MSH6 alone (2.9%, 2/70), and PMS2 alone (1.4%, 1/70).

SC case linkage to germline DNA MMR testing results was identified in 56 patients, 25 of whom had MMR IHC testing of their tumor. In 54% (30/56), germline testing identified MMR deficiency consistent with MTS/LS (germline pathogenic variants of *MSH2/MSH6/MLH1/PMS2*). Of the patients, 50% (12/24) with dMMR tumors by IHC were identified to have germline pathogenic variants; one patient was found to have a germline pathogenic variant despite IHC MMR being reported as proficient. Ninety percent of germline tests were done after the diagnosis of SC. The most common germline pathogenic variants were identified in *MSH2* (80%, 24/30), followed by *MSH6* and *MLH1* (both 10%, 3/30) (Table IV).

DISCUSSION

In this national study of SC with genetic testing data and cancer diagnoses, we found that one-third of SC cases tested had MMR deficiency and that cancer risk among patients with SC is high. Currently, MMR screening is infrequent among patients with

Table IV. Cancer association and genetic testing of patients with SC stratified by MMR status

	Overall (N = 1077)	MMR deficient (n = 70)	MMR proficient (n = 150)	MMR not tested (n = 857)
Presence of LS-associated cancer, No. (%)				
Patients	219 (19.5%)	21 (30.0%)	22 (14.7%)	167 (19.5%)
Cancers	274	28	24	222
Germline testing, No. (%)				
Present	56 (5.2%)	24 (34.3%)	1 (0.7%)	31 (3.6%)
Absent	1021 (94.8%)	46 (65.7%)	149 (99.3%)	826 (96.4%)
Germline deficiency, No.				
<i>MSH2</i>	24	9	1	14
<i>MSH6</i>	3	2	0	1
<i>MLH1</i>	3	1	0	2
<i>PMS2</i>	0	0	0	0
None	26	12	0	14
Unknown	1021	46	149	826

LS, Lynch syndrome; MMR, mismatch repair; SC, sebaceous carcinoma.

SC, and our findings provide data to recommend that all patients with SC tumors should be offered MMR screening.

We found increased rates of LS-associated cancers in extraocular SC but not periocular SC.³ Extraocular SC was mainly associated with colorectal cancers, which showed significantly increased rates in both men and women. Upper urinary tract cancers also showed increased rates that reached statistical significance in the cohort of extraocular SC patients. Based on this finding that³ only a small proportion of periocular SC (8%) were MMR deficient, we consider MMR screening and genetic testing should be focused on extraocular SC if testing resources are limited.

A high proportion of cases undergoing MMR IHC were identified to be dMMR (32%). dMMR cancers do not always imply a germline MMR gene defect; MMR deficiency may be confined to the tumor itself (ie, somatic mutation)^{22,23} or be due to false-positive results of MMR assays.²⁴ However, compared with sporadic colorectal cancer screening where 3% of cases are linked to LS,¹⁰ high yields of underlying MTS/LS are expected in SC cohorts, with recent reviews estimating a rate between 18.8% and 33.3%.^{10,11} In the current study, 24 patients with tumors identified to be dMMR by IHC also had a germline test, and 50% (12/24) were identified to have an underlying genetic pathogenic variant, the most frequent of which was in *MSH2*. We did not test for very rare associations with germline biallelic pathogenic variants in *MUTYH*²⁵ or heterozygous *RBI*²⁶ pathogenic variants. The low rate of genetic testing in this cohort may be due to multiple

factors including access to and thresholds for testing and limited interpretation of rates of genetically confirmed LS patients in sporadic SC cohorts.

SC is a cancer that presents in the 7th decade in our and other cohorts, yet almost a third of patients presented with an LS-associated cancer after the presentation of SC. The lower than expected survival shown is likely to be in part due to the presentation of other cancers in undiagnosed LS-associated with SC. Up to 1 in 279 people in the US population are thought to carry a germline MMR gene pathogenic variant,²⁷ and MMR deficiency screening of SC can have implications for cancer screening if LS is confirmed. Furthermore, LS is a dominantly inherited genetic condition with a 50% risk of transmission to children of parents with LS, and cascade testing of family members will detect further LS carriers, expanding the benefit of early LS detection.

Our study has limitations. In keeping with other national registries, variations in practice may be seen in terms of thresholds for MMR deficiency testing. Linkage to germline testing is dependent on NHS molecular genetic laboratories that test for LS to extract retrospective data for submission to NCRAS; registry data for MMR germline testing is complete at national level from 2015 onwards and goes back substantially further in most of England. Due to the rarity of SC and, in particular, low MMR deficiency screening incidence, identifying a significant association is limited. In our study, insufficient tumors with normal IHC underwent germline testing in order to reliably calculate sensitivity and specificity.

Conclusions

dMMR SC can be a presenting feature of MTS/LS and thus may reveal a predisposition to other associated cancers. Incorporation of tumor IHC MMR screening into clinical practice guidelines for the management of SC will increase the opportunity for MTS/LS diagnoses for patients and family members who may benefit from cancer surveillance, chemoprevention with aspirin, and immunotherapy treatment targeted to MTS/LS cancers. Reflex testing of SC, as seen with colorectal and endometrial cancer in England, may help address inequity of care, which is a recognized feature across rare cancers.²⁸

This work uses data that has been provided by patients and collected by the NHS as part of their care and support. The data is collated, maintained and quality assured by the National Cancer Registration and Analysis Service, which is part of NHS Digital.

Conflicts of interest

None disclosed.

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