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.


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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 1995.11,12 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 1993, 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 [93% 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 procedures13 to estimate cumulative survival rates after irradiation and Cox regression14 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,15 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:

\[ h_{0}(B_{1}Z_{1} + B_{2}Z_{2}(t)), \]

where \( Z_{1} \) is an indicator variable denoting group membership, and \( Z_{2}(t) = Z_{1}(\log \text{survival time}) \). 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 \( B_{2} \) should be close to 0.16 Equality of survival curves was evaluated using the Wilcoxon rank sum test.17
elevated in the next interval (>36 to 72 months), and beyond 6 years, the protective influence for parity disappeared. Results of a test for nonuniformity in RRs across time intervals (comparing parous women with remaining patients) were of borderline statistical significance (P = .07).

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).

This study provides evidence that a history of childbearing affords protection from metastatic death in intraocular melanoma. Our results support a role specific to childbearing; death rates were higher in nulliparous women than in those who had ever given birth, in a similar magnitude to the excess observed in men relative to parous women. In addition, there was an apparent dose response for parity, with death rates inversely proportional to the number of children delivered. These results were unconfounded by stage at diagnosis and other established clinical prognostic factors in this disease. Given the high level of surveillance in this population, the results are unlikely to reflect differential follow-up by sex or according to parity. Our data provide support for studies in cutaneous melanoma suggesting that the survival advantage for women noted in many studies is likely to be secondary to childbearing.

These results suggest that the benefit associated with childbearing may be transitory, in effect only during the early years following diagnosis and treatment. However, since the preponderance of deaths occur in this early period (K.M.E., J.L.Q., E.S.G., unpublished data), the advantage in parous women extends for a decade or more following treatment in terms of cumulative death rates. This temporary nature of parity-associated immunity is
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 = 0.03) 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.^{16} 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 incidence, followed within several years by a gradually declining incidence relative to nulliparity.^{22} 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 concerning the possibly aggravating effect of concurrent pregnancy^{21} and our findings suggesting a possible increase in death rates for recent childbearing. In a previous analysis^{23} 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.

### CONCLUSIONS

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 mechanisms 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.

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### REFERENCES


