Childbearing History Associated With Improved Survival in Choroidal Melanoma

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Background: Research in cutaneous melanoma suggests that women may experience better tumor-dependent survival than men, and some studies have shown that the advantage is specific to childbearing.

Objective: To examine whether childbearing may be a favorable prognostic factor in melanoma of the uveal tract.

Design: Prospective follow-up study.

Setting: Hospital.

Main Outcome Measure: Death from metastatic choroidal melanoma.

Methods: We evaluated a consecutive series of 1818 patients with choroidal melanoma, 748 parous and 165 nulliparous women and 905 men, after treatment with proton irradiation. Three hundred fifty-two deaths from metastasis were documented in follow-up.

Results: Overall multivariate-adjusted death rates from metastasis were approximately 25% higher in nulliparous women (relative risk [RR], 1.23; 95% confidence interval [CI], 0.83-1.82) and men (RR, 1.25; 95% CI, 1.00-1.56) than in women who had given birth. The protective influence of parity was strongest in the early period following diagnosis and treatment (RR, 1.58; 95% CI, 0.88-2.86, and RR, 1.51; 95% CI, 1.04-2.19, in nulliparous women and men, respectively, during the first 36 months of follow-up). The level of protection increased with the number of live births ($P$ for trend, .04).

Conclusion: These data provide support for the hypothesis that a history of childbearing confers protection from death in choroidal melanoma.


INTRAOCULAR MELANOMA is the only potentially fatal eye tumor in adults. Established prognostic factors include tumor size, patient age, and histologic cell type, among others. The current investigation was motivated by studies in which cutaneous melanoma showed women to have a better prognosis than men. In a few studies, the advantage was limited to women who had given birth. To investigate the possible role of childbearing in melanoma of the uveal tract, we prospectively evaluated a large cohort of individuals with these tumors after a detailed reproductive history had been collected from the women during baseline examination.

RESULTS

Of the 1818 patients evaluated, 905 were men and 913 were women; among the women, 748 (82%) were parous. Patients ranged in age from 14 to 93 years (median, 61 years); 10% of women were under the age of 40 years at presentation. Table 1 shows follow-up statistics by parity and sex. Approximately 20% of patients died from metastasis an average of 3.6 years after irradiation (range, 3 months to 16 years). Median follow-up in the 1226 surviving patients was 8.5 years (12 years or more in 25% of patients). Most survivors had recent follow-up; survival status was known within 10 months of study closeout (April 30, 1997) in 90% of the surviving patients.

Overall 10-year survival rates were 61%, 59%, and 66% for men, nulliparous women, and parous women, respectively. Tumor-specific survival curves are displayed in the Figure according to parity and sex, and corresponding survival estimates are given in Table 2. Parous women had modestly though significantly better survival rates than men ($P = .02$) throughout follow-up; death rates were also reduced among women with a prior birth compared with the nulliparous women, although the difference was not significant ($P = .29$). Tumor-specific survival at 10 years was 77% in parous women compared with 75% in the other groups.

Table 3 shows a comparison of baseline prognostic factors according to sex and parity. Groups were comparable on most factors. However, nulliparous women were younger than the other patients. In addition, men were more likely to present with ocular symptoms (eg, vision loss, photophobia). We used...
SUBJECTS AND METHODS

The analysis was based on a cohort of 1843 patients with a diagnosis of unilateral choroidal and/or ciliary body melanoma who had undergone proton irradiation for the tumor at the Harvard cyclotron, Cambridge, Mass, between July 1975 and December 1995. The patients were all US or Canadian citizens who had not previously been treated for the tumor and showed no evidence of metastatic disease at pretreatment workup. All were treated with a total dose of 70 cGy under the care of one of us (E.S.G.). A detailed parity history was available for all but 13 eligible women.

Patients were evaluated at regular intervals after irradiation. Most returned to our institution for routine follow-up care. The remaining patients were followed up through the referring ophthalmologist or local primary care physicians. In 1991 and in 1995, all surviving patients were mailed a follow-up questionnaire to collect interim data on reproductive history and current menstrual status; these surveys were returned by an estimated 85% of surviving patients. We excluded the 12 women who gave birth after irradiation treatment for the tumor, bringing the total for analysis to 1818 subjects.

Patients were followed up until April 30, 1997. Five hundred ninety-two deaths were documented, 352 caused by metastatic melanoma (primarily to the liver), 78 caused by another primary tumor, and 159 caused by noncancer causes; in 3 additional cancer deaths, the site of the primary tumor could not be determined, and these were classified as non–tumor-related causes. For most patients, cause of death was confirmed with medical records, including biopsy reports and results of liver scans, hospital discharge summaries, and autopsy reports (83% overall [90% of metastatic deaths] and/or death certificates [total with documentation, 90% overall [95% of metastatic deaths]). The remaining deaths were classified based on information given by next of kin.

For analysis, we evaluated survival as a function of sex and parity using Kaplan-Meier procedures to estimate cumulative survival rates after irradiation and Cox regression to estimate multivariate-adjusted relative risk (RR) ratios for melanoma-related death, the end point in all analyses (10 patients were alive with metastasis at the time of analysis). Multivariate models included terms for known prognostic factors, including largest tumor diameter and patient age as continuous variables, location of the anterior margin of the tumor (ciliary body, anterior to the equator without ciliary body involvement, or posterior to the equator), presence or absence of extrascleral extension, and symptoms vs screen-detected tumor diagnosis. The RR ratios were estimated for tumor-related death in nulliparous women and men relative to parous women. To test formally for uniformity of RR ratios over time (eg, the proportional hazards assumption), we constructed separate models that included product terms for sex and parity multiplied by the logarithm of the survival time, such that:

\[ h(t) = \exp(B_1 Z_1 + B_2 Z_2(t)) \]

where \( Z_1 \) is an indicator variable denoting group membership, and \( Z_2(t) = \log(t) \) (logarithmic survival time). If the ratio of the hazard functions for the 2 groups (parous women vs the remaining patients) is nearly constant for any value of survival time, then \( B_1 \) should be close to 0. Equality of survival curves was evaluated using the Wilcoxon rank sum test.

Cox regression to examine relative death rates as a function of sex and parity while accounting for these baseline differences (Table 4). Tumor-associated death rates were approximately 25% higher in men (RR, 1.25; 95% CI, 1.00-1.56) and nulliparous women (RR, 1.23; 95% CI, 0.83-1.82) than in women who had ever given birth.

The protective influence of parity was largely confined to the early period following diagnosis and treatment (Table 4); partitioning follow-up intervals (0-36, >36 to 72, and >72 months), multivariate-adjusted death rates were elevated by 50% and 60% in men and nulliparous women, respectively, during the first 3 years after treatment. Relative risk ratios were not materially different among groups.

### Table 1. Survival and Follow-up Statistics by Sex and Parity

<table>
<thead>
<tr>
<th>Sex</th>
<th>Parous (n = 748)</th>
<th>Nulliparous (n = 165)</th>
<th>Men (n = 905)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decedents</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total No.</td>
<td>216</td>
<td>56</td>
<td>320</td>
</tr>
<tr>
<td>Metastasis, No. (%)</td>
<td>130 (17)</td>
<td>31 (19)</td>
<td>191 (21)</td>
</tr>
<tr>
<td>Time to death, y†</td>
<td>3.9 (2.6-6.1)</td>
<td>3.0 (2.5-5.2)</td>
<td>3.6 (1.9-5.3)</td>
</tr>
<tr>
<td>Other causes, No. (%)</td>
<td>86 (11)</td>
<td>25 (15)</td>
<td>129 (14)</td>
</tr>
<tr>
<td>Survivors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total No.</td>
<td>532</td>
<td>109</td>
<td>585</td>
</tr>
<tr>
<td>Follow-up time, y†</td>
<td>8.4 (4.5-11.7)</td>
<td>7.1 (4.0-11.5)</td>
<td>8.8 (4.7-11.9)</td>
</tr>
<tr>
<td>Time since last contact, mo</td>
<td>0 (9.9)</td>
<td>0 (9.9)</td>
<td>0 (9.5)</td>
</tr>
</tbody>
</table>

* Prior to study closeout; 90% of subjects were known to be alive within 10 months after that date, and 50% were followed up after study closeout. †Values are median (interquartile range). ‡Values are median (90th percentile).
Results according to number of liveborn children and time since most recent birth are given in Table 5. There was a significant inverse relationship between number of children and degree of protection associated with childbearing. This trend was most evident in the first 3 years after treatment; death rates in women who had more than 4 children were approximately one third those of nulliparous women and men (multivariate RR, 0.35; 95% CI, 0.10-1.12). Each live birth reduced death rates by 6% overall (RR, 0.94), and by 14% for deaths in the first 36 months (RR, 0.86) (data not shown). No consistent patterns were observed according to years since last completed pregnancy; for early deaths (≤36 months), the greatest protection was afforded for childbirth ending 11 to 30 years prior to treatment (RR, 0.33; 95% CI, 0.16-0.70). Relative risk ratios were nonsignificantly elevated (RR, 1.7; 95% CI, 0.50-5.62) in association with recent childbirth (within 10 years of treatment).

The influence of parity on survival was generally absent among younger patients (data not shown). In those patients over age 50 years (278 deaths), adjusted overall RR ratios were 1.37 (95% CI, 0.88-2.12) and 1.38 (95% CI, 1.07-1.79) for nulliparous women and men, respectively; in younger patients (74 deaths), these estimates were 0.67 (95% CI, 0.25-1.80) and 0.88 (95% CI, 0.54-1.44), respectively. Relative risk ratios in the older group according to numbers of births were 0.85, 0.73, 0.75, and 0.62 for 1, 2, 3 or 4, and 5 or more births, respectively (RR per birth, 0.92; P for trend, .02). There was no similar trend among the younger patients (RR per birth, 1.03; P = .74).

**Table 2. Actuarial Tumor-Specific Survival Rates After Irradiation by Sex and Parity**

<table>
<thead>
<tr>
<th>Time Following Irradiation, y</th>
<th>Survival Rate (95% CI)</th>
<th>Parous Women</th>
<th>Nulliparous Women</th>
<th>Men</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>(%)</td>
<td>(n = 748)</td>
<td>(n = 165)</td>
<td>(n = 905)</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>(%)</td>
<td>86 (84-89)</td>
<td>83 (76-89)</td>
<td>84 (81-86)</td>
<td>.13</td>
</tr>
<tr>
<td></td>
<td>77 (73-81)</td>
<td>75 (66-82)</td>
<td>75 (71-78)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*P = .29 for parous vs nulliparous women. P = .02 for men vs nulliparous women.

**Table 3. Prognostic Factors for Melanoma-Related Death According to Sex and Parity**

<table>
<thead>
<tr>
<th>Women</th>
<th>Parous</th>
<th>Nulliparous</th>
<th>Men</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age at treatment, y</td>
<td>60.4</td>
<td>57.0</td>
<td>58.4</td>
<td>.003</td>
</tr>
<tr>
<td>Mean largest tumor diameter, mm</td>
<td>13.2</td>
<td>13.3</td>
<td>13.4</td>
<td>.50</td>
</tr>
<tr>
<td>Involving ciliary body, %</td>
<td>28</td>
<td>30</td>
<td>26</td>
<td>.36</td>
</tr>
<tr>
<td>Extrascal, %</td>
<td>3.6</td>
<td>5.4</td>
<td>3.8</td>
<td>.53</td>
</tr>
<tr>
<td>Symptomatic, %</td>
<td>70</td>
<td>68</td>
<td>77</td>
<td>.001</td>
</tr>
<tr>
<td>Darkly pigmented, %</td>
<td>45</td>
<td>55</td>
<td>47</td>
<td>.70</td>
</tr>
<tr>
<td>Light iris color, %</td>
<td>45</td>
<td>47</td>
<td>48</td>
<td>.56</td>
</tr>
</tbody>
</table>

**Table 4. Cox Regression for Influence of Sex and Parity on Melanoma-Related Survival After Irradiation**

<table>
<thead>
<tr>
<th>Time After Irradiation</th>
<th>Parous Women</th>
<th>Men</th>
<th>Nulliparous Women</th>
<th>Deaths/No. evaluated</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-36 mo</td>
<td>RR (95% CI)</td>
<td>P</td>
<td>RR (95% CI)</td>
<td>P</td>
</tr>
<tr>
<td>Parous women</td>
<td>1.0</td>
<td></td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>1.51 (1.04-2.19)</td>
<td>.03</td>
<td>1.25 (0.87-1.78)</td>
<td>.22</td>
</tr>
<tr>
<td>Nulliparous women</td>
<td>1.58 (0.88-2.86)</td>
<td>.13</td>
<td>1.09 (0.57-2.10)</td>
<td>.79</td>
</tr>
<tr>
<td>Deaths/No. evaluated</td>
<td>137/1818</td>
<td></td>
<td>141/1445</td>
<td></td>
</tr>
</tbody>
</table>

*P = .07 for interaction by test for heterogeneity in relative risk (RR) ratio across time intervals for parous women vs nulliparous women and men. Relative risk ratios were adjusted for largest tumor diameter, patient age at irradiation, extrascleral extension, anterior extent of the tumor in relation to equator (posterior or anterior, with or without ciliary body involvement), and symptoms at presentation. CI indicates confidence interval.
nancy21,22 and our findings suggesting a possible in-
ging the possibly aggravating effect of concurrent preg-
light of the literature on cutaneous melanoma concern-
tolerance during pregnancy. The theory is intriguing in
term promotional effect is attributed to maternal immune
present similar antigens.19 The theory was put forth to
provide immunity to cancerous cells that theoretically
explanation in breast cancer of pregnancy
cause a short-term increase in breast cancer inci-
dence, followed within several years by a gradually de-
clining incidence relative to nulliparity.23 This short-
term promotional effect is attributed to maternal immune
tolerance during pregnancy. The theory is intriguing in
light of the literature on cutaneous melanoma concern-
ing the possibly aggravating effect of concurrent preg-
nancy21,22 and our findings suggesting a possible in-
crease in death rates for recent childbearing. In a previous
analysis23 we found nonsignificantly higher death rates in
women of reproductive age (<45 years) than in men
(RR, 1.28), which may be in line with a risk-enhancing
influence of concurrent or recent pregnancy.

These results constitute the first evidence that a remote
history of childbearing may improve survival rates in uveal
melanoma, albeit temporarily. These findings, if confirmed,
offer new potential insights into the mecha-
nisms by which metastatic cells may lie dormant in
the liver for extended periods and provide further rationale
for seeking immune or vaccine therapies as a means of
extending survival in patients with melanocytic tumors.

Accepted for publication January 22, 1999.

This study was supported in part by the Melanoma
Research Fund, Massachusetts Eye and Ear Infirmary, Bos-
ton, Mass, and by the Retina Research Foundation, Hous-
ton, Tex (Dr Gragoudas). Dr Gragoudas is a Research to
Prevent Blindness Senior Scientific Investigator, Research to
Prevent Blindness Inc, New York, NY.

Presented at the annual meeting of the Association for
Research in Vision and Ophthalmology, Fort Lauderdale,
Fla, May 1998.

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Table 5. Cox Regression for Influence of Parity Factors on Melanoma-Related Survival Rates After Proton Irradiation*  

<table>
<thead>
<tr>
<th>No. of births</th>
<th>Combined No. of Deaths RR (95% CI)</th>
<th>First 36 Months No. of Deaths RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>222</td>
<td>93</td>
</tr>
<tr>
<td>1</td>
<td>21</td>
<td>9.01 (0.45-1.82)</td>
</tr>
<tr>
<td>2</td>
<td>41</td>
<td>0.52 (0.27-0.99)</td>
</tr>
<tr>
<td>3-4</td>
<td>41</td>
<td>0.71 (0.42-1.20)</td>
</tr>
<tr>
<td>&gt;4</td>
<td>16</td>
<td>0.36 (0.11-1.13)</td>
</tr>
<tr>
<td>P for trend</td>
<td>.04</td>
<td>.01</td>
</tr>
<tr>
<td>Time since</td>
<td></td>
<td></td>
</tr>
<tr>
<td>first birth, y</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>222</td>
<td>93.0</td>
</tr>
<tr>
<td>&gt;30</td>
<td>56</td>
<td>0.71 (0.45-1.12)</td>
</tr>
<tr>
<td>11-30</td>
<td>45</td>
<td>0.33 (0.16-0.70)</td>
</tr>
<tr>
<td>≤10</td>
<td>9</td>
<td>1.67 (0.50-5.62)</td>
</tr>
<tr>
<td>P for trend</td>
<td>.25</td>
<td>.88</td>
</tr>
</tbody>
</table>

* Relative risk (RR) ratios were adjusted for largest tumor diameter, patient age at irradiation, extrascleral extension, anterior extent of the tumor in relation to equator (posterior or anterior, with or without ciliary body involvement), and symptoms at presentation. The total number of children was missing for 69 women (11 deaths from metastasis); age at most recent birth was missing for 54 women (20 deaths from metastasis). CI indicates confidence interval.

Further supported by the analysis of time since most recent
childbirth; the lowest death rates occurred in women who had given birth within 11 to 30 years. Considering
only the parous women, overall age-adjusted death rates
were significantly lower (by 40%; RR, 0.58; P = .03) in
the women who had given birth within 11 to 30 years
compared with 30 or more years before the tumor was
diagnosed.

Several potential mechanisms have been advanced
to explain how pregnancy and childbearing might affect the
pathogenesis of cancer.22,23 Exposure to fetal tissue could
provide immunity to cancerous cells that theoretically
present similar antigens.19 The theory was put forth to
explain the phenomenon in breast cancer of pregnancy
causing a short-term increase in breast cancer inci-
dence, followed within several years by a gradually de-
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tolerance during pregnancy. The theory is intriguing in
light of the literature on cutaneous melanoma concern-
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(RR, 1.28), which may be in line with a risk-enhancing
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CONCLUSIONS

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