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“CARCINOMA BASOCELULAR: RELACIÓN ENTRE FACTORES EXTERNOS Y CARACTERÍSTICAS CLÍNICO-HISTOLÓGICAS. CAUSAS DE RETRASO DIAGNÓSTICO Y DE EXTIRPACIÓN INCOMPLETA”

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TESIS PARA OPTAR AL GRADO DE DOCTOR EN MEDICINA Y CIRUGÍA

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Granada, 2012

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CERTIFICAN

que la Tesis Doctoral titulada **"CARCINOMA BASOCELULAR: RELACIÓN ENTRE FACTORES EXTERNOS Y CARACTERÍSTICAS CLÍNICO-HISTOLÓGICAS. CAUSAS DE RETRASO DIAGNÓSTICO Y DE EXTIRPACIÓN INCOMPLETA"**, ha sido llevada a cabo por **D. Husein Husein ElAhmed** bajo nuestra supervisión, con el fin de alcanzar el GRADO DE DOCTOR en Medicina y Cirugía por la Universidad de Granada.

M.Teresa Gutierrez Samerón Jose Aneiros Cachaza Ramón Naranjo Sintes

Granada, 2012

A mis padres y hermanos, por ser mi máximo apoyo.

A todos aquellos que han creído en mi.

Desearía expresar mi agradecimiento a todas aquellas personas que de alguna forma han colaborado en la realización de esta Tesis Doctoral. Podría ocurrir que existiera alguna omisión involuntaria, por lo que pido disculpas de antemano.

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En el actual contexto universitario, la calidad de la formación así como de los resultados de la misma tiene un papel relevante. Teniendo en cuenta que una de las competencias básicas que debe adquirir el doctorando es la capacidad de comunicación con la comunidad académica y científica, las publicaciones en revistas especializadas garantizan la adquisición de esta competencia, además de otras relacionadas con ella.

Por ello y con el consentimiento de mis directores, he creído conveniente que la Tesis Doctoral que aquí se presenta tenga este formato por las siguientes razones: (I) Porque permite comunicar a la comunidad científica los resultados obtenidos de una forma rápida, no teniendo que esperar varios años hasta la finalización del proyecto de Tesis, lo cual puede provocar que los hallazgos pierdan originalidad e interés; (II) Porque uno de los principales criterios por los que se mide la calidad de un trabajo científico es a través del nivel de impacto de las revistas en las que éste es publicado. El conjunto de trabajos presentados en esta Tesis, y que he realizado con la ayuda de mis directores y otros compañeros, se ha publicado en revistas internacionales con impacto, tras estrictas revisiones llevadas a cabo por expertos en el área de la dermatología, lo cual creemos que es motivo de satisfacción, puesto que se trata de un importante indicador de la calidad del trabajo realizado.

Los miembros del tribunal comprobarán que los trabajos publicados están firmados por varios autores. Este hecho se debe a que dichos trabajos han sido realizados en colaboración con otros compañeros de distintos departamentos, sin los cuales la tarea habría sido difícilmente abordable.

Husein Husein ElAhmed

Las revistas en las que se han publicado los trabajos que forma parte de esta Tesis presentan los siguientes factores de impacto (año 2012):

- **Journal of the European Academy of Dermatology and Venereology: 2.98**
- **Dermatology: 2.71**
- **European Academy of Dermatology: 2.52**
- **Journal of Cutaneous Medicine and Surgery: 1.16**

Los artículos de los que consta esta Tesis por compendio de publicaciones son los siguientes:

1. **Factors related to delay in the diagnosis of Basal Cell Carcinoma.**

Husein-ElAhmed H, Gutierrez-Salmeron MT, Aneiros-Cachaza J, Naranjo-Sintes R.

J Cutan Med Surg. doi:10.2310/7750.2012.12030

2. **Relationship between food intake and cutaneous solar elastosis adjacent to basal cell carcinoma.**

Husein-ElAhmed H, Aneiros-Fernandez J, Gutierrez-Salmeron MT, Aneiros-Cachaza J, Naranjo-Sintes R.

J Eur Acad Dermatol Venereol. 2011 Nov 24

3. **Basal cell carcinoma: a comparative study between outdoor versus indoors workers.**

Husein-ElAhmed H, Aneiros-Fernandez J, Gutierrez-Salmeron MT, Aneiros-Cachaza J, Naranjo-Sintes R.

Enviado para publicación

4. **Alcohol intake and risk of aggressive histological basal cell carcinoma: a case-control study.**

Husein-ElAhmed H, Aneiros-Fernandez J, Gutierrez-Salmeron MT, Aneiros-Cachaza J, Naranjo-Sintes R.

Eur J Dermatol. 2012 Apr 19

5. **Effect of non-steroidal anti-inflammatory drugs on the histology of basal cell carcinomas.**

Husein-ElAhmed H, Aneiros-Fernandez J, Gutierrez-Salmeron MT, Aneiros-Cachaza J, Naranjo-Sintes R.

Eur J Dermatol. 2012 Jan 12

6. **Assessment of incompletely excised basal cell carcinomas in six facial areas. Influence of elastosis.**

Husein-El Ahmed H, Aneiros-Fernandez J, Gutierrez-Salmeron MT, Aneiros-Cachaza J, Naranjo-Sintes R.

Dermatology. 2012 Mar 31

7. **Analysis of Factors associated with incomplete excision at a referral hospital in Southern Spain.**

Husein-ElAhmed H, Aneiros-Fernandez J, Gutierrez-Salmeron MT, Aneiros-Cachaza J, Naranjo-Sintes R. Basal Cell Carcinoma.

Enviado para publicación

IV. PUBLICACIONES

V. DISCUSIÓN

ABREVIATURAS

ABREVIATURAS

AINEs	Antiinflamatorios no esteroideos
CBC	Carcinoma basocelular
CBC-HA	Carcinoma basocelular histológicamente agresivo
COX-1	Ciclooxigenasa 1
COX-2	Ciclooxigenasa 2
IFN	Interferon
IL	Interleuquina
PG	Prostaglandinas
RUV	Radiación ultravioleta

INTRODUCCIÓN

1.1. EPIDEMIOLOGÍA

1.1.1. CONCEPTO

El carcinoma basocelular (CBC) es un tumor de origen epitelial que se desarrolla en los queratinocitos basales de la epidermis y de la vaina radicular externa del pelo[1]. Se considera el tumor cutáneo más prevalente y el de mayor incidencia en la población blanca mundial[2,3,4], y representa el 75% de las enfermedades malignas de la piel[5].

1.1.2. INCIDENCIA

A pesar de su alta prevalencia, existen pocos datos sobre este tumor procedentes de registros de cáncer en la mayoría de paises europeos: tan solo Finlandia[6], Suiza[7], Holanda[8] y Francia[9] han publicado sus datos epidemiológicos sobre CBC. Aproximadamente 200 a 600/100.000 personas de raza blanca lo padecen, mientras que en la raza negra la incidencia es más baja: 3.5/100.000 habitantes[10]. El CBC aparece generalmente en adultos, y su incidencia aumenta significativamente a partir de los 50 años. En los últimos años se ha detectado un aumento de casos en pacientes con edad menor de 50 años debido a la exposición solar por razones sociales o de ocio. La aparición de un CBC en un paciente menor de 30 años obliga a descartar la presencia de una genodermatosis.

Este tumor se presenta por igual en ambos sexos, y el 80 a 90% de los casos se localizan en cabeza y cuello. Actualmente la incidencia del CBC aumenta un 10% por año en todo el mundo y causa una importante morbilidad en los pacientes. Por otro lado, la probabilidad de aparición de un segundo carcinoma basocelular u otras patologías tumorales cutáneas es mayor en pacientes con historia previa de CBC.

1.1.3. RELEVANCIA CLÍNICA Y DIAGNÓSTICO

Puesto que en la mayoría de las ocasiones se trata de una neoplasia de crecimiento lento y con agresividad local que excepcionalmente ocasiona diseminación metastásica, los pacientes no suelen otorgarle la importancia adecuada. Este hecho puede determinar que exista un retraso temporal desde la aparición del CBC hasta que el paciente acude a la consulta médica. Se ha observado que distintos factores asociados al paciente son los responsable del retraso diagnóstico en el caso de otros tumores internos[11-16]. En oncología cutánea, la mayoría de estudios que abordan este aspecto se han centrado en el melanoma[17-27]. Alam et al[28] fueron los primeros autores en analizar las causas del retraso en el tratamiento del cáncer cutáneo no melanoma y la variación en el crecimiento del tumor durante ese intervalo de tiempo. El conocimiento de estas causas constituye una interesante maniobra de prevención secundaria, ya que un diagnóstico precoz de la enfermedad puede minimizar su impacto en el paciente[29,30]. Por todo ello, nosotros realizamos un estudio en la población de nuestra área de trabajo para conocer los factores de retraso en el diagnóstico del CBC. Como resultado de este estudio, obtuvimos la primera publicación que aparece en esta Tesis (**Factors related to delay in the diagnosis of Basal Cell Carcinoma. Husein-Elahmed H, Gutierrez-Salmeron MT, Aneiros-Cachaza J, Naranjo-Sintes R, J Cutan Med Surg. doi:10.2310/7750.2012.12030)**

1.2. ETIOLOGÍA

1.2.1. FACTORES DE RIESGO

Los factores que se han implicado en el desarrollo de esta neoplasia se pueden agrupar en 2 categorías:

A. *Constitucionales:*

- *Fototipo I y II*
- *Hamartomas y tumores epiteliales benignos*: Nevus sebáceo de Jadassohn y algunos dermatofibromas.
- *Genodermatosis*: Xeroderma pigmentoso, albinismo, síndrome de nevus basocelular nevoide, síndrome de Bazex, síndrome de Rombo y epidermólisis ampollosa congénita.

B. *Ambientales:*

- *Exposición solar, fototerapia y cámaras de bronceado.*
- *Radiación ionizante*
- *Exposición a arsénico*
- *Tratamiento inmunosupresor* en trasplante de órgano
- *Mostaza nitrogenada tópica*

1.2.2. ELASTOSIS SOLAR

De todos estos factores, el principal factor de riesgo para el desarrollo de CBC es la exposición a la radiación ultravioleta (RUV). Ésta radiación es además responsable de la alteración de las fibras elásticas de la piel conocida como *Elastosis Solar*. Estos cambios elástóticos de la piel son un signo primario del proceso de envejecimiento

cutáneo y se piensa que son un indicador esencial de la exposición solar acumulativa, la cual guarda una relación causal con el desarrollo del CBC. Existen evidencias crecientes que muestran que la piel dañada por la RUV puede ser modificada gracias al consumo de factores dietéticos como la vitamina C, vitamina E y carotenoides[31,32]. Este hecho nos motivó a realizar un estudio que dio lugar a la segunda publicación que aparece en la sección central de esta Tesis (**Relationship between food intake and cutaneous solar elastosis adjacent to basal cell carcinoma. Husein-Elahmed H, Aneiros-Fernandez J, Gutierrez-Salmeron MT, Aneiros-Cachaza J, Naranjo-Sintes R. J Eur Acad Dermatol Venereol. 2011 Nov 24**). El objetivo de este estudio era analizar el efecto del consumo de nutrientes en el proceso de elastosis cutánea observada en la piel de pacientes con CBC.

1.2.3. RELACIÓN ENTRE LA RADIACIÓN ULTRAVIOLETA Y LA HISTOLOGÍA DEL CBC

Los factores etiológicos previamente expuestos son factores de riesgo largamente estudiados, sin embargo su asociación con la histología del tumor no se ha analizado. De hecho, a pesar de que la RUV juega un papel clave en la patogénesis, la relación de ésta con el tipo histológico y la localización clínica no está bien definida[33]. Aunque muchos pacientes intervenidos de un primer CBC no desarrollan más, en otro grupo de pacientes aparecen nuevos tumores[34-38]. Se ha calculado que el riesgo acumulado de desarrollar nuevos CBC tras 3 años después del primero es del 33% al 77%[39]. Se postula que la localización del primer tumor también puede asociarse con la aparición o no de sucesivos basaliomas. No se sabe si esta asociación se correlaciona a su vez, con el tipo histológico. Hasta 1990, la mayoría de estudios sobre CBC se centraban en el

grado de invasión y recurrencia de los distintos subtipos histológicos; y aunque la mayoría de series de CBC no tenían en cuenta estos subtipos, tres trabajos arrojaban nuevos datos sobre los distintos subtipos de CBCs sugiriendo que el CBC superficial podría tener diferentes factores causales a los del CBC nodular[40-42]. Los estudios sobre las características demográficas y clínicas de las variantes histológicas de CBC no se publicaron hasta después de 1995[42-44.] Actualmente, se debate sobre la relevancia de la exposición solar asociada al ámbito laboral y el desarrollo y la progresión de CBC en trabajadores expuestos a la RUV durante el horario de trabajo[45]. Esta situación nos motivó a analizar la influencia de la radiación solar en el lugar de trabajo y las características histológicas y clínicas de los CBC. Como resultado de este análisis, se derivó el tercer trabajo publicado que se presenta en esta Tesis (**Basal cell carcinoma: a comparative study between outdoor versus indoors workers. Husein-Elahmed H, Aneiros-Fernandez J, Gutierrez-Salmeron MT, Aneiros-Cachaza J, Naranjo-Sintes R.)**. En este estudio, se comparan las características clínicas e histológicas de los CBC desarrollados en 2 cohortes: trabajadores expuestos a RU y trabajadores no expuestos a RUV.

1.3. CLÍNICA

1.3.1. VARIANTES CLÍNICAS

Se distinguen varias formas de presentación de CBC que se pueden clasificar en 2 grupos en función de la delimitación de sus márgenes: <u>*Circunscritos*</u> *(con márgenes bien definidos).* Incluyen: nodular, nódulo-ulcerativo y fibroepitelioma de pinkus. <u>*Difusos*</u> *(con márgenes mal definidos).* Incluyen: superficial, terebrante y esclerodermiforme.

Todas estas variedades clínicas pueden pigmentarse, dando lugar al CBC pigmentado que supone un 5% del total de CBC. La presencia de pigmento es un hallazgo anecdótico en el CBC sin que ello signifique un mejor o peor pronóstico.

1.3.2. LOCALIZACIÓN

Aproximadamente el 80% de los CBC, aparecen en la cabeza y el cuello. La localización en tronco y extremidades inferior no es habitual, y en las áreas distales, como manos y pies, la aparición de este tumor es rara. La presencia de un CBC supone un factor de riesgo para el desarrollo de más CBC, con una estimación que va del 33% al 77%[39]. Aunque el CBC suele aparecer como una lesión indolente y de lento crecimiento, algunos tumores pueden mostrar un comportamiento localmente agresivo, sin que se conozca con exactitud el motivo de ello. La capacidad de metástasis del CBC es limitada, con una tasa de metástasis del 0.0028% al 0.55%[46]. Los tumores metastásicos tienden a ser de gran tamaño, localmente agresivos y que han recurrido a pesar de tratamientos repetidos.

1.4. HISTOLOGÍA

1.4.1. VARIANTES HISTOLÓGICAS

El CBC muestra distintos subtipos histológicos. El subtipo *nodular o sólido* es el más frecuente y se compone de una estructura formada por islotes sólidos de células basalioides en disposición aleatoria y con agrupamiento de células en la periferia a modo de empalizada, rodeados por unos espacios claros de “retracción”. Las células tumorales presentan un núcleo hipercromático con citoplasma relativamente pequeño y mal definido. El subtipo *micronodular* es similar al sólido, pero con nidos de menor

tamaño. Cuando los nidos de células basalioides están unidos a la porción inferior de la epidermis y confinados a la dermis papilar, se denomina subtipo *superficial*. El subtipo *adenoide* está formado por bandas finas de células basalioides en un patrón reticular, con abundante mucina estromal. El subtipo *esclerosante* está constituido por bandas elongadas y estrechas y pequeños islotes de células neoplásicas rodeadas por un estroma fibroso denso. El subtipo *queratósico* es similar al tipo nodular, pero con diferenciación escamosa y queratinización de los centros de los islotes, sin diferenciación folicular. Si esta diferenciación está presente, se denomina carcinoma basocelular tipo *folicular*. Otros subtipos histológicos son: *Basoescamoso, fibroepitelioma de Pinkus, con diferenciación anexial o neuroendocrina, pleomórfico, de células claras, granulares, en anillo de sello, etc.*

1.4.2. CLASIFICACIÓN POR PATRÓN DE CRECIMIENTO

En la actualidad, se da una relevancia creciente al patrón de crecimiento y a los bordes de progresión de esta neoplasia, puesto que juega un papel en el pronóstico. Por ello, los subtipos histológicos se clasifican en 2 grupos: A) *De límites bien definidos*: nodular o sólido, basoescamoso y adenoide. B) *De límites mal definidos*: superficial, micronodular, morfeiforme e infiltrativo.

Los subtipos histológicos de CBC con límites mal definidos generalmente muestran un comportamiento agresivo definido por: una extensión subclinica del tumor, un crecimiento localmente destructivo, alta tasa de recurrencias y difícil respuesta al tratamiento[47]. Estudios de centros de referencia indican que la incidencia de estos CBC histológicamente agresivos va del 2.5 al 44%[48-52].

1.4.3. CONSUMO DE ALCOHOL Y RADIACIÓN ULTRAVIOLETA. EFECTOS EN LA PIEL.

Como se ha expuesto previamente, la asociación de la RUV con la histología del CBC no está bien definida, así como la dosis de RUV necesaria para desarrollar el tumor. En este sentido, estudios recientes sugieren que una dosis mínima de RUV en asociación con factores comportamentales o ambientales puede aumentar la incidencia de CBC[53-56], y por tanto aumentar el riesgo de desarrollar CBC histológicamente agresivos (CBC-HA).

El consumo de alcohol es muy frecuente en los paises occidentales, especialmente en relación con actividades al aire libre y exposición a la luz solar. Distintos estudios han sugerido que los consumidores de alcohol presentan mayor prevalencia de quemaduras solares en la piel[57] y mayor incidencia de CBC[53,58]. Además, 2 estudios epidemiológicos con grandes muestras poblacionales sugieren una asociación positiva entre la incidencia de CBC y el consumo diario de alcohol[59,60]. Tras revisar la literatura publicada hasta el momento, observamos que no hay estudios que analicen la relación entre el consumo de alcohol y el desarrollo de CBC-HA, por lo que decidimos investigar esta posible asociación. Esta investigación dió lugar a la cuarta publicación que se presenta en esta Tesis (**Alcohol intake and risk of aggressive histological basal cell carcinoma: a case-control study. Husein-Elahmed H, Aneiros-Fernandez J, Gutierrez-Salmeron MT, Aneiros-Cachaza J, Naranjo-Sintes R. Eur J Dermatol. 2012 Apr 19)**. Este trabajo consiste en un estudio de casos y controles en el que se analiza el consumo de alcohol de los participantes.

1.4.4. LA ENZIMA CICLOOXIGENASA Y SUS IMPLICACIONES EN LA PIEL

Un mecanismo posible por el cual la RUV promueve la carcinogénesis es por su capacidad para inducir la formación de prostaglandinas (PGs). Las PG actúan como promotores y/o iniciadores tumorales[61-64]. La síntesis de PGs a partir del ácido araquidónico consiste en un proceso químico que está catalizado por la enzima ciclooxigenasa (COX). En el organismo, se conocen dos isoformas de COX. La COX-1 es la forma constitutiva que se encuentra en la mayoría de los tejidos. La COX-2 es la forma inducida que se expresa en presencia de agentes proinflamatorios y mitógenos[65]. Existen evidencias que muestran que la COX-2 está implicada en los procesos de carcinogénesis y progresión tumoral. Liu et al[66] fueron los primeros autores en mostrar que la sobreexpresión de la COX-2 se asociaba la carcinogénesis: estos autores observaron que la inserción del gen que expresa la COX-2 en las células de las glándulas mamarias de ratas era suficiente para inducir el tumor. En tumores de órganos internos tales como páncreas[67,68], endometrio[69], pulmón[70], hígado[71], vejiga[72], y glioma[73], la expresión de COX-2 está aumentada en comparación con los tejidos normales. En la piel fotodañada, existe una sobreexpresión de COX-2 con un excesiva producción de PGs[74,75]. Los antiinflamatorios no esteroideos (AINE) son fármacos que bloquean la síntesis de PGs proinflamatorias al inhibir la acción de la COX, y por ello, se ha postulado que estas sustancias podrían tener un efecto preventivo en el proceso de tumorogénesis. Estudios de laboratorio han mostrado que los AINE ejercen un efecto protector en del desarrollo de CBC tanto en modelos in vitro[76,77] como en modelos animales[78-81]. Los resultados de los distintos estudios llevados a cabo en humanos para analizar la asociación entre el consumo de AINE y el riesgo de CBC son contradictorios[82-86]. Este hecho puede ser debido a los diferentes modos utilizados para

cuantificar el uso de AINE[82,83,85] o por potenciales variables confundentes no ajustadas, como la sensibilidad al sol.

Existen pocos trabajos científicos sobre el efecto del consumo de AINE en la histología del CBC. Por ello, nos propusimos analizar la relación entre el consumo de AINE y el desarrollo de CBC-HA. Nuestro análisis se muestra en la quinta publicación que aparece en la sección central de esta Tesis (**Effect of non-steroidal anti-inflammatory drugs on the histology of basal cell carcinomas. Husein-El Ahmed H, Aneiros-Fernandez J, Gutierrez-Salmeron MT, Aneiros-Cachaza J, Naranjo-Sintes R. Eur J Dermatol. 2012 Jan 12**). En este trabajo se analiza el consumo de AINE en pacientes con CBC-HA y pacientes con CBC histológicamente no agresivos.

1.5. TRATAMIENTO

La localización, el tamaño y el subtipo histológico (agresivo versus no agresivo) del tumor son consideraciones importantes a tener en cuenta a la hora de decidir la técnica de tratamiento más adecuada[87,88]. Otros aspectos a considerar son el estado del paciente y el objetivo terapéutico, funcional y estético.

1.5.1. MODALIDADES TERAPEÚTICAS

Además de la excisión quirúrgica, existen múltiples modalidades no invasivas de tratamiento del CBC como: uso de radiación electromagnética (Terapia fotodinámica), quimioterápicos tópicos e intralesionales (5-fluororuacilo) y tratamientos inmunomoduladores (Imiquimod). El uso de estas técnicas no invasivas ha aumentado en popularidad en los últimos años, ya que además de ser efectivas, producen unos resultados cosméticos excelentes[89].

1.5.2. LA EXTIRPACIÓN QUIRÚRGICA

La extirpación quirúrgica es una técnica relativamente sencilla de realizar, económica y con tasas de curación del 95-99%[90,91]. Por ello, continúa siendo la modalidad terapéutica más utilizada para tratar el CBC a nivel mundial[92]. Además, tiene la ventaja de permitir el estudio histológico de la pieza extirpada. Todos estos aspectos han hecho que la extirpación quirúrgica del cáncer cutáneo no melanoma sea considerada un importante indicador de excelencia clínica y quirúrgica[93]. No hay trabajos recientes que evalúen este indicador en nuestra área de trabajo. Esta situación nos motivó a realizar un estudio prospectivo sobre la tasa de extirpación incompleta de CBC en pacientes intervenidos en nuestro hospital. Aunque la mayoría de los CBC son subsidiarios de extirpación quirúrgica mediante técnica estándar, algunos casos (debido a la localización o la histología) requieren el uso de cirugía micrográfica de Mohs. Esta técnica quirúrgica especializada no está disponible en nuestro hospital, y esta carencia no ha afectado a práctica quirúrgica diaria en nuestro servicio, gracias principalmente, a la larga tradición quirúrgica con la que cuentan nuestros dermatólogos. Los resultados en el tratamiento quirúrgico del CBC que obtuvimos se muestran en la sexta publicación que aparece en esta Tesis (**Basal Cell Carcinoma: Analysis Of Factors Associated With Incomplete Excision At A Referral Hospital In Southern Spain. Husein-El Ahmed H, Aneiros-Fernandez J, Gutierrez-Salmeron MT, Aneiros-Cachaza J, Naranjo-Sintes R.).**

1.5.3. LA CIRUGÍA DEL CARCINOMA BASOCELULAR FACIAL

El CBC se desarrolla en cualquier zona de la piel y existen casos atípicos de localización en el pene[94] y en región perianal[95]. La cabeza es la región afectada con más frecuencia, puesto que en ella aparecen más del 80% de los CBC. El tratamiento

quirúrgico de los CBC que aparecen en la cara y su posterior reconstrucción mediante plastia o colgajo constituyen un reto terapéutico debido a la proximidad de estructuras vitales y funcionales como el ojo, nariz o el labio. Este hecho es especialmente relevante en el caso de CBC faciales invasivos por su comportamiento local agresivo y riesgo de desfiguración. Por este motivo, es importante que la excisión quirúrgica en la cara se realice de forma que los márgenes no estén afectos por el tumor. Identificar aquellas áreas faciales en las que existe más riesgo de que la resección quirúrgica se realice de forma incompleta puede ser de utilidad para establecer estrategias terapéuticas adecuadas. Por ello, nos decidimos a realizar un análisis de los CBC faciales intervenidos en nuestro servicio con objeto de conocer las zonas dentro de la cara que presentan más riesgo de extirpación incompleta. Además, valoramos la influencia de la elastosis solar en este hecho. La elastosis solar a nivel facial es intensa debido a la exposición casi continua a la RUV y debido a ello, la delimitación de los márgenes quirúrgicos del tumor puede ser dificultosa, con el consecuente riesgo de extirpación incompleta. Como fruto de nuestro análisis, obtuvimos la séptima publicación que aparece en la sección central de esta Tesis (**Assessment of incompletely excised basal cell carcinomas in six facial areas. Influence of elastosis. Husein-El Ahmed H, Aneiros-Fernandez J, Gutierrez-Salmeron MT, Aneiros-Cachaza J, Naranjo-Sintes R. Dermatology. 2012 Mar 31**).

JUSTIFICACIÓN

Y

OBJETIVOS

2.1. JUSTIFICACIÓN

Teniendo en cuenta la magnitud, incidencia y prevalencia del CBC, así como su posible repercusión en términos de morbilidad, la realización de estudios sobre diferentes aspectos de este tumor que permitan un mayor conocimiento del mismo resulta de gran interés en el ámbito sanitario.

Si bien la literatura científica sobre el CBC ha ido en aumento en las últimas décadas, existen aún cuestiones no aclaradas.

Pensamos que esta investigación será de utilidad ya que permite aportar nuevos datos que ayuden a conocer y entender mejor la naturaleza de esta enfermedad.

2.2. OBJETIVO GENERAL

El objetivo principal de esta Tesis Doctoral es conocer si existe una relación entre determinados factores externos y las características clínicas e histológicas del CBC, así como estudiar los posibles factores asociados al retraso diagnóstico; por último, analizar los resultados quirúrgicos de los tumores intervenidos en nuestro centro.

2.3. OBJETIVOS ESPECÍFICOS

1. Identificar factores asociados al retraso en el diagnóstico del CBC

2. Analizar la relación entre la dieta y la presencia de elastosis solar adyacente al CBC

3. Comparar las características clínico-histológicas de CBC en trabajadores expuestos a RU y trabajadores no expuestos

4. Analizar la asociación del consumo de alcohol y el desarrollo de CBC de histología agresiva.

5. Analizar la asociación del consumo de AINE y el desarrollo de CBC de histología agresiva

6. Analizar los resultados del tratamiento quirúrgico del CBC en nuestra área de trabajo y factores implicados

7. Analizar los resultados del tratamiento quirúrgico de CBC faciales en nuestra área de trabajo y la posible implicación de la elastosis solar.

MATERIAL Y MÉTODO

Para cumplir con los objetivos, se realizaron 3 subestudios que se presentan en formato de 7 artículos científicos. En este apartado se resumen los métodos empleados, y en cada uno de los artículos se describe con más detalle los análisis específicos realizados.

3.1. SUBESTUDIO 1: DIETA Y ELASTOSIS SOLAR CUTÁNEA ASOCIADA AL CBC. ANÁLISIS DE ASOCIACIÓN ENTRE ALCOHOL, AINEs y LA HISTOLOGÍA DEL CBC.

3.1.1. DIETA Y ELASTOSIS SOLAR CUTÁNEA ASOCIADA AL CBC

Fuente de información

Pacientes intervenidos de CBC en el hospital Universitario San Cecilio entre el día 1 de Enero y el día 1 de Mayo de 2010.

Variables

Las variables de exposición eran el consumo de frutas, verduras, grasas, carnes rojas, café y té. Mediante una entrevista, se les pedía a los participantes que estimaran la frecuencia de consumo medio en términos de porciones estándar. Este consumo se clasificaba en 3 categorías: *Diario, Semanal* y *Mensual*.

La variable resultado era el grado de elastosis solar. La elastosis se clasificó en 3 grados: *Ausente o Leve* (sin elastosis o hasta dermis superficial), *Moderada* (hasta dermis media) y *Severa* (hasta dermis profunda).

Además, se controlaron posibles variables que pudieran actuar como factores de confusión: edad, sexo, fototipo, exposición a RUV y tabaco.

3.1.2. CONSUMO DE ALCOHOL Y RIESGO DE CBC HISTOLÓGICAMENTE AGRESIVO

Fuente de información

Pacientes intervenidos de CBC en el hospital Universitario San Cecilio entre el día 1 de Enero y el día 1 de Mayo de 2010.

Variables

La variable de exposición fué el consumo de alcohol. Para determinar este consumo, se preguntó a los participantes cuantas bebidas alcohólicas (cerveza, vino o destilados) consumían en una semana normal. Posteriormente, el consumo de alcohol se dividió en 3 categorías: *Ligero* (≤ 5 bebidas por semana), *Moderado* (> 5 y $\leq$ bebidas por semana) y *Severo* (> 10 bebidas por semana). Para obtener los gramos de alcohol consumido por semana, multiplicamos el consumo semana referido, por el contenido en gramos de alcohol de cada bebida: 10 gr para la cerveza, 9.6 gr para el vino y 9.8 gr para los destilados. Para calcular el grado de exposición al alcohol de cada sujeto, se le pedía a los pacientes que proporcionasen información sobre la cantidad mínima, habitual y máxima consumida y el tiempo de consumo.

La variable resultado era la histología agresiva del tumor. Las piezas extirpadas fueron analizadas por un patólogo de nuestro hospital y clasificadas en: *CBC histológicamente no agresivos* (superficial y nodular) y *CBC-HA* (morfeiforme, infiltrativo y micronodular).

Además, se estudiaron otras variables que pudieran actuar como factores de confusión: edad, sexo, fototipo, color de ojos y de cabello, antecedentes de quemaduras solares en la infancia y en la adultez, café y tabaco.

3.1.3. EFECTO DE LOS AINEs EN LA HISTOLOGÍA DEL CBC

Fuente de información

Pacientes intervenidos de CBC en el hospital Universitario San Cecilio entre el día 1 de Enero y el día 1 de Mayo de 2010.

Variables

La variable de exposición fue el consumo de AINEs durante los últimos 15 años. Esta información se obtuvo mediante una entrevista dirigida por el mismo dermatólogo. La variable de exposición se categorizó en: *SI* o *NO*. Puesto que el CBC se desarrolla en muchas ocasiones en personas mayores con problemas de memoría, las respuestas proporcionadas por los pacientes se comprobaron en la base de datos farmacológica de nuestro hospital. Investigamos la exposición a los siguientes AINEs: acemetacina, aspirina, celecoxib, diclofenaco, diflunisal, etodolaco, fenoprofeno, ibuprofeno, indometacina, meloxicam, naproxeno, piroxicam, rofecoxib and tenoxicam. En aquellos sujetos con consumo de más de un AINE, se consideraba aquel de mayor duración de consumo.

La variable resultado era la histología agresiva del tumor. Las piezas extirpadas fueron analizadas por un patólogo de nuestro hospital y clasificadas en: *CBC histológicamente no agresivos* (superficial y nodular) y *CBC-HA* (morfeiforme, infiltrativo y micronodular).

Además, se estudiaron otras variables que pudiera actuar como factores de confusión: edad, sexo, fototipo, color de ojos y de cabello, antecedentes de quemaduras solares en la infancia y en la adultez y consumo de tabaco.

3.2. SUBESTUDIO 2: COMPARACIÓN DEL CBC EN TRABAJADORES EXPUESTOS A RU Y TRABAJADORES NO EXPUESTOS.

Fuente de información

Pacientes intervenidos de CBC en el hospital Universitario San Cecilio entre el día 1 de Mayo de 2010 y el día 1 de Mayo de 2011.

Variables

La variable de exposición era el tipo de trabajo realizado: *Expuesto* o *No expuesto a la RU*. El primer grupo lo constituían sujetos donde la totalidad o parte de la jornada era realizada expuesto a la RUV ($\geq$ 6 horas al día durante $\geq$ 6 meses) sin ningún tipo de protección. La mayoría de los sujetos de esta categoría lo formaban granjeros y pescadores. El segundo grupo lo formaban sujetos que pasaban la mayor parte de la jornada laboral en lugares no expuestos a la RUV: tiendas, fábricas, bancos, oficinas, hospitales, escuelas…

La variable resultado era la histología del tumor. Utilizando el registro electrónico de muestras anatomopatológicas de nuestro hospital, se identificaron las piezas quirúrgicas que fueron analizadas por un patólogo de nuestro hospital y clasificadas en los siguientes subtipos histológicos: *Superficial, Nodular, Morfeiforme* y *Micronodular*. Las piezas con características mixtas fueron clasificadas por el subtipo más predominante.

Además, se estudiaron otras variables que pudieran actuar como factores de riesgo independientes: edad, sexo, fototipo, color de ojos y de cabello, antecedentes de quemaduras solares en la infancia y en la adultez.

3.3. SUBESTUDIO 3: FACTORES ASOCIADOS A RETRASO DIAGNÓSTICO Y A EXTIRPACIÓN INCOMPLETA DEL CBC

3.3.1. *ANÁLISIS DE FACTORES ASOCIADOS AL RETRASO DIAGNÓSTICO*

Fuente de información

Pacientes intervenidos de CBC en el hospital Universitario San Cecilio entre el día 1 de Enero de 2010 y el día 31 de Diciembre de 2010.

Variables

Mediante una entrevista dirigida por el mismo dermatólogo los sujetos incluidos en el estudio aportaban información referente a la detección de la lesión, características de la misma, síntomas asociados, antecedentes personales y familiares de cáncer cutáneo no melanoma y presencia de enfermedades crónicas.

La variable resultado era el retraso diagnóstico. El "tiempo hasta el diagnóstico" se definió como el tiempo (en meses) desde que la lesión era notada por el paciente hasta que el médico la examinaba y la diagnosticaba. Como nota aclaratoria, indicar que el que este tiempo se iniciaba en el momento en que el paciente, basado en los síntomas, en la apariencia inusual o en la persistencia de la lesión, era consciente de que podía existir un problema, y no simplemente con la aparición de una "mancha" en la piel. El "retraso diagnóstico" se definió como un tiempo hasta el diagnóstico superior a 12 meses. Este dato fue analizado como variable contínua y como variable dicotómica ($\leq$ 12 meses, > 12 meses).

3.3.2. ANÁLISIS DE FACTORES ASOCIADOS A EXTIRPACIÓN QUIRÚRGICA INCOMPLETA DEL CBC

Fuente de información

Pacientes intervenidos de CBC en el hospital Universitario San Cecilio entre el día 1 de Enero de 2010 y el día 31 de Diciembre de 2010.

Variables

Utilizando el registro electrónico de muestras anatomopatológicas de nuestro hospital, se identificaron las piezas quirúrgicas que fueron analizadas por un patólogo de nuestro hospital. Se consideraba *Extirpación Incompleta* cuando al menos uno de los márgenes o el fondo de la pieza estaban infiltrados por el tumor. Las piezas se clasificaron en los siguientes subtipos histológicos: superficial, nodular, morfeiforme y micronodular. Se determinó la presencia de elastosis y se clasificó en grados: *Grado 0 (Ausencia), Grado I (Dermis papilar), Grado II (Dermis reticular media) y Grade III (Dermis reticular profunda).* Además se obtuvo información sobre: Presencia de necrosis, espesor del tumor, distancia al margen quirúrgico más próximo, tamaño y localización de la lesión.

Del informe operatorio, se obtuvo información del tipo de anestesia utilizada y el método de cierre de la herida quirúrgica.

3.3.3. EXTIRPACIÓN QUIRÚRGICA INCOMPLETA DE CBC FACIALES. INFLUENCIA DE LA ELASTOSIS SOLAR

Fuente de información

Ver sección 3.3.2

Variables

Ver sección 3.3.2

PUBLICACIONES

*4.1.**Husein-Elahmed H**, Gutierrez-Salmeron MT, Aneiros-Cachaza J, Naranjo-Sintes R.* ***Factors related to delay in the diagnosis of Basal Cell Carcinoma**. **J Cutan Med Surg. doi:10.2310/7750.2012.12030***

Factors Related to Delay in the Diagnosis of Basal Cell Carcinoma

Husein Husein-ElAhmed, Maria-Teresa Gutierrez-Salmeron, Ramon Naranjo-Sintes, and Jose Aneiros-Cachaza

Background: **There is often a delay between the clinical emergence of a basal cell carcinoma (BCC) and the point in time at which the patient presents for definitive diagnosis and treatment. Previously published studies on delays regarding skin cancer have focused on melanoma rather than BCC. We conducted a study aimed at identifying factors associated with the detection of BCC and reasons for the delay in diagnosis.**

Method: **A monocentric study was performed. Patients with a primary BCC diagnosed in 2010 were included in the study. They were asked about factors concerning BCC awareness and detection, tumor characteristics, previous history of nonmelanoma cutaneous cancer, family history of nonmelanoma cutaneous cancer, and the presence of comorbidities. Data were analyzed using *SPSS* software.**

Results: **The mean diagnostic delay for BCC in our hospital setting was estimated at 19.79 ± 14.71 months. Delayed diagnosis was significantly associated with patients over 65 years, those without a previous history of BCC, those without a family history of BCC, those with BCC located elsewhere than the head or neck, and those with lesions not associated with itching or bleeding.**

Conclusion: **This study revealed considerable delay in the diagnosis of BCC. The main reason for delay in the diagnosis seems to be the initial decision of the patient to seek medical advice. These data suggest a need for greater information for the general public on the symptoms and signs that should prompt suspicion of a BCC.**

Contexte: **Il s'écoule souvent un certain temps entre l'apparition clinique d'un carcinome basocellulaire (CBC) et le moment où le patient connaît le diagnostic définitif et est soumis à un traitement. Les études publiées antérieurement sur ce temps d'attente, dans le contexte du cancer de la peau, portaient surtout sur le mélanome plutôt que sur le CBC. Aussi notre étude vise-t-elle à cerner les facteurs associés à la détection du CBC et les raisons à l'origine du temps écoulé avant la pose du diagnostic.**

Méthode: **Il s'agit d'une étude monocentrique. Des patients chez qui un diagnostic de CBC primitif avait été posé en 2010 ont participé à l'étude. Ils ont répondu à différentes questions sur les facteurs relatifs à la prise de conscience de l'existence du CBC et de sa détection, les particularités de la tumeur, les antécédents de cancer de la peau non mélanique, les antécédents familiaux de cancer de la peau non mélanique, et la présence de maladies concomitantes. Les données recueillies ont été analysées à l'aide du logiciel *SPSS*.**

Résultats: **Le temps moyen avant la pose du diagnostic de CBC dans notre établissement hospitalier a été évalué à 19.79 ± 14.71 mois. Le retard dans la pose du diagnostic était fortement associé à un âge supérieur à 65 ans, à l'absence d'antécédents de CBC, à l'absence d'antécédents familiaux de CBC, à des sièges de CBC autres que la tête et le cou, et à l'absence de démangeaison ou de saignement des lésions.**

Conclusions: **L'étude a fait ressortir l'existence d'un retard considérable dans la pose du diagnostic de CBC. La principale raison de ce retard serait liée à la décision tardive des patients à consulter un médecin. Les données laissent penser qu'il faudrait informer davantage le public sur les signes et symptômes potentiellement révélateurs d'un CBC.**

BASAL CELL CARCINOMA (BCC) is the most common tumor in whites.[1] Although its incidence varies depending on the geographic area—for example, in Australia, the incidence is higher than in the United States or Europe[2]—the number of new cases per annum is increasing all over the world. BCC can occur at any age, but its incidence increases dramatically in people over 40 years. Most BCCs are not fatal, but they can cause severe morbidity, destroying facial sensory organs such as the

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nose, ear, lips, and eyelids. Management of this condition depends on many factors, with surgical excision being the treatment of choice as it reaches a cure rate between 95 and 99%.[3,4]

There is often a delay between the clinical emergence of a BCC and the point in time at which the patient presents for definitive diagnosis and treatment. Delayed treatment may lead to larger and more disfiguring surgical excisions. Diverse patient-related factors seem to be the causes for the delay in the treatment of cancer in general and BCC in particular.[5–23] In some cases, patients misunderstand the symptoms of their lesions, which are considered unimportant or likely to go away. Other patients experience denial or fear. Previously published studies on delays regarding skin cancer diagnosis and treatment have focused on melanoma rather than BCC. In view of this, we conducted a study aimed at identifying factors associated with the detection of BCC and reasons for the delay in diagnosis.

Material and Method

Subjects and Source of Data

Patients with a primary BCC (one o more) diagnosed and operated on between January and December 2010 were included in the study. Written informed consent was obtained from each patient. They were interviewed by a single dermatologist using a questionnaire. The interview consisted of questions concerning BCC awareness and detection, tumor characteristics, previous history of nonmelanoma cutaneous cancer, family history of nonmelanoma cutaneous cancer, the presence of comorbidities, and other personal factors that might have influenced the period of time between the first observation and diagnosis of the tumor. Elderly patients and those with limited sensory were assisted by staff members, who explained questionnaire items in detail.

Statistical Analysis

Time to diagnosis was defined as the patient-reported time in months from when the lesion was first noted to when the doctor examined and diagnosed the lesion. For clarification, the initial time was when, based on symptoms, persistence, or unusual appearance, the patient realized that something troublesome was occurring rather than when a spot was first noted. A cutoff for duration of symptoms of at least 12 months before the visit to the doctor for diagnosis was used to define patient delay. These data were analyzed as both a continuous variable and a categorical variable ($\leq$ 12 months, $>$ 12 months). The continuous time measure was compared between categories of demographic and patient history characteristics (all of them dichotomous) using the Student *t*-test. A multivariable analysis of factors possibly related to a delay in BCC diagnosis was performed by multiple regression analysis. Data evaluation was performed using the statistical package *SPSS* version 15 for Windows (SPSS Inc, Chicago, IL). A $p < .05$ was regarded as statistically significant.

Results

Two hundred ninety-two patients with BCC were interviewed (147 women and 145 men). No incomplete responses or missing data were obtained. The median age of the patients was 69.13 $\pm$ 10.74 years. The overall median waiting time to diagnosis was 19.79 $\pm$ 14.71 months. In 48.8% of our sample, the waiting time to diagnosis was $\leq$ 12 months, whereas 51.2% waited $>$ 12 months to seek medical advice.

The frequency of the clinical symptoms and signs of BCC is given in Table 1. The three predominant symptoms were feeling (37.9%), bleeding (32.7%), and itching (29.1%), whereas the most common signs were telangiectasias (75.5%), ulceration (66.1%), and crusts (39.4%).

The median/mean time elapsed between first noticing a suspicious lesion and diagnosis was related to demographic and medical history characteristics (Table 2). The median waiting time to visit a doctor was longer in patients over 65 years ($p = .024$), those without a previous history of BCC ($p = .017$), those without a family history

Table 1. Frequency of Signs and Symptoms Observed in the Sample

Signs and Symptoms	*Cases %*	n
Itching	29.1	84
Pain	1.8	6
Bleeding	32.7	95
Feeling	37.9	110
Homogeneous surface	31.8	93
Crusts	39.4	115
Ulcerated	66.1	193
Telangiectasias	75.5	220
Pigmentation	15.8	47
Perilesional actinic keratosis	18.8	54

Multiple responses were possible.

Table 2. Time to Diagnosis (mo) by Demographic and Patient History Characteristics

Characteristic	*Minimum*	*Mean*	*Maximum*	p *Value* (95% CI)*
Age (yr)				
≥ 65	3	17.07	43	.024 (−7.39 to −0.65)
> 65	2	21.45	69	
Gender				
Female	3	19.89	72	.56
Male	4	20.87	62	
History of skin cancer				
No	2	22.13	57	.017 (0.881–8.91)
Yes	6	17.77	46	
Family history of skin cancer†				
No	2	21.73	64	.01 (1.02–7.61)
Yes	5	16.41	60	
Comorbidities‡				
No	3	21.89	63	.12
Yes	2	19.73	61	
Location of BCC				
Head/neck	2	18.21	52	.035 (1.42–5.69)
Remaining body	4	21.41	62	
Itching				
No	4	22.87	63	.04 (1.82–7.32)
Yes	2	17.75	61	
Bleeding				.
No	3	19.94	63	005 (2.31–7.89)
Yes	2	16.87	54	
Feeling				
No	4	23.87	68	.19
Yes	5	21.64	61	

*Student *t*-test.
†Including natural parents, brothers, and sisters only.
‡Presence of chronic diseases that may lead to the patient being more likely to seek medical advice, such as diabetes, arterial hypertension, and dyslipidemia.

of BCC ($p = .01$), those with BCC located elsewhere than the head or neck ($p = .035$), and those with lesions not associated with itching or bleeding ($p = .04$ and .005). No differences in waiting time were observed regarding gender ($p = .56$) and the presence of comorbidities ($p = .12$)

Multiple regression analysis confirmed the results observed in the univariable test and revealed the following factors to be significantly related to a delay in BCC diagnosis: age over 65 years ($p = .024$), absence of a previous history of BCC ($p = .017$), absence of a family history of BCC ($p = .01$), lesions located elsewhere than the head or neck ($p = .035$), and lesions with bleeding ($p = .011$). No statistical significance in waiting time was observed regarding gender, the presence of comorbidities, histologic BCC subtype, and tumor thickness ($p = .32, .21, .65$, and .78, respectively). In the same way, lesions with itching and feeling did not show differences in waiting time ($p = .34$ and .23). Odds ratios and confidential intervals are shown in Table 3.

Discussion

Skin cancer information campaigns and screening programs are based on the presumption that earlier disease diagnosis can minimize the impact of disease.[24] An approach that does not have an impact on BCC incidence but that reduces BCC-associated mortality is to increase secondary prevention. Given the unique visible nature of BCC, this tumor can be more readily discovered than other types of cancer. Despite this fact, our study indicates that most patients with BCC delay going to physicians for a definitive diagnosis after noticing the lesion: in 48.8% of the patients in our sample, over 1 year elapsed between the first observation of skin changes and the diagnosis. We

Table 3. Factors Related to Delayed Diagnosis of Basal Cell Carcinoma on Multiple Regression Analysis

Factor	*Odds Ratio*	p *Value (95% CI)*
Location of BCC, head/neck vs remaining body	.53	.016 (0.38–0.74)
Previous history of BCC, yes vs no	.48	.003 (0.29–0.78)
Previous family history of BCC,* yes vs no	.49	.003 (0.31–0.79)
Comorbidities,† yes vs no	.43	.21
Gender, M vs F	1.27	.32
Age, younger vs older	.61	.05 (0.36-0.91)
Itching, yes vs no	.98	.34
Bleeding, yes vs no	.73	.011 (0.43-0.82)
Feeling, yes vs no	.66	.23
Histologic type, nodular/superficial vs other types	1.18	.65
Thickness, ≤ 10 mm vs > 10 mm	1.53	.78

BCC = basal cell carcinoma.
*Including natural parents, brothers, and sisters only.
†Presence of chronic diseases that may lead to the patient being more likely to seek medical advice, such as diabetes, arterial hypertension, and dyslipidemia.

consider this figure excessive for the most common cancer in humans. It is even more surprising than in recent years, despite clear improvements in patient access to medical information.[25]

The problem of delayed reporting for diagnosis of patients with BCC was analyzed by Blackford and colleagues.[26] These authors conducted a study on patients with BCC and found that the mean time from the appearance of a skin lesion to the doctor's visit was over 2 years. A study conducted by Antoszewski and colleagues indicated an even longer delay, with a time interval of 2.7 years on average.[27] In the present study, we obtained slightly lower figures, with an overall median waiting time to diagnosis of 19.79 ± 14.71 months (1.64 years on average).

Reasons for the delay in diagnosis of BCC have not been well studied previously. Most relevant research has focused on melanoma and, to a lesser extent, other types of cancer.[28] In our research, we observed that patients who were younger (≤ 65 years), those with lesions located in the head and neck, those with a previous BCC history, and those with a family history of skin cancer waited a relatively shorter time before seeking medical care after noticing the lesion. Multivariable analysis confirmed these findings, and the significance of the results for age, BCC location, and personal and family history of BCC remained unchanged.

Denial of illness has been found to result in delayed diagnosis and treatment of BCC.[28] The results of the present study indicate that patients with a personal or family history of BCC wait a shorter period before seeking the diagnosis of the skin condition. This may be explained by the fact that these subjects are more concerned about skin malignancies and trained in the recognition and understanding of the cutaneous signs and symptoms, with no denial of their disease. This is in line with other work that has shown that a previous history of BCC can determine medical help-seeking behavior.[28]

Regarding age, we observed that older patients (≥ 65 years) seemed significantly at higher risk for a delay in the diagnosis. This is consistent with results from other studies.[28,29]

The head and neck are the most common locations of BCC.[30] One interesting finding of our study is that the delay to diagnosis was significantly shorter for patients who presented with lesions on visible areas such as the head and neck compared to patients with BCC elsewhere. One plausible explanation may be that lesions in these areas are more easily recognized, so patients seek medical advice earlier.

Our data did not show an association between delay and tumor thickness. The most likely explanation is that the growth of BCC is not fast enough to show a significant increase in tumor thickness for extra months in diagnosis. Our finding is consistent with the results of a study on the dimensions of BCC conducted by Kirkup and de Berker.[31] These authors found a poor correlation between tumor growth and time, suggesting that the growth of a small BCC is not linear; therefore, it is not possible to predict the effect of longer delays on tumor dimensions.

Of the symptoms examined, bleeding and itching were the most prevalent in our sample. We found that patients with bleeding and itching lesions sought medical advice earlier. However, this was not essential for the prognosis according to other studies that have demonstrated a lack of

benefit of early referral of patients with symptomatic BCC.[31,32]

Studying the factors associated with a delayed diagnosis presents unique methodologic challenges. What constitutes a delay in seeking medical attention for cancer has been defined differently in studies that have addressed this issue. We chose a priori the cut point of 12 months to distinguish between delayers and nondelayers. We chose the time period from first concern to when the diagnosis was made because many "marks" are noticed several months prior to the development of BCC and do not pose a problem until suspicious changes occur.

Our study suffers from a few limitations. First, the retrospective nature of the data collection on the duration of symptoms, which is intrinsic to any study of patient delay, poses a potential threat to bias (owing to the patient's memory). Second, we do not know if there were difficulties surrounding the reason for the referral of suspected skin lesions.[33] Third, there may be other sources of delay that we did not adequately assess, such as a patient's personal priorities.

The main advantage of our study is that this is one of the few studies considering the time period before the diagnosis of BCC and factors associated with the delayed diagnosis, a measure of BCC morbidity. All cases were obtained from the practice of a single referral dermatologist and are felt to be representative of BCC in Granada, Spain. The use of a single dermatologist reduces provider-associated variability. Moreover, the homogeneous general practice structure throughout our country makes our results generalizable to other areas in our country where the health care systems are comparable, but differences in health care systems, especially levels of gatekeeping and cultural factors, should be considered before extrapolating our findings to other countries.

This study shows that a substantial level of awareness (a previous history of BCC) did prevent a delay in the diagnosis of BCC. In a substantial number of cases, absence of symptoms and lesions not located on the head and neck exacerbated the delay. Thus, it seems that, as for malignant melanoma,[34] the main delay in the diagnosis pathway is the initial decision of the patient to seek medical advice, and further approaches targeting the public are necessary to improve awareness, behavior, and recognition of BCC.

Conclusion

This study shows a considerable delay in the diagnosis of BCC. Delayed diagnosis was seen mainly in patients over 65 years, those without a previous history of BCC, those without a family history of BCC, those with BCC located elsewhere than the head or neck, and those with lesions not associated with itching or bleeding. The main reason for a delay in the diagnosis seems to be the initial decision of the patient to seek medical advice. Our findings suggest that the public needs to be further educated about BCC symptoms to seek medical advice earlier. Thus, early diagnosis and treatment can lead to briefer surgeries, smaller scars, and overall decreases in morbidity.

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4.2. ***Husein-Elahmed H****, Aneiros-Fernandez J, Gutierrez-Salmeron MT, Aneiros-Cachaza J, Naranjo-Sintes R.*
Relationship between food intake and cutaneous solar elastosis adjacent to basal cell carcinoma*. J Eur Acad Dermatol Venereol. 2011 Nov 24*

ORIGINAL ARTICLE

Relationship between food intake and cutaneous solar elastosis adjacent to basal cell carcinoma

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Abstract

Background/Objective Studies suggest that diet may influence in skin ageing and skin appearance. However, the effect of diet in the elastotic changes of dermis, which is the main histological sign of ageing, has not been studied previously. The objective was to investigate if the dietary habits influence the dermal elastosis observed in BCCs.

Materials and methods The 136 patients with facial BCCs, who underwent surgery, were interviewed to assess the consumption of fruit, vegetables, fat, red meat, coffee and tea. We reviewed 136 specimens of BCC to identify the presence of solar elastosis. We also analysed clinical variables such as gender, age, phototype and smoking.

Results Severe solar elastosis was found in 22 patients (16%), middle reticular dermis in 37 (27 %) and 77 patients (57%) had abscence or light elastosis. Fat consumption was reported by most of participants from our sample, while fruit and tea consumption was less common. Intakes of fat, vegetables and coffee were not associated with the grade of elastosis whereas Vitamin E and C-rich fruits and tea were correlated with less risk of elastosis. Smokers showed higher grades of elastosis than non-smokers.

Conclusion Our study provides evidence that the presence of dermal elastosis and cutaneous ageing may be influenced by the type of food intake: Vitamin E and C-rich fruit and tea are positively associated with less elastosis.
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Conflict of interest

The authors have no conflict of interest to declare. All the authors approved the final version of manuscript and submission. All authors have participated sufficiently to take public responsibility for appropriate portions of the work.

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Introduction

Sking ageing is a process which remains partially unresolved and particularly important due to its social impact. Clinical changes of aged skin are xerosis, laxity, wrinkles, slackness and the occurrence of benign neoplasms such as seborrhoeic keratoses and cherry angiomas. One of the most relevant histological features that accompany these clinical changes is the solar elastosis.

Solar elastosis is the deposit of altered elastin in the dermis. Elastotic changes of the dermis are the primary sign of cutaneous ageing process and thought to be an essential indicator of the cumulative sun exposure which is associated with non-melanoma skin cancer, such as basal cell carcinoma (BCC). BCC is the most common cancer in humans with more incidences in the elderly population. The exposure to ultraviolet (UV) light is the first environmental cause of skin ageing and the main risk factor of BCC. Both UVB (290–320 nm) and UVA (320–400 nm) are responsible of skin ageing; however, the exact mechanism of how UV radiation causes skin ageing is not completely clear. UVA penetrates more deeply than UVB damaging both epidermis and dermis, and plays an essential role in the pathogenesis of ageing.

There are increasing line of evidences that show that the photo-damaged skin can be modified by dietary factors such as vitamin C, vitamin E and carotenoids.[1,2] However, these studies present limitations by the use of supplements, which makes it difficult to determine if dose of nutrient is enough to display an effect.

The purpose of this study is to assess the possible effect of nutrient intakes, rather than supplement, in the ageing process through the assessment of cutaneous elastosis, observed in the skin immediately adjacent to the dermal portion of BCC.

Table 1 Food groups investigated in our study

*Fat and oils (Margerine, Butter, Eggs, Cheese, Oils dressing, Oils – corn, satflower or soybean-, Fried food – hot dog or hamburger)
†Red meat (Beef, Pork, Lamb)
‡Vegetables (Green leafy vegetables, Onions, Corn, Peas, Garlic, Cauliflower, Carrots, Tomatoes)
§Vitamin E or C-rich fruits (Mango, Orange, Grapefruits, Strawberry, Pineapple, Watermelon, Apple, Apricot, Kiwi, Banana, Peach)
¶Tea (Green and black tea)
¶Coffee

*Standard portion size: Margerine and Butter: 1 Tablespoon; Eggs: 1; Cheese: 1 Ounce; Oil dressing: 1 Teaspoon; Oil: 1 Teaspoon; Fried food: 1 unit.
†Standard portion size: 2–3 ounces.
‡Standard portion size: Green leafy vegetables, Cauliflowers, Carrots, Tomatoes: 1 Cup; Onions, Corn, Peas: Garlic: ½ cup; Garlic: 1 slide or 1 teaspoon (garlic powder).
§Standard portion size: Mango, Orange, Apple, Kiwi, Banana, Peach: 1 unit. Grapefruit: ½ cup; Strawberry: 1 and ¼ cup; Pineapple: ¾ cup, Watermelon: 1 slide; Apricot: 4 whole.
¶Standard portion size: 1 cup.
Data obtained from The University of North Caroline and Chapel Hill Campus Health Services, Medicine Specialty Services: Nutrition.

Materials and methods

The 136 patients with facial BCC undergoing surgery were included in the study. They were interviewed to assess the consumption of fruit, vegetables, fat and oils, red meat, coffee and tea. Participants were asked to estimate the average frequency of consumption of each food over the past 5 years in terms of a standard portion size. The sizes of portions were expressed in appropriate units of the each food. From the average intakes of different items, subjects were classified into three frequency categories, ranging from daily to weekly and monthly, in each food group. All food groups (with the items) are shown in Table 1. We reviewed 136 specimens of BCC to identify the presence of solar elastosis associated with the tumouration. Elastosis is readily recognized with the routine haematoxilin & eosine stain as an increase in the coalescence of light blue to grey elastin fibres and in photodamaged skin, elastosis displaces ordinary colagen. Three grades of elastosis were considered using immediately adjacent to the dermis in the tumour: Abscense or Light (Without elastosis or to superficial dermis), Moderate (to mild dermis) and Heavy (to deep dermis) (Figs 1,2). Histological variant of BCC was also identified (data not included). We analysed others clinical variables which could be confounding factors such as gender, age, phototype, average lifetime exposure to UV-light and smoking.

Statistical analysis

Using the SPSS version 15 software (SPSS, Chicago, IL, USA) we performed Pearson's chi-squared test to evaluate the association between qualitative variables and elastosis. We used a *P*-value

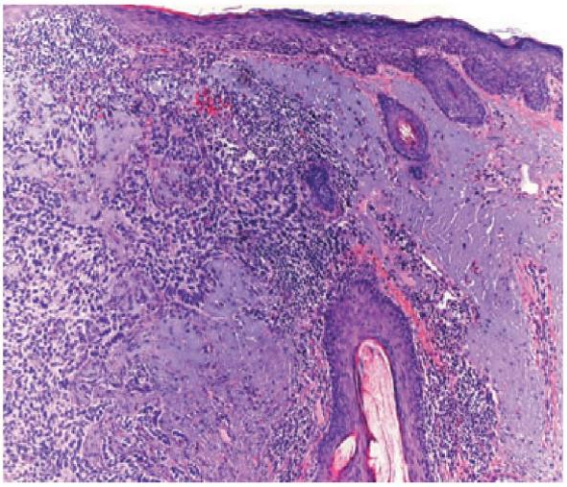

Figure 1 Basal cell carcinoma with overlying dermis with mild elastosis.

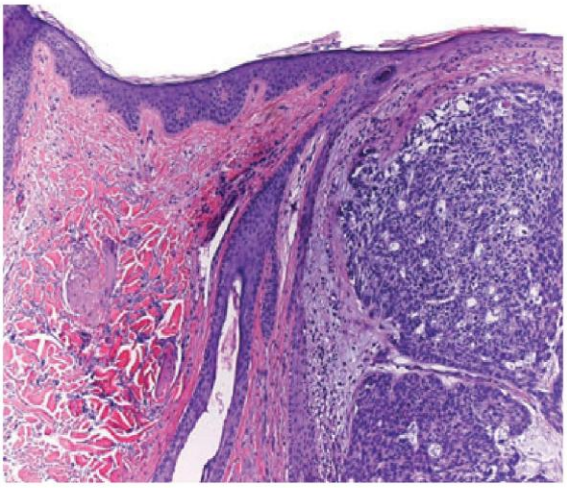

Figure 2 Basal cell carcinoma with overlying dermis with heavy elastosis.

<0.05 for significance and all tests were two-sides. To assess the relative risk a binary logistic regression test was performed for those variables with significance.

Results

Table 2 shows the distribution of cutaneous elastosis by gender, age, phototype and average exposure to UV-light. Of 136 participants, 77 (56%) participants showed abscence or light elastosis in the specimens, 37 (27%) mild elastosis and 22 (17%) heavy elastosis. The grade of elastosis was independent of sex ($P = 0.64$). While it is well-established that grade of elastosis is heavier in lower phototypes of skin, we found no significant difference amongst the cutaneous phototypes. Nevertheless, statistical

Table 2 Distribution of cutaneous elastosis by gender, age, phototype and average UV-exposure

	Abscence or light elastosis (%)	Mild elastosis (%)	Heavy elastosis (%)	Total (%)	*P*-value
Sex					
Female	22 (29)	8 (22)	7 (32)	37 (27)	0.64
Male	55 (71)	29 (78)	15 (68)	99 (73)	
Total	77 (100)	37 (100)	22 (100)	136 (100)	
Age	70.82 (±11.60)	73.11 (±11.29)	76.86 (±8.16)		
Phototype					
I	9 (12)	6 (16)	7 (32)	22 (16)	0.06
II	41 (53)	16 (44)	13 (59)	70 (52)	
III	20 (26)	8 (21)	1 (5)	29 (21)	
IV	7 (9)	7 (19)	1 (5)	15 (11)	
Total	77 (100)	37 (100)	22 (100)	136 (100)	
Average exposure to UV-light (h/week)	7.5	15.3	20.6		0.05

significance was almost reached ($P = 0.06$). We found statistical differences ($P = 0.05$) in grade of elastosis when considering the average exposure to UV-light. Data regarding food intake of participants are shown in Table 3. No differences in grade of elastosis was observed between patients taking fat and oils ($P = 0.739$), vegetables ($P = 0.387$), red meat ($P = 0.204$) and coffee ($P = 0.441$). Consumption of fruit ($P = 0.0001$; RR: 0.231; 95% CI: 0.096–0.557) and tea ($P = 0.001$; RR: 0.34; CI 95%: 0.139–0.831) were correlated with less grade of cutaneous elastosis. Fruit consumption was associated with 23% less risk of mild and heavy elastosis, while tea with 34% less risk. We found significant differences in skin elastosis between non-smoker participants and smoker and former participants ($P = 0.016$; RR: 0.253; 95% CI: 0.109–0.584). Non-smokers have 25% less risk of higher grades of elastosis.

Discussion

Skin ageing is determined by several causes including ageing obviously, but also by environmental factors, such as smoking, pollution, psychological stress, menopause-induced oestrogen deficiency, but exposure to sunlight is the most important risk factor particularly in fair-skinned individuals. Solar elastosis is the most prominent histological feature of photoageing change and is visible on the face as a yellowish skin criss-crossed by wrinkles. On limbs and neck, the skin shows atrophic and dyschromic changes. Excessive exposure to the sun is also responsible for most skin cancers. These cancers occur mainly on exposed parts, with BCC as the most prevalent type.

In this study, we investigated the possible association between diet intake and the grade of elastosis, and therefore skin ageing.

According to our results, a high dietary intake of fats was very common amongst participants of our samples. However, fat intake had no effect in grade of cutaneous elastosis independent of gender, age and phototype. To our knowledge this is the first work studying this possible association. In a well-designed study, Cosgrove et al[3] found that a high intake of fats had a negative effect in the wrinkled appearance, senile dryness and skin atrophy in 4025 middle-aged women. Although a large sample was studied, those studied outcomes might be difficult to be measured objectively and men were not included in the study.

Animal experiments have consistently showed that high fat intake may increase the sensitivity of the skin towards ageing.[4] In addition, lutein and zeaxanthin (carotenoids contained in eggs) have been shown to protect the skin of mice against photoageing by decreasing the inflammation.[5,6] In humans, results are inconsistent, showing that the issue of fat intake and skin ageing is apparently more complex and may involve several other factors such as family history and genetics, action of other nutrients such as vitamins, minerals, antioxidants and the composition of dietary fats. Nevertheless, our findings have to be interpreted with caution and more researches are needed to clarify this association, particularly regarding composition of dietary fats.

Intrinsic factors regarding skin ageing and solar elastosis are correlated with different markers of oxidative stress including the accumulation of lipid peroxidation and glycation products.[7,8] Antioxidants provide protection against this oxidative stress, especially in stratum corneum lipids. These antioxidants include superoxide dismutase, catalase, alpha-tocopherol, ascorbic acid, ubiquinone (Coenzyme Q10) and glutathione. Many of them are inhibited by UV and visible light.[9] Alpha-tocopherol (vitamin E) and ascorbic acid (vitamin C) are antioxidants in the superficial epidermal layers, participating in collagen synthesis, the regeneration process and wound repair.[10] Air pollutants such as nitrogen oxides and volatile organic compounds created from fossil fuel combustion reduces these antioxidants of the skin in the superficial epidermal layers leading to an accelerated skin ageing.[11] Our results suggest that a higher dietary intake of vitamin C and E-rich fruit was associated with lower grades of skin elastosis. However, it is possible that the effect of fruit may not be explained by their

Table 3 Distribution of the study population by food and tobacco consumption considering the grade of cutaneous elastosis

	Abscence or light elastosis (%)	Mild elastosis (%)	Heavy elastosis (%)	*P-value
Fat and oils				
Daily	15 (20)	7 (19)	3 (14)	0.739
Weekly	35 (45)	21 (57)	12 (55)	
Monthly	27 (35)	9 (24)	7 (31)	
Red meat				
Daily	2 (3)	0 (0)	0 (0)	0.204
Weekly	19 (25)	14 (37)	3 (14)	
Monthly	56 (72)	23 (62)	19 (86)	
Vegetables				
Daily	9 (12)	6 (16)	4 (18)	0.387
Weekly	24 (31)	16 (43)	5 (23)	
Monthly	44 (57)	15 (41)	13 (59)	
Vitamin E or C-rich fruits				
Daily	25 (33)	19 (51)	11 (50)	0.0001
Weekly	16 (21)	16 (43)	3 (14)	†RR: 0.231
Monthly	36 (46)	2 (6)	8 (36)	(95% CI: 0.096–0.557)
Tea				
Daily	29 (38)	2 (5)	7 (32)	0.001
Weekly	14 (18)	16 (43)	3 (14)	‡RR: 0.34
Monthly	34 (44)	19 (52)	12 (54)	(95% CI: 0.139–0.831)
Coffee				
Daily	12 (16)	7 (19)	5 (23)	0.441
Weekly	24 (31)	8 (22)	9 (41)	
Monthly	41 (53)	22 (59)	8 (36)	
Smoking				
Yes	22 (29)	17 (46)	12 (55)	0.016
Former	16 (21)	11 (30)	6 (27)	§RR: 0.253
No	39 (50)	9 (24)	4 (18)	(95% CI: 0.109–0.584)

*Obtained with Pearson's chi-squared test. *P*-value <0.05 for significance, and all tests were two-sides.

†,‡Relative risk of daily consumption vs. montly consumption (Category reference: Montly consumption). The relative risk was assessed by performing a binary logistic regression test (abscence/ light elastosis vs mild/heavy elastosis).

§Relative risk of smoker vs. non-smoker (Category reference: Smoker). The relative risk was assessed by performing a binary logistic regression test (abscence/ light elastosis vs. mild/heavy elastosis).

provision of vitamin C and E and other candidate components, or synergies which fruits provide are more likely to be relevant such as phenolics and flavonoids. In this way Liu *et al.*[12] has suggested that the antioxidant activity of fruit may not come from the amount of vitamins, but from the synergistic effect of these phytochemicals. Previous works regarding vitamin C supplements and skin ageing are inconsistent: Findings from a cross-sectional study suggested that low intakes of vitamin C were associated with wrinkled appearance.[3] Furthermore, in other studies vitamin C decreased the presence of wrinkles and senile dryness by its actions as antioxidants.[10] Different studies about vitamin C as topical application or oral supplementation trials showed similar results.[13,14] In the other hand, Martalena *et al.*[15] found that vitamin C supplements may have a harmfull effect on skin.

High intake of red meat has been associated with cardiovascular diseases and other disorders involving chronic inflammation and oxidative stress.[16–18] With respect to the relation of red meat with cutaneuous inflammation and ageing, the evidence remains unclear. Martalena *et al.*[15] found that high intake of processed red meat was associated with higher grades of skin wrinkling. Our results are inconsistent and show that red meat (beef, pork and lamb) are not correlated with the grade of elastosis. There is insufficient evidence to draw solid conclusions of red meat and skin ageing, and more research is needed.

Vegetables provide several of the antioxidants referred above, particularly carotenoides and Coenzyme Q10 (CoQ10). CoQ10, also known as ubiquinone, is a naturally occurring antioxidant found in spinach, parsley and broccoli.[19] The cellular levels of CoQ10 decreases with age.[20] In addition, CoQ10 is the first skin antioxidant agent which is destroyed by UV light in epidermis and dermis.[19] In our study, no association of vegetables intakes and elastosis was found. Nevertheless, other work suggests onions, garlic and spinach have a preventive effect on skin wrinkling.[15] A potential explanation of the lack of effects of vegetables in our

study is the minor reported consumption of them in our sample, leading to a type II error (false negative result).

Green and black tea demonstrate anti-inflammatory activity even when administered after UV exposure in animal models.[21,22] Both types of tea contain polyphenols, antioxidants that scavenge reactive oxygen and nitrogen species. Green tea contains a lower proportion of caffeine than black tea and a higher proportion of polyphenols, of which epigallocatechin-3-gallate may have the greatest antioxidant activity.[23] Given this knowledge about tea consumption, there appears to be plausible grounds for considering that tea may influence in skin ageing. Although tea consumption is relatively low in Spain and so on in our sample, we found that those subjects who take it showed a protector effect against skin ageing. This may be explained by the presence of polyphenols in tea leaf, which exert a much stronger oxygen free radical scavenging effect than vitamin C and E,[24,25] giving the tea consumption one of the highest preventive effect in skin ageing from dietary, even higher than fruit and vegetables. Other study in mice have found the similar results: The use of tea pigment reduced the skin photoageing.[26]

Recent studies have found that coffee consumption reduces the effect of UVB on the skin preventing non-melanoma skin cancers by inducing the apoptosis in photodamaged keratinocites[27] and inhibing the synthesis of PGE.[28] Whether these effects in the keratinocites have an impact on the skin ageing is unclear. No works have investigated the possible correlation of coffee consumption and human skin ageing in the current literature. UV-induced infiltration of neutrophils into the skin is relevant to the process of photoageing.[29] In this way, Mitani *et al.*[30] found that topical application of plant extracts with xanthine derivates prevented UV-induced wrinkling in mice by suppressing that infiltration of neutrophils. Coffee is well-known to contain xanthines. Nevertheless, our study shows no significant differences in cutaneous elastosis between participants who had coffee and those who did not. One possible explanation is that the oral consumption of coffee does not reach enough concentrations of xanthines in the skin to suppress the neutrophil cells. More investigations in this way are needed.

It is important to highlight that the future researches investigating the association of coffee and skin ageing should include one confounding factor which is strongly associated with coffee consumption and may lead to misinterpret the results: Smoking.

Smoking is a well-established environmental factor contributing to premature skin ageing. 'Smoker's face' or 'cigarette skin' is characteristic and implies increased facial wrinkling and an ashen and grey skin appearance.[31,32] A premature old appearance with yellow and irregularly thickened skin is a symptom of long-term smokers. Smoking was collected amongst participants of our study as being a possible cofounding factor. We found smoking is an independent factor of skin elastosis. Our results support the contributing role of smoking in skin ageing with smokers showing heavier grades of elastosis than non-smokers.

Major strengths of this study are, first, data regarding food intake were obtained by a physician-conducted interview and second, the analysis of skin ageing was performed by obtaining skin specimen and assessing the histological dermal elastosis. We assessed the presence of elastosis depending on depth in the dermis instead of thick and fine elastic fibres. We think this assessment is more objective and reprodutible and avoid possible bias induced by phototype and history of burns. Main limitations of our study are the small sample and the possibility of false-negative findings for some food, such as vegetables, as this study was carried out in a population in which low or no consumption of some food group was relatively common.

Our findings add more evidence to the hypothesis that, what we eat affects our skin ageing appearance; eating healthy food such as fruit, dark green leafy vegetables and black and green tea prevents cutaneous elastosis and improves skin ageing appearance, and this may motivate people for healthy life style.

Conclusion

Our study provides evidence that the presence of dermal elastosis and cutaneous ageing may be influenced by the type of food intake. Vitamin E and C-rich fruit and tea are positively associated with less elastosis.

An intervention study is warranted to investigate whether the skin ageing could be prevented in part with higher intakes of Vitamin E and C-rich fruit, tea and possible green-leaf vegetables.

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4.3. ***Husein-Elahmed H****, Aneiros-Fernandez J, Gutierrez-Salmeron MT, Aneiros-Cachaza J, Naranjo-Sintes R.* ***Basal cell carcinoma: a comparative study between outdoor versus indoors workers.***

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BASAL CELL CARCINOMA: A COMPARATIVE STUDY BETWEEN OUTDOOR VERSUS INDOORS WORKERS

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ABSTRACT:

Background: Basal cell carcinoma (BCC) is the most prevalent malignancy in humans and it remains a significant health problems. UV-exposure subjects are at highest risk to develop this cancer.

Aim: To compare the features of BCC in occupational UV-exposure patients and non-occupational UV-light exposure patients.

Method: The study was conducted in our referral hospital. The population cohorts were patients with diagnosis of primary BCC. Data were analyzed using SPSS software.

Results: 308 subjects comprised 178 (58%) outdoor workers (OW) and 130 (42%). indoor workers (IW). In IW, the history of sunburns during childhood was significantly higher than in OW. When considering the adult period, the OW group had a significant higher rate of sunburns. The majority of BCC arised in sun-exposed areas of the head and neck in both cohorts, and only 8 (4.5%) in OW and 19 (14.6%) in IW were located in trunk or extremities. The nodular was the most common subtype in both cohorts, followed by the superficial.

Conclusion: According to the results of our study, OW are more likely to develop nodular BCC, with no increased risk for superficial BCC. The age of onset in OW is older than IW. Some areas such as the trunk are more commonly involved in IW. Truncal BCC may have etiological factors different than UV-exposure, such as a genetic predisposition

KEY WORDS: Basal cell carcinoma; occupational exposure; histology; site

WHAT IS ALREADY KNOWN

- BCC is the most common cancer in Caucasians with rapidly increasing incidence rates and huge cost for society
- Despite lots of epidemiologic studies in BCC, and the known importance of UV exposure in its carcinogenesis, there are no clear conclusions regarding the role of chronic and acute sun exposure related to BCC subtypes
- It is reasonable to assume that outdoors workers with a history of UV-exposure works may develop BCC with different features than those observed in indoors workers.

WHAT THIS STUDY ADDS

- Outdoors workers are more likely to develop nodular BCC, with no increased risk for superficial BCC.
- The age of onset in OW is older than IW.
- Some areas such as the trunk are more commonly involved in IW.
- Truncal BCC may have etiological factors different than UV-exposure, such as a genetic predisposition
- This study may be useful to inform occupational safety representatives, stimulate the implementation of prevention strategies and encourage further research in this important field.

INTRODUCTION

Basal cell carcinoma is the most prevalent malignancy in the Caucasian humans and its incidence is rising rapidly. Despite the low mortality, this condition cause severe

morbidity and it remains as a significant healthy problem with huge cost for healthcare systems. Those who have red/blonde hair, light eye colour and skin type 1 & 2 show higher incidence. Besides, the likely of developing this skin cancer increases parallely with the age, and men are more frequently affected than women[1,2]. Although several factors have been implicated in the etiology of this condition such as ionizing radiation, trauma, chemical carcinogenesis, immunosupression, predisposing syndromes and host factors[3-5], UV radiation is considered to be the major risk factor with most BCC presenting in sun-exposure body areas such as face or neck. Prolongate suberythrodermal UV doses can lead to pyrimidine dimer formation in dermal and epidermal tissues and cause DNA mutation with a potential carcinogenic effects. Considering the occupational environment, a relevant percentage of workers are exposed to varying levels of UV-radiation related to outdoors work settings and it may be plausible to think that subjects with a history of UV-exposure works may develop BCC with different features than those observed in indoors workers. However, there is a debate about the relevance of this occupational UV-exposure for the development and growth of this cancer in outdoors occupations[6,7].

The aim of this study is to compare the clinical and histological features of BCC in outdoor versus indoor workers in a referral hospital in southern Spain.

METHOD

We designed a study which was conducted between May 1st 2010, and May 1st 2011. Using the electronic pathology records of our hospital, we identified records of specimens containing the word "skin" in the specimen box and "basal cell carcinoma" in the diagnosis box. We excluded those subjects with concomitant or previous history of squamous cutaneous carcinoma. Reexcisions for incompletely excised lesions,

punch, shave or incisional biopsies as well as palliative excisions were also excluded. The specimens were reviewed and classified according to the differentiation pattern of BCC (superficial, nodular, micronodular, morpheiform). BCC with mixed features were classified according to the most predominant subtype.

We recorded information on participants' work history, i.e. any job held during their lifetime with a minimum duration of 6 months. They were asked about the type of work, the starting and finishing dates. Furthermore, in participants on outdoor works we evaluated hours per day and months, whether subjects worked partly unclothed, whether they wore a head covering, and lastly whether they wore socks and stocking during work done in summer. Each individual was assigned on the basis of stated occupation to outdoor and indoor workers. The first group included those where all or a large part of the work (≥ 6 hour per day for ≥ 6 months) was performed outdoors daylight without any covering. Most subjects of this group included farmers and fishermen. Indoor workers were those who spent most of the day in indoor environment such as shop, factory, office, hospital, library, bank, school and laboratory. Most subjects of this group included mechanics and shop assistants. A small group of occupations could not be classified and was excluded from the study.

We included variables that could be considered independent risk indicators, namely: age, sex, colour of eyes, natural hair colour, phototype, and history of sunburns. All the data were collected with a personal interview performed by a single dermatologist during the follow-up of the patients.

The study was approved by the ethics committee of our hospital and written consent was obtained from every recruited subject, in order to both analyzing the data acquired and accessing the relevant diagnostic documents (e.g.pathology reports).

Chi-square test and Student T test were performed to compare the two cohorts using the SPSS version 15 software. We used a P value < 0.05 for significance, and all tests were two-sides.

RESULTS

The total of 308 subjects comprised 178 (58%) outdoor workers (OW) and 130 (42%). indoor workers (IW). Table 1 summarizes the characteristics of each cohort with the statistical outcomes.

The mean age of OW was significantly older than IW (75.17±10.74 vs 69.73±9.98, P<0.001). The sex distribution in the two cohorts were significantly different (p<0.001): OW group featured a slightly higher proportion of men than women (92 vs 86), whereas in the IW group women were clearly more prevalent than men (85 vs 45).

Skin type II was the most frequent in the two cohorts (82 subjects among OW and 75 among IW), but no statistical differences regarding the proportions of each skin type were found (P>0.05).

No differences regarding the colour of eyes (Blue/Gray vs Brown/Black) between the two cohorts were found (P>.05). In the same way, the two cohorts did not show differences in the hair colour (Red /Blond vs Brown/Black)

The history of sunburns was significantly different between the two groups: In childhood period the incidence of 2º grade sunburns was higher in IW, while in adult period, the OW group showed more incidence of 2º grade sunburns (≥2 episodes).

In the OW, most of subjects had a positive family history of BBC (91 cases), while in the majority of IW participants, the family history of BCC was negative (90 cases). This difference was statistically significant (P=.03).

Table 2 show the distribution of anatomic sites affected with BCC in OW and IW. The nose was the most frequently affected area in OW [35 cases (19%)] while in IW the cheek was the most common location [23 (18%)]. Comparisons of frequencies for each anatomical locations revealed that only the rate for truncal BCC was significantly different: IW had more incidence of truncal BCC than OW. Although the differences between groups were not statistically significant, there were trends towards higher frequencies for BCC of the forehead in OW.

In both groups, the most prevalent histological subtype was the nodular (133 cases in OW and 90 cases in IW) followed by the superficial (17 cases in OW and 29 cases in IW). The rate of nodular subtype of BCC was statistically different between the 2 cohorts, with the OW showing higher incidence compared to IW. Regarding the superficial subtype, the opposite was observed: IW had significant increased risk compared to OW. There were trends towards higher frequencies for morpheic pattern in OW than IW, but the differences were not statistically significant.

DISCUSSION

Skin cancer due to occupation is more common than is generally recognized[6,7], but the relevance of occupational UV-exposure in outdoor occupations as a risk factor of BCC is still an ongoing debate. In this study, we analyzed the different clinical and histological outcomes of BCC in two cohorts: indoor workers versus outdoor workers.

We found that the mean age of IW was lower than OW, which means that the subjects working indoors developed BCC at younger age than those subjects working outdoors. This is consistent with recent studies which show that occupational cumulative sun exposure has been associated with the developing of BCC in older age group, while the acute intermittent recreational sun exposure particularly in childhood and adolescence is linked with BCC in patients with younger age[6].

The role of gender as risk factor for BCC remains unclear. Some reports show that BCC is more frequent in men than in women[8-10]. In our study, the sex distribution was statistically significant: Proportion of women was higher in IW, while the opposite was observed in OW. These differences may be explained by cultural and lifestyle patterns: Women in IW tend to have office-jobs in urban settings and wear modern fashion clothes at work and at recreations. In rural settings, women have agricultural works and tend to wear more traditional clothes which offer sun protection.

The positive family history has been suggested to be a constitutional risk factor in the development of BCC [11-13]. In our study, we observed that positive family history was more common in OW, while in IW subjects had a negative family history. These differences were significant, and the OW had a 2.6-fold increased chance to have a positive family history of BCC compared to IW. The cultural and lifestyle patterns may partially explain this finding: In rural setting, workers tend to have the same job of parents as a traditional way of life and their skins have the same pattern of UV exposure than their parents'. Whereas in urban settings this is no usual and subjects may have other jobs compared to parents' and therefore, the pattern of UV exposure in the skin may be different. However, a genetic predisposition of developing BCC cannot be

excluded. In addition, we have to consider that the information on family history of BCC was self-reported and not validated, which may bias the results.

One interesting finding of our study is the differences regarding the history of sunburns between the two cohorts: In IW, the history of sunburns during childhood was significantly higher than in OW. When considering the adult period, the OW group had a significant rate of sunburns. The relation between UV radiation and BCC is complex and it remains highly controversial regarding the patterns of sun exposure and their occurrence in different periods of lifetime[14]. The overall history of severe sunburns seems to be more important than simply the tendency of burn or tan[15,16] and besides, the history of sunburn in childhood and teenager periods is associated with early onset of BCC[6]. This is consistent with our findings: The age of onset of the tumor was lower in the group which had the significant history of sunburns in childhood: the IW. BCC developed at older ages in the OW who had more incidence of sunburns in adult period. However, we have to consider that retrospective nature of the data collection on childhood and adult burns has a potential threat to bias as the information is based on the memory of the patients. In addition, other non-UV risk factors for BCC, such as ionizing radiation exposure, were not analyzed

The majority of BCC arised in sun-exposed areas of the head and neck in both cohorts, and only 35 (19%) in OW and 28 (22%) in IW were located in trunk or extremities. One interesting outcomes of our study is that in the OW group, the rate of trunk BCC was significantly lower than in IW. The BCC on trunk have been suggested to be linked to a genetic susceptibility[17,18] and a reduced DNA repair capacity[19] rather than sun exposure. Our finding supports that hypothesis and suggests that the occupational sun exposure has no direct relation with truncal BCC. This outcome is consistent with the

result of a case-control study conducted by Pelucchi et al[20] in 528 cases of BCC and 512 controls. These authors concluded that the occupational sun exposure was not associated with truncal BCC, but with head/neck BCC, indicating that there may differential etiological mechanisms between truncal and head/neck BCC. In the largest series of BCC published in the literature with 13457 specimens, the authors state that the tumours of the trunk may represent a particular variant of BCC, in which the theory of chronic versus intermittent sun exposure cannot be simply extrapolated as it is for the rest of BCC sites. Other factors such as genetic predisposition could be involved in the development of truncal BCC[21]. In the same way, Ramos et al[22] suggest that non-melanoma skin cancer of sun-protected anatomic sites may occur in individuals with impairment in DNA repair process.

The classification of the BCC in histological subtype helps to predict the tumor behavior[23] which has a prognosis value. In our study, the nodular was the most common subtype in both cohorts, followed by the superficial. The nodular subtype was increased in OW compared to IW, while the superficial subtype was most common in IW. Bastiaens et al[24] and McCormack et al[25] have suggested that the most frequent subtypes of BCC (nodular and superficial) may represent different tumours with distinct causal factors. According to these authors, nodular subtypes are associated with accumulative sun exposure, while superficial subtypes are more intense and intermittent sun exposure. The results of the current study support this hypothesis, in order that the cohort of OW with accumulative sun exposure showed more incidence of nodular BCC than IW, while the subjects with intense and intermittent sun exposure (the IW) showed more risk of superficial BCC.

The importance of occupational UV-exposure in outdoor occupations as a risk factor of BCC is still an ongoing discussion. Our data show that occupational sun exposure may be considered an etiological factor for BCC according to histological subtypes and anatomic site.

Our study has the following limitations: First, the retrospective nature of the data collection on occupation and childhood burns poses a potential threat to bias (memory of the patient). Second, the information on family history of BCC was self-reported and not validated. Third, other non-UV risk factors for BCC, such as ionizing radiation exposure, were not considered. Fourth, the limited sample size may have lead to obtain negative results.

Among the strengths of the study are the complete response rate and the similar catchment area of OW and IW: the common hospital setting of the two cohorts, and hence the similar attention to medical history, may improve the comparability of information. All cases were obtained from the practice of a single referral dermatologist and are felt to be representative of our working area. The use of a single dermatologist reduces provider-associated variability.

1. According to our results, OW are more likely to develop nodular BCC, with no increased risk for superficial BCC. The age of onset in OW is older than IW.

2. Some areas such as the trunk are more commonly involved in IW. Truncal BCC may have etiological factors different than UV-exposure, such as a genetic predisposition

3. This study is useful to occupational safety representatives and physicians in order to stimulate the implementation of prevention strategies for this easily preventable tumor, and encourage further research in this important field.

The authors have no conflict of interest to declare.

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Table 1. Distribution of the variables in each cohort with the statistical outcomes.

		OUTDOOR WORKERS (n=178)	**INDOOR WORKERS (n=130)**	***P Value* (CI95%)***
Age		75.17 (±10.74)	69.73 (±9.98)	<0.001 **Mean Difference: 5.44 (3.10-7.78)
SEX	***Female***	86	85	.002 OR: .56 (.35-.90)
	Male	92	45	
COLOUR OF EYES	***Blue & Gray***	87	62	>.05
	Brown & Black	91	68	

HAIR COLOUR	***Red & Blond***	82	57	>.05
	Brown & Black	96	73	
PHOTOTYPE[a]	***II***	82	75	>.05
	III	67	33	>.05
	IV	29	22	>.05
CHILDHOOD[b]	***0***	92	62	.45
2º GRADE SUNBURNS	***≤ 2***	69	42	.05
	> 2	18	26	<.00001 (OR: 2.13; CI: 1.64-2.79)
2º GRADE SUNBURNS	***0***	95	53	.13
	≤ 2	67	42	.067

	> 2	19	35	.002 (OR:1.39; CI:1.21-1.92)
FAMILY HISTORY OF BCC[c]	***No***	77	90	.03 (OR:2.66; CI: 1.9-3.3)
	Yes	91	40	
HISTOLOGICAL SUBTYPE	***Nodular***	133	90	.024 (OR:1.92; CI:1.4-2.72)
	Superficial	17	29	.05 (OR:1.42; CI:1.29-1.72)
	Morpheic	16	6	.07
	Micronodular	15	9	.23

[a] Reaction of skin after exposure to 1 hour of midday sun for the first time in the summer with: 1 indication painful or blistering sunburn with no tan; 2, painful sunburn followed by a light tan; 3, mild suburn followed by a moderate tan; and 4, no sunburn followed by a deep tan.

[b] Under age of 18.

[c] Including natural parents, brothers and sisters only.

* For those variables with significant outcomes, the OR is calculated with a CI95%.

**Student's T test, with CI95%

Table 2. Distribution of anatomic sites affected by BCC in the two cohorts.

	OUTDOOR WORKERS (n=178)	**INDOOR WORKERS (n=130)**	***P Value* (IC95%)**
Scalp	7 (4%)	18 (14%)	.08
Cheek	11 (6%)	23 (18%)	.26
Inner Canthus	14 (8%)	10 (8%)	.71
Outer Canthus	11 (6%)	6 (5%)	.21
Forehead	10 (5%)	1 (1%)	.06
Nose	35 (21%)	18 (13%)	.47
Periocular Region	18 (10%)	8 (6%)	.88
Auricular Region	14 (8%)	9 (7%)	.91
Temple	11 (6%)	3 (2%)	.18
Chin	6 (3%)	1 (1%)	.81
Neck	6 (3%)	5 (4%)	.23
Upper extremity	18 (10%)	9 (7%)	.58
Lower extremity	9 (5%)	0 (0%)	.83

Trunk	8 (4%)	19 (14%)	0.0035

4.4. ***Husein-Elahmed H****, Aneiros-Fernandez J, Gutierrez-Salmeron MT, Aneiros-Cachaza J, Naranjo-Sintes R.* ***Alcohol intake and risk of aggressive histological basal cell carcinoma: a case-control study****. Eur J of Dermatol. 2012 Apr 19*

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Alcohol intake and risk of aggressive histological basal cell carcinoma : a case-control study

Background: Aggressive basal cell carcinomas (BCC) are not rare. These subtypes of skin cancer are characterized by an infiltrative behavior and rapid progression. Often, management may be difficult. Recent evidence suggests that minimal UV exposure in combination with other behavioral and/or environmental factors may lead to higher incidence of BCC and, therefore, more risk of aggressive subtypes of this malignancy. Alcohol is a very commonly consumed beverage in Western societies, especially in association with outdoors activities. *Objective*: To investigate a possible relationship between alcohol intake and aggressive histological variants of BCC. *Materials and Method*: We designed a prospective study. Patients who underwent surgery for BCC in our hospital were interviewed to collect data regarding alcohol intake. The specimens were reviewed by a pathologist and classified into aggressive and non-aggressive subtypes. Statistical analysis was performed using SPSS software. *Results*: 136 patients were included. Of participants with aggressive BCCs, 10 (26.3%) were abstainers, 4 (10.4%) had light consumption, 18 (47.5%) moderate consumption and 6 (15.8%) heavy consumption, while among participants with non-aggressive BCCs, 57 (58.2%) were abstainers, 29 (29.5%) had light consumption, 10 (10.2%) moderate consumption and 2 (2.1%) heavy consumption. In the multivariate analysis we found a positive significant association between alcohol consumption and the presence of aggressive BBCs. *Conclusions:* According to our results, alcohol intake may be linked with a higher incidence of aggressive subtypes of BCC

Key words: Aggressive basal cell carcinoma, alcohol intake

Basal cell carcinoma (BCC) is the most common malignancy in humans and the incidence is increasing: in the USA population an increase of 10% a year has been found, leading to a 30% lifetime risk of developing a BCC [1]. The most important causes are sun-exposure and the sun sensitivity characteristics of the individual, such as eye and hair color, skin pigmentation and propensity to tan or burn.

The cure rate of BCC is high, with low mortality and morbidity. However, this tumor carries a considerable cost for health care services. Aggressive histology is not rare in BCC. Large studies from referral centers report the incidence of aggressive histology BCC ranging from 2.5 to 44% [2-6]. These aggressive BCC are characterized by subclinical extension, invasive behavior, local recurrence and challenging treatment [7].Although UV radiation is the main risk factor of BCC, recent evidence suggests that minimal UV exposure in combination with other behavioral and/or environmental factors may lead to a higher incidence of BCC [8-11] and, therefore, more risk of aggressive subtypes of this malignancy. Regarding alcohol consumption, several studies have found that alcohol drinkers have a higher prevalence of sunburns [12] and incidence of BCC [8, 13]. In addition, two epidemiological studies with large samples reported a significant positive association between risk of BCC and daily alcohol intake [14, 15]. However, to the best of our knowledge, there are no studies investigating a link between alcohol intake and the development of an aggressive form of BCC in the current literature. In view of these data, we conducted a study to examine the relationship between aggressive BCC and alcohol consumption.

Materials and method

Study design and selection of subjects

The study was conducted between January 1st 2010, and May 1st 2010. Using the electronic pathology records of our hospital, we identified records of specimens containing the word "skin" in the specimen box and "basal cell carcinoma" in the diagnosis box. We excluded those subjects with relapsed BCC and a concomitant or previous history of squamous cutaneous carcinoma. The specimens were reviewed by a trained pathologist from our hospital and classified into non-aggressive BCC and aggressive BCC.

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Two cohorts were formed: One including patients with pathologically confirmed non-aggressive BCC: superficial and nodular, and another with aggressive BCC: micronodular, morpheiform and infiltrative (angular nests infiltrating throughout the dermis with minimal to absent desmoplastic stromal host response).

Assessment of alcohol and co-variables

Using a questionnaire administered by a trained dermatologist, detailed information regarding age, sex, skin phototype, eye and hair color, history of sunburn before and after the age of 20 years, cigarette smoking and coffee consumption was collected. Alcohol intake was explored by asking subjects how many alcoholic beverages (beer, wine or liquor), on average, they consumed in a typical week. Thus, the questions did not differentiate between types of alcoholic beverage.

Total alcohol intake was divided into three categories: Light drinkers ($\leq$5 standard drinks per week), moderate drinkers (>5 and $\leq$10 standard drinks per week) and heavy (>10 standard drinks per week).

The answers provided were considered as a quantitative variable. To obtain the grams of intake of alcoholic beverage per week, we multiplied the reported consumption frequencies by the serving size for each alcoholic beverage specified in the Netherlands Nutrition Center: 10 g for beer, 9.6 g for wine, and 9.8 g for liquor [16].

To measure the subjects' lifetime alcohol exposure, we asked participants to provide information on their minimum, typical, and maximum quantity and frequency of consumption and the duration of each exposure. We operationally defined high cumulative (lifetime) consumption as at least two drinks/day for twenty-five or more years. Although no formal criteria are available to define a significant level of cumulative consumption in older age, we selected the above threshold based on its face validity.

All these data were obtained during an interview during the follow up of the patients. Subjects gave their informed consent before enrolling in the study and the study was approved by the ethics committee of our hospital. *Figure 1* shows the original survey questionnaire used to collect the information.

QUESTIONNAIRE*

1. What is your age?
2. What is your gender?
3. Phototype/Hair color/Eye color:
4. Have you ever suffered 2° grade sunburns (with blisters)?
5. If you answered yes to the previous question, how many episodes of 2° grade sunburns have you suffered?
6. Have you ever suffered 2° grade sunburns in childhood (before 20 years old)?
7. If you answered yes to the previous question, how many episodes of 2° grade sunburns have you suffered?
8. Have you ever smoked?
9. If you answered yes to the previous question, are you a current smoker?
10. Do you usually have coffee?
11. Do you usually drink alcohol (not counting small tastes or sips of alcohol)?
12. If you answer yes to the previous question, about how often did you USUALLY drink alcoholic beverages (beer, wine or liquor) during the last 12 months?
13. How many of alcoholic beverages (beer, wine or liquor), on average, do you USUALLY consume in a typical week during the last 12 months?
14. During the last 12 months, about how often did you drink FIVE or MORE drinks in a single day?†

14b. During the last 12 months, about how often did you drink FOUR or MORE drinks in a single day? (Women only)†

*Adapted from the National Epidemiologic Survey on Alcohol and Related Conditions of the National Institute on Alcohol Abuse and Alcoholism. United States.

† This questions are used to screen abuse consume and alcohol-related problems. None of the participants were detected to have any of them.

Figure 1. Original survey questionnaire used to collect the information.

Statistical analysis

We undertook two statistical analyses. First we performed a univariate test to analyze a possible association between the BCC histological aggressiveness and alcohol consumption. In a second step, a multivariate logistic regression analysis was performed, which included the alcohol consumption (No *vs* Light *vs* Moderate *vs* Heavy), the histological subtype of BCC (Aggressive *vs* Non-aggressive) and possible confounders. The size and the thickness of aggressive and non-aggressive BCC were compared using the Student-T test for independent samples.

Secondly, among alcohol-exposed subjects, we compared the amount of alcohol consumed (in grams per week) in patients with aggressive and non-aggressive histological subtypes of BCC, using the Student-T test for independent samples.

The normality of the two compared populations was tested by the Kolmogorov-Smirnov test. All statistical tests were two-sided with a level of significance of P $\leq$0.05. Analyses were conducted using SPSS version 15 software.

Results

A total of 136 patients with histologically confirmed BCC were enrolled in the study. 98 of the specimens (74.6%) were non-aggressive subtypes while 38 (25.4%) were aggressive subtypes. Within the overall sample (n=136), 65 (48%) subjects reported alcohol intake, while 71 (52%) were abstainers, without considering the histology of the tumors. Among participants with aggressive BCCs, 10 (26.3%) were abstainers, 4 (10.4%) had light consumption, 18 (47.5%) moderate consumption and 6 (15.8%) heavy consumption, while within participants with non-aggressive BCCs, 57 (58.2%) were abstainers, 29 (29.5%) had light consumption, 10 (10.2%) moderate consumption and 2 (2.1%) heavy consumption. A significant positive association was observed between alcohol consumption and the risk of aggressive BCC (P=0.028. OR: 1.32; CI95%: 1.14-1.53). This association remained unchanged in the multivariate analysis for two categories of alcohol consumption: moderate and heavy. The demographic characteristics of the study population with the P value obtained in the analysis are shown in *Table 1*. Although it was not the purpose of this study, we found that aggressive BCC were thicker than non-aggressive BCC (P<0.001), while no differences were found regarding the tumoral size (P=0.12). *Figure 2* shows the distribution of alcohol grams per week in the three patterns of consumption. Among

Table 1. Baseline characteristics of patients with aggressive and non-aggressive BCCs.

Covariates†	Non-aggressive BCCs (n=98)	Aggressive BCCs (n=38)	P value[a] OR; IC95%
Sex (Female/Male)	25/73	17/21	.051
Age (Mean)	73.7	66.9	.21
Size of tumor (mm)	11.34 (±5.32)	13.36 (±7.68)	.12*
Thickness of tumor (mm)	2.59 (±1.10)	4.00 (±2.46)	<.001*
Skin type[b]			
1	16	3	.3
2	56	14	.8
3	16	17	.19
4	10	4	.76
Hair color (Red/Blond vs Brown/Black)	38/60	13/25	.714
Eye color			
blue/gray	80	24	.25
brown	17	14	.12
black	1	1	.39
2nd grade sunburns[c]			
0	49	19	.77
≤ 2	33	15	.65
>2	16	4	.52
Childhood			
2nd grade sunburns[c]	43	15	.48
0	41	15	.26
≤ 2	14	8	.34
>2			
Smoking			
no	42	18	.34
current	27	11	.93
former[d]	29	9	.2
Coffee consumption (No *vs* Yes)	53 / 45	22 / 16	.42
Alcohol consumption[e]			
abstainer	57	10	.59
light	29	4	.09
moderate	10	18	.043 (1.29; CI95%: 1.1-1.51)
heavy	2	6	.039 (1.45; CI95%: 1.23-1.77)

BCCs, basal cell carcinomas

† *The variable high cumulative (lifetime) consumption was not included in the multivariate analysis, because only 1 patient was categorized as having high cumulative consumption.*

[a] *Adjusted for sex, eye color (blue/grey vs brown vs black), hair color (red/blond vs brown/black), skin type (1-4 as described in [b]), history of smoking (no vs current vs former), history of sunburns (0 vs ≤2 vs>2), history of sunburns in childhood (0 vs ≤2 vs>2) and Coffee consumption (No vs Yes). Ninety-five percent CI values are Wald estimates.*

[b] *Reaction of skin after exposure to 1 hour of midday sun for the first time in the summer with: 1 indication painful or blistering sunburn with no tan; 2, painful sunburn followed by a light tan; 3, mild suburn followed by a moderate tan; and 4, no sunburn followed by a deep tan.*

[c] *Under age of 18.*

[d] *≥ 12 months without smoking.*

[e] *Light drinkers (≤5 standard drinks per week), moderate drinker (>5 and ≤10 standard drinks per week) and heavy (>10 standard drinks per week)*

* *Compared using the Student-T test for independent samples.*

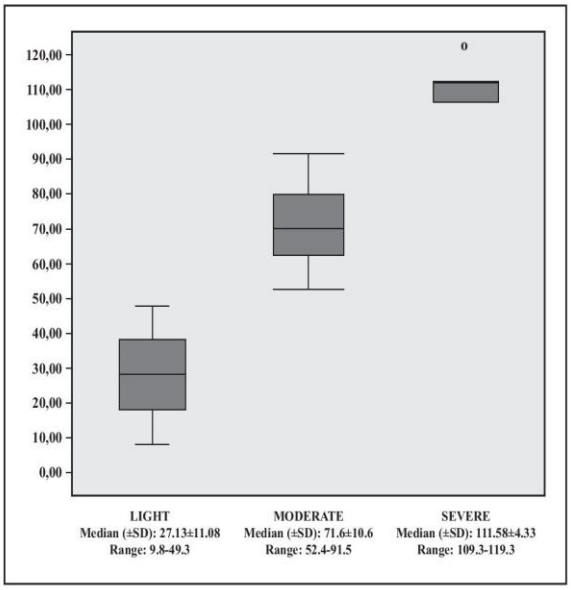

Figure 2. Graphic describing alcohol consumption for each class.

the 65 alcohol-exposed subjects, we found statistical differences in the amount of alcohol consumed (in grams per week) considering the histology of the lesions (Mean difference: 26.03±8.30; P=0.006; CI 95%: 43.50- 8.56.): Those patients with aggressive BCCs showed a higher amount of alcohol consumption compared to those with non-aggressive BCCs (*table 2).*

From the sample of 136 patients included in our study, only 14 (10.29%) showed positive surgical margins and none of them showed relapse.

Discussion

In this analysis, we observed a positive association between alcohol consumption and the risk of developing an aggressive form of BCC after adjustment for the main co-variables. Although different studies have found a positive association between risk of BCC and alcohol intake [8, 11-15], to our best knowledge there are no studies investigating the effects of alcohol on the histology of skin malignancies in the current literature.

Epidemiological evidence suggests that factors in the diet may modify skin cancer incidence and aggressiveness [17]. We found that there may be a potential influence of alcohol intake in the growth and the behavior of BCC. Alcohol is a very commonly consumed beverage in Western societies, so it is reasonable to expect that the potential effect of alcohol in BCC might occur in association with UV exposure. This concept of an interaction between nutrients and histology /cell mechanisms has been studied recently in other epithelial tumors. In an interesting study conducted in patients with colorectal cancer, those subjects with a high alcohol intake had more aggressive histologies in the biopsy specimens [18]. We found similar results in relation to BCC. Alcohol consumption is common during outdoor activities in western countries. Saladi *et al* found that alcohol intake in the presence of UV substantially enhances the cellular damage caused by UV, leading to skin malignancies [19]. Most of the alcohol (ethanol) entering the body is metabolized to acetaldehyde: a highly reactive product that acts as a photosensitizer, generating reactive oxygen species (ROS). These ROS potentiate the UV- promoting carcinogenetic effect and cell proliferation by enhancing the DNA damage and the signal-transduction cascade [19]. Therefore, alcohol and UV have a synergic effect in cell proliferation and migration and this may be a plausible explanation for our finding. UV exposure is the main risk factor for BCC and may be considered the trigger factor for tumor initiation and development [20], while alcohol intake might have an effect in the progression and aggressive behavior of the tumor.

Because of its implications in therapy and prognosis, it is important to consider the histological subtype of BCC. There are important differences in the surrounding tumor-associated connective tissue in aggressive BCC compared to non-aggressive BCC. These differences in the structure modify the border of the lesion and create highly irregular and spiculated outlines [21].

According to the histological stepwise theoretical model of BCC, aggressive subtypes derive from incipient low-aggressive forms (superficial-to-nodular-to-micronodular and superficial-to-nodular-to-infiltrative-to-morpheic BCC types). This concept suggests that BCC evolution reflects a dynamic histological continuum determined by the host-tumor interactions [22]. The stromal reaction, including the inflammation and immune response, constitutes the peritumoral microenvironment, which will determine the progression of an incipient BCC to an aggressive form. Thus, immunity plays a key role in blocking the tumor progression. We hypothesize that alcohol may exert a progression effect in basal cell carcinoma cells due to its effects in impairing cell-mediated and humoral immunity [23, 24]. Kaporis *et al.* [25] demonstrated a dynamic state in the immune microenvironment associated with BBC by microarray analysis. The presence of immature dendritic cells, Th2 cytokines (IL-4, IL-10) and Tregs (T cells that control the immune response, such as CD4, CD 25 and

Table 2. Comparison of alcohol grams consumed per week between subjects with aggressive and non-aggressive BBCs.

	Non-aggressive BCCs (n=45)	Aggressive BCCs (n=20)	P value[a] mean difference (CI 95%)
Grams of alcohol consumed (Mean± SD)	49.35 (±27.95)	75.38 (±25.50)	0.006 26.03±8.30 (8.56-43.50)

Abbreviation: BCCs, basal cell carcinomas; CI: Confidence Interval
[a] Obtained using the Student-T test for independent samples.

FoxP3 cells) would allow tumor invasion and aggressive behavior. In contrast, abundant CD8 T cells, expression of interferon-associated genes (IFI-27, IRF-1, IRF-7 and G1P2) and IL-12/IL-23 would lead to an antitumoral host response. Aggressive BCCs use Treg cells to successfully evade the host immune system. Alcohol intake has been found to inhibit the expression of interferon-associated genes [26-28], and increase levels of Th2 cytokines [24, 29, 30]. Furthermore, human studies have shown that both acute and prolonged alcohol intake inhibit dendritic cell functions in the dermis [29], including antigen presentation [30-32]. These data provide possible mechanisms for which alcohol intake would enhance evasion of the host immune system and progression of the tumoral cells, resulting in aggressive variants of BCC.
Interferon -α and -γ (IFN) have key roles in host cell innate immunity against tumoral cells. Regarding BCC cells, these two molecules have demonstrated several effects:

– initiate apoptosis in BCC cells through the CD-95 ligand-receptor interaction [33],
– reverse the observed low levels INF-γ receptors [34],
– anti-angiogenic activities [35],
– decrease vascularity surrounding BCCs [36].

Anasagasti *et al* [37], successfully treated 9 histologically aggressive variants of BCC with an intralesional formulation of IFN-α and -γ. This formulation promoted an antitumoral host response, achieving the block of the malignant progression and turning it to curation. Alcohol has been found to suppress the intracellular expression of IFN-α [26] and -γ [38]. This fact adds another possible explanation to our finding of aggressive histological subtypes of BCC in alcohol-exposed subjects.
Figure 3 summarizes the possible underlying mechanisms by which alcohol consumption influences the histology of BCC. All these alcohol-induced abnormalities collectively contribute to reduce the immune response and to enhance the progression of tumoral cells in the alcohol-exposed host. Therefore, we think that the proposed hypothesis may be considered to have a good rationale.

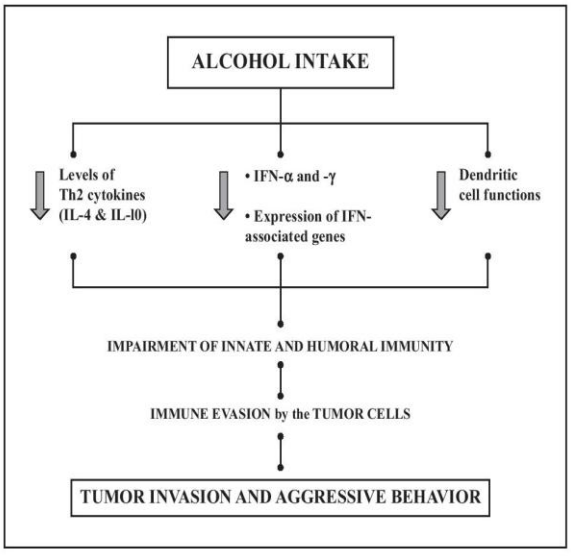

Figure 3. Possible mechanisms of alcohol in modulation of the peritumoral micro-environment.

The association we found is not a linear cause-effect correlation, but alcohol intake may be one contributing factor which, added to other unknown factors, increases the risk of developing an aggressive BCC. In general terms, the clinical course of diseases in patients with alcoholism has been noted to be more aggressive than in abstainers [39]. Thus, alcohol has been shown to have a direct enhancing effect in metastasis and the growth of breast cancer by stimulating expression of nuclear proteins [40]. Furthermore, alcohol increased melanoma metastasis in lymph nodes by impairing the trafficking of NK cells [41].
We think our study has strengths. First, it is the first study to establish a link between alcohol intake and the presence of more aggressive histological subtypes of BCC. Second, the consumption of alcohol was obtained by a direct interview instead of a questionnaire. This approach gives the opportunity for clarification or further explanation, assuring better data. Third, we obtained a statistically significant association in both the Student-T test and the multivariate analysis, despite limitations in the sample size. Fourth, most of the possible confounding factors between the histology of BCC and the alcohol intake were considered in the statistical analysis. The main limitations of our study are the impossibility of stating when the potential negative effect of alcohol starts, with what dose of consumption, and if that effect might be reversed when alcohol is discontinued. Furthermore, we were unable to differentiate between types of alcoholic beverage.
Alcohol consumption, including excessive consumption, is common in western societies and BBC is the most prevalent cancer in humans, with an important morbidity/mortality, particularly for the aggressive subtypes. Therefore, we think more research is warranted to confirm the association we found.

Conclusion

According to our findings, alcohol consumption is associated with aggressive forms of BCC. This may be due to modulation of the peritumoral micro-environment associated with alcohol consumption, which may be considered as a contributing factor to the progression and the malignant behavior of the tumoral cells. ■

Disclosure. *Conflict of interest The authors have no conflict of interest to declare. All the authors approved the final version of manuscript and submission. All authors have participated sufficiently to take public responsibility for appropriate portions of the work. No founding sources.*

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Effect of non-steroidal anti-inflammatory drugs on the histology of basal cell carcinomas

Background: Aggressive histology is not rare in BCC. Large studies from referral centers report incidences of aggressive histology BCC ranging from 2.5- 44%. These aggressive BCC are characterized by subclinical extension, invasive behavior, local recurrence and challenging treatment. ***Objectives:*** To examine the association between non-steroidal anti-inflammatory drug (NSAID) use and the different histological subtypes of basal cell carcinoma (BCC). ***Methods:*** The design was a nested case-control study. The two population-based cohorts were of patients with a primary BCC diagnosis during January and May 2010 (n=136) and NSAID use in the 15 years prior to baseline. All the lesions were excised and analyzed to determinate the histological subtype of BCC as aggressive or non-aggressive. Odds ratios (ORs) and 95% confidence intervals (CIs), using conditional logistic regression, were calculated with the SPSS software to estimate the association of aggressive histological subtypes of BCC and use of NSAID. We controlled the potential confounding factors. ***Results:*** The rate of non-aggressive BCC associated with exposure to NSAID was increased (OD: 0.34; 95% CI: 0.14-0.84) after adjusting for covariants. *Limitations*: our sample is small. We collected data regarding use of NSAID over a wide time ranges, so that we are unable to propose when the potential benefits of NSAID on the histology of BCC would happen. ***Conclusion:*** According to our data, NSAID exposure is associated with a decreased risk of aggressive BCC.

Key words: basal cell carcinoma, non-steroidal anti-inflammatory drugs

Non-steroidal anti-inflammatory drugs (NSAID) block the synthesis of pro-inflammatory prostaglandins by inhibiting the cyclooxygenase (COX). There is evidence suggesting that the enzyme COX-2 is involved in the development and growth of cutaneous and non-cutaneous cancers [1]. Liu *et al.* [2] first reported that COX-2 over-expression induces tumorigenesis by inserting the murine COX-2 gene into rat mammary gland epithelial cells. Other evidence showed that COX-2 is over-expressed in a variety of human solid cancers compared to normal tissues [3-11]. NSAID can, therefore, be used as chemopreventive agents because the potential mechanism of action for NSAID is to inhibit COX activity. In this way, laboratory studies have suggested that NSAID exert protective effects against basal cell carcinoma (BCC) both *in vitro* [1, 12] and in animal models [13-16]. In humans, there are conflicting results about associations between the use of NSAID and the risk of BCC [17-21] which may result from different methods for calculating NSAID use [17, 18, 20] or potentially confounding variables not adjusted for, such as sun sensitivity. In view of these data, we conducted a study to determine whether NSAID are associated with aggressive histological subtypes of BCC.

Methods

Subjects and source of data

The study cohorts were identified from the electronic pathology records of our hospital by examining all electronic pathology reports of specimens collected between January 1st 2010 and May 1st 2010 that contained the word "skin" in the specimen box and "basal cell carcinoma" in the diagnosis box. Subjects with squamous cutaneous carcinoma were excluded. All specimens included in the study were reviewed by a trained pathologist from our hospital and classified as non-aggressive BCC or aggressive BCC. We formed two cohorts, one of all patients with pathologically confirmed non-aggressive BCC: superficial and nodular, and the other with patients with aggressive BCC: micronodular, morpheiform and infiltrative (angular nests infiltrating throughout the dermis with minimal to absent desmoplastic stromal host response).

Exposure assessment

For all subjects included in the study we investigated the consumption of NSAID over the previous 15 years with an

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interview performed by a dermatologist during the patient's follow up. NSAID were categorized as Yes or No. Because BCC presents in an elderly population with frequent memory issues, the answers provided by the patients were checked in the prescription Database of our hospital. This approach allowed for inclusion of current NSAID use and avoided memory bias as well as the inclusion of wrong data. We identified all NSAID prescriptions over the previous 15 years using the Prescription Database of our hospital. We identified exposure to the following NSAID: acemetacin, aspirin, celecoxib, diclofenac, diflunisal, etodolac, fenoprofen, ibuprofen, indomethacin, meloxicam, naproxen, piroxicam, rofecoxib and tenoxicam. For subjects with use of more than one NSAID, the longest reported duration was used for the exposure variable. Patients took these drugs for conditions such as osteoarthritis, cardiovascular diseases and lower back pain.

Covariates in the full models were age, sex, eye color, hair color, skin type, family history of BCC, history of smoking, history of sunburns and history of sunburns in childhood. Data regarding these covariates were obtained by a trained dermatologist during an interview in the follow up of patients.

Statistical analysis

All analyses were stratified by cohort. Logistic regression was used to estimate the adjusted rate ratios of use of NSAID (with their 95% confidence intervals) in each cohort of aggressive or non-aggressive basal cell carcinomas. We adjusted for the above-referenced covariates. All the statistical analysis was performed using SPSS version 15 software.

Results

We identified a cohort of 136 subjects with BCCs. Of these patients, 111 had non-aggressive and 25 had aggressive forms of BCC. Baseline characteristic of the patients, considered for adjustment, are presented in *table 1*.

Eighty-eight (64%) patients from our sample were current NSAID users, while forty-eight (36%) did not use them. Aspirin was the most commonly consumed NSAID (42 subjects), followed by: ibuprofen (10), naproxen (9), diclofenac (8), piroxicam (6), indomethacin (5), celecoxib (3), meloxicam (2) and fenoprofen (1). The mean duration of consumption was: 8.12 $\pm$ 2.68 years, ranging from 2 years to 14 years.

Table 2 shows the crude and adjusted rate ratios of use of NSAID (with their 95% confidence intervals) in relation to the histology of the BCC. Among patients with aggressive BCC, 44% had current exposure to NSAID. In patients with non-aggressive BCC, 69% had a current exposure to NSAID. The adjusted ratio of aggressiveness in BCC associated with exposure of NSAID was 0.246 (0.065-0.928).

Discussion

NSAID have been shown to have a protective effect in certain cancers such as colorectal [22, 23], breast [24], prostate [25] and lung [26]. In relation with BCC, some epidemiological studies have suggested an association between use of NSAID and the incidence of BCC: Recently, Elmets *et al.* found celecoxib to be a chemopreventive agent against BCC [27]. The results of these studies were inconsistent, maybe due to presence of confounding factors or the use of different measure methods [17-21]. However, few studies have investigated the influence of NSAID in the histology of BCC. We found that the use of NSAID is associated with the presence of nodular and superficial variants of BCC, which are considered the least aggressive variants of BCC, after adjustment for age, sex, eye color, hair color, skin type, family history of BCC, history of smoking, history of sunburns and history of sunburns in childhood.

Possible mechanisms involving the effect of NSAID in the histology and behavior of BCC are dependent on the COX enzyme. Two isoforms of COX have been described. COX-1 is a constitutive isoform expressed in most normal tissues, whereas COX-2 is an inducible isoform up-regulated by signs such as inflammation or carcinogenesis.

The key factor in chemoprevention as a strategy for reducing cancer incidence and aggressive behavior seems to be the COX-2 inhibitor drugs [28-30]. The interest of these drugs lies in their influence on multiple components of the carcinogenesis pathway, from initiation to progression. Overexpression of the COX-2 enzyme has an anti-apoptotic effect on tumoral cells [31] and increases levels of angiogenesis [32-35]. Inhibition of COX-2 is reported to inhibit tumor angiogenesis [35-37]. Therefore, the primary effects of COX-2 inhibitor drugs in the invasive potential of BCC may be to starve the blood supply to the tumor and to promote tumor cell apoptosis, leading to a non-infiltrative behavior of the tumor. In the skin, overexpression of COX-2 has been observed after UVB injury [38, 39], which is known as the main risk factor for BCC. In addition, COX-2 increases tumoral invasiveness [40]. Our hypothesis is that in nodular and superficial BCCs the expression of COX-2 may be lower than in aggressive variants of BCC, such as morpheiform, micronodular and infiltrative, which might be explained by the use of NSAID. Supporting our hypothesis, Yu *et al.* [41] recently found differences in COX-2 expression in pathologic specimens of BCC: morpheiform BCCs have elevated COX-2 levels when compared with other BCC subtypes, such as superficial ones, where low or no COX-2 was seen, and nodular, where the expression was moderate. For that reason they are clinically more aggressive and recurrent, being particular candidates for topical NSAID.

The exact mechanism of cancer protection associated with these drugs remains unclear, but it may be related to alteration of arachidonic acid metabolites, such as prostaglandins (PGs), which modulate several signal transduction pathways that may affect angiogenesis, apoptosis, immune response, cellular adhesion, proliferation, differentiation and tumor invasion.

Bennett [42] and Jaffe [43] were the first authors to report an elevated concentration of PG E2 in colorectal cancer tissue compared to the surrounding normal mucosa, and therefore the positive effect of these drugs. Similarly, elevated PG E2 has also been observed in photodamaged skin, associated with increased levels of prostaglandin F2 and J2 [44]. PG E2, which is induced by COX-2, exerts an effect on immune tolerance during the process of cancer development and progression [45] and suppresses dendritic cell

Table 1. Distribution of covariates among patients with aggressive and non-aggressive BCCs.

Covariates	Non-aggressive BCCs (n=111)	Aggressive BCCs (n=25)	P Value
Sex			
(Female/Male)	33/78	4/21	0.031
Age			
(Mean)	73.7	66.9	0.018
Skin type[a]			
1	19	3	0.37
2	61	9	0.786
3	19	10	0.323
4	12	3	0.719
Hair color			
(red/blond *vs* brown/black)	44/67	7 / 18	0.714
Eye color			
Blue/gray	93	15	0.326
Brown	17	9	0.145
Black	1	1	0.385
Smoking			
No	51	8	0.118
Current	28	11	0.704
Former[b]	32	6	0.166
2° Grade sunburns[c]			
0	53	15	0.82
≤ 2	42	8	0.868
>2	16	2	0.528
Childhood			
2° Grade sunburns[c,d]	50	10	0.662
0	41	10	0.364
≤ 2	20	5	0.668
> 2			
Family history of BCCs[e]			
(No *vs* Yes)	87/24	22/3	0.187

BCCs: basal cell carcinomas

[a] *Reaction of skin after exposure to 1 hour of midday sun for the first time in the summer with: 1, indication of painful or blistering sunburn with no tan; 2, painful sunburn followed by a light tan; 3, mild sunburn followed by a moderate tan; and 4, no sunburn followed by a deep tan.*

[b] *≥ 12 months without smoking.*

[c] *First grade sunburns were collected in the study, but data are not shown due to most participants reported not remembering if they had this kind of sunburns.*

[d] *Under the age of 18.*

[e] *Including natural parents, brothers and sisters only.*

functions and antitumor T-cell responses [46]. The inhibition of PG production by NSAID might lead to a decrease in the malignant progression of cancer and enhance the suppressive response of immune cells. Furthermore, PGs are known to play a role in multiple cell-regulatory functions, such as DNA synthesis and cell division [47].

Besides these COX-dependent mechanisms, we suggest that COX-2- induced chronic inflammation may be a critical component in the aggressive and pathogenesis histology of BCC. Kaporis *et al.* [44] demonstrated by microarray analysis a dynamic state in the immune microenvironment associated with BBC: the presence of immature dendritic

Table 2. Use of NSAID among patients with aggressive and non-aggressive BCCs.

	Aggressive BCCs (%) n=25	Non-aggressive BCCs (%) n=111	Crude or (95% CI); P value	Ajusted or[a] (95% CI); P value
Use of NSAID	11 (44%)	77 (69%)	0.347 (0.143-0.842); 0.016	0.246 (0.065-0.928); 0.038
No use of NSAID	14 (56%)	34 (31%)		

CI, confidence interval; NSAID, non-steroidal anti-inflammatory drugs; OD, odds ratio; BCCs, basal cell carcinomas

[a] *Adjusted for age, sex, eye color (blue/grey vs brown vs black), hair color (red/blond vs brown/black), skin type (1-4 as described in table 1), family history of BCC (no vs yes), history of smoking (no vs current vs former), history of sunburns (0 vs ≤2 vs >2) and history of sunburns in childhood (0 vs ≤2 vs >2). Ninety-five percent CI values are Wald estimates.*

cells, Th2 cytokines (IL-4, IL-10) and Tregs (T cells that control the immune response, such as CD4, CD 25 and FoxP3 cells) would allow tumor invasion and aggressive behavior. In contrast, abundant CD8 T cells, the expression of interferon-associated genes (IFI-27, IRF-1, IRF-7 and G1P2) and IL-12/IL-23 would lead to an antitumoral host response. Aggressive BCCs use Treg cells to successfully evade the host immune system. We suggest that aggressive variants of BCCs express the former inflammatory partner which would be induced by COX-2, while non-aggressive variants would express the second partner. Supporting the role of the immune microenvironment in the aggressiveness of tumoral cells, Anasagasti *et al.* [48] successfully treated 9 histologically aggressive variants of BCC with an intralesional formulation of IFN-α and IFN-γ. This formulation promoted an antitumoral host response, achieving a blocking of the malignant progression and turning it to curation. IFN-α and IFN-γ have been demonstrated to have several effects on BCC cells: (1) to initiate apoptosis in BCC cells through the CD-95 ligand-receptor interaction [49], (2) to reverse the observed low level INF-γ receptors [50], (3) anti-angiogenic activities [51], (4) to decrease vascularity surrounding BCC [52].

Bergmann *et al.* [53] showed, in squamous carcinoma cells, that the expression of COX-2 induced IL-10 and CD4, CD25A and FoxP3 cells, which are responsible for immunosuppression and that the use of an NSAID, such as diclofenac, impaired the production of these enzymes. We hypothesize that the same mechanisms may occur in BCC.

Regarding the histology of BCC, it is important to highlight that, in aggressive BCC, there are important differences in the surrounding tumor-associated connective tissue compared to non-aggressive BCC, which modify the lesion border and create highly irregular and spiculated outlines [54]. According to the histological stepwise theoretical model of BCC, aggressive subtypes derive from incipient low aggressive forms (superficial-to-nodular-to-micronodular and superficial-to-nodular-to infiltrative-to-morpheic BCC types). This concept suggests that BCC evolution reflects a dynamic histological continuum determined by the host-tumor interactions [55].

Inflammatory and immune responses play an important role in this dynamic process of host-tumor interactions, which determines the development of aggressive or non-aggressive BCCs and enhances or limits the spread of these tumors. Data from studies by Kaporis *et al.* [44], Anasagasti *et al.* [48] and Bergmann *et al.* [53] support the hypothesis that overexpression of COX-2 at sites of chronic inflammation in human malignancies is accompanied by suppression of the immune system. The effects of NSAID on the histology of BCC might result in the establishment of a more efficient and long-lasting control of tumoral cells via the activation of innate and adoptive immune responses. This effect may comprise dendritic cell activation, tumor antigen presentation and T-cell cytotoxicity and interferon-associated genes. Such mechanisms have been demonstrated for other conditions with the administration of NSAID – *e.g.*, COX-2 inhibitor drugs enhance levels of IFN-γ, obtaining an inhibitory effect on the angiogenesis and tumor invasion in mice with colorectal cancer [56], promote antitumor responses by inducing IFN-γ and IL-12 in murine lung carcinoma [57], strengthen the inhibitory function of T cells against human renal carcinoma [58], inhibit Tregs, decreasing the immune tolerance of cancer with a reduction of tumor mass and metastasis [41], and limit tumor metastasis by enhancing MHC-mediated cytotoxicity of natural killers [59]. *Figure 1* shows the possible pathways by which COX-2 influences a more aggressive cancer behavior.

These studies support the concept of immunorestorative strategies via COX-2 inhibition in cancer. All these properties of NSAID and many others likely contribute to controlling the behavior of BCC cells, leading to a benign histological variant of this condition. The association with NSAID use was present regardless of the indication for use, across age and gender and for all sites of BCC.

Aggressive histology is not rare in BCC. Large studies from referral centers report the incidence of aggressive histology BCC ranging from 2.5- 44% [60-64]. These aggressive BCC are characterized by subclinical extension, invasive behavior, local recurrence and challenging treatment [65]. Therefore, preventive strategies for this type of BCC are warranted, and NSAID might be one of them.

We acknowledge several limitations to our study. First, our sample is small. We collected data regarding the use of NSAID over a wide range of time (15 years), so that we are unable to propose either when the potential benefit of NSAID on the histology of BCC would happen, or if a dose-response effect is plausible. Skin type II was the most common type in the non-aggressive BCC cohort, while the most prevalent skin type in Southern Europe is type III [66]. This might have led to bias, but was controlled adequately in the stratificated analysis, in which no differences between the two cohorts were found.

Nonetheless, our analysis has several strengths. To our knowledge, this study is the first to address an association between use of NSAIDs and the histology of BCC. Data of BCC histology and the use of NSAID are from a carefully controlled database. Once collected from the database, the specimens were reviewed by a trained pathologist from our hospital. Data regarding NSAID over the previous 15 years gives a sufficiently long-term use for patients to be affected by the potential protective effect of these drugs. For colorectal cancer, for example, 10-20 years of consistent use may be required for a preventive effect [67].

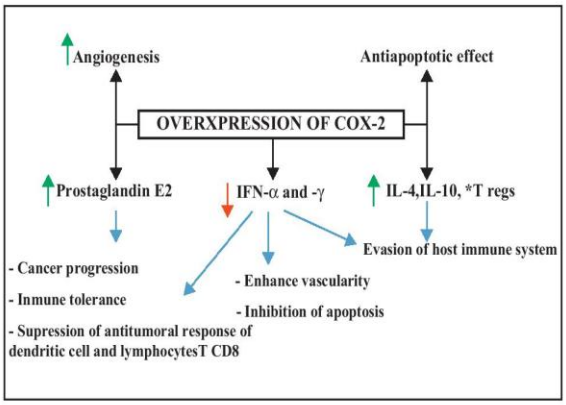

Figure 1. Possible mechanisms involving the effects of non-steroidal anti-inflammatory drugs in the histology of basal cell carcinoma.

Conclusions

These results indicate that NSAID play a role and may help in understanding the complex behavior of subtypes of BCC, thus eventually may lead to new therapy strategies. Further research is needed to confirm these findings. ■

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4.6. ***Husein-El Ahmed H****, Aneiros-Fernandez J, Gutierrez-Salmeron MT, Aneiros-Cachaza J, Naranjo-Sintes R.* ***Basal Cell Carcinoma: Analysis of Factors associated with incomplete excision at a referral hospital in Southern Spain.***

BASAL CELL CARCINOMA: ANALYSIS OF FACTORS ASSOCIATED WITH INCOMPLETE EXCISION AT A REFERRAL HOSPITAL IN SOUTHERN SPAIN

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BASAL CELL CARCINOMA: ANALYSIS OF FACTORS ASSOCIATED WITH INCOMPLETE EXCISION AT A REFERRAL HOSPITAL IN SOUTHERN SPAIN

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ABSTRACT:

Background: Basal cell carcinoma (BCC) is the most prevalent malignancy in human being, with the excision as the best therapeutic approach. Incomplete excision of non-melanoma skin cancer is a clinical indicator of surgical care. The purpose of this study is to assess the rate of incomplete excision at a tertiary referral hospital in the Southern Mediterranean area of Spain, and to determinate factors that may influence this.

Method: The design was a retrospective study. The population cohorts were patients with a primary BCC diagnosis during January and December 2010. Data were collected retrospectively and analyzed using SPSS software.

Results: The percentage of incomplete excision was 14.01%. Risk factors for incomplete excision are periocular and periauricular locations, large and thick tumors, morpheic and superficial subtypes and tumors with moderate-severe elastosis.

Conclusion: This study analyses the therapeutical results from a tertiary referral hospital in Southern Spain. We have obtained percentage of incomplete excision similar to other studies. Noeithstanding, a better marking of correct surgical margins, considering the size of the lesion, should be performed to improve our figures.

KEYWORDS: Basal cell carcinoma; incomplete excision

WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT:

- Previous studies have measured the percentage of incomplete excisions in basal cell carcinomas and its relationship with anatomic factors such as site and size of tumors, and histological factors such tumoral subtype.
- Most of the published studies are from North Europe, USA and Australia. Few works from Mediterranean area have been published.
- Role of elastosis and its impact in the surgery of BCC have not been investigated previously

WHAT THIS STUDY ADDS

- This study present the rate of incomplete excision from a referral hospital in Mediterranean area (Spain) and factors associated with it.
- The presence of severe elastosis adjacent to the lesion is associated with more risk of incomplete excision
- Those tumors with invasion in depth are more likely to be incompletely excised

IMPACT ON CLINICAL PRACTICE

- BCC associated with moderate-severe elastosis are difficult to delimite and therefore a careful demarking of the borders should be performed to avoid incomplete excisions.

BASAL CELL CARCINOMA: ANALYSIS OF FACTORS ASSOCIATED WITH INCOMPLETE EXCISION AT A REFERRAL HOSPITAL IN SOUTHERN SPAIN

INTRODUCTION

Basal cell carcinoma is the most prevalent malignancy in the humans, with an incidence of 200-600 cases/100,000 in Caucasian population and 3.5 cases/100,000 in Black population[1]. UV radiation has been found the major etiological factor, producing DNA alterations, with higher risk for those subjects with excessive UV light in childhood or receiving heavy and sporadic exposure[2]. Despite of multiple recent treatment modalities such as imiquimod cream, criotherapy and laser excision, surgical resection remains as the golden standard approach reaching cure rate between 95-99%[3,4]. It has the advantages of the economy and the availability of histological exam. In addition, incomplete excision of non-melanoma skin cancer is a clinical indicator of surgical care. The purpose of this study is to assess the rate of incomplete excision in a tertiary referral hospital in the Southern Mediterranean area of Spain, and its relationship with tumor location, histological and surgical features.

MATERIAL AND METHOD

SUBJECTS AND SOURCE OF DATA

We designed a retrospective study which was conducted between January 1st 2010, and December 31st 2010. Using the electronic pathology records of our hospital, we identified records of specimens containing the word “skin” in the specimen box and

"basal cell carcinoma" in the diagnosis box. We excluded those subjects with concomitant or previous history of squamous cutaneous carcinoma. Reexcisions for incompletely excised lesions, punch, shave or incisional biopsies as well as palliative excisions were also excluded. The specimens were reviewed by a trained pathologist of our hospital and considered incompletely excised when showed positive margins at the sides and/or the bottom. Furthermore, all the specimens were evaluated to obtain information regarding: presence of necrosis, depth of the lesion and distance to the surgical margin. Presence of elastosis was assessed and classified in one of the following category: *Grade 0 (Absence), Grade I (Papillary dermis), Grade II (Middle reticular dermis)* and *Grade III (Deep reticular dermis).* The specimens were also classified according to the differentiation pattern of BCC (superficial, nodular, micronodular and morpheiform). BCC with mixed features were classified according to the most predominant subtype.

From the operation notes we obtained additional information about the site and size of the lesion, type of anesthetic used and the method of wound closure, which indirectly signifies the complexity of the lesions.

STATISTICAL ANALYSIS

For statistical analysis, a multivariate logistic regression analysis was performed with the categorical variable "Incomplete excision" (Yes or No) as the outcome variable using the SPSS version 15 software. The previous variables were fitted in the final model. We used a P value < 0.05 for significance, and all tests were two-sides.

RESULTS

323 lesions from 292 subjects were included in the study. 282 patients had 1 lesion, while 13 and 5 patients had 2 and 3 BCCs respectively. The incidence of incomplete excision was 14.01 %. Table 1 summarizes the results from the multivariate statistical analysis.

Age and Sex

The median age was 72.98(±10.72) years (range 37 to 89 years); 161 (55%) were women and 131 (45%) were men. There was no significant differences in the rate of incomplete excision regarding sex (P>0.05).

Site of the lesion

Most of the lesions were located on the head (69.5%), with the nose as the most involved area. We found a significant difference in the rate of incomplete excision in head compared with other locations: trunk, neck and limbs (P=0.008; CI95%: 0.005-0.445).

Although not statistical differences were obtained, the site with more risk of incomplete excision within the head were inner canthus (23.1 % of incompletely excised), cheek (20%), auricular region (18.2%) and periocular region (17.3%). Distribution of incomplete excision in the facial area is summarized in Table 2.

Size of the lesion

212 of specimens were <10 mm, 96 measured from 10 to 20 mm, while 22 were larger than 20 mm. Lesions larger than 20 cm and those between 10 a 20 mm had a significant higher rate of incomplete excision (P=0.014 and P=0.001 respectively) than those < 10 cm.

Depth of the lesion

The distribution of the tumor depths was: n=247 (0 to 3.0 mm), n=70 (3.1 to 6.0 mm) and n=13 (>6.0 mm). The median tumor depth was 2.64±1.34. Tumor deeper than >6.0 mm showed statistically higher rate of incomplete excision compared to those ≤ 3 mm (P=0.025). This statistical finding was not observed for tumor depths ranging 3.1 to 6.0 mm (P=0.311).

Histological subtype of BBC

The most prevalent histological form was nodular (n=248), followed by morpheic (n=33), superficial (n=28) and micronodular (n=14). The percentage of incomplete excision was: 13.7% for nodular BCC, 17.9% for superficial BCC, 15.6% for morphemic BCC and 14.3% for micronodular BCC. There were significant differences in the rate of incomplete excision for morpheic BCC and superficial BCC compared to nodular BCC (P=0.001 and P=0.01 respectively). This outcome was not observed for micronodular BCC (P=0.57).

Necrosis

The presence of necrosis in the tumor specimen was observed in 148 lesions, while in 175 lesions the necrosis was absent. This feature did not affect to rate of incomplete excision (P=0.96).

Elastosis

24.1% of the tumors had no elastosis (grade 0), while 33.7%, 24.8% and 17.3 % had grade I, grade II and grade III of elastosis respectively. We found statistical differences for incomplete excision regarding the grade of elastosis. Those specimens with grade II

and III of elastosis were more likely to be incompletely excised compared to specimens without elastosis (Grade 0): P=0.001 and P=0.0001 respectively. However, lesions with light elastosis (grade I) showed not differences in margins affected by tumoral cells compared to lesions with grade 0 of elastosis (P=0.45)

Margin of surgical excision

Surgical margins ranged from 1 mm to 10 mm (Mean margin: 2.04±1.31). Margins greater than 10 mm were not used. In head-located BCC, the margin was 1.98±1.37, while in the other location was 2.43±1.65.

Site of tumor invasion and infiltration

The lateral margin was infiltrated by tumoral cells in 20 specimens (6.3%), while in 22 lesions (6.8%) the deep margin was involved. No nerve invasion was observed. The ratio of deep to lateral margin involvement was 1:1.1.

Method of surgical closure

Direct closure was the most frequent way of repair, with 285 lesions (86.4%) closured by this method. Flap repair was used in 26 lesions (7.6%), while in only 12 tumors (3.6%) skin graft was required. No statistical correlation was observed between the rate of incomplete excision and the method of repair (P>0.05).

Type of Anesthetic

Local anesthetic was used in 285 patients (97.6%), while general anesthetic was required in 7 patients (2.4%). There was no difference in the percentage of incomplete excision between local and general anesthetic (P>0.05).

DISCUSION

The present study aims to establish the rate of BCC incompletely excised in a tertiary referral hospital in Southern Spain, and factors associated with this outcome. In previous retrospective studies, the reported incidence of incomplete excision of BCC ranged from 6.3 to 25%[5-15]. In our study, the rate of incomplete excision was 14.01%, which is compatible with the reported literature (Table 3).

San Cecilio University Hospital is a tertiary referral hospital with a catchment area that includes the surrounding metropolis and the South of the province of Granada (South Mediterranean coast of Spain). According to the Cancer Registry of Granada, this tumor is quite prevalent with an annual incidence of 240 cases per 100,000 (men) and 110 cases per 100,000 (women). Usually, the skin tumors which are referred to our unit are deemed to be difficult and beyond the therapeutic capacity of the primary doctor. So that, our result of 14.01% of incomplete excision is in part a reflection of the complexity of lesions treated in our hospital.

Those BCC located in areas different from head showed lower risk of incomplete excision compared to head-located BCC. Within the head area, the inner canthus (23.1 % of incompletely excised), cheek (20%), auricular region (18.2%) and periocular region (17.3%) were particularly difficult to treat, while the other location in the head had average proportions of incomplete excision (Table 1). This finding is consistent with other published studies[7,8,16-18]. Possible explanations may be the proximity of vital structures and the cosmetic considerations that should be taken into account when treating lesions on the face. The average surgical margin was slightly lower in head-located BCCs compared with those tumors located in other areas. Head lesions

constitute 63.5% of all BCCs excised in our hospital. This figure is similar to that observed in other center such as Peter MacCallum Cancer Center (Australia)[18], but lower than the 80% - 90% at other centers[7,16].

Most of the BCC (65.6%) were smaller than 10 mm in diameter and, overall 34.6 % were larger than 10 mm. Those tumors > 20 mm were more likely to be incompletely excised compared to those lesions < 10 mm. This outcome is consistent with published reports stating that the risk of subclinical extension increases with the size of the tumor[15]. In addition, in our study we found that BBCs measured between 10-20 mm have more risk of positive margins than tumors < 10 mm.

Regarding histological subtype, morpheic and superficial BBCs were significantly more likely to be excised incompletely. This finding is consistent with results from other published works[16-18-20]. Morpheic BBC is usually presented as a yellowish-white, flesh colored lesion with induration and borders that are not sharply demarcated. All these characteristics contribute to the difficulty in delineating the correct surgical margins. Equally, superficial BBCs spread within the epidermis and show poorly demarcated margins, again contributing to a higher rate of incomplete excision. Micronodular BBC is a histological form of BBC without any distinctive clinical characteristics and it was not found as a risk factor of incomplete excision in our study.

One interesting finding of our work is the positive correlation between incomplete excision and the depth of the tumor invasion. In the same way that larger lesions have more risk of being incompletely excised, we found that the invasion in depth was an independent risk factor for incomplete excision. Thick tumors (>6.0 mm) showed statistically higher rate of incomplete excision compared to thin lesions (≤ 3 mm). This

outcome might be considered confounding factor for incomplete excision, where the thicker tumors would predominate in high risk areas such as periorbital or periauricular areas. However, from the 13 BBCs > 6.0 mm in our study, only 2 were located in the face (forehead and nose), while 3 lesions were located in the scalp, 1 in the neck, 3 in the arms and 4 in the back (Data not shown). Large and infiltrative BCCs, which are lesions with more likely to be completely excised[15,18], have an asymmetrical infiltrative growth in depth[19]. This feature adds difficulty to the complete excision in depth, although the lesion is correctly excised in the superficial level, contributing to higher percentage of positive margins. Therefore, this invasive growth in depth may be considered one contributing risk factor for incomplete excision in BCCs independently of the size and infiltration. This finding is very interesting from a surgical perspective because the deep-margin involvement is often more concerning as the reexcision of deep margins is more difficult and recurrences are only detectable in the later stages.

Guidelines suggest that to perform a complete excision the surgical margin should be 3-mm margin for non-morpheic BCC < 20 mm and 10-mm margin for morpheic and infiltrative BBC and BBC> 20 mm[21]. In our study, small BBC (<20 mm) accounted for 95.4% of all excisions, but only 12.2% were excised with margins ≥3 mm. While large BBC (> 20 mm) were 6.8% of all excisions and only 9 % were excised with margins ≥10 mm.

In the majority of BBCs (86.4%), the way of repair was the direct closure, which is related to small lesions. In our study, the method of surgical closure was not a factor for incomplete excision. In other studies, graft repair has been found associated with higher

percentage of incomplete excision[18]. This method of closure was required in only 12 lesions in our work.

Necrosis is a histological feature present in some BCCs. We analyzed the presence of this feature in our sample and found that it was not correlated with more incidence of incomplete excision. In the same way, the presence of elastosis was measured and classified in 4 possible grades. We observed that the presence of higher grade of elastosis (Grade II and III) was associated with higher rate of incomplete excision. Solar elastosis is the deposit of altered elastin in the dermis. Elastotic changes of the dermis are thought to be an essential indicator of the cumulative sun exposure, which is associated with the risk of developing BCC. Solar elastosis is visible on the face as a yellowish skin associated with atrophic and dyschromic changes. All these changes add difficulty in delineating the borders of the lesion, particularly in those with severe elastosis, and may explain our finding. In the same way, those lesions with light elastosis (Grade I) are easier to demark and in our study they resulted in a similar percentage of incomplete excision to tumors without elastosis (Grade 0).

The choice of anesthetic type depends on tumor and patient factors. There were not statistical differences in the percentage of incomplete excision between local and general anesthesia. Results from other studies are consisted with our finding[18].

Our study suffers from a few limitations: First we did not consider the variations in experience among the surgeons of our clinic. Secondly, this is the first study analysing the rate of incomplete excision in BCC at our hospital, so that, it may be interesting to compare the figures obtained in our work with the results of future researches conducted at the same center.

In conclusion, this study analyses the surgical therapeutic results in BCC excised at a tertiary referral hospital in Southern Spain. We have obtained percentages of incomplete excision similar to other studies. Noeithstanding, a better marking of the correct surgical margins, particularly considering the size of the lesion, should be performed to improve our figures.

CONCLUSION

We have obtained a percentage of incomplete excision of 14.01 %, which is an acceptable figure at a tertiary teaching hospital and it is similar to other published figures. However, this result can be improved. Some risk factors associated with incomplete excision have been found such as the periocular and periauricular locations, large and thick tumors, morpheic and superficial subtypes and tumors with moderate-severe elastosis

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TABLES:

TABLE 1. Multivariate statistical analysis. For each covariable the category reference is the first one.

COVARIABLE	**ODDS RATIO**	**P value (IC95%)**
SITE		

(Head vs Other)	1.8	0.008 (1.25-2.31)
BCC subtype - *Nodular* - *Morpheic* - *Superficial* - *Micronodular*	 2.1 2.2 1.2	 0.001 (1.55-2.58) 0.01 (1.33-2.83) 0.57 (0.16-1.9)
SIZE - < 10 mm - 10-20 mm - > 20 mm	 1.2 2.4	 0.001 (1.01-1.32) 0.014 (1.62-3.31)
TUMOR DEPTH - < 3 mm - 3-6 mm - > 6mm	 1.3 1.9	 0.311 (0.57-2.21) 0.025 (1.61-2.34)
NECROSIS *(Presence vs Absence)*	 1.02	 0.96 (0.56-2.3)

ELASTOSIS - *Grade 0* - *Grade 1* - *Grade 2* - *Grade 3*	 1.89 1.36 2.21	 0.45 (0.35-3.82) 0.001 (1.13-1.78) 0.0001 (1.74-2.78)
METHOD OF CLOSURE - *Direct* - *Flap* - *Skin graft*	 0.84 0.92	 0.23 (0.34-1.28) 0.38 (0.76-1.19)
ANESTHETIC *(Local vs General)*	 1.08	 0.42 (0.22-1.89)

TABLE 2: Distribution of incomplete excisions in the facial areas.

	COMPLETE EXCISIONS	**INCOMPLETE EXCISIONS;**	**TOTAL**

		(%)	
Scalp	20	4 (16.7%)	24
Cheek	20	4 (20%)	24
Inner Canthus	10	3 (23.1%)	13
Outer Canthus	15	2 (11.7%)	17
Forehead	13	2 (13.3%)	15
Nose	44	7 (13.7%)	51
Periocular Region	24	5 (17.3%)	29
Auricular Region	27	6 (18.2%)	33
Temple	14	1 (6.6%)	15
Chin	5	0 (0%)	5
TOTAL	192	34	226

TABLE 3. Percentage of incomplete excision in the current literature

AUTHORS	YEAR	TOTAL Nº OF LESIONS	% OF INCOMPLETE EXCISION
Lawrence et al.[22]	1986	58	17.2
Kumar el al.[16]	2002	757	4.5
Bisson el al.[23]	2002	100	4
Thomas el al.[24]	2002	71	2.8
Hsuan et al.[25]	2004	55	18.2
Bhatti el al.[26]	2006	900	14
Su et al.[18]	2007	1214	11.2
Griffiths et al.[27]	2007	1539	8
Farhi et al.[28]	2007	362	10.3
Twist et al.[29]	2009	124	1.6
Macbeth et al.[30]	2009	1419	14
Hansen et al.[31]	2009	6881	6.4
Sherry et al.[32]	2010	3006	3.2
Malik et al.[33]	2010	1832	14

Santiago et al.[34]	2010	947	9.5

4.7. ***Husein-El Ahmed H****, Aneiros-Fernandez J, Gutierrez-Salmeron MT, Aneiros-Cachaza J, Naranjo-Sintes R.* ***Assessment of incompletely excised basal cell carcinomas in six facial areas. Influence of elastosis.*** *Dermatology. 2012 Mar 31*

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Assessment of Incompletely Excised Basal Cell Carcinomas in Six Facial Areas: Influence of Elastosis

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Key Words
Facial basal cell carcinoma · Incomplete excision · Elastosis

Abstract
Background: Incomplete excision of non-melanoma skin cancer is a clinical indicator of surgical care. With most basal cell carcinomas arising on the face and considering the cosmetic and functional structures involved, it is interesting to identify what are the areas within the face with more likelihood of incomplete excision and the factors implicated. The aim of this study was to identify those areas and possible predictive factors. Six anatomical regions were considered and studied selectively. ***Method:*** A monocentric study was performed reviewing all facial basal cell carcinomas excised at our center during 2010. Data were analyzed using SPSS software. ***Results:*** 202 lesions from 202 subjects were studied. The percentage of incomplete excision was 17.07%. ***Conclusion:*** Lesions located in the orbitopalpebral and auricular areas and those with moderate to severe grade of associated elastosis are more likely to be incompletely excised. Wider surgical margins are observed in frontal, malar and labial areas which are distant from functional structures. The following tumor features were found to be a risk factor for incomplete resection: morpheic or superficial histology, large lesions (>20 mm) and thick lesions (>6 mm).

Introduction

Basal cell carcinoma (BCC) is the most common tumor in humans [1]. Its incidence varies depending on geographic area: in Australia the incidence is higher than in the USA or Europe [2]. UV exposure, mainly UVB, is the major etiological factor producing DNA alterations. Other genetic predispositions such as Gorlin syndrome have been found as risk factors [3]. This tumor may occur at any age, but its incidence increases dramatically in people over 40 years. Despite this, cases in people younger than 40 are increasing because of the use of tanning devices and the practice of sunbathing. This tumor may occur in any skin area, with published cases of atypical location such as the penis [4] and penianal location [5], but the head is the most frequent site. Although BCCs are relatively indolent and rarely metastasize, local destruction and disfigurement may occur in some cases of invasive facial BCCs, which are a challenge for complete excision and optimal reconstruction due to the proximity of vital structures such as eyes or lips.

The aim of the present study was (1) to assess the possible influence of facial solar elastosis in the rate of incomplete excision, and (2) to identify those areas within the face associated with a higher rate of incomplete excision and possible predictive factors, in order to establish a proper therapeutic strategy.

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Table 1. Multivariate statistical analysis

Covariable	Odds ratio	p value (95% CI)
Sex (female vs. male)	1.3	0.38 (0.73–2.29)
Facial area		
Frontal		
Orbitopalpebral	1.4	0.037 (1.08–1.83)
Nasal	1.2	0.08 (0.97–1.59)
Labial	1.01	0.14 (0.57–1.51)
Malar	1.8	0.21 (0.31–3.23)
Auricular	1.5	0.048 (1.13–1.94)
BCC subtype		
Nodular		
Morpheic	2.5	0.021 (1.35–3.82)
Superficial	1.9	0.049 (1.23–2.67)
Micronodular	1.3	0.69 (0.89–1.96)
Size		
<10 mm		
10–20 mm	1.7	0.025 (1.16–2.4)
>20 mm	2.1	0.039 (1.08–3.19)
Tumor depth		
<3 mm		
3–6 mm	3.1	0.17 (0.62–5.67)
>6 mm	2.3	0.024 (1.2–3.34)
Necrosis (presence vs. absence)	1.9	0.68 (0.87–3.31)
Elastosis		
Grade 0		
Grade 1	1.52	0.37 (0.61–3.83)
Grade 2	1.38	0.04 (1.09–1.69)
Grade 3	2.46	0.021 (1.79–3.19)
Method of closure		
Direct		
Flap	0.81	0.46 (0.25–1.41)
Skin graft	0.44	0.08 (0.18–1.15)
Anesthetic (local vs. general)	1.7	0.39 (0.48–3.19)

For each covariable the category reference is the first one.

Subjects and Methods

Subjects and Source of Data

We designed a retrospective monocentric study conducted between January 1st 2010 and December 31st 2010. We used the electronic pathology records of our hospital to identify records of specimens containing the word 'skin' in the specimen box and 'basal cell carcinoma' in the diagnosis box. We excluded those subjects with non-facial BCCs (including lesions located in the scalp) and those with a concomitant or previous history of squamous cutaneous carcinoma. Re-excisions for incompletely excised lesions, punch, shave or incisional biopsies as well as palliative excisions were also excluded.

The specimens were reviewed by a trained pathologist of our hospital and considered incompletely excised when they showed pathologically positive margins at the sides and/or bottom. Furthermore, all specimens were evaluated to obtain information regarding presence of necrosis, depth of the lesion and distance from the surgical margin. Presence of elastosis was assessed and classified in one of the following categories: grade 0 (absence), grade I (papillary dermis), grade II (middle reticular dermis) and grade III (deep reticular dermis). The specimens were also classified according to the differentiation pattern of BCC (superficial, nodular, micronodular, morpheiform). BCCs with mixed features were classified according to the most predominant subtype.

Six anatomical regions were considered and studied selectively: nasal region, orbitopalpebral region, labial region, malar region, frontal region and auricular region. All facial BCCs in the study were included in one of these six areas. From the operation notes we obtained additional information on the size of the lesion, type of anesthetic used and the method of wound closure, which indirectly indicate the complexity of the lesions.

Statistical Analysis

A binary logistic regression test was performed with the categorical variable 'incomplete excision' (yes or no) as the outcome variable to assess the rate of incomplete and relative risk among the six anatomical areas considered. The ANOVA test was performed to evaluate differences in the distance from the surgical margin among the six anatomical areas. We used a p value <0.05 for significance, and all tests were two-sided. The SPSS version 15 software was used for statistical analysis.

Results

202 lesions from 202 subjects were included in the study. The incidence of incomplete excision was 17.07%. Table 1 summarizes the data from the multivariate analysis.

Age and Sex

The median age was 74.73 ± 9.11 years (range 45–89 years); 108 (53.4%) were women and 94 (46.6%) were men. There was no significant difference in incomplete excision rate regarding sex ($p > 0.05$).

Site of the Lesions

The most common involved area was the orbitopalpebral region with 59 lesions (29.1%), followed by the nasal region (n = 51, 25.4%), the auricular region (n = 33, 16.5%), the frontal region (n = 30, 14.8%), the malar region (n = 24, 11.8%) and the labial region (n = 5, 2.4%). We found a significant difference in the rate of incomplete excision in the orbitopalpebral (p = 0.037, 95% CI 1.08–1.83) and auricular (p = 0.048, 95% CI 1.13–1.94) regions compared with the frontal region (region of reference). Although no

statistical differences were obtained, the nasal area was near significance regarding involved margins (p = 0.08, 95% CI 0.97–1.59). The distribution of incomplete excision in the overall facial area is summarized in table 2.

Size of the Lesions

167 of specimens were <10 mm, 30 measured 10–20 mm, while 5 were >20 mm. Lesions >20 mm and those between 10 and 20 mm had a significantly higher rate of incomplete excision (p = 0.039 and p = 0.025, respectively) than those <10 cm.

Depth of the Lesions

Tumor depths were 0–3.0 mm (n = 153), 3.1–6.0 mm (n = 47) and >6.0 mm (n = 2). The median tumor depth was 2.72 ± 1.16 mm. Tumor deeper than 6.0 mm showed a statistically higher rate of incomplete excision compared to those ≤3 mm (p = 0.024). This statistical significance was not observed for tumor depths ranging 3.1–6.0 mm (p = 0.17).

Histological Subtype of BCC

The most prevalent histological form was nodular (n = 158), followed by superficial (n = 20), morpheic (n = 17) and micronodular (n = 7). The percentage of incomplete excision was 13.7% for nodular BCC, 17.9% for superficial BCC, 15.6% for morpheic BCC and 14.3% for micronodular BCC. There were significant differences in the rate of incomplete excision for morpheic BCC and superficial BCC compared to nodular BCC (p = 0.021 and p = 0.049, respectively). This outcome was not observed for micronodular BCC (p = 0.69).

Necrosis

Presence of necrosis in the tumor specimen was observed in 105 lesions, while in 97 necrosis was absent. This feature did not affect the rate of incomplete excision (p = 0.68).

Elastosis

15.4% of the tumors had no elastosis (grade 0), 33.1% were grade I, 32.3% were grade II and 19.3% were grade III. We found statistical differences for incomplete excision regarding the grade of elastosis. Those specimens with grade II and III of elastosis were more likely to be incompletely excised compared to specimens without elastosis (grade 0): p = 0.04 and p = 0.021, respectively. However, lesions with light elastosis (grade I) showed not differences in margins affected by tumor cells compared to lesions with grade 0 of elastosis (p = 0.37).

Table 2. Distribution of incomplete excisions in the face

	Complete excisions	Incomplete excisions	Total
Frontal	27	3 (10.0%)	30
Orbitopalpebral	49	10 (16.9%)	59
Nasal	44	7 (13.7%)	51
Labial	5	0 (0%)	5
Malar	20	4 (16.6%)	24
Auricular	27	6 (18.2%)	33
Total	172	30	202

Margin of Surgical Excision

Surgical margins ranged from 1 to 7 mm (mean 2.04 ± 1.31). Margins >7 mm were not used. The facial area with the widest margins was the labial area (3.71 ± 1.21) followed by the frontal area (3.21 ± 1.34), the malar area (2.95 ± 0.93), the nasal area (2.27 ± 1.07), the auricular area (2.20 ± 1.25) and the orbitopalpebral area (2.13 ± 0.65). We found that surgical margins in the frontal and labial areas were statistically wider than those in the orbitopalpebral area (p < 0.001 and p < 0.001, respectively), the nasal area (p = 0.009 and p < 0.001) and the auricular area (p < 0.001 and p = 0.02). The malar area showed significantly wider margins compared with the auricular area (p = 0.05). Details about differences in surgical distances among the six facial areas are shown in table 3.

Site of Tumor Invasion and Infiltration

The lateral margin was infiltrated by tumor cells in 13 specimens (6.4%), while in 16 lesions (7.9%) the deep margin was involved. No nerve invasion was observed. The ratio of deep to lateral margin involvement was 1:1.23.

Method of Surgical Closure

Direct closure was the most frequent way of repair, with 170 lesions (84.2%) closed by this method. Flap repair was used in 26 lesions (12.9%), while in only 6 tumors (2.9%) skin graft was required. No statistical correlation was observed between the rate of incomplete excision and the method of repair (p > 0.05).

Type of Anesthetic

Local anesthesia was used in 186 patients (92.1%), while general anesthesia was required in 16 patients (7.9%). There was no difference in the percentage of incomplete excision between local and general anesthesia (p > 0.05).

Table 3. Differences in surgical margins (mean ± SD) among the six facial areas (ANOVA test)

Facial areas	Differences in surgical margins	p value (95% CI)
Frontal versus		
Orbitopalpebral	1.31 ± 0.30	0.0001 (0.61 to 2.23)
Nasal	1.13 ± 0.55	0.009 (0.37 to 1.56)
Labial	0.61 ± 0.41	0.85 (–0.81 to 3.24)
Malar	0.72 ± 0.32	0.91 (–0.62 to 2.53)
Auricular	2.13 ± 0.70	0.0001 (0.81 to 1.78)
Orbitopalpebral versus		
Frontal	–1.31 ± 0.30	0.0001 (–2.23 to 0.61)
Nasal	–0.69 ± 0.44	0.82 (–2.02 to 0.62)
Labial	–2.44 ± 0.57	0.0001 (–4.17 to –1.72)
Malar	–0.34 ± 0.15	0.78 (–1.17 to 1.31)
Auricular	0.85 ± 0.42	0.65 (–0.69 to 1.67)
Nasal versus		
Frontal	–1.13 ± 0.55	0.009 (–1.56 to 0.37)
Orbitopalpebral	0.69 ± 0.44	0.82 (–0.62 to 2.02)
Labial	–2.15 ± 0.24	0.0001 (–3.66 to –0.83)
Malar	–1.85 ± 0.77	0.26 (–0.45 to 4.16)
Auricular	0.85 ± 0.24	0.19 (–1.3 to 2.32)
Labial versus		
Frontal	–0.61 ± 0.41	0.85 (–3.24 to 0.81)
Orbitopalpebral	2.44 ± 0.57	0.0001 (1.72 to 4.17)
Nasal	2.15 ± 0.24	0.0001 (0.83 to 3.66)
Malar	–1.6 ± 0.91	0.31 (–0.88 to 2.47)
Auricular	2.75 ± 0.89	0.02 (1.09 to 4.21)
Malar versus		
Frontal	–0.72 ± 0.32	0.91 (–2.53 to 0.62)
Orbitopalpebral	0.34 ± 0.15	0.78 (–1.31 to 1.17)
Nasal	1.85 ± 0.77	0.26 (–4.16 to 0.45)
Labial	1.6 ± 0.91	0.31 (–2.47 to 0.88)
Auricular	1.97 ± 0.52	0.05 (1.02 to 2.38)
Auricular versus		
Frontal	–2.13 ± 0.70	0.0001 (–1.78 to 0.81)
Orbitopalpebral	–0.85 ± 0.42	0.65 (–1.67 to 0.69)
Nasal	–0.85 ± 0.24	0.19 (–2.32 to 1.3)
Labial	–2.75 ± 0.89	0.02 (–4.21 to 1.09)
Malar	–1.97 ± 0.52	0.05 (–2.38 to 1.02)

Discussion

Although BCCs of the face are generally easily recognized, their treatment remains subject to schools of thought of individual practices, which are often difficult to define. Our study assesses the rate of incomplete excision of facial BCCs according to topographical localization in a tertiary referral hospital, and factors associated with it. Six anatomical regions were studied selectively to define the rate of incomplete excision: nasal region, orbitopalpebral region, labial region, malar region, frontal region and auricular region. The facial location of BCCs is important, as tumors that arise in this cosmetically and functionally delicate area are best managed with therapies that minimize the amount of tissue removed while ensuring the highest chance of complete cure. Identifying factors associated with incomplete excision is useful to improve the outcomes of surgery and to avoid recurrences.

We observed an incomplete excision rate of 17.07%. Our figure is slightly higher than others from previous studies: Bogdanov-Berezovsky et al. [6] had a rate of incomplete excision of 15.74%, while Bhatti et al. [7] and Su et al. [8] obtained rates of 14.1 and 14.5%, respectively. However, we think that our rate of incomplete excision may be considered a good overall outcome considering that some facial BCCs may be a surgical challenge and that Mohs' micrographic surgery is not available in our hospital.

Among the six anatomical areas analyzed, the orbitopalpebral and auricular areas showed a high rate of incomplete excision in our study. This is consistent with other studies in which tumors situated in these regions presented a higher rate of positive margins compared to other localizations [9–11]. These two areas are part of the so-called H-zone of the face (fig. 1). The H-zone of the face corresponds to locations of embryonic fusion plates which are linked with a high risk of incomplete excision and recurrence. There appears to be a certain difficulty in assessing these regions clinically with excessive adjustment of the surgical margin, and also pathologically, when taking into account spatial orientation, thin skin, fragmentation of margins and tissue shrinkage after formalin fixation [12]. These may be plausible explanations of our results of incomplete excision in these two areas. When incomplete excision occurs on the face there is good evidence to support the need for re-excision. Boulinguez et al. [13] report a 24% chance of incompletely excised BCCs becoming more aggressive when they recur, with the likelihood being higher for perinasal, periocular and periauricular lesions. Our findings of more risk of incomplete excisions in the orbitopalpebral and auricular areas may be interesting and helpful to dermatologic surgeons, because performance of a more acute surgery in these regions may avoid incomplete excision and later aggressive recurrence. In an interesting work, Wetzig et al. [14] found that resection of BCCs with complete margin control using paraffin-embedded sections achieved excellent

cure rates for both primary and recurrent BCCs. Considering our result of more risk of incomplete excision in the orbitopalpebral and auricular areas, the implementation of this technique to control surgical margins is warranted for lesions in these areas.

Guidelines suggest performing complete excision, a 3-mm margin for non-morpheic BCCs <20 mm and a 10-mm margin for morpheic and infiltrative BCCs and BCCs >20 mm [15]. However, as a result of the importance of a good cosmetic outcome when tumors arise on the face, surgery may differ significantly from those that would be made for BCCs arising elsewhere. In our study, the varying surgical margin range (1–7 mm) depended on the anatomical site of the lesions: in some cases, facial BCC arose in close contact with functional structures which made it difficult to perform an excisional margin following the guidelines. In fact, in our study large BCCs (>20 mm) were 2.5% of all excisions and none of them were excised with margins ≥10 mm, while small BCCs (<20 mm) accounted for 97.5% of all excisions, but only 12.5% were excised with margins ≥3 mm.

If we consider the six facial areas analyzed we observe that wider margins (≥3 mm) were performed in the frontal, labial and malar areas, which can be considered locations relatively distant from vital structures. On the other hand, the orbitopalpebral, nasal and auricular areas had the narrowest margins. This is because having to remove facial lesions near functional structures with adequate excision margins can be disfiguring as a result of loss of tissue, grafting and subsequent scarring. Besides, there are also important key structures for self-recognition and esthetics which make surgeons prudent with security margins in these regions. Another important point to consider when performing an excision of facial BCC is that BCCs on the face may have a higher degree of subclinical spread than tumors arising elsewhere. For all these reasons, the use of Mohs' micrographic surgery is a good alternative to traditional surgery in these regions based on the highest cure rates and maximum tissue conservation reached with this technique. Batra and Kelley [16] retrospectively analyzed 1,131 cases of Mohs' surgery on the face and found higher rates of extensive subclinical spread on the eyelid, ear and nose than the cheek. This extensive subclinical spread may be a reasonable explanation for our results of high incomplete excision in the oculopalpebral and auricular areas. While it would seem sensible to take larger margins at the sites where subclinical spread is known to be more extensive, these sites are all of great cosmetic and functional importance, and therefore striking the correct balance is necessary.

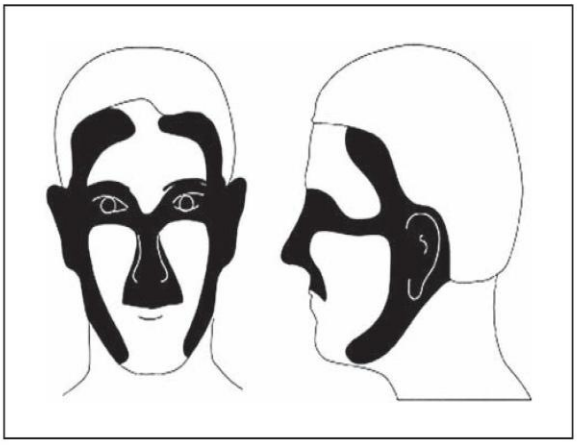

Fig. 1. Areas in the H-zone of the face.

We observed that BCCs measuring >20 mm and 10–20 mm have more risk of positive margins than tumors <10 mm. This is consistent with previous reports stating that the risk of subclinical extension increases with the size of the tumor [17].

When considering histological subtype, morpheic and superficial BCCs were statistically more likely to be excised incompletely. This finding is consistent with results from other published works [8, 11, 18]. Morpheic BCCs usually present as yellowish-white, flesh-colored lesions with induration and borders that are not sharply demarcated. All these characteristics contribute to difficulty in delineating the correct surgical margins. In the same way, superficial BCCs spread within the epidermis, with poorly demarcated margins contributing to a higher likelihood of incomplete excision. Micronodular BCC is a histological form of BCC with not distinctive clinical characteristics and was not found to be a risk factor of incomplete excision in our study.

One interesting outcome of our work is the positive correlation between incomplete excision and the depth of tumor invasion. In the same way that larger lesions are more likely to be excised incompletely, we observed that invasion depth was an independent risk factor for incomplete excision. Thick tumors (>6.0 mm) showed statistically more likelihood of incomplete excision compared to thin lesions (≤3 mm). Although there are few data regarding the correct deep surgical margin and excision through the subcutaneous fat is generally considered right, it has been observed that infiltrative BCCs have an asymmetrical infiltrative growth in depth [19], and this may be one reason why these lesions are more likely to be

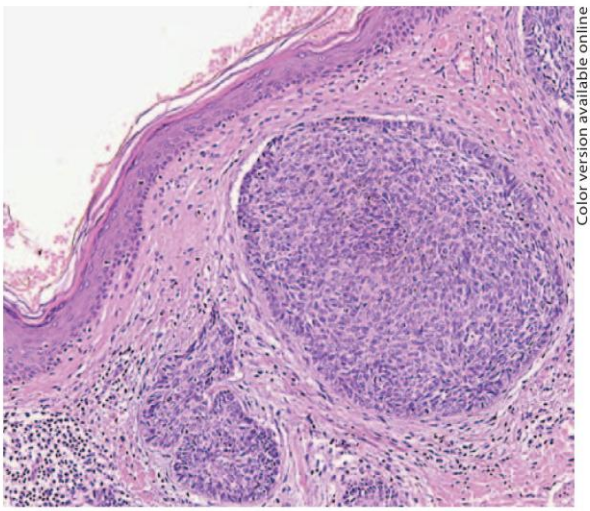

Fig. 2. BCC with light elastosis.

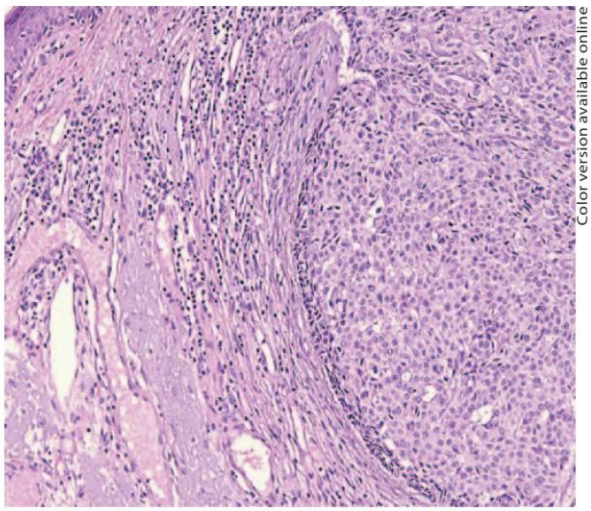

Fig. 3. BCC with moderate elastosis.

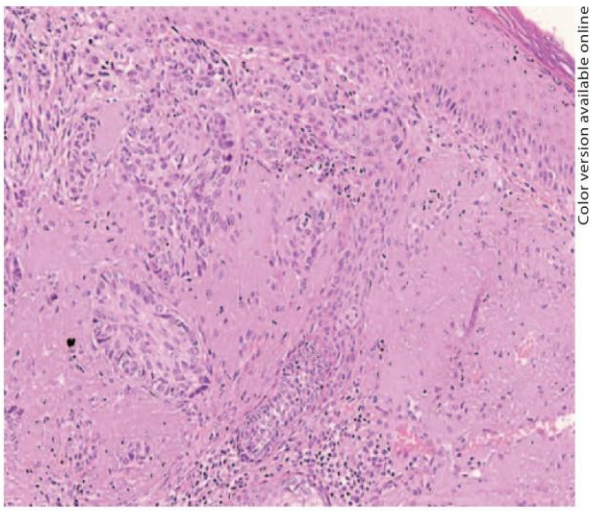

Fig. 4. BCC with severe elastosis.

completely excised [8, 17]. This feature adds difficulty to complete excision in depth, although the lesion is correctly excised at the superficial level, contributing to a higher risk of positive margins. Therefore, this invasive growth in depth may be considered one contributing risk factor for incomplete excision in BCCs independently of size and infiltration. This finding is very interesting from a surgical perspective, as long as the deep margin involvement is often more concerning as the re-excision of deep margins is more difficult to perform on facial areas. Besides, recurrences are only detectable in the later stages with the potential risk of invasion into functional and vital structures such as nose, eye, lips or ears.

The most common way of repair was direct closure (84.2%), which is related to smaller lesions. In our study, the method of surgical closure was not a factor for incomplete excision. In other studies, graft repair has been found to be associated with a higher percentage of incomplete excision [8]. This method of closure was required in only 6 lesions in our work. In the same way, there were not statistical differences in the percentage of incomplete excision between local and general anesthesia, which is consistent with result from other studies [8].

Necrosis is a histological feature present in some BCCs. We analyzed the presence of this feature in our sample and found that it was not correlated with a higher incidence of incomplete excision. Equally, the presence of elastosis was measured and classified into four grades. We observed that higher grades of elastosis (grade II and III) were associated with more likelihood of incomplete excision. Solar elastosis is the deposit of altered elastin in the dermis. Elastotic changes of the dermis are thought to be an essential indicator of cumulative sun exposure, which is associated with the risk of developing BCC. Solar elastosis is particularly visible on the face as yellowish skin associated with atrophic and dyschromic changes. All these changes add difficulty in delineating the borders of lesions arising on facial locations, particularly in those with severe elastosis, and may explain our finding. A pilot study conducted by Skaria [20] obtained results

consistent with ours. These data support the idea that tumor surgery is a dermatologic speciality for accuracy where severe elastosis is a key feature in the rate of incomplete excision. This factor should be considered during daily surgical practice in order to perform complete excision of the lesion. In the same way, lesions with light elastosis (grade I) were easier to demarcate and resulted in a similar percentage of incomplete excision as tumors without elastosis (grade 0) in our study. Figures 2–4 show BCCs with different grades of elastosis.

Our study suffers from a few limitations. First we did not consider the experience of the surgeons in the analysis. Second, as it was the first work studying the rate of incomplete excision in BCCs arising on face at our center, we are unable to establish a comparison with previous data.

Conclusion

This study analyzed what areas of the face have a higher likelihood of incomplete excision and what factors may be implicated. Considering that most BCCs arise on the face and the cosmetic and functional structures involved at this location, this analysis may represent a good surgical tool to improve figures of facial BCC surgery. According to our study, facial BCCs with higher grades of elastosis (grade II and III) were associated with more likelihood of incomplete excision. We identified that tumors located in the orbitopalpebral and auricular areas and those with moderate to severe grade of associated elastosis are more likely to be incompletely excised. Wider surgical margins are observed in the frontal, malar and labial areas, which are distant to functional structures. The following tumor features were found to be risk factors for incomplete resection: morpheic or superficial histology, large lesions (>20 mm) and thick lesions (>6 mm).

Disclosure Statement

The authors have no conflict of interest to declare.

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DISCUSIÓN

En esta Tesis Doctoral, hemos estudiado distintos aspectos de la epidemiología y la histología del CBC. Pensamos que nuestros análisis aporta interesantes datos para el conocimiento de esta neoplasia que, como hemos comentado en el capítulo de introducción, tiene una incidencia en pleno ascenso en los últimos años, principalmente en los países occidentales[96,97]. A continuación se discuten los hallazgos más importantes observados en cada trabajo. Para más detalles, se remite a las publicaciones científicas.

5.1. FACTORES ASOCIADOS A RETRASO EN EL DIAGNÓSTICO DEL CBC

El primer aspecto analizado es el retraso en el diagnóstico del tumor y los posibles factores implicados. Aquellos CBC diagnosticados de forma precoz y tratados mediante una técnica quirúrgica adecuada tienen en general un pronóstico excelente, con una morbilidad asociada mínima. Las estrategias de salud orientadas a la prevención secundaria del cáncer buscan la detección y aplicación de tratamiento en estadíos muy tempranos para detener la progresión de la enfermedad[98]. Gracias a la accesibilidad del CBC, este tumor presenta la ventaja de ser más fácilmente reconocido que otro tipo de tumores. Por ello, la aplicación de estrategias de prevención secundaria está justificada. A pesar de ello, en nuestro análisis hemos observado que en el 48.8% de los pacientes el intervalo de tiempo desde la aparición de la lesión y la consulta médica fue superior al año.

El problema de las consultas tardías para el diagnóstico del CBC ha sido analizado por diferentes autores: Blackford y colaboradores[99] observaron que el tiempo medio desde la aparición de la lesión hasta la consulta con el médico era de 2 años; Antoszewski y colaboradores[100] llevaron a cabo un estudio en Polonia y obtuvieron un intervalo de

tiempo incluso mayor (2,7 años de media). En nuestro trabajo, las cifras obtenidas son similares a las previamente descritas en la literatura: 1,64 años de media.

Las razones del retraso en el diagnóstico de este tumor no han sido bien definidas. Como hemos expuesto previamente en la introducción, en oncología cutánea la mayoría de trabajos que estudiaban las causas de retraso diagnóstico se han centrado en el melanoma[17-27]. En nuestro análisis, observamos que la presencia de determinados factores determinaba un menor intervalo de tiempo hasta acudir a la consulta del especialista y por tanto, un diagnóstico más precoz de la enfermedad. Estos factores son los siguientes:

- Edad < 65: En pacientes jóvenes el riesgo de retraso en el diagnóstico del tumor fue menor. Este dato es similar al obtenido en otros trabajos publicados[28,101]

- CBC de localización en cabeza o cuello: Las localizaciones más frecuentes del CBC coincidían con las asociadas a menor riesgo de retraso diagnóstico. Una posible explicación es el reconocimiento fácil de la lesión al presentarse en áreas visibles.

- Historia personal de cáncer de piel: Estos pacientes están más concienciados del riesgo de aparición de una lesión cutánea maligna, de modo que consultaban antes ante la presencia de una lesión sospechosa. Este hallazgo es similar al obtenido en otros trabajos publicados recientemente[28]

- Antecedentes familiares de cáncer de piel: Del mismo modo, la historia de cáncer de piel en un familiar, hace que los pacientes sean más conscientes del riesgo de desarrollar

esta enfermedad y consulten precozmente. Este hallazgo es similar al obtenido en otros trabajos publicados recientemente[28]

- Presencia de síntomas asociados (sangrado, picor…): Las lesiones asintomáticas presentaban más riesgo de retraso diagnóstico. Sin embargo, este factor no parece tener utilidad pronóstica, a la luz de estudios que no muestran beneficio en la derivación y tratamiento precoz de CBC sintomáticos[102,103]

El retraso en el diagnóstico de la lesión no se asoció a tumores más profundos en nuestro análisis. La explicación más plausible es que el crecimiento del CBC no es lo suficientemente rápido como para determinar un incremento significativo en su tamaño a lo largo de meses, y requeriría años para mostrar aumentos llamativos de tamaño. Estos resultados son similares a los obtenidos por Kirkup y colaboradores[102]: Estos autores observaron que no existía una correlación entre el crecimiento del tumor y el tiempo de evolución, sugiriendo que el CBC no presenta un crecimiento lineal, y que por tanto, es difícil determinar los efectos del retraso en el diagnóstico en las dimensiones de la lesión.

5.2. DIETA Y ELASTOSIS SOLAR ASOCIADA AL CBC

La elastosis solar es determinada por la exposición de la piel a la RUV y constituye la característica histológica más llamativa del proceso de envejecimiento cutáneo. Desde el punto de vista clínico, se manifiesta como zonas de piel amarillentas con presencia de arrugas. La RUV también representa el principal factor de riesgo para el desarrollo de CBC.

En este estudio analizamos si la dieta podía influir en el grado de elastosis solar en pacientes con CBC.

El consumo de grasas era muy prevalente en la muestra analizada, pero no se asociaba con el grado de elastosis solar. Estudios de experimentación en animales han mostrado que el consumo elevado de grasa puede aumentar la sensibilidad de la piel al envejecimiento[104]. Además, se ha observado que los carotenoides del huevo disminuyen el fotoenvejecimiento en la piel de ratones gracias a un efecto antiinflamatorio[105,106]. En humanos, los resultados son contradictorios, lo que sugiere que la asociación de consumo de grasas y envejecimiento cutáneo es un proceso complejo que puede implicar otros factores como son la genética familiar, la acción sinérgica con otros nutrientes, como vitaminas y antioxidantes, y la composición cualitativa de las grasas.

Dentro de los factores intrínsecos implicados en el envejecimiento cutáneo y la elastosis solar, destaca el estrés oxidativo de los lípidos de la capa córnea[107,108]. Existen sustancias que actúan como antioxidantes al inhibir este proceso de estrés oxidativo: Catalasa, alfa-tocoferol (vitamina E), ácido ascórbico (vitamina C), coenzima Q10 y glutatión. Muchos de estos agentes antioxidantes se inactivan por la RUV[109]. Nuestros datos sugieren que una dieta rica en alimentos con vitamina C y E se asocia a menor elastosis cutánea. Los estudios previos sobre suplementos de vitamina C y envejecimiento cutáneo son contradictorios: Existen trabajos que muestran que el déficit de vitamina C se asocia a la aparición de arrugas[110], y su aporte disminuye la profundidad de las arrugas y la sequedad cutánea gracias a su acción antioxidante[111]. Sin

embargo, Martalena y colaboradores[112] observaron que los suplementos de vitamina C podían ejercer un efecto nocivo sobre la piel.

En nuestro trabajo el consumo de carnes rojas no mostró ninguna relación con la elastosis solar. La evidencia científica en este aspecto no es concluyente, y se necesitan más estudios para aclarar esta cuestión.

El consumo de ajo, espinacas y cebollas tiene un efecto preventivo sobre el envejecimiento cutáneo gracias a su contenido en Coenzima Q10[112,113]. En nuestro análisis, el consumo de verduras no se asoció con el grado de elastosis. Esto puede ser explicado por el bajo consumo referido por los pacientes de nuestra cohorte, dando lugar a un error tipo II (resultado falso negativo).

Aunque el consumo de té no es habitual en España, y tampoco resultó serlo en la cohorte estudiada, observamos que los pacientes que consumían té presentaban menor grado de elastosis cutánea. Una explicación plausible es la presencia de polifenoles en las hojas del té, que tienen un efector antioxidante muy superior al de la vitamina C y E[114,115], y convierten a estas sustancias en uno de los agentes más potentes frente al estrés oxidativo.

Estudios recientes han mostrado que el consumo de café reduce el efecto de la RUV tipo B en la piel a través de la inducción de la apoptosis de los queratinocitos fotodañados[116] y de la inhibición de la síntesis de prostaglandina E[117]. La repercusión de estos fenómenos en el proceso de envejecimiento cutáneo no está bien definida. Uno de los efectos más relevante de la RUV tipo B en el envejecimiento de la piel es la inducción de un infiltrado de neutrófilos[118]. Mitani y colaboradores[119] observaron que la

aplicación de extractos de plantas ricas en xantinas en la piel de ratones era capaz de disminuir las arrugas gracias a la reducción del infiltrado neutrofílico. El café contiene altos niveles de xantinas, sin embargo, en nuestro análisis no observamos diferencias en el grado de elastosis cutáneas entre los participantes que consumían café y los que no. Una explicación posible puede ser que el consumo de café no permite alcanzar en la piel concentraciones de xantinas significativas para inhibir el infiltrado inflamatorio.

5.3. COMPARACIÓN DEL CBC EN TRABAJADORES EXPUESTOS A RU Y TRABAJADORES NO EXPUESTOS

Hemos analizado las diferencias clínicas e histológicas en el CBC de 2 cohortes: Trabajadores expuestos a la RUV (TE) y trabajadores no expuestos a la RUV (TNE).

Observamos que la edad media de desarrollo del tumor era menor en los TNE que en los TE. Este hallazgo es similar al obtenido por otros estudios recientes que muestran que la exposición a la RUV de forma acumulativa se asocia a la aparición de CBC a mayor edad, mientras que la exposición de forma intermitente, sobre todo en la infancia y adolescencia, se asocia a aparición precoz de CBC[120].

El fototipo bajo, el color de cabello y ojos claros son características fenotípicas asociadas a elevado riesgo de CBC. En nuestro trabajo, observamos que estas características eran similares en las 2 cohortes, sin diferencias significativas.

La historia familiar de CBC se ha sugerido como un factor de riesgo constitucional de desarrollo de CBC[121-123]. En nuestro análisis, la historia familiar positiva era más frecuente en TE, mientras que en la cohorte de TNE la mayoría de sujetos no tenía

historia familiar de CBC positiva. Aunque indudablemente la predisposición genética al desarrollo de CBC ayuda a explicar este hallazgo, también puede ser debido a los patrones de hábitos de vida y culturales: En los medios rurales, los trabajadores tienden a tener los mismos oficios que sus padres como modo de vida tradicional, de modo que la piel sufre el mismo patrón de exposición a la RUV que sus progenitores. En los medios urbanos, esto no es habitual y los sujetos pueden tener trabajos diferentes, y por tanto, con distinto patrón de exposición a la RUV.

Un hallazgo interesante de nuestro trabajo es la diferencia de historia de quemaduras entre las 2 cohortes: En los TNE, la historia de quemaduras en la infancia era más elevada, mientras en los TE se observó esta situación para las quemaduras en la edad adulta. La relación entre la RUV y el CBC es compleja y existen controversias sobre el patrón de exposición solar y el desarrollo del tumor durante diferentes etapas de la vida[124]. La historia de quemaduras severas parece ser más importante que la tendencia a quemarse o al bronceado[125,126], y además, la historia de quemaduras durante la infancia se asocia a aparición precoz del tumor. Esta situación la observamos en nuestro análisis puesto que la edad de desarrollo del tumor fue menor en sujetos con historia positiva de quemaduras en la infancia: la cohorte de TNE. En los TE, el CBC se desarrollaba a edades más tardías y en esta cohorte, como hemos expresado anteriormente, la incidencia de quemaduras en la edad adulta era más prevalente.

Otro dato de interés obtenido de nuestro análisis es la mayor presencia de CBC en el tronco en la cohorte de TNE frente a TE. Se ha sugerido que el CBC localizado en el tronco pueda deberse más a una susceptibilidad genética[127,128] y una reducción en la capacidad de reparación del ADN[129] que a la exposición a la RUV. Nuestros resultados

apoyan esta hipótesis y muestran que la exposición solar laboral no tenía una relación con el CBC localizado en tronco. Otros trabajos publicados han obtenido resultados similares: Pelucchi y colaboradores[130] compararon 528 casos de CBC con 512 controles y observaron que la RUV no se asociaba al CBC de localización en tronco, sugiriendo que los factores etiológicos de este subtipo de CBC pueden ser diferentes a los de CBC en otras localizaciones. En la mayor serie de CBC publicada en la literatura con 13457 piezas, los autores sugieren que el CBC de localización en tronco puede representar una variante particular de CBC, en la que la RUV no sería tan decisiva en la etiología, sino que estaría más en relación con la predisposición genética[131]. En este sentido, Ramos y colaboradores[132] sugieren que los carcinomas de piel no melanoma en áreas no expuestas a la RUV pueden deberse a una incapacidad para reparar el ADN dañado.

Desde el punto de vista histológico, el subtipo nodular fue el más prevalente, seguido del superficial en ambas cohortes. En el grupo de TE la variante nodular fue estadísticamente más frecuente comparado con el grupo TNE, mientras que el resultado opuesto se observaba para la variante superficial. En dos trabajos dirigidos por Bastiaens[133] y McCormack[134], se indica que los 2 subtipos histológicos de CBC (nodular y superficial) pueden representar distintos tumores con distintos factores causales. Según estos autores, los CBC nodulares se asociarían a la RUV acumulada, mientras que los CBC superficiales estarían más en relación con la exposición intermitente e intensa a la RUV. Los resultados de nuestro trabajo apoyan esta hipótesis, ya que en la cohorte de TE con mayor RUV acumulada, el tipo nodular fue significativamente más prevalente, mientras que el tipo superficial lo era en la cohorte de TNE con exposición solar más intermitente. Estos hallazgos aportan más evidencia a

la consideración cada vez más aceptada de que los tipos histológicos de CBC no son simplemente variedades arquitecturales, sino diferentes subtipos tumorales con distintos factores causales. Aunque la importancia de la RUV en el ámbito laboral es una incógnita aún por resolver, nuestros datos indican que puede tener relevancia en la localización y el tipo histológico del tumor.

5.4. CONSUMO DE ALCOHOL Y RIESGO DE CBC HISTOLÓGICAMENTE AGRESIVO

En este estudio, observamos una relación positiva entre el consumo de alcohol y el riesgo de desarrollar CBC-HA. Existen estudios epidemiológicos que proponen que algunos factores de la dieta pueden modificar la incidencia y agresividad de los cánceres de piel[135]. Nosotros observamos que el alcohol puede modificar el comportamiento y crecimiento del CBC. Este concepto de interacción entre nutrientes y mecanismos celulares e histológicos ha sido recientemente estudiado en otros tumores de origen epitelial: En pacientes con cáncer de colon se ha observado que aquellos sujetos con consumo de alcohol elevado presentaban histologías más agresivas en los estudios de biopsia[136]. Nosotros hemos observado un resultado similar para el CBC.

El consumo de alcohol es habitual en las sociedades occidentales durante actividades al aire libre. En este sentido, Saladi y colaboradores han observado que el consumo de alcohol en presencia de la RUV aumenta el daño celular producido por éstas, y aumenta por tanto, el riesgo de cáncer de piel[137]. El alcohol (etanol) ingerido es metabolizado en a acetaldehído: un producto altamente reactivo que actúa como sensibilizante generando radicales libres. Estos radicales potencian el efecto carcinogénico de la RUV y la

proliferación celular debido al daño ejercido sobre el ADN[137]. Por lo tanto, este efecto sinérgico entre el alcohol y la RUV en la proliferación y migración celular podría explicar nuestros hallazgos: La RUV es considerada el factor desencadenante de la iniciación y desarrollo tumoral[138], mientras que el alcohol tendría un efecto en la progresión y agresividad de la lesión.

Según el modelo de desarrollo histológico del CBC, los CBC-HA se derivan de formas incipientes más indolentes, de manera que la evolución del CBC reflejaría un estado histológico dinámico determinado por las interacciones entre el tumor y el huésped[139]. La reacción estromal, formada por la inflamación y la respuesta inmune, constituyen el microambiente peritumoral el cual determina la progresión o no de un CBC incipiente a un CBC-HA. De este modo, la inmunidad juega un papel clave en el bloqueo de la progresión tumoral. Nosotros planteamos que el alcohol induciría la progresión del las células del CBC gracias a su efecto inhibitorio de la inmunidad celular y humoral[140,141].

Analisis de microarrays han demostrado un estado dinámico en el microambiente inmune asociado al CBC[142]: La presencia de células dendríticas inmaduras, citoquinas Th2 (IL-4, IL-10) y reguladores T (linfocitos T CD4, CD25 y células FoxP3) permitirían la invasión y agresividad del tumor. Por el contrario, la presencia de linfocitos CD8, la expresión de genes asociados al interferón (IFI-27, IRF-1, IRF-7 and G1P2) y las IL-12 y IL-23 determinaría una respuesta antitumoral por parte del huésped. Los CBC-HA utilizarían los reguladores T para evadir el sistema inmune del huésped.

Se ha observado que el consumo de alcohol:

1. Eleva los niveles de citoquinas Th2[141,143,144].

2. Inhibe la expresión de genes asociados a interferon[145-147]

3. Suprime la expresión intracelular de IFN-alfa[145] e IFN-gamma[148]

4. Inhibe las funciones de las células dendríticas en la dermis[143], entre ellas, la presentación de antígenos[144,149,150]

Todos estos datos proporcionan mecanismos posibles a través de los cuales el consumo de alcohol reduciría la respuesta inmune del huésped frente a las células tumorales, permitiendo su evasión, progresión y comportamiento agresivo, y finalmente resultando en variantes de CBC-HA.

La asociación que hemos encontrado no es una correlación lineal causal, sino que el consumo de alcohol puede ser un factor contribuyente, que asociado a otros factores aún no conocidos incrementa el riesgo de desarrollar CBC-HA.

5.5. EFECTO DE LOS AINEs EN LA HISTOLOGÍA DEL CBC

Los fármacos antiinflamatorios no esteroideos (AINEs) han mostrado tener un efecto protector en distintos tipos de cáncer como: colorectal[151,152], mama[153], próstata[154] y pulmón[155]. Diferentes estudios epidemiológicos han obtenido resultados contradictorios en relación con el uso de AINEs y la incidencia de CBC[156-160]. Nosotros hemos observado que entre los sujetos con CBC, el consumo de AINEs se asociaba con mayor presencia de CBC nodular y superficial, 2 variantes histológicas de baja agresividad. Los posibles mecanismos implicados en la influencia de los AINEs en la histología y comportamiento de las células del CBC depende de la enzima ciclooxigenasa (COX). Se distinguen 2 isoformas de COX:

- COX-1 *(Isoforma constitutiva):* Se expresa en la mayoría de los tejidos del organismo.

- COX-2 *(Isoforma inducida):* Se expresa en respuesta a señales como la inflamación o la carcinogénesis.

El factor clave en la quimioprevención como estrategia para reducir la incidencia y agresividad de los tumores parecen ser los fármacos inhibidores de la COX-2[161-163]. El interés en estos fármacos radica en su efecto en múltiples pasos del proceso de carcinogénesis: desde la iniciación hasta la progresión tumoral. La sobreexpresión de COX-2 tiene un efecto antiapoptótico sobre las células tumorales[164] y estimula la angiogénesis en el tejido tumoral[165-168].

En la piel, se ha observado que el daño producido por la RUV determina una sobreexpresión de COX-2[169,170]. Nuestra hipótesis plantea que las variantes histológicas superficial y nodular de CBC presentan expresiones más bajas de COX-2 que otras variantes más agresivas, como la morfeiforme, micronodular o infiltrativa, lo cual puede ser debido al uso de AINEs. En apoyo de esta hipótesis, un estudio reciente en muestras histológicas de CBC ha mostrado que la expresión de COX-2 es más alta en CBC morfeiformes en comparación con otros subtipos histológicos como el superficial, en el cual la expresión de COX-2 era baja o nula. Estos autores sugieren que esta sobreexpresión de COX-2 puede ser una de las causas de que estas variantes tumorales sean más agresivas y recurrentes[171].

El mecanismo exacto por el que estos fármacos ejercen un efector preventivo en oncología no está claramente definido, pero parece estar relacionado con la alteración de los metabolitos derivados del ácido araquidónico, como las prostaglandinas (PGs),

que modulan distintas señales de transducción en múltiples procesos como: angiogénesis, apoptosis, respuesta inmune, adhesión celular, proliferación, diferenciación e invasión tumoral. En la piel fotodañada, se han observado niveles elevados de PG E2, F2 Y J2[142]. La PG E2 es inducida por la COX-2 y ejerce un efecto de tolerancia inmune durante el proceso de desarrollo y progresión tumoral[172], así como una supresión de las funciones de las células dendríticas y de la respuesta antitumoral de los linfocitos T[173]. La inhibición de la producción de PGs con AINEs podría reducir la progresión maligna del tumor y aumentar la supresión ejercida por las células inmunológicas.

Junto a todos estos mecanismos dependientes de COX-2, la COX-2 induce un estado crónico de inflamación que puede ser crucial en la agresividad histológica del CBC. Como hemos expuesto previamente, análisis de microarrays han demostrado un estado dinámico en el microambiente inmune asociado al CBC[142]: La presencia de células dendríticas inmaduras, citoquinas Th2 (IL-4, IL-10) y reguladores T (linfocitos T CD4, CD25 y células FoxP3) permitirían la invasión y agresividad del tumor. Por el contrario, la presencia de linfocitos CD8, la expresión de genes asociados al interferón (IFI-27, IRF-1, IRF-7 and G1P2) y las IL-12 y IL-23 determinaría una respuesta antitumoral por parte del huésped. Nuestra hipótesis plantea que los CBC-HA expresarían el primer patrón de inflamación inducido por la COX-2, mientras que los CBC más indolentes expresarían el segundo patrón.

En el carcinoma espinocelular, se ha observado que la expresión de COX-2 inducía la producción de IL-10, linfocitos T CD4, CD25 y células FoxP3 que son responsables del estado de inmunosupresión local[174]. El uso de AINEs, como el diclofenaco, bloquea la

producción de COX-2. Nuestra hipótesis es que el mismo mecanismo podría suceder en el CBC.

La inflamación y la respuesta inmune juegan un papel clave en el dinámico proceso de interacciones huésped-tumor, el cual determina la agresividad o no del CBC, limitando o permitiendo su progresión. La evidencia científica apoya la hipótesis de que la sobreexpresión de COX-2 en los tumores humanos con inflamación crónica asociada se acompaña de una supresión de la respuesta inmune[142,174]. El efecto de los AINEs en la histología del CBC podría responder al establecimiento de un control más eficiente y duradero sobre las células tumorales gracias a la activación de la inmunidad, tanto innata como adaptativa. Esta efecto incluiría la activación de las células dendríticas, la presentación de antígenos tumorales, la citotoxicidad ejercida por los linfocitos T y la activación de genes asociados a interferon.

5.6. ANÁLISIS DE FACTORES ASOCIADOS A EXTIRPACIÓN QUIRÚRGICA INCOMPLETA DEL CBC

Como hemos expuesto previamente en la introducción de esta tesis, la extirpación quirúrgica continúa siendo el "*golden estándar*" del tratamiento de CBC: Es la modalidad de tratamiento más utilizada a nivel mundial[92] y además, se considera un importante indicador de excelencia clínica y quirúrgica[93].

En este trabajo hemos estudiado la tasa de extirpación incompleta de nuestro hospital, y hemos obtenido una cifra del 14.01%. Estudios previos publicados arrojan cifras del 6.3 al 25%[175-185], por lo que consideramos que nuestros resultados son compatibles con los de la literatura previa.

Aquellos tumores localizados en áreas diferentes de la cabeza presentaban menos riesgo de extirpación incompleta que los localizados en la cabeza. Las áreas de máximo riesgo dentro de la cabeza fueron: canto interno (23.1% de extirpaciones incompletas), mejilla (20%), región auricular (18.2%) y región periocular (17.3%). Estos hallazgos son compatibles con los publicados en la literatura[93,177,178,186,187], y pueden deberse a la proximidad de estructuras vitales y a consideraciones cosméticas a la hora de proceder a la intervención.

Aquellos tumores con diámetro > 20 mm tenían más riesgo de ser extirpados de forma parcial comparados con los de diámetro < 10 mm. Este hallazgo es compatible con otros trabajos previos, que sugieren que el crecimiento subclinico del CBC es mayor cuanto mayor es el tamaño de la lesión[185].

En cuanto a las variantes histológicas, el riesgo de márgenes positivos fue significativamente más elevado en el morfeiforme y en el superficial. Estos mismos hallazgos se han obtenido en publicaciones previas[93,186,187]. La variante morfeiforme de CBC se presenta clínicamente como lesiones blanco-amarillentas, de bordes indurados y poco definidos. Estas características hacen que la delimitación de los márgenes no sea clara, lo que explica que la extirpación de este tumor sea incompleta en ocasiones. Del mismo modo, la variante superficial presenta márgenes pobremente definidos y muestra tasa altas de escisión incompleta.

Un hallazgo interesante de nuestro análisis es la relación positiva entre el espesor tumoral y el riesgo de extirpación incompleta. Del mismo modo que las lesiones de mayor tamaño tenían más riesgo de ser extirpadas parcialmente, observamos que la

invasión en profundidad del tumor era un factor de riesgo independiente de extirpación incompleta: Los tumores de mayor grosor (> 6.0 mm) estadísticamente tenían más tasa de extirpación incompleta que los tumores más delgados (< 3.0 mm). Este hallazgo puede ser considerado un factor de confusión, donde los tumores de mayor grosor predominarían en áreas anatómicas de reconocido riesgo de excisión parcial, como el área periocular o periauricular. Sin embargo, de los 13 tumores de grosor > 6.0 mm en nuestro trabajo, solo 2 se localizaban en la cabeza (frente y nariz). Los CBC grandes e infiltrativos, de reconocido riesgo de extirpación incompleta[93,185], tienen un crecimiento asimétrico en profundidad[188]. Esta característica añade dificultad a la excisión en profundidad, aunque la lesión haya sido extirpada correctamente en superficie, contribuyendo de este modo al aumento de márgenes positivos en este tipo de lesiones. Este hallazgo es interesante desde el punto de vista quirúrgico puesto que la afectación del margen profundo por el tumor hace que las recurrencias se detecten más tardíamente y la reexcisión de estas lesiones sea más complicada.

Otro hallazgo de interés observado fue el hecho de que la presencia de elastosis solar en la piel perilesional se asociaba con mayor riesgo de excisión parcial de la lesión. Como hemos expuesto previamente, la elastosis cutánea se manifiesta clínicamente como zonas de piel amarillentas con presencia de arrugas, áreas discrómicas y atróficas. Estos cambios cutáneos añaden dificultad para la delimitación de los márgenes de la lesión, sobre todo en aquellas pieles con elastosis cutánea severa, y pueden explicar los hallazgos observados en nuestro análisis. Un estudio piloto llevado por Skaria y colaboradores[189] obtuvo resultados similares a los nuestros: estos autores concluyen que la elastosis solar es un factor clave en la cirugía dermatológica y que debería tenerse en

cuenta en la práctica quirúrgica diaria con objeto de reducir la tasa de extirpación incompleta.

5.7. EXTIRPACIÓN QUIRÚRGICA INCOMPLETA DE CBC FACIALES. INFLUENCIA DE LA ELASTOSIS SOLAR

En la última publicación que aparece en esta tesis, analizamos la tasa de extirpación incompleta de CBC faciales intervenidos en nuestro centro. Seis áreas anatómicas faciales diferentes se definieron para realizar este estudio: Nasal, Orbitopalpebral, Labial, Malar, Frontal y Auricular.

Obtuvimos una tasa de extirpación incompleta de 17.07%. Esta cifra es ligeramente superior a la publicada por estudios previos: Bogdanov-Berezovsky y colaboradores[184] obtuvieron una tasa de 15.74%, mientras que Bhatti et al[190] y Su et al[93] de 14.1% y 14.5% respectivamente. Sin embargo, pensamos que esta cifra se puede considerar buena, teniendo en cuenta que en nuestro centro de trabajo la técnica micrográfica de Mohs no se encuentra disponible, lo que hace que la intervención de algunas lesiones faciales sea un desafio terapeútico.

De las seis áreas anatómicas analizadas, la orbitopalpebral y la auricular mostraron las tasas de extirpación incompleta más altas en nuestro trabajo. Este hallazgo es similar al obtenido por estudios previos[191-193]. Estas dos áreas forman parte de la llamada "zona H" facial. La zona H hace referencia a localizaciones de fusión embrionaria cutánea, de modo que los tumores que asienta en esta zona tienen mayor riesgo de excisión incompleta y recurrencia[177]. Cuando se realiza una excisión parcial de un CBC facial, la evidencia científica apoya la reexcisión de la lesión, puesto que se ha observado que un

24% de los CBCs faciales extirpados de manera parcial se transforman en formas histológicas más agresivas, especialmente los localizados en áreas periocular, periauricular y perinasal[194]. Por ello, en los CBCs faciales localizados en la zona H, se debe llevar a cabo una intervención quirúrgica con especial atención a los márgenes quirúrgicos, con objeto de evitar una excisión parcial y una posterior recurrencia agresiva del tumor. En la cirugía de los CBCs en la zona H se ha observado que el grado de extensión subclínica de estos tumores puede ser mayor que en otras localizaciones: En un estudio retrospectivo de 1131 casos de CBCs faciales intervenidos mediante cirugía de Mohs, los autores concluyen que el grado de invasión subclínica es mayor en el párpado, nariz y oreja comparado con la mejilla[195]. Esta invasión subclínica más avanzada en determinadas áreas puede explicar el mayor riesgo de extirpación parcial en las áreas orbitopalpebral y auricular observadas en nuestro centro.

Para realizar una extirpación completa del tumor las guías terapeúticas aconsejan márgenes de **3 mm** para los CBC de pequeño tamaño (< 20 mm) que no sean morfeiformes ni infiltrativos, y márgenes de **10 mm** para los CBCs morfeiformes, infiltrativos y CBC de gran tamaño (> 20 mm)[196]. Sin embargo, debido a la importancia del resultado cosmético final en los CBCs faciales, la cirugía puede diferir significativamente comparada con la llevada a cabo en CBC localizado en otras áreas. En nuestro estudio el margen quirúrgico de resección varíaba de 1 a 7 mm. Este amplio rango responde a la localización anatómica de las lesiones: En algunos casos, el tumor asienta en contacto directo con estructuras funcionales que dificultan la resección del modo indicado por las guías terapéuticas. De hecho, en nuestro estudio los CBC de gran tamaño (> 20 mm) constituían el 2.5% de las lesiones intervenidas, y ninguna de ellas

fueron extirpadas con márgenes ≥ 10 mm; los CBC de pequeño tamaño sumaban el 97.5% de todos los tumores, pero solo el 12.5% fueron extirpadas con márgenes ≥ 3 mm.

En nuestro análisis, los márgenes más amplios (≥ 3mm) se realizaron en las áreas frontal, labial y malar, que pueden considerarse localizaciones relativamente distantes de estructuras funcionales. En el lado opuesto, las áreas auricular, nasal y orbitopalpebral tenían los márgenes de excisión más estrechos. Esto se explica porque la extirpación de lesiones faciales cerca de estructuras funcionales con márgenes de resección adecuados puede resultar en una pérdida de tejido sano excesiva, y la posterior secuela cosmética, máxime en centros sin disponibilidad de cirugía micrográfica de Mohs.

Otros factores asociados a márgenes quirúrgicos positivos de CBCs faciales son similares a los observados en el estudio ***"Análisis de factores asociados a extirpación quirúrgica incompleta del cbc"***. A continuación, se presentan de manera breve estos factores, y para más detalle, se remite a la discusión de dicho trabajo expuesta previamente:

- ***Tamaño tumoral:*** Los CBC >20 mm y CBC 10-20 mm mostraron estadísticamente más riesgo de extirpación incompleta que los CBC < 10 mm.

- ***Variantes histológicas:*** Los subtipos morfeiforme y superficial tenían mayor riesgo de extirpación con márgenes quirúrgicos positivos.

- *Espesor tumoral*: Los tumores de mayor grosor (> 6.0 mm) estadísticamente tenían más tasa de extirpación incompleta que los tumores más delgados (< 3.0 mm).

- *Elastosis solar:* La presencia de elastosis moderada y severa en la piel adyacente al tumor se asociaba significativamente con mayor riesgo de extirpación parcial del tumor.

CONCLUSIONES

1. Existe un retraso en el diagnóstico del Carcinoma Basocelular en nuestra área de trabajo. El principal motivo de retraso es la decisión inicial del paciente de acudir a consulta. Otros factores asociados son: Edad mayor de 65 años, localización en áreas diferentes de cabeza y cuello, lesiones asintomáticas, y ausencia de historia personal y familiar de Carcinoma Basocelular.

2. La elastosis solar y el envejecimiento de la piel, factores importantes en la etiopatogenia del Carcinoma Basocelular, se modifican con la dieta: El consumo de té y de alimentos ricos en vitamina E y C se asocia a menor elastosis.

3. En los trabajadores expuestos a RUV es mayor el riesgo de desarrollar Carcinoma Basocelular nodular y la edad de aparición es más tardía. En los trabajadores no expuestos el tumor se desarrolla a edad más temprana y la forma clínica más frecuente es la superficial.

4. El consumo de alcohol se asocia a formas histológicas más agresivas de Carcinoma Basocelular.

5. El uso de AINEs se asocia a formas histológicas menos agresivas de Carcinoma Basocelular.

6. La tasa de extirpación incompleta de Carcinoma Basocelular en nuestro hospital es de 14.01%. Los factores asociados son: Localización periocular y periauricular, tamaño mayor de 20 mm., espesor mayor de 6 mm., subtipos superficial y morfeiforme y elastosis solar moderada y/o severa.

7. Los tumores localizados en las áreas orbitopalpebral y auricular, y aquellos asociados a elastosis moderada y/o severa se asocian a mayor riesgo de extirpación incompleta.

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