J Korean Med Sci 2000; 15: 545-50
ISSN 1011-8934

Sebaceous Carcinoma of the Eyelids: Frequent Expression of c-erbB-2 Oncoprotein

Ocular sebaceous carcinoma (OSC) is an uncommon malignancy with a potential to recur and metastasize. Some characteristics of sebaceous carcinoma, such as female preponderance, shown in the present series during 11-year period at Korea Cancer Center Hospital, led us to study their hormone receptors and c-erbB-2 expression. c-erbB-2 overexpression was very common (83%) in OSC, and was not associated with pathologic findings or clinical outcome. Interestingly, estrogen and progesterone receptor was detected in 4 and 2 cases, respectively, suggesting a role of hormonal influence on this neoplasm. Immunohistochemical and clinicopathologic features of 18 cases of OSC in Korea are presented.

Key Words: *Carcinoma; Sebaceous Glands; Eyelids; Immunohistochemistry; erbB-2; Receptors, Estrogen; Receptors, Progesterone*

Kyung-Ja Cho, Shin-Kwang Khang, Jae-Soo Koh*, Jin-Haeng Chung*, Seung-Sook Lee*

Department of Pathology, University of Ulsan College of Medicine, Seoul, Korea
Department of Anatomic Pathology*, Korea Cancer Center Hospital, Seoul, Korea

Received: 23 March 2000
Accepted: 9 June 2000

Address for correspondence
Kyung-Ja Cho, M.D.
Department of Pathology, University of Ulsan College of Medicine, 388-1 Poongnap-dong, Songpa-gu, Seoul 138-040, Korea
Tel: +82.2-2224-4545, Fax: +82.2-472-7898
E-mail: kjc@www.amc.seoul.kr

INTRODUCTION

Sebaceous carcinoma is an uncommon malignant tumor of the skin adnexae, which occurs most frequently in the eyelids, where it accounts for up to 5.5% of malignancy (1, 2). The incidence appears to be greater in women than men in many reported series (1-4). In addition to the female preponderance, which prompted us to suspect a hormonal influence on sebaceous carcinoma, this neoplasm shares a tendency for intraepithelial pagetoid spread with ductal carcinoma of the breast. Paget's disease of the breast is known to show high incidence of c-erbB-2 overexpression (5, 6), and a hypothesis that c-erbB-2 oncoprotein mediates the influence of a chemotactic factor released by epidermal keratinocytes has been proposed (6). Literature review shows only one study on c-erbB-2 expression of sebaceous carcinoma, with results of low positive rate (7). We present 18 cases of sebaceous carcinoma of the eyelids from Korea Cancer Center Hospital, with immunohistochemical study for c-erbB-2 oncoprotein, estrogen receptor and progesterone receptor.

MATERIALS AND METHODS

Eighteen cases of sebaceous carcinoma of the eyelids, treated at Korea Cancer Center Hospital from 1987 through 1998, were examined. Clinical data including age, sex, location of the tumors, treatment modalities and outcome were obtained from the medical records. Histological review was focused on the presence of sebaceous differentiation with abundant vacuolated cytoplasm, nuclear pleomorphism, squamous or basaloid differentiation, and intraepithelial pagetoid spread, and on the type of the gland of origin. Immunohistochemical staining for c-erbB-2, estrogen receptor (ER), and progesterone receptor (PR) was performed on formalin-fixed, paraffin-embedded tissue sections using avidin-biotin-peroxidase complex method. Briefly, after deparaffinization and rehydration, all sections were subjected to microwave retrieval in 5% citrate buffer. Endogenous peroxidase activity was blocked with hydrogen peroxide. After treatment with normal serum to minimize background staining, the sections were incubated for 60 min with primary antibodies: rabbit anti-human c-erbB-2 oncoprotein (Dako, Denmark), mouse anti-human ER (Dako, Denmark), and mouse anti-human PR (Dako, Denmark). Visualization with streptavidin-HRP complex (Dako, Denmark) and diaminobenzidine followed. The results were interpreted as positive only when cytoplasmic membrane staining for c-erbB-2, and nuclear staining for ER and PR were distinct in more than 5% of tumor areas. Statistical comparison of clinico-pathologic features

between c-erbB-2 positive and negative cases, and between hormone receptor positive and negative cases was done using chi-square test.

RESULTS

Clinical findings and outcome

The patients were 14 females and 4 males, with a mean age of 59 years (range 39-86). The tumors occurred at the same ratio in the upper and lower (9:9), and the right and left (9:9) eyelids. Four patients had initially presented as recurrent disease with histories of tumor excision and/or radiation 2-10 years previously. Duration of initial symptom in the remaining 14 patients, mostly of eyelid mass, ranged from 1 month to 6 years. Surgical excision was done in all cases. One patient had neck metastasis at the time of operation and was given adjuvant radiotherapy. Another patient developed local recurrence 30 months after the operation, and was treated with excision and radiation. Despite adjuvant therapy, the aforementioned four patients with recurrent presentation developed repeated recurrences, leading to a fatal outcome in one. Except for this case, 17 patients are alive, with or without disease, after a follow-up period of 6 months to 17 years.

Pathologic findings

The tumors appeared to have arisen from the meibomian glands in 11, from the glands of Zeis in 4, and from undetermined origin in 3 cases. They were histologically characterized by invasive solid nests or lobules consisting of rather large round cells with distinct cytoplasmic membrane, abundant pale basophilic, foamy, or vacuolated cytoplasms, and round vesicular nuclei with prominent nucleoli (Fig. 1). Some cases contained occasional areas featuring small cells with peripheral palisading, resembling basal cell carcinoma (Fig. 2). Foci of keratinization was observed in 3 cases (Fig. 3). Comedo-type necrosis was not uncommon, being noted in 7 cases (Fig. 4). The proportions of typical sebaceous differentiation and the degree of nuclear pleomorphism varied case by case. According to the current classification based on degree of sebaceous differentiation (5), 5, 6 and 7 cases were classified as well, moderately and poorly differentiated groups, respectively. Intraepithelial pagetoid spread of the tumor cells was present in 5 cases.

Immunohistochemical findings

Fifteen cases (83%) showed c-erbB-2 overexpression of the tumor cells (Fig. 5). c-erbB-2 positive (15 cases) and negative (3 cases) groups did not show significant difference in differentiation, presence of pagetoid spread, and clinical ourcome. ER and PR were focally detected in 4 and 2 cases, respectively (Fig. 6). ER or PR-positive group (6 cases) showed no specific clinico-pathologic fea-

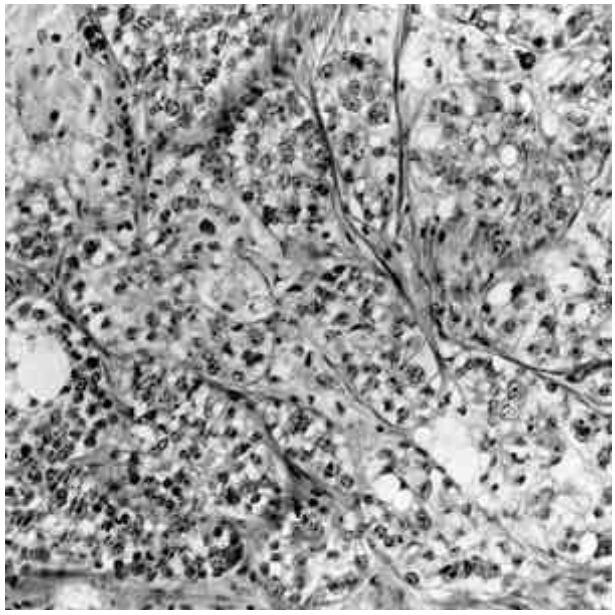

Fig. 1. Photomicrograph of ocular sebaceous carcinoma shows solid lobular growth of large round cells with round vesicular nuclei, distinct cytoplasmic membrane and abundant foamy cytoplasm (Case 12, H&E, ×600).

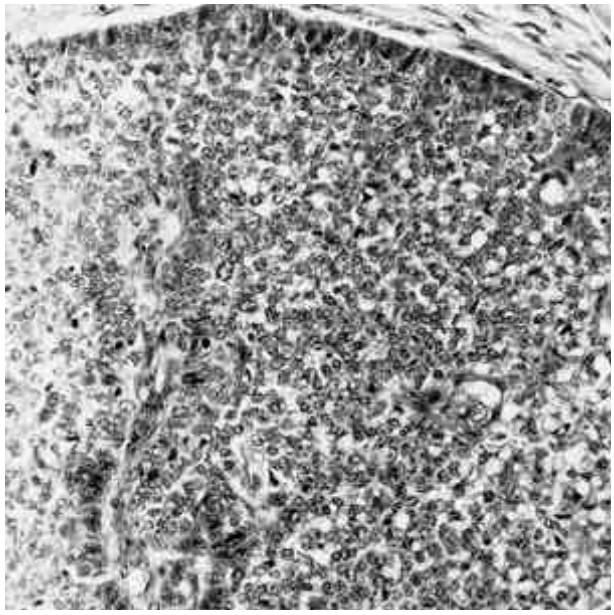

Fig. 2. Peripheral palisading of small uniform cells in sebaceous carcinoma, resembling basal cell carcinoma (Case 15, H&E, ×600).

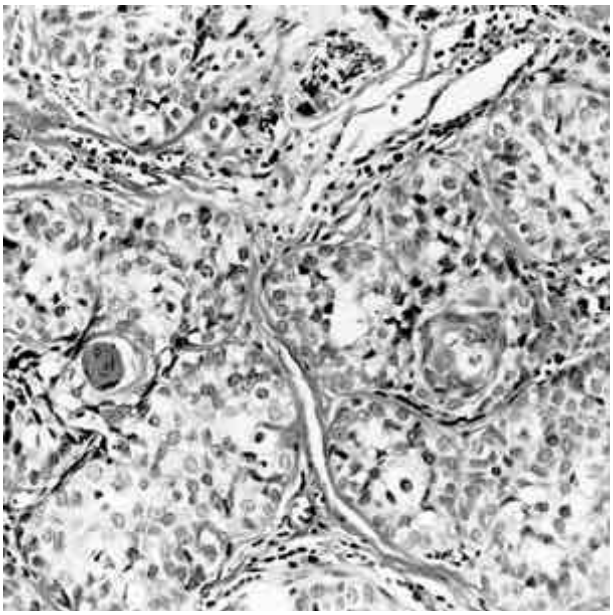

Fig. 3. Foci of keratinization in sebaceous carcinoma (Case 9, H&E, ×600).

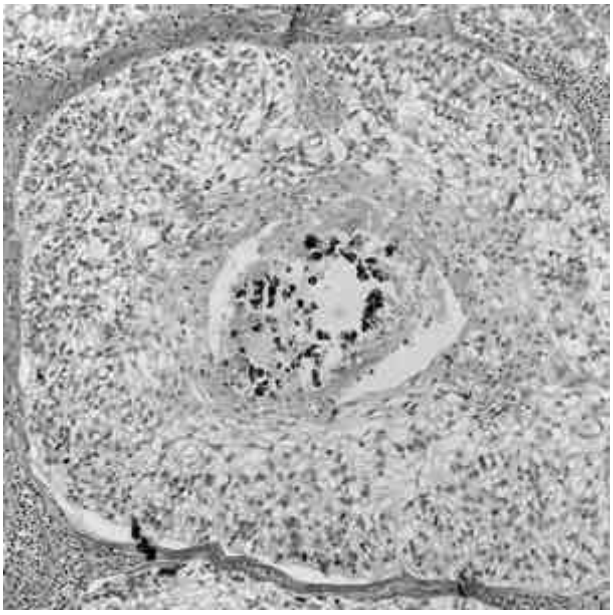

Fig. 4. Comedo-type necrosis at center of tumor cell nests in sebaceous carcinoma (Case 14, H&E, ×400).

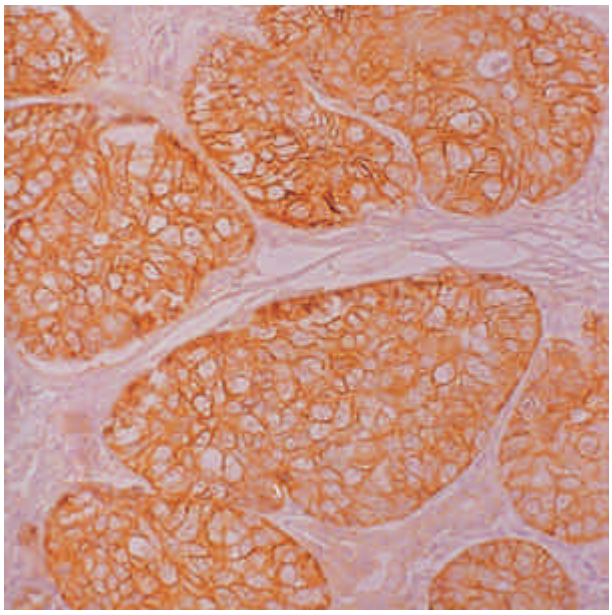

Fig. 5. Diffuse and strong reaction for c-erbB-2 oncoprotein along cell membrane of sebaceous carcinoma (Case 9, immunostain, ×600)

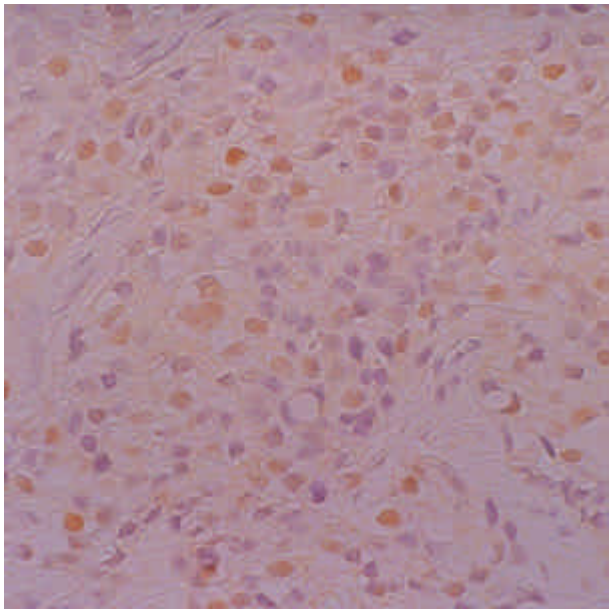

Fig. 6. Nuclear positivity for progesterone receptor in sebaceous carcinoma (Case 18, immunostain, ×800).

tures, except for their female gender in all. Clinical, pathologic and immunohistochemical findings are listed in Table 1.

DISCUSSION

Ocular sebaceous carcinoma (OSC) was known to have a higher incidence in the Asian population, however, this assumption was based on one large series from Shanghai (3), which comprised 156 cases in a 22-year period. Other reports from Japan and Singapore, and our series has not shown significantly higher incidence than those from U.S.A. or U.K. (8-14). Globally, sebaceous carcinoma of the eyelids appears to be a rare neoplasm.

The etiology of sebaceous carcinoma is unknown, however, reported cases following radiation therapy for retinoblastoma or other diseases (15-19) suggest a role of

Table 1. Summary of clinical, pathologic and immunohistochemical findings in 18 patients with ocular sebaceous carcinoma

Case No.	Sex/Age	Site	Differentiation	Paget	c-erbB-2	ER/PR	Recurrence	Outcome
1	F/50	RLL, M	W	-	-	-/-	-	NED
2	F/63	LLL, U	W	-	±	-/-	+ (L)	NED
3	F/65	RUL, Z	M	-	++	-/-	-	NED
4	F/59	RLL, M	W	-	++	+/-	-	NED
5	F/51	LUL, M	M	+	++	+/-	-	NED
6	F/56	LLL, M	M	-	++	-/-	+ (L)	AWD
7	M/56	LUL, M	P	-	-	-/-	-	NED
8	F/60	RUL, Z	M	+	+	-/-	-	NED
9	M/67	RLL, M	M	-	+++	-/-	+ (L)	NED
10	M/50	RUL, U	P	-	++	-/-	+ (S)	DOD
11	F/53	LUL, M	P	+	++	+/-	-	NED
12	F/66	RUL, M	W	-	++	-/-	-	NED
13	M/55	LUL, Z	P	+	++	-/-	-	NED
14	F/51	RLL, M	W	-	+	-/+	*	NED
15	F/39	LLL, Z	P	+	+	-/-	-	NED
16	F/79	RLL, M	P	-	+	-/-	-	NED
17	F/86	LUL, M	M	-	+	+/-	-	NED
18	F/53	LUL, U	P	-	++	-/+	+ (L)	AWD

Paget, intraepithelial pagetoid spread; ER, estrogen receptor; PR, progesterone receptor; RLL, right lower lid; LLL, left lower lid; RUL, right upper lid; LUL, left upper lid; M, meibomian gland; Z, gland of Zeis; U, undetermined origin; L, local; S, systemic; *, initial neck metastasis; NED, alive with no evidence of disease; AWD, alive with disease; DOD, died of disease

irradiation as a risk factor for sebaceous carcinoma. OSC is a disease of the elderly, with reported averages of 57-74 years. It could be assumed that a life-long exposure to minor x-rays or UV lights might have contributed to the development of this neoplasm. A study from Japan has reported a high percentage (61.9%) presence of HPV DNA in OSC (20), but the fact does not necessarily place the HPV as a cause of OSC. We could not detect HPV DNA using in situ hybridization on this series (data not shown).

It is worthy to note that OSC is more common in females than in males. This tendency was marked in this series (female to male ratio 3.5:1), ranking as one of the highest ratios among the published series, which have shown the ratio of 1.0-3.3:1. The female preponderance for OSC, anatomical proximity of the sebaceous glands to the breast, and histologic resemblance of carcinomas from each organ led us to suspect a role of endocrine influence on OSC.

Fraser et al. observed consistent expression of estrogen-related protein (ERP) in normal epidermis, sebaceous glands, hair follicles and sweat ducts, thus concluding these organelles must be considered as estrogen target tissues (21). However, in a study on 114 sebaceous and sweat gland neoplasms, ERP was not found in 24 sebaceous carcinomas (22). We applied ER and PR immunohistochemistry on 18 OSC, resulting in a focal but unequivocal positivity in 4 and 2 cases, respectively. These 6 patients were all female. To our knowledge, this is the first report to document the presence of ER and PR in sebaceous carcinoma, and the results suggest a hormonal influence on this neoplasm and a possibility of hormonal therapy.

c-erbB-2 oncoprotein, which is an important oncogene in breast ductal carcinoma, has been known to be expressed in the sebaceous glands of the fetal and adult skin, but in a cytoplasmic form (23). There has been one other study on c-erbB-2 expression of sebaceous carcinoma showing membrane positivity in only 3 out of 13 cases (7). In our study, c-erbB-2 overexpression was common in OSC (15/18), suggesting c-erbB-2 oncogene plays a significant role in the development or progression of sebaceous carcinoma.

In regards to breast cancer, the incidence of c-erbB-2 overexpression has been known to be higher in Paget's disease and intraductal carcinoma than in invasive ductal carcinoma (5, 6). de Potter et al. asserted that the Paget cells spread through the epidermis due to motility induced by epidermal keratinocytes, whose influence is mediated by c-erbB-2 protein (6). Intraepithelial pagetoid spread is one of the characteristics of sebaceous carcinoma, with reported frequencies of 16-80% (2-4, 10-13). Our series included 5 cases (27%) with pagetoid spread, of which only 3 cases showed c-erbB-2 overexpression. This result was unexpected and different from the breast cases. In the breast, negative association of

hormone receptor and c-erbB-2 expression is frequently described (24), but all 6 OSCs with positive hormone receptor were also c-erbB-2 positive in this study.

The histology of sebaceous carcinoma can be nonspecific, but the hallmark is the presence of sebaceous differentiation, featuring abundant foamy cytoplasm which positively stains on fat staining. Classification schemes based on growth patterns, i.e. lobular, comedocarcinoma, papillary and combined (25); on histologic pattern, i.e. differentiated, squamoid, basal cell, adenoid and spindle cell (3); and on the degree of sebaceous differentiation, i.e. well, moderately and poorly differentiated (4) or grade I-IV (10) have been proposed. As these classifications indicate, sebaceous carcinoma can be poorly differentiated, or resemble squamous cell carcinoma or basal cell carcinoma. Since fat staining result is usually unsatisfactory on paraffin-embedded tissue, differential diagnosis can be difficult, especially on small biopsies which show limited features of the lesions.

According to a review of 43 cases from the Mayo Clinic, only 16 cases were initially diagnosed as sebaceous carcinoma (10). Our series also included 6 cases which had been initially diagnosed as basal cell carcinoma or squamous cell carcinoma with or without sebaceous differentiation. In comparison with basal cell carcinoma, the undifferentiated cells of sebaceous carcinoma are known to show more eosinophilic cytoplasm, greater cytologic atypia and greater invasiveness (1). Sebaceous carcinoma can show focal keratinization, but not true squamous differentiation with glassy cytoplasm and intercellular bridges (2).

OSC is an aggressive neoplasm with a tendency to recur locally or metastasize by lymphatics, hematogenously or by lacrimal systems. Factors reported to be related to poor prognosis include multicentric origin, poor sebaceous differentiation, intraepithelial pagetoid distortion, highly infiltrative growth, vascular or lymphatic invasion, longer duration and large size (1, 4, 13). The significance of histologic differentiation and pagetoid involvement has been debatable (9, 11). Another practical prognostic factor appears to be the treatment modality. Aggressive surgical excision with frozen section monitoring of resection margins is recommended (11), with significantly better outcome with surgical margin of more than 5 mm having been described (8, 12). The Korea Cancer Center Hospital has also been carrying out wide excision with frozen section monitoring for eyelid malignancy, and the importance of wide excision is acknowledged since only one patient among 14 developed local recurrence. Prognostic significance of histologic or immunohistochemical findings could not be tested in this series, since the patient outcome did not vary significantly.

ACKNOWLEDGMENT

We are grateful to Dr. Tai Won Lee and Dr. Sung Wook Yang, who formerly worked at the Department of Ophthalmology, Korea Cancer Center Hospital, for their contribution to the patients with ocular sebaceous carcinoma.

REFERENCES

1. Nelson BR, Hamlet KR, Gillard M, Railan D, Johnson TM. *Sebaceous carcinoma. J Am Acad Dermatol 1995; 33: 1-15.*
2. Kass LG, Hornblass A. *Sebaceous carcinoma of the ocular adnexa. Surv Ophthalmol 1989; 33: 477-90.*
3. Ni C, Kuo PK. *Meibomian gland carcinoma. A clinicopathological study of 156 cases with long-period follow-up of 100 cases. Jpn J Ophthalmol 1979; 23: 388-401.*
4. Rao NA, Hidayat AA, McLean IW, Zimmerman LE. *Sebaceous carcinomas of the ocular adnexa: a clinicopathologic study of 104 cases, with five-year follow-up data. Hum Pathol 1982; 13: 113-22.*
5. De Potter CR. *The neu-oncogene: more than a prognostic indicator? Hum Pathol 1994; 25: 1264-8.*
6. De Potter CR, Eeckhout I, Schelfhout AM, Geerts ML, Roels HJ. *Keratinocyte induced chemotaxis in the pathogenesis of Paget's disease of the breast. Histopathology 1994; 24: 349-56.*
7. Hasebe T, Mukai K, Yamaguchi N, Ishihara K, Kaneko A, Takasaki Y, Shimosato Y. *Prognostic value of immunohistochemical staining for proliferating cell nuclear antigen, p53, and c-erbB-2 in sebaceous gland carcinoma and sweat gland carcinoma: comparison with histopathological parameter. Mod Pathol 1994; 7: 37-43.*
8. Dogru M, Matsuo H, Inoue M, Okubo K, Yamamoto M. *Management of eyelid sebaceous carcinomas. Ophthalmologica 1997; 211: 40-3.*
9. Tan KC, Lee ST, Cheah ST. *Surgical treatment of sebaceous carcinoma of eyelids with clinico-pathological correlation. Br J Plast Surg 1991; 44: 117-21.*
10. Wolfe JT III, Campbell RJ, Yeatts RP, Waller RR, Wick MR. *Sebaceous carcinoma of the eyelid. Errors in clinical and pathologic diagnosis. Am J Surg Pathol 1984; 8: 597-606.*
11. Doxanas MT, Green WR. *Sebaceous gland carcinoma. Review of 40 cases. Arch Ophthalmol 1984; 102: 245-9.*
12. Epstein GA, Putterman AM. *Sebaceous adenocarcinoma of the eyelid. Ophthalmic Surg 1983; 14: 935-40.*
13. Zurcher M, Hintschich CR, Garner A, Bunce C, Collin JR. *Sebaceous carcinoma of the eyelid: a clinicopathological study. Br J Ophthalmol 1998; 82: 1049-55.*
14. Pickford MA, Hogg FJ, Fallowfield ME, Webster MH. *Sebaceous carcinoma of the periorbital and extraorbital regions. Br J Plast Surg 1995; 48: 93-6.*
15. Howrey RP, Lipham WJ, Schultz WH, Buckley EG, Dutton

JJ, Klintworth GK, Rosoff PM. *Sebaceous gland carcinoma. A subtle second malignancy following radiation therapy in patients with bilateral retinoblastoma. Cancer 1998; 83: 767-71.*

16. Rumelt S, Hogan NR, Rubin PA, Jakobiec FA. *Four-eyelid sebaceous cell carcinoma following irradiation. Arch Ophthalmol 1998; 116: 1670-2.*
17. Draper GJ, Sanders BM, Kingston JE. *Second primary neoplasms in patients with retinoblastoma. Br J Cancer 1986; 53: 661-71.*
18. Hood IC, Qizilbash AH, Salama SS, Young JE, Archibald SD. *Sebaceous carcinoma of the face following irradiation. Am J Dermatopathol 1986; 8: 505-8.*
19. Lemos LB, Santa Cruz DJ, Baba N. *Sebaceous carcinoma of the eyelid following radiation therapy. Am J Surg Pathol 1978; 2: 305-11.*
20. Hayashi N, Furihata M, Ohtsuki Y, Ueno H. *Search for accumulation of p53 protein and detection of human papillomavirus genomes in sebaceous gland carcinoma of the eyelid. Virchows Arch 1994; 424: 503-9.*
21. Fraser D, Padwick ML, Whitehead M, Coffer A, King RJ. *Presence of an oestradiol receptor-related protein in the skin: changes during the normal menstrual cycle. Br J Obstet Gynaecol 1991; 98: 1277-82.*
22. Swanson PE, Mazoujian G, Mills SE, Campbell RJ, Wick MR. *Immunoreactivity for estrogen receptor protein in sweat gland tumors. Am J Surg Pathol 1991; 15: 835-41.*
23. De Potter CR, Daele SV, Van de Vijver MJ, Pauwels C, Maertens G, De Boever J, Vandekerckhove D, Roels H. *The expression of the neu oncogene product in breast lesions and in normal fetal and adult human tissues. Histopathology 1989; 15: 351-62.*
24. Poller DN, Snead DRJ, Roberts EC, Galea M, Bell JA, Gilmour A, Elston CW, Blamey RW, Ellis IO. *Oestrogen receptor expression in ductal carcinoma in situ of the breast: relationship to flow cytometric analysis of DNA and expression of the c-erbB-2 oncoprotein. Br J Cancer 1993; 68: 156-61.*
25. Rao NA, McLean JW, Zimmerman LE. *Sebaceous carcinoma of the eyelid and caruncle: correlation of clinicopathologic feature with prognosis. In: Jacobiec FA, ed. Ocular and adnexal tumors. Birmingham: Aesculapuis, 1978; 461-7.*