The burden of cutaneous adnexal carcinomas and the risk of associated squamous cell carcinoma: a population-based study

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The burden of cutaneous adnexal carcinomas and the risk of associated squamous cell carcinoma: a population-based study

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What's already known about this topic?

Cutaneous adnexal carcinomas are rare tumors, but their incidence is increasing. Their rarity prevents from gaining sufficient clinico-pathological experience: CACs can be a diagnostic challenge due to mostly non-specific clinical presentation and histopathological variety that often requires specific expertise for a definite diagnosis.

What does this study add?

CAC incidence increased from 2.5in 1985-87 to 19per million person-years in 2009-10; from 1997 it constantly increased rising up to 159% in 2010. In patients with cutaneous adnexal carcinoma, the risk of SCC is 34-times higher than in general population. Considering demographic evolution with progressive population's ageing and higher CACs' incidence among elderly, it is reasonable to expect a further increase in the future.

Abstract

Background: Recent studies have shown an increasing incidence of cutaneous adnexal carcinomas (CACs) over the years.

Objective: The aim of our study was to evaluate incidence and survival of CACsand investigate their association with other skin neoplasms.

Methods: Population based study. Data on incident cases of CACs were obtained from the Tuscany Cancer Registry (TCR) between 1985 and 2010. In order to determine if the occurence of squamous cell carcinoma (SCC) among patients with CAC is higher or lower than expected in the general population, standardized incidence ratio (SIR) was calculated.

Results: 242 patients with CAC were observed; age–standardized incidence rate was 3.8 cases per millionperson-years. From 1997 to 2010, crude-incidence rates increased by 159%. Age-specific incidence was higher in males over 80 year-oldthan females of the same age and younger individuals. Carcinomas of sweat gland originprevailed; the most common histotype was porocarcinoma and the most frequentlyaffected site was the head-neck. 88% of CACs was diagnosed at a localized stage. 5-year overall survival and disease-specific survival rates were 59% (95%CI 53-65) and 94% (95%CI 91-98), respectively. In observation cohort, number of SCC was significantly higher than expected as SIR resulted 33.7 ($p<0.0001$).

Conclusion: Increasing incidence warrants awareness and early diagnosis of cutaneous adnexal carcinomas. Increased SCC incidence among patients with these tumors highlights relevance of careful skin examination and follow-up.

INTRODUCTION

Cutaneous adnexal carcinomas (CACs) are a wide and heterogeneous group of malignant skin neoplasms that differentiate towards one or more appendageal structures: apocrine and eccrine sweat glands, hair follicle and sebaceous gland.[1] Classification is based on apocrine-eccrine, follicular or sebaceous differentiation displayed on histopathological examination. CACs most often present as single nodules or asymmetric plaques, sometimes ulcerated, with variable growth-rate, lacking in distinctive dermoscopical features.[2-5] They are rare tumors with age-standardized incidence rateof 5.1 per million person-years in the USA and 2.8 in Europe (5.3 in the Netherlands).[6-9] In Italy crude-incidence rate is 6.1 per million (1343 cases observed in 2000-10) with 424 new cases diagnosed in 2015 (3.4% of all skin tumors registered in the same period).[5]Theirrarity prevents from gaining sufficient clinico-pathological experience and definite diagnosis oftenrequires specific expertise.[10,11] However incidence of these tumors has increased in recent years both in the USA and in Europe.[6,7,12] Remarkably theincidence temporal trend has been similar to that of basal cell carcinoma (BCC), squamous cell carcinoma (SCC), and melanoma.[6] Complete surgical excision is the treatment of choice; treatment of metastatic disease is described only in case-reports and there is no consensus about the most suitabletherapeutic regimen being CACs often poor responsive to traditional chemotherapy.[13] The role of target therapy is under investigation.[14]Adjuvant radiotherapy may play a role for regional or distant disease control.[15] Therefore prognosis is generally good when the neoplasm is localized to the skin, but deteriorates when distant organs are involved.[7,16,17]

The present study examined a 25-years time period (1985-2010) in order to evaluate the burden of CACs in terms of incidence and survival. Based on Tuscany Cancer Registry (TCR) reports, we evidenced the registration of multiple skin cancers in several patients with CAC. Since all occurred cases of SCC have been registered by TCR (1985-2010), while BCC casesare not registered regularly

yet, we decided to investigate the association between CAC and SCC. In order to determine if the incidence of SCC among patients with CAC is higher or lower than expected, given the general population and age distribution, standardized incidence ratio (SIR) was calculated.

MATERIALS AND METHODS

We obtained and reviewed all cases of CACscollected from January 1st 1985 to December 31st 2010 by the Tuscany Cancer Registry (TCR), a population-based cancer registry active in the Italian area of Florence and Prato(inhabitants 1.2 million, area 3879 square kilometers). The source population was 30.720.481 individuals. One participant could contribute with several CACs. Cases were followed-up until December 1st 2016 considering the date of death or the date of last access to regional health services for any reason.Registry structure and methods have been previously reported.[18] The following morphological codes, according to World Health Organization's International Classification of Diseases for Oncology Third Edition (ICD-O-3), were considered: 8102/3, 8110/3, 8200/3, 8211/3, 8400-03/3, 8407-10/3, 8413/3, 8420/3, 8480-81/3, 8940/3.[19]Cases with topographic code C44 (skin) were included. Paget's disease was excluded for non-homogeneous coding. The variables considered for each patient were gender, age, tumor stage, anatomical localization, treatment, metastasis, and other neoplasms. All data were de-identified and tracked using a registry code number. According to Surveillance, Epidemiology and End Results Program Registries (SEER) summary staging system, tumor stage was classified in localized, regional, and distant.[20]*In situ* tumors were also considered.

Statistical analysis

Incidence rates were expressed per 1 million person-years and age-adjusted to the European Standard Population using the direct method.[21,22]Age-specific incidence rates and incidence rate ratios (IRR) were calculated. Age-standardized incidence rate (ASR) confidence interval (CI) was calculated using binomial approximation. The survival end points were 5-year overall survival (OS) and 5-year disease-specific survival (DSS) rates; these were calculated using the life-table method.[23] OS defines the time from CAC's diagnosis to death from any cause or last follow-up; DSS the time from diagnosis to death from CAC; disease-free survival (DFS) the time after primary treatment for CAC

ends that the patient survives without any signs or symptoms of that cancer.Disease-specific survival rates at 1 and 5 years indicate the proportion of patients who have not die due to CAC at 1 and 5 years from the date of diagnosis of the neoplasm; patients who died from other causes were censored.
In order to investigate if the occurence of SCC among patients with CAC was higher or lower than expected, standardized incidence ratio (SIR) was calculated. SIR is defined as the ratio between the number of SCC observed in patients with CAC and the number of SCCexpected inthe observation period (1985-2010)based on general population age-specific incidence rates. Only first SCCs were included in calculating the SIR.Statistical analysis was performed using Stata software version 11 (Stata Corp, College Station, TX, USA). For evaluation of statistical significance, χ-square test was used.

RESULTS

242 CACs were registered, 132 (55%) males and 110 (45%) females (Table I). ASR was 3.8 per million person-years(95%CI 3.2-5.2) and 7.8 was the crude incidence rate. Incidence increased from 2.5 in 1985-87 to 19 in 2009-10; from 1997 it constantly increased rising up to 159% in 2010 (Figure 1). Age-specific incidence rates remarkably rose from 0.9 in people ageing 30-34 years to 118 in those aged 85 or older (Figure 2). The incidence was higher in males (8.9) than females (6.8) with an IRR of 1.3. No cases were found inunder25.No patients had multiple CACs.

Carcinomas with sweat gland differentiation prevailed (198 cases,82%), followed by carcinomas with sebaceous differentiation (32 cases,13%).Porocarcinoma represented the most common histotype (55%, Table II) and the most frequent entity among both males and females (50.8% and 60% of CACs diagnosed respectively). Other recorded histotypes were: sebaceous carcinoma (13%), hidradenocarcinoma (12%), apocrine carcinoma (5%), adenoid cystic carcinoma, microcystic adnexal carcinoma and adnexal carcinoma with follicular differentiation (3.7% each), eccrine carcinoma (2%), cutaneous adnexal carcinoma NOS (1.2%), mucinous carcinoma (0.4%, Table II).

Age at diagnosis ranged from 26 to 99 years and mean age was 76.5 (SD = 14.1), 81 considering porocarcinoma.

56% of CACs was localized on the head-neck region, especially the face, including eyelid, lip, and ear (Figure 3). In males most neoplasms presented on scalp (23% vs 10% in females), whereas in females on lower limbs (16% vs 8% in males) and on trunk (21% vs 14% in males, Table I). Considering all histotypes the most common site was the head-neck (Table II), except from apocrine carcinoma that in 5 out of 12 cases was localized on trunk, preferentially in axillary region (Figure 3).By all anatomical sites the most common histotype was porocarcinoma: it represented almost half of carcinomas arising on face (47%) and trunk (49%), 63% of those arising on scalp, and more than 80% of CACs on extremities (Table II).

88% of CACs was localized to the skin at diagnosis while 4.5% extended directly into surrounding tissues and/or involved regional lymph nodes (Table I). Only 2.5% was diagnosed at distant stage. In situ tumors represented 3.7% and they were all intraepidermal porocarcinomas (Table II).

During follow-up period (mean follow-up time 85 months), 11 CACs (5 localized and 6 regional) metastasized. Taking into account all CACs that metastasized during follow-up, DFS was 70.6 months (median 25). Regional stage carcinomas had 32 months DFS (median 22).

Metastases were more commonly observed in males (Table I), mainly due to CACs primitively located on head-neck (9/17) and with sweat gland differentiation, particularly porocarcinoma (Table II). Lung (7/17), skin (4/17), brain (3/17), and liver (2/17) where more commonly involved.
3 porocarcinomas and 1 sebaceous carcinoma of the upper eyelid (that invaded orbital structures), treated by radical surgical excision with negative margins, relapsed after 48.7 months (median 43.5).

Surgery was performed in 99% of patients. In selected cases adjuvant chemotherapy and/or radiotherapy were performed (Table I).

5-year OS and DSS rate were 59% (95%CI 53-65) and 94% (95%CI 91-98), as shown in Figure 4. The median DSS was 27 months.

123 (50.8%) patientspresented one or more other malignant tumor in their medical history: 61 patients had or had had an extracutaneous tumor, 96 a further skin cancer (including BCC, SCC, melanoma, Bowen disease, actinic keratosis, and Merkel cell carcinoma).

During observation period (TCR, 1985-2010), 36 (14.9%) patientspresented at least one SCC, while 1.07 cases of SCC would beexpected in the present cohort based on age-specific incidence rates. SIR resulted 33.71, *p*-value <0.0001 (i.e. observed SCCs were 33.71 times higher than expected). The histotypes of CACs associated with SCC are described in Table III. Taking into consideration SCC observed in patients with porocarcinoma, the two neoplasms arose on same anatomical region in 76% of cases, particularly on head region. Similar anatomical site concordance was equally observed in patients with other histological types.In 1/3 of cases SCC was diagnosed before CAC, in 1/3 at the same time and in 1/3 after (Table III). Mean age at diagnosis of SCC in patients with CAC was 82 years.

DISCUSSION

Even in the Italian area of Florence and Prato (TCR, 1985-2010), CACs are rare tumors as ASR is 3.8 per million person-years, which is higherthan ASR reported in Southern Europe (2.5) but overlaps with that registered in Northern Europe(p <0.01). [6,7,8]Crude-incidence is 7.8although it resulted 12.6 in 2000-10 twice the rate (6.1) described by Italian cancer report.[9] Crude-incidence has increased over the years and fewer cases in1994-96 arelikely to be attributed to lower registration or coding system shift. There has been a steady increase in incidence with 159% change between 1997-98 and 2009-10(Figure 1).

Different factors may justify increasing temporal trend as real increase of incident cases,but also diagnostic techniques' improvement via histopathological confirmation of all excised skin lesions, demographic evolution with population ageing (age-specific incidence peaks over 85 year-old) and finally greater awareness to skin cancer registration in recent decades. In support of real incidence boost of these tumors rather than improved diagnostic ability, Blake et al. demonstrated that such an increase applies to all tumor stages.[6] In addition since their incidence trend is comparable to that reported for BCC, SCC, and melanoma it has been hypothetized that UV radiation may be implicated in CACs pathogenesis.[6,7,24,25,26]

The excellent 5-year DSS (94%)can be explained by diagnosis of CACs predominantly at localized stage and efficacy of excisional surgery. It is higher than 5-year OS (59%) because more than half ofCACs are found in people over 80 year-old who died for other causes not related to CAC. In general our survival rates are lower than those reported in the USA.[16] This discrepancy may be due toolder population (73% over 70 year-old in present studyvs 49% in Martinez et al.) and delayed diagnosis(2.5% distant stage vs 1.7%). It is worth mentioning that our study populationdiffers onsample size being that of Martinez et al. considerably bigger, nevertheless older age is a known cancer risk factor and elderly people have worse prognosis than younger ones. In fact DNA damage accumulates over time, resulting in malignant cellular transformation and immunosenescence that determines deficit of adaptive immunity and a protumorigenic inflammatory microenvironment.[27]Evenfibroblasts' ability to scavenger oxygen free radicals is reduced in older skin with less protection against oxidative stress.[28]Diagnostic delay may also impact on survival, especially in elderly population where slow-growing skin lesions are often underestimated.

CACs' clinical presentation is heterogeneous, thus histopathological examination is mandatory representing the diagnostic gold standard. Incisional biopsy may not be representative of the tumor in its entirety, so an excisional biopsyis preferable. In the suspect of an adnexal carcinoma, it is necessary to avoid inappropriate destructivetreatments,as there is risk of recurrence and metastasis. Pathological examination provides information about histotype, lymphatic and/or vascular

invasion, status of deep and lateral excision margins.Classification of CACs poses many difficulties considering synonyms and dignity of definition of some entities.[29-31] In our study carcinomas with sweat gland differentiationare the most common category (82%), followed by tumors with sebaceous differentiation(Table II) according to previous epidemiological studies. [6,7,9] Among tumors with sweat gland differentiation, the most frequent histotype is porocarcinoma representing 55% of all CACs, far above 7% reported by SEER Registries.[6]Porocarcinoma is also more common than sebaceous carcinoma that is the most frequent CAC diagnosed in both Dutch and American populations (13% vs 25% and 35% respectively).[6,7]Since etiology of CACs remains still unknown, the comparison of different epidemiological patterns for specific histological types can provide useful insights.[6] Different histotype distribution may depend on selection and diverse composition of observed population as a result of exposure to different risk factors both environmental (geographic area, exposure to solar UV radiation, atmospheric pollution) and individual (concomitant diseases, immunosuppression, viral infections).[32-36]

The most frequent localization in sun-exposed areas (head-neck region with predominant onset on male scalp) as happensinNMSC,suggests a possible common etiopathogenesis represented by chronic sun-exposure.[6,7,37]

An interesting result is that in the examined population we found a higher number of SCCs than expected based on age specific population incidence rates with a SIR of 33.7. It means thatpatients with CAC have a risk of developing an SCC 34-times higher than general population.Surprisingly,SCC were localized in the same anatomic region of CAC, particularlythe head (Table III). To date only a few case reports have described the association of CAC and SCC in the same patient and in only one case, an 86-year-old patient history of cumulative solarUV-exposure has been documented.[38,39]Cases in association with Bowen's disease or arising in the site of a previous Bowen have also been reported;[40-42]this finding, difficult to explain, may be due to the close histologic resemblance between Bowen’s disease and *in situ* porocarcinoma. Concomitant onset of CAC and SCC in sun-exposed areasand independent distribution over time in the way that now SCC and now

CAC arises, emphasizes the concept of field cancerization.[43,44]Strong site coincidence could be related to exposure to common risk factorssuch as solar UV radiation or other factors (i.e. genetic) not yet known. Recently,mutations compatible with sun radiation damage (UV mutational signature) and similar to those found in melanoma of the skin, SCC, and Merkel polyomavirus-negative cell carcinoma have been identified in porocarcinomas of the head.[37,45]In the present study, surveillance bias could also represent part of the explanation for the similar anatomical localizations of CAC and SCC. However, the TCR does not collect information about neither initial nor follow-up visits, so it is not known how much closely or with what frequencypatients have been followed-up or how much carefuleness was put in the medical examination. Being male and elder represents risk factor for both CAC and SCC: this is important in guiding dermatologists in clinically approaching these patients at initial visit and follow-up.

To date for patients with CAC neither modality nor duration of follow-up has been established; on the basis of our results we propose to investigate patients as described in Figure 5. During follow-up other skin lesions eventually associated should be checked, especially considering SCC higher incidence in patients with CAC. Attention should be drawn to elderly male patients with porocarcinoma arising on head and patients with regional tumor stage at diagnosis. Disease-specific deaths' concentration in the first 3 years from diagnosis (median DSS 27 months) highlights the opportunity of a close follow-up. It would be wise to prolong follow-up until 5 years from diagnosis given that recurrences observed occurred after 48.7 months. In patients with regional stage tumor attention should be kept in the first 2 years of follow-up, as median DFS was 22 months in this group. However, these considerations should be evaluated in the light of two main limits: relatively small sample size, which determines a strong statistical oscillation and influence of competitive mortality for other causes.

It would be desirable to create a global register of rare skin cancersin order to allow a precise knowledge of the burden of CACs worldwide,[47,48]and include a section dedicated to these tumors in the guidelines of leading dermatology societies so to achieve uniform treatment and management, since rarity of CACs must not be excuse of less attention.

CONCLUSION

Considering demographic evolution with progressive population'sageing and higher CACs'incidence among elderly, it is reasonable to expect a further increase in the future. Therefore early diagnosis and propertreatment is crucial. Do never underestimate new onset of skin lesions in sun-exposed areas in elderly, especially in those who have history of adnexal carcinoma.

Abbreviations

ASR age-standardized incidence rate

CAC cutaneous adnexal carcinoma

CI confidence interval

DFS disease-free survival

DSS disease-specific survival

IRR incidence rate ratio

NMSC non melanoma skin cancer

OS overall survival

SCC squamous cell carcinoma

SD standard deviation

SIR standardized incidence ratio

TCR Tuscany Cancer Registry

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Figure legend

Figure 1. "Trends in crude-incidence rates of cutaneous adnexal carcinomas in Tuscany Cancer Registry, 1985-2010."

Figure 2. "Age-specific incidence curves for cutaneous adnexal carcinomas in males, females and both genders in Tuscany Cancer Registry, 1985-2010."

Figure 3. "Anatomic location by gender and histotype of cutaneous adnexal carcinomas in Tuscany Cancer Registry, 1985-2010."

Figure 4. "Overall survival and disease-specific survival rates among patients with cutaneous adnexal carcinoma in Tuscany Cancer Registry, 1985-2010."

Figure 5. "Follow-up scheme based on TCR analysis, 1985-2010. Patients with CAC should be followed up every 6 months in the first 2 years and every year up to 5 years after initial diagnosis. Follow-up should include: complete history account, status andskin examination with palpation of main lymph node stations; ultrasonography of loco-regional draining lymph nodes and instrumental investigation of most common metastatic sites (i.e. lung, chest x-ray at diagnosis and the following year). Patient clinical status must guide choice and appropriateness of instrumental examination."

Table legend

Table I. “Features of cutaneous adnexal carcinomas in Tuscany Cancer Registry, 1985-2010”

Table II. “Cutaneous adnexal carcinomas according to histological type: cases distribution by gender, anatomical localization, tumor stage at diagnosis and metastases (TCR, 1985-2010).”

Table III. “Association between cutaneous adnexal carcinoma and squamous cell carcinoma in Tuscany Cancer Registry, 1985-2010: SCC cases observed by CAC histological type, temporal relation of SCC with CAC’s diagnosis and site match.”

Table I. “Features of cutaneous adnexal carcinomas in Tuscany Cancer Registry, 1985-2010”

	Gender		
	Males and Females No. (%)	Males No. (%)	Females No. (%)
Year of diagnosis			
1985-1990	27 (11)	17 (13)	10 (9)
1991-1995	27 (11)	19 (14)	8 (7)
1996-2000	31 (13)	15 (11)	16 (15)
2001-2005	63 (26)	27 (20)	36 (33)
2006-2010	94 (39)	54 (41)	40 (36)
All years	242 (100)	132 (100)	110 (100)
Age at diagnosis			
<55	20 (8)	7 (5)	13 (12)
55-69	39 (16)	26 (20)	13 (12)
70-84	94 (39)	57 (43)	37 (34)
>85	89 (37)	42 (32)	47 (43)
Primary site (topographical code ICD-O-3)			
Lip (C440)	3 (1)	2 (2)	1 (1)
Eyelid (C441)	12 (5)	7 (5)	5 (5)
Ear (C442)	15 (6)	12 (9)	3 (3)
Head and neck (C443-4)	105 (43)	59 (45)	46 (42)
Trunk (C445)	41 (17)	18 (14)	23 (21)
Upper limb (C446)	18 (7)	11 (8)	7 (6)
Lower limb (C447)	28 (12)	10 (8)	18 (16)
Overlapping (C448)	2 (1)	1 (1)	1 (1)
Unknown (C449)	18 (7)	12 (9)	6 (5)
Stage			
In situ	9 (4)	5 (4)	4 (4)
Localized	214 (88)	118 (89)	96 (87)
Regional	11 (4)	3 (2)	8 (7)
Distant	6 (2)	5 (4)	1 (1)
Unknown	2 (1)	1 (1)	1 (1)
Treatment			
Surgery	230 (95)	126 (95)	104 (95)
Surgery + chemotherapy	4 (2)	2 (2)	2 (2)
Surgery + radiotherapy	4 (2)	2 (2)	2 (2)
Surgery + chemotherapy + radiotherapy	1 (0)	0 (0)	1 (1)
Radiotherapy	1 (0)	1 (1)	0 (0)
No treatment	2 (1)	1 (1)	1 (1)
Metastasis*	17 (7)	10 (8)	7 (6)
Lymph node dissection*	14 (6)	3 (2)	11 (10)

*include: at time of diagnosis and during follow-up

Table II. "Cutaneous adnexal carcinomas distribution according to histological type: cases distribution by gender, anatomical localization, tumor stage at diagnosis and metastases (TCR, 1985-2010)."

Histological type (ICD-O-3)	No.cases	Gender		Anatomical localization					Tumor stage at diagnosis					Metastases
		Males	Females	Face	Scalp	Trunk	Limbs (upper; inferior)	Multisite/ NOS	In situ	Localized	Regional	Distant	Unknown	
Porocarcinoma (8409/3)	133	67	66	44	26	20	38 (15;23)	5	9	114	7	2	1	8
Sebaceous carcinoma (8410/3)	32	20	12	17	3	3	1 (1;0)	8	0	31	0	0	1	0
Hidradenocarcinoma (8400/3, 8402/3)	29	16	13	12	4	8	5 (1;4)	0	0	26	2	1	0	3
Apocrine carcinoma (8401/3)	12	6	6	3	1	5	1 (0;1)	2	0	9	1	2	0	3
Adenoid cystic carcinoma (8200/3)	9	5	4	5	0	3	0	1	0	8	1	0	0	2
Microcystic adnexal carcinoma (8407/3)	9	6	3	4	3	2	0	0	0	9	0	0	0	0
CAC with follicular differentiation (8102/3, 8110/3)	9	7	2	5	1	0	1 (1;0)	2	0	9	0	0	0	0
Eccrine carcinoma (8413/3)	5	3	2	3	2	0	0	0	0	4	0	1	0	1
CAC NOS (8390/3)	3	1	2	1	1	0	0	1	0	3	0	0	0	0
Mucinous carcinoma (8480/3)	1	1	0	0	0	0	0	1	0	1	0	0	0	0
Total (all histological types)	242	132	110	94	41	41	46 (18;28)	20	9	214	11	6	2	17

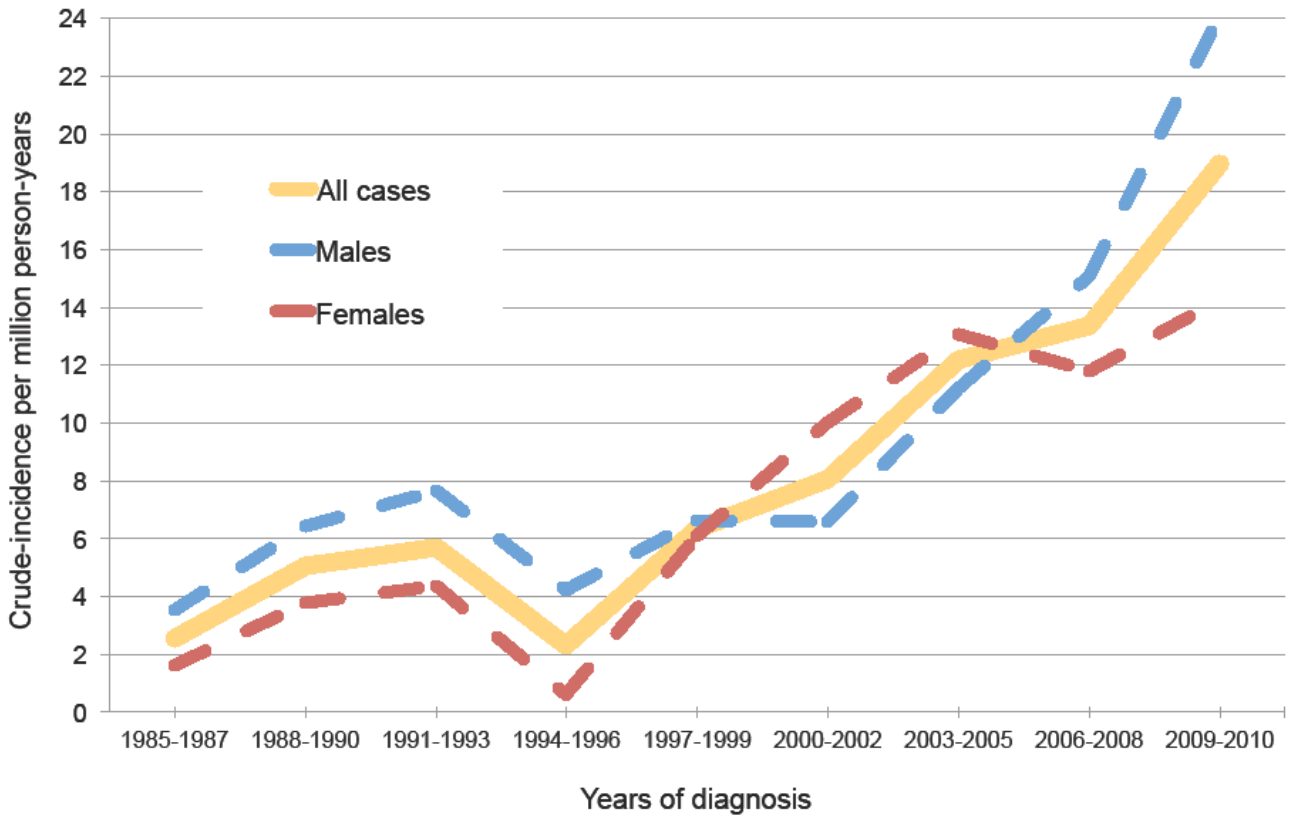
NOS, *not otherwise specified*

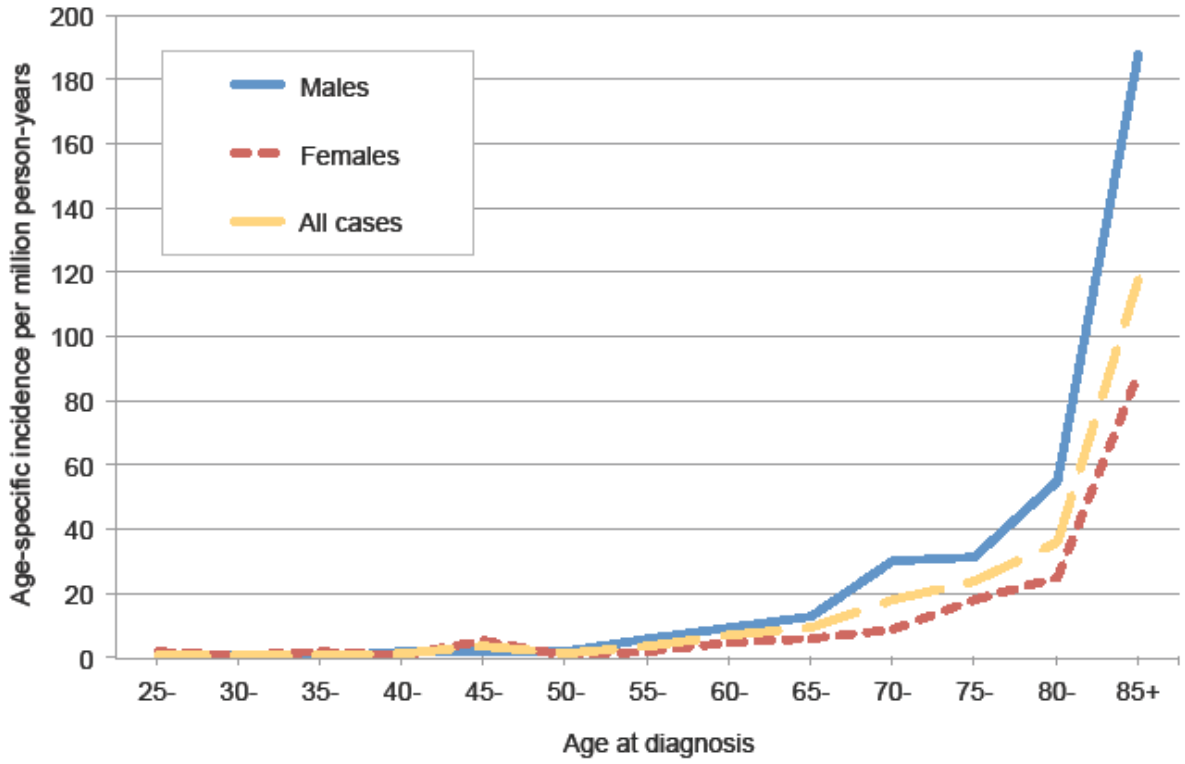
Table III. "Association between cutaneous adnexal carcinoma and squamous cell carcinomain Tuscany Cancer Registry, 1985-2010: SCC cases observed by CAC histological type, temporal relation of SCC with CAC's diagnosis and site match."

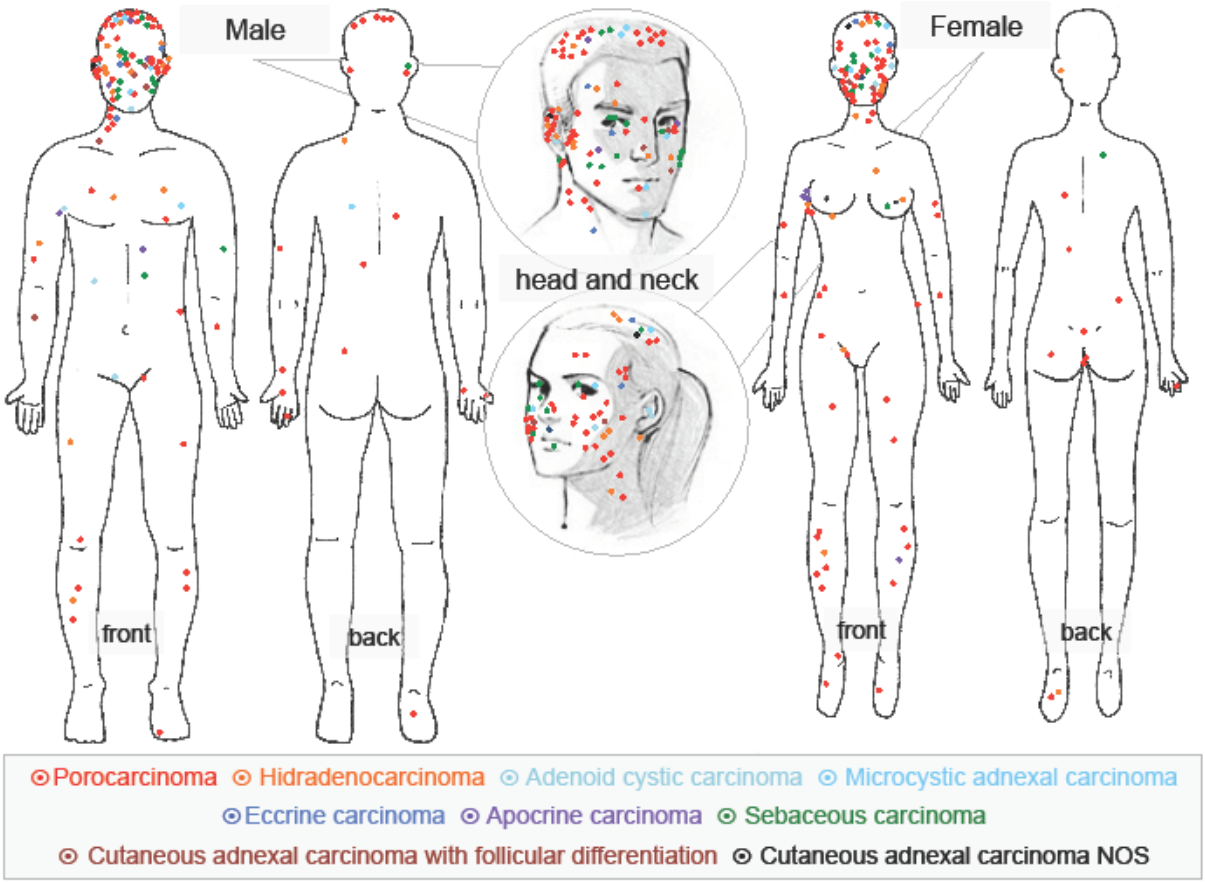
Histological type	SCC observed (males;females)	SCC diagnosis (compared to CAC)			SCC and CAC site match(SCC observed per site)		
		Earlier	Concomitant	Later	All sites	Head	Limbs
Porocarcinoma	21 (15;6)	8	8	5	16(19*)	15(16)	1(3)
Hidradenocarcinoma	7 (6;1)	1	2	4	6(7)	6(7)	0(0)
Sebaceous carcinoma	6 (4;2)	2	1	3	3(6)	2(4)	1(2)
CAC with follicular differentiation	1 (1;0)	1	0	0	1(1)	1(1)	0(0)
Microcystic adnexal carcinoma	1 (1;0)	1	0	0	1(1)	1(1)	0(0)
All histological types	36 (27;9)	13	11	12	27(34*)	25(29)	2(5)

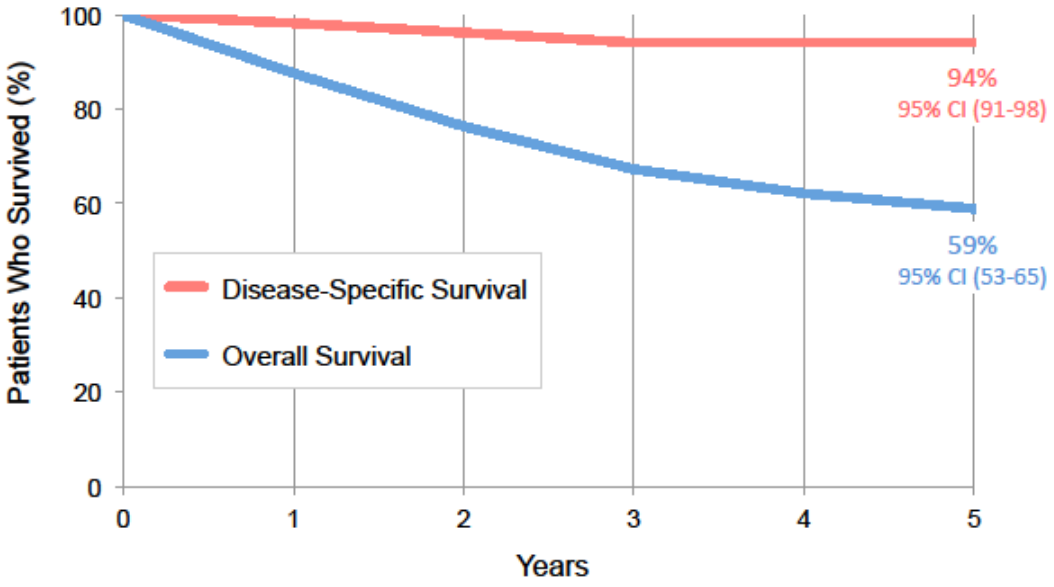
SCC, *squamous cell carcinoma*; CAC, *cutaneous adnexal carcinoma*

*Unknown localization for 2 porocarcinomas.

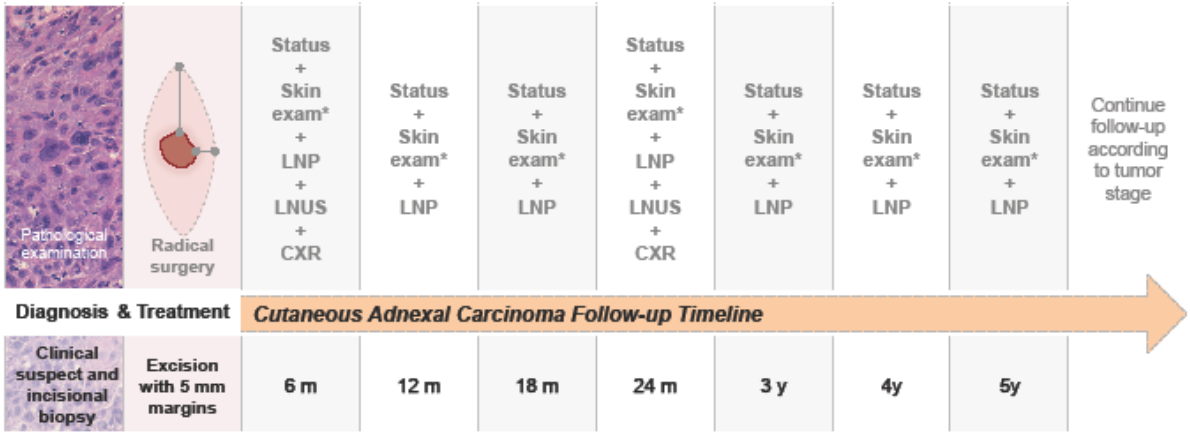








Disease-Specific Survival					
No. at Risk	228.5	199.5	174.5	155	144.5
No. of Events	4	4	4	0	0
Overall Survival					
No. at Risk	241.5	211	183.5	161	148.5
No. of Events	30	27	22	12	8



LNP lymphnodes palpation; LNUS regional lymphnodes ultrasound; CXR chest x-ray.
* At skin examination attention should be drawn to new-onset lesion, especially in the elderly and on the head region.