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Case-Control Study of Female Hormones and Eye Melanoma[1]

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ABSTRACT

In a case-control study, we compared 238 women with intraocular malignant melanoma to 223 matched controls with detached retinas to evaluate the influence of hormonal factors on the risk of this cancer. We observed increased risk among women who had ever been pregnant (relative risk, 1.4; 95% confidence interval, 0.8, 2.2) and women who used replacement estrogens (relative risk, 2.0; 95% confidence interval, 1.2, 3.1), decreased risk among women who had undergone oophorectomy (relative risk, 0.6; 95% confidence interval, 0.4, 1.0), and no change in risk among women who had used oral contraceptives. Compared to hormonal effects on risk of reproductive tumors, these effects were weaker and less consistent, suggesting that hormonal factors may play only a limited role in causing melanomas of the eye.

INTRODUCTION

Although intraocular malignant melanoma is a rare tumor (1), it nonetheless holds considerable interest because of the rapid and unexplained rise in incidence of the related but more common melanomas of the skin (2). Sunlight exposures may influence risk of intraocular (3) as well as cutaneous melanoma (4). Several lines of evidence suggest that hormones also may influence the development of melanomas, including eye melanomas. Hyperpigmentation, reflecting increased activity of the melanocytes, can be induced by hormonal stimuli, including pregnancy, topical estrogens, oral contraceptives, and menopausal replacement estrogens (5). In several surveys, the rates of eye cancer were higher in premenopausal women than in men at similar ages (6, 7). Eye melanomas are also seen more frequently than expected among survivors of breast cancer (8), and breast cancers occur more often than expected among survivors of melanoma of the skin (but not the eye) (9). Oral contraceptive use has also been suggested as a possible cause of skin melanoma (10, 11). We have, therefore, estimated the risk of eye melanoma according to various hormonal factors by using interview and medical record data from a case-control study of intraocular melanoma.

SUBJECTS AND METHODS

Study Population. The cases were 509 consecutive patients with melanoma of the uveal tract (iris, ciliary body, and choroid) seen at the Ocular Oncology Service at Wills Eye Hospital from January 1974 through June 1979. All cases were examined and evaluated by at least one of the authors (J. S. and J. A.). The diagnosis (uveal tract melanoma) was confirmed histopathologically in 298 cases treated by surgery, or was based on reliable ancillary studies in the other 211 cases managed by radiotherapy or other conservative means (12). Ten of the cases were excluded because they did not fulfill the diagnostic criteria.

The controls were patients with detached retinas not due to tumors who were seen at Wills Eye Hospital during the same time period. One control matched by age (within 2 years), sex, race, and date of diagnosis was selected for each case. Details of the ophthalmological examination and medical history were abstracted from the medical records of all cases and controls. Patients with a history of eye tumors or "pseudomelanoma" were not included as controls.

Data Collection. All eligible subjects were asked to participate in a telephone interview in 1979-1980. A total of 444 (89%) of the cases and 424 (85%) of the controls agreed to the 45-min telephone interview which obtained details of past medical history, family history, employment, and exposure to various environmental agents, including sunlight. If the subject was deceased, the next of kin was interviewed, if willing. Next of kin interviews were conducted for 17% of the cases and 14% of the controls. For each group, approximately one-half of the next of kin interviews (8 and 6%, respectively) were with spouses; most of the rest were with first-degree relatives (7 and 7%, respectively. The subjects who declined interview did not differ appreciably in age, sex, race, or location of residence from those who participated in the study.

Hormonal exposures were not the primary focus of the study, but we queried subjects about ages at menarche, at first and last oral contraceptive use, at last pregnancy, and at menopause. We asked whether the ovaries (or an ovary) had been removed, what brands of oral contraceptives and other hormones had been taken, and for how long and what tumors had been diagnosed in the subject or her family. We lacked data on hysterectomy and age at first birth, and we could not distinguish bilateral and unilateral oophorectomies. Exposures occurring after diagnosis were not considered.

Analysis. Assuming that all cases occurring in the Wilmington, DE-Philadelphia, PA Standard Metropolitan Statistical Area were seen at the Wills Eye Hospital, we computed incidence rates, using Bureau of Census estimates of the population. Comparisons were made with incidence rates from the Surveillance, Epidemiology, and End Results Program of 1973-1977 (13).

We measured the effect of a host or environmental factor using the relative risk (RR), the ratio of disease incidence in the exposed to the incidence in the unexposed as estimated by the odds ratio. Following standard methods for analysis of case-control data (14), we used stratified contingency table analysis to adjust for the effect of potentially confounding variables, including the sun exposure variables and matching variables. For multiple levels of exposure, we calculated the P value of the test for linear trend. When it was necessary to control simultaneously for three or more confounding variables, we fitted a logistic regression model with intraocular melanoma as the dependent variable.

The present analysis is restricted to women (237 cases, 223 controls), except as specifically noted in the text. All of the subjects were white. The mean ages were 58.2 among cases (SD = 15.0) and 59.3 among controls (SD = 14.4). We also analyzed some of the exposures, *e.g.*, estrogen use, oophorectomy, and age at menopause, excluding data provided by surrogate respondents. We found the estimates similar to the data provided by all respondents, except as noted in the text, and present only the latter in this report.

RESULTS

The incidence rates for eye melanoma in the white population of greater Philadelphia, PA, and Wilmington, DE, during 1974–1978, are shown in Fig. 1. The age-specific curves were similar for men and women. As shown in Table 1, the incidence rates estimated from our study were similar to those measured in the much larger Surveillance, Epidemiology, and End Results Program for 1973–1977. Men had slightly lower rates of both cutaneous and ocular melanoma before the age of 40 and generally higher rates than women at ages 40–54. At older ages, men had slightly higher skin melanoma rates than women, but

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Table 1 *Age-adjusted incidence of ocular and cutaneous melanoma by sex (cases/million person-years)*

	Male				Female				Sex ratio (male/female)			
	<40	40–54	>55	All ages	<40	40–54	>55	All ages	<40	40–54	>55	All ages
All ocular melanoma												
SEER[a] (1973–1977)	1.3	10.7	22.6	7.6	1.5	6.2	21.0	7.7	0.9	1.7	1.1	1.0
Study (1974–1978)	1.3	11.0	22.6	7.2	2.0	8.3	25.0	7.6	0.7	1.3	0.9	0.9
Cutaneous melanoma												
SEER (1973–1977)	28.5	124.3	167.0	64.9	33.2	107.3	121.5	63.3	0.9	1.2	1.4	1.0

[a] SEER, Surveillance, Epidemiology, and End Results Program.

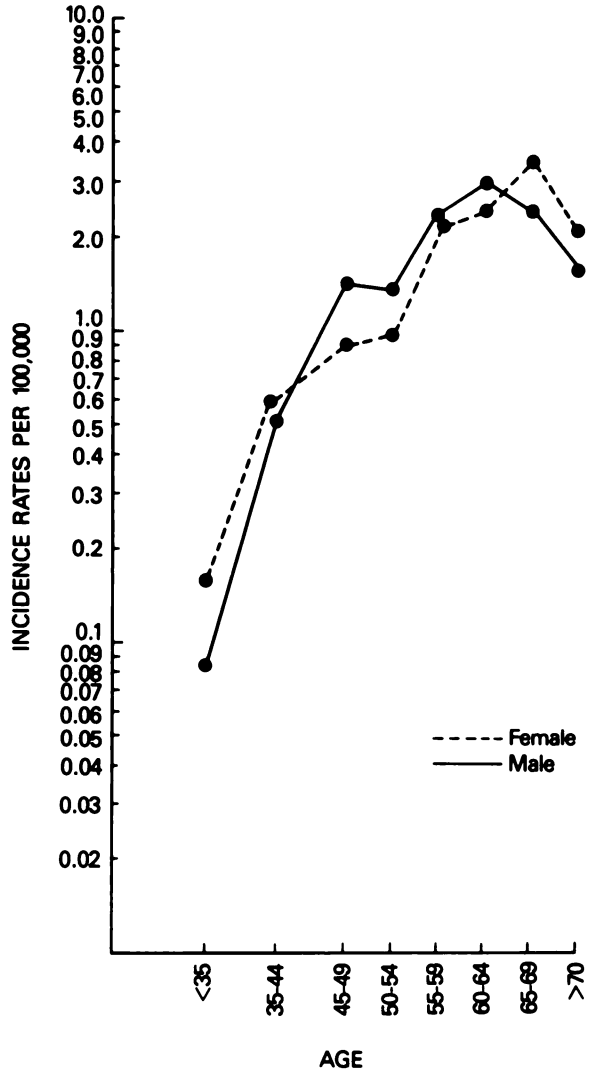

Fig. 1. Incidence rates for eye melanoma in white population of greater Philadelphia and Wilmington during 1974–1978.

similar eye melanoma rates. As expected, more cases than controls resided outside of the Philadelphia and Wilmington metropolitan areas. These cases were included in the case-control analysis, but not in the computation of incidence rates. A comparison of postal codes suggested that, within the Philadelphia and Wilmington Standard Metropolitan Statistical Areas, residential patterns were similar.

In the case-control data, pregnancy was related to eye melanoma risk. Women who had ever been pregnant had a 40% increase in risk (RR[3] = 1.4, 95% CI = 0.8, 2.2), but there was no relation between the number of pregnancies and the level of risk (Table 2). Pregnancy was associated with increased risk regardless of whether the outcome was live birth, stillbirth, or

[3] The abbreviations used are: RR, relative risk; CI, confidence interval.

Table 2 *Estimated RR of intraocular melanoma according to parity, gravidity, and pregnancy losses*

	Cases	Controls	RR[a]	95% CI
Pregnancies				
0	41	48	1.0	
1–2	89	78	1.4	0.8–2.4
3–4	76	67	1.4	0.8–2.5
5+	30	28	1.3	0.6–2.7
P for trend test			0.21	
Live births[b]				
0	47	56	1.0	
1–2	112	91	1.5	0.8–2.6
3–4	60	62	1.2	0.6–2.2
5+	18	14	1.4	0.5–4.0
P for trend test			0.32	
Miscarriages, stillbirths[c]				
0	169	172	1.0	
1–2	61	46	1.3	0.8–2.1
3+	7	5	1.5	0.4–5.8
P for trend test			0.10	

[a] Adjusted for age at diagnosis.
[b] Also adjusted for miscarriages and stillbirths.
[c] Also adjusted for live births.

miscarriage. The interval between last pregnancy and diagnosis was unrelated to melanoma risk. The pregnancy effect was not confounded by the influence of exogenous estrogens, history of ovarian surgery, or other risk factors.

We examined the relation between menstrual factors and risk of intraocular melanoma (Table 3). Age at menarche was not consistently related to risk. Women who reported having undergone menopause had a slightly higher risk than premenopausal women, after adjustment for age at diagnosis, and history of oophorectomy. Among the menopausal women, there was no clear relation between age at menopause and risk. To examine the effect of age at menopause with greater statistical power, we used life table analysis to combine data from premenopausal and postmenopausal women. The median estimated age at menopause was 47.5 among cases and 47.7 among controls.

Twenty % of the cases and 24% of the controls reported having their ovary or ovaries removed. After adjustment for age at diagnosis, age at menopause, and use of menopausal estrogens, the RR for women who reported an oophorectomy was 0.6 (95% CI 0.4, 1.0) (Table 3). The protective effect of oophorectomy was highest in the group of women who reported early menopause. Women who reported oophorectomy and menopause before age 40 showed a 70% lower risk than women who reported no oophorectomy and menopause in their 40s.

Use of menopausal replacement estrogens was related to risk, but use of oral contraceptives was not (Table 4). Thirteen % of the cases and an equal proportion of controls reported using oral contraceptives. A history of using oral contraceptives was related to age at diagnosis, and the age-adjusted RR was 0.9. Estimated risk was not related to duration of oral contraceptive use or to interval from either first or last use.

Women who reported using replacement estrogens showed a significant RR of 2.0 (95% CI 1.2, 3.1). Among the users, the level of risk did not rise consistently with longer use (Table 4).

Table 3 *Estimated RR of intraocular melanoma according to menarche, menopause, and oophorectomy*

	Cases	Controls	RR[a]	95% CI
Age at menarche (yr)[a]				
<12	28	25	1.0	
12	54	39	1.3	0.6–2.7
13	59	59	1.0	0.5–2.0
14–15	60	63	0.9	0.4–1.8
≥16	16	20	0.9	0.3–2.4
P, trend test			0.11	
Menopausal status[b]				
Premenopausal	50	44	1.0	
Menopausal	165	158	1.2	0.6–2.6
Age at menopause (yr)[b]				
<40	24	32	1.0	
40–44	42	27	2.1	0.9–3.0
45–49	43	43	1.4	0.6–3.0
50–54	44	43	1.4	0.6–3.2
≥55	11	13	0.9	0.3–3.1
P, trend test			0.44	
Oophorectomy[c]				
No	184	162	1.0	
Yes	45	52	0.6	0.4–1.0
Age at menopause and oophorectomy (yr)[a]				
No oophorectomy, <40 at menopause	13	13	0.7	0.3–1.8
No oophorectomy, 40–49 at menopause	64	46	1.0	
No oophorectomy, ≥50 at menopause	42	43	0.7	0.4–1.3
Oophorectomy, <40 at menopause	9	18	0.3	0.1–0.8
Oophorectomy, 40–49 at menopause	19	21	0.6	0.3–1.4
Oophorectomy, ≥50 at menopause	12	11	0.8	0.3–2.3

[a] Adjusted for age.
[b] Adjusted for history of oophorectomy and age.
[c] Adjusted for age at menopause, use of menopausal estrogens, and age.

Table 4 *Estimated RR of intraocular melanoma according to use of exogenous estrogens*

	Cases	Controls	RR	95% CI
Oral contraceptives[a]				
Never used	205	191	1.0	
Ever used	30	29	0.9	0.4–1.7
≤1 yr	12	11	0.9	0.3–2.4
2–9 yr	16	9	1.4	0.5–4.3
≥10 yr	2	8	0.2	0.3–1.2
P, trend test			0.165	
Menopausal estrogens[b]				
Never used	131	154	1.0	
Ever used	83	55	2.0	1.2–3.1
≤1 yr	39	26	1.9	1.0–3.5
2–5 yr	16	14	1.6	0.7–3.8
≥6 yr	16	9	2.2	0.9–5.8
P, trend test			0.08	

[a] Adjusted for age.
[b] Adjusted for age and history of oophorectomy.

There was virtually no use of exogenous estrogens among women over age 60 at diagnosis. Too few women recalled particular brands of menopausal estrogens other than Premarin to permit stable estimates of brand-specific risks, but an effect was present for users of Premarin as well as all other brands combined. We lacked data to assess the effects of interval between last use or first use and date of diagnosis. When surrogate respondents were excluded from the analysis, the relative risk associated with ever using replacement estrogens was 1.6 (95% CI = 1.04, 2.5).

As Table 5 shows, the effects of pregnancy and menopausal estrogens appeared in the subgroups of women who did or did not report oophorectomies. The opposing effects of replacement estrogens and oophorectomy tended to cancel out, with a

Table 5 *Estimated relative risks among women with and without oophorectomy*

	With oophorectomy			Without oophorectomy		
	Cases	Controls	RR[a]	Cases	Controls	RR[a]
Age at menopause (yr)						
<40	9	18	1.0	13	13	1.0
40–44	10	10	2.1	32	16	2.0
45–49	9	11	2.2	32	30	1.1
50–54	10	8	2.5	33	34	1.0
55+	2	3	1.6	9	9	0.8
P, trend test			0.10			0.17
Menopausal estrogens						
Never	23	31	1.0	125	132	1.0
Ever	22	21	1.5	59	30	2.1
95% CI			0.6–3.8			1.2–3.6
Oral contraceptives						
Never	16	19	1.0	155	27	1.0
Ever	3	2	1.1	136	26	0.9
95% CI			0.2–8.0			0.4–1.8
Pregnancy						
Never	5	9	1.0	36	148	1.0
Ever	40	43	1.7	37	125	1.2
95% CI			0.5–6.6			0.7–2.1

[a] Adjusted for age in two groups (<60, ≥60).

Table 6 *Estimated RR of intraocular melanoma according to history of prior gynecological cancers and family history of gynecological or prostate cancers*

Type of cancer (ICD-9 codes)	Cases	Controls	RR	95% CI
Self				
No gynecological cancer	205	201	1.0	
Any gynecological cancer (174–184)	32	22	1.6[a]	0.8–3.0
Breast cancer (174)	14	16	1.0	0.4–2.1
Ovary cancer (183)	8[b]	4[b]	2.8	0.7–12
Uterine corpus cancer (182)	1	1	1.0	0.02–34
Uterine cervix cancer (180)	4	0	∞	1.0–∞
First-degree relative[c]				
No gynecological or prostate cancer	334	337	1.0	
Any gynecological or prostate cancer (174–185)	108	83	1.3	0.9–1.8
Breast cancer (174–185)	66	48	1.4	0.9–2.1
Ovary cancer (183)	3	7	0.4	0.09–1.9
Uterine cervix cancer (180)	5	6	0.8	0.2–3.2
Prostate cancer (185)	21	12	1.7	0.8–3.8

[a] Adjusted for history of oophorectomy.
[b] Includes six cases and four controls with a history of oophorectomy.
[c] Includes male and female study subjects; RR adjusted for age.

relative risk of 1.1 (95% CI 0.6, 2.2) for women with oophorectomy and replacement hormones compared to women with natural menopause and no hormones. Life table estimates of the median ages at menopause without oophorectomy were 47.9 and 49.1 for cases and controls, respectively. Median ages at menopause with oophorectomy were 49.4 and 46.9 for cases and controls, respectively.

We also estimated the risks of intraocular melanoma according to the woman's own history of gynecological cancers and to the history of cancer in first degree relatives (Table 6). After adjusting for a history of oophorectomy, we observed increased risk among the women who reported prior ovarian cancer. Women reporting prior breast cancer did not show an increased risk. Cirrhosis of the liver, a disease that increases circulating estrogens in both sexes, was associated with increased risk in the total study group of men and women (RR = 2.4, 95% CI = 0.5, 20.8).

The hormonal risk factors suggested in this study were not confounded by the effects of southern birthplace or use of eye protection in the sun, the two major sunlight-related factors in these data, nor were the hormonal effects significantly different between the lower-risk group of women who always used eye shade and the higher-risk group of women who did not. There were too few women born in the south to produce stable estimates of the hormonal effects in that higher-risk group.

DISCUSSION

In this study, some hormonal variables were related to the risk of developing intraocular melanoma. Our results do not implicate a particular hormone, but the findings on gravidity, menopausal estrogens, and oophorectomy, seem compatible with an ovarian hormonal mechanism. Early menarche and late menopause should increase risk, if estrogens are involved, but they did not in this study. By themselves, our observations on gynecological and prostatic cancer histories among subjects and their families provide only weak evidence of hormonal factors. In addition, the recollection of cancers in subjects or their first degree relatives may be inaccurate; the reported prevalence in this study was substantially higher than the estimated prevalence in the Connecticut Tumor Registry data (15).

It is possible that our estimates were distorted by the use of controls with detached retinas, misclassification of hormonal exposures, or by the play of chance. Few of the conditions leading to a detached retina are related to hormone exposure, with the possible exception of diabetes, a history of which was mentioned by 15% of controls and 10% of cases. If any hormonal variables were also correlated with diabetes, they would be more common among controls than among the general population. The attendant bias probably would be rather small. Some misclassification of oophorectomy status and other exposures almost certainly occurred, but there is no particular reason for misclassification to vary between cases and controls. Random misclassification may have biased some of the estimates toward the null value.

Finally, random variation may have produced some of the associations observed in this study of 237 cases. The associations with oophorectomy and replacement estrogens were the least likely to have been produced by chance.

Only one other analytic study of ocular melanoma has provided data on hormonal variables. The Western Canada Melanoma Study (16), involving 38 male and 27 female cases with matched population controls, reported no significant effect of oral contraceptives, menopausal estrogens, or parity, but the statistical power was too low to distinguish the levels of risk seen in the present study from chance.

Descriptive surveys of intraocular melanoma have raised the possibility of hormonal factors. United States data (6) show greater incidence in women than men at ages younger than 45 in 1969–1971, and Scandinavian and Japanese data (7) show a similar pattern. On the other hand, data from England for 1952–1978 (17) reveal no sex difference. Hormonal factors have also been suggested by surveys of second primary cancers, indicating associations between melanomas and female reproductive tumors, such as ovarian cancer in our study. Breast cancer survivors (8) had elevated rates of skin melanoma (RR = 1.5) and eye melanoma (RR = 2.5). Eye cancer survivors (9) showed excesses of endometrial cancer (RR = 2) and skin melanoma (RR = 3.7), but not breast cancer (RR = 0.9). Skin melanoma survivors (9) also had excesses of breast, endometrial, and eye cancers.

Studies of cutaneous melanoma have produced limited information on hormonal risk factors, with attention centered on the possible role of contraceptives (10, 11, 18–21). The best available data suggest that the oral contraceptive association is very weak, if present at all. Two of these studies revealed an increased risk of skin melanoma among parous women (11, 20). In addition, estrogen receptors have been detected on melanomas and on nevi, with increases during pregnancy and while taking oral contraceptives (21, 22).

In summary, this case-control study of intraocular melanoma revealed excess risks associated with gravidity and replacement estrogens, and decreased risks with oophorectomy. No influence of oral contraceptives, menarche, or age at menopause was detected. Further studies are needed to verify these findings.

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