Association of MDM2 SNP309, Age of Onset, and Gender in Cutaneous Melanoma

Eliaz F. Firoz, 1,7 Melanie Warycha, 1 Jan Zakrzewski, 1 Danuta Pollens, 1 Guimin Wang, 1 Richard Shapiro, 2 Russell Berman, 2 Anna Pavlick, 1,3 Prashiela Manga, 1 Harry Ostrer, 3,4,5 Julide Tok Celebi, 7 Hideko Kamino, 1,5 Farbod Darvishian, 6 Linda Rolnitzky, 6 Judith D. Goldberg, 6 Iman Osman, 1,3 and David Polsky 1,5

Abstract

Purpose: In certain cancers, MDM2 SNP309 has been associated with early tumor onset in women. In melanoma, incidence rates are higher in women than in men among individuals less than 40 years of age, but among those older than 50 years of age, melanoma is more frequent in men than in women. To investigate this difference, we examined the association among MDM2 SNP309, age at diagnosis, and gender among melanoma patients.

Experimental Design: Prospectively enrolled melanoma patients (N = 227) were evaluated for MDM2 SNP309 and the related polymorphism, p53 Arg72Pro. DNA was isolated from patient blood samples, and genotypes were analyzed by PCR-restriction fragment length polymorphism. Associations among MDM2 SNP309, p53 Arg72Pro, age at diagnosis, and clinicopathologic features of melanoma were analyzed.

Results: The median age at diagnosis was 13 years earlier among women with a SNP309 GG genotype (46 years) compared with women with TG+TT genotypes (59 years; P = 0.19). Analyses using age dichotomized at each decade indicated that women with a GG genotype had significantly higher risks of being diagnosed with melanoma at ages <50 years compared with women ≥50 years, but not when the comparison was made between women <60 and ≥60 years. At ages <50 years, women with a GG genotype had a 3.89 times greater chance of being diagnosed compared with women with TG+TT genotypes (P = 0.01). Similar observations were not seen among men.

Conclusions: Our data suggest that MDM2 may play an important role in the development of melanoma in women. The MDM2 SNP309 genotype may help identify women at risk of developing melanoma at a young age.

Melanoma incidence rates vary dramatically with gender and age. According to National Cancer Institute’s Surveillance, Epidemiology and End Results (SEER) data (1), melanoma incidence rates are greater among women than men between the ages of 20 and 40 years, and among women in this age group melanoma incidence rates rise steeply. After the age of 40 years, melanoma incidence rates continue to rise in women, but at a slower pace. In men, the most rapid increase in incidence rates occurs between the ages of 50 and 80 years. As a result of these trends, the incidence rates of melanoma are greater among women than men at ages <40 years, equal in both sexes between the ages of 40 and 44 years, and greater among men than women at ages >45 years. Interestingly, the natural incidence of menopause prior to 40 years of age is quite low; however, nearly 10% of postmenopausal women in the United States are between the ages of 40 and 50 years, with many others entering the menopause transition or perimenopause during this decade (2). The average age of menopause in the United States and other Western countries is 51 years (3). Given these observations, it is possible that the discordance in melanoma incidence rates between men and women, both above and below the age of 50 years, is related in part to estrogen signaling.

Recently, a single nucleotide polymorphism (SNP) at position 309 in the P2 promoter of MDM2 (rs2279744; T/G) has been associated with the onset of several different cancers among younger women. For example, women with an MDM2 SNP309 G allele display earlier-onset soft tissue sarcoma, diffuse large B-cell lymphoma, colorectal cancer, and non–small cell lung cancer compared with patients lacking the G allele (4–10). In these studies, the differences in tumor onset were observed when patients were divided into “premenopausal” and “postmenopausal” groups using the age of 51 years as...
One of the principles of cancer medicine is early detection of localized disease to prevent metastatic disease. Ideally, early detection efforts are best applied to those patients at highest risk of a given cancer. This article describes a statistically significant relationship between age-related melanoma risk in women and an inherited genetic polymorphism. Although these results need to be replicated, the risk estimate is substantial for women <50 years of age, but not for older women, suggesting a role of female hormones in melanoma pathogenesis. On the clinical side, these findings may lead to a genetic test to identify women <50 years of age who are at increased risk of melanoma. These patients may benefit from more careful early detection screening. In the laboratory, these results may stimulate research into the role of female hormones in melanoma.

**Translational Relevance**

The characteristics of melanoma patients were summarized using medians with interquartile ranges (IQR) for continuous variables and percentages for categorical variables. Wilcoxon rank sum tests (for continuous variables) and Fisher’s exact tests (for categorical variables) were used to identify differences between men and women.

The associations between the SNP309 and Arg72Pro genotypes were evaluated using Fisher’s exact tests. Histopathologic features of melanoma were compared by genotype separately for men and women using boxplots. The odds of being diagnosed with melanoma by a specified age for patients with the SNP309 GG genotype were compared to the odds of diagnosis by this age for patients with SNP309 TG or TT genotypes. This was done using odds ratios with 95% confidence intervals. These odds ratios were estimated for selected cutoffs of the age distribution.

Statistical analyses were done at a significance level of 0.05 (two-sided). No adjustments were made for multiple comparisons. SAS 9.1 and SPSS 14.0 were used for statistical analyses.

**Results**

**Patient characteristics.** Table 1 presents a summary of patient and tumor characteristics. A total of 227 primary
MDM2 SNP309, Age of Onset, and Gender in Melanoma

Table 1. Characteristics of study population

<table>
<thead>
<tr>
<th>A. Patient Characteristics</th>
<th>Total</th>
<th>Women</th>
<th>Men</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>All melanoma patients</td>
<td>227 (100)</td>
<td>93 (41.0)</td>
<td>134 (59.0)</td>
</tr>
<tr>
<td>Median age at diagnosis (y)</td>
<td>58</td>
<td>57</td>
<td>58.5</td>
</tr>
<tr>
<td>History of multiple melanoma</td>
<td>29 (12.8)</td>
<td>12 (12.9)</td>
<td>17 (12.7)</td>
</tr>
<tr>
<td>Family history of melanoma</td>
<td>23 (10.1)</td>
<td>11 (11.8)</td>
<td>12 (9.0)</td>
</tr>
<tr>
<td>Stage of disease at recruitment</td>
<td>171 (75.3)</td>
<td>74 (79.6)</td>
<td>97 (72.4)</td>
</tr>
<tr>
<td>I</td>
<td>38 (16.7)</td>
<td>14 (15.1)</td>
<td>24 (17.9)</td>
</tr>
<tr>
<td>II</td>
<td>18 (7.9)</td>
<td>5 (5.4)</td>
<td>13 (9.7)</td>
</tr>
<tr>
<td>B. Tumor Characteristics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>Histologic type</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Superficial spreading</td>
<td>111 (48.9)</td>
<td>46 (49.5)</td>
<td>65 (48.5)</td>
</tr>
<tr>
<td>Nodular</td>
<td>49 (21.6)</td>
<td>16 (17.2)</td>
<td>33 (24.6)</td>
</tr>
<tr>
<td>Other*</td>
<td>32 (14.1)</td>
<td>16 (17.2)</td>
<td>16 (11.9)</td>
</tr>
<tr>
<td>Unclassified</td>
<td>35 (15.4)</td>
<td>15 (16.1)</td>
<td>20 (14.9)</td>
</tr>
<tr>
<td>Median thickness (mm)</td>
<td>0.85</td>
<td>0.72</td>
<td>0.9</td>
</tr>
<tr>
<td>Anatomic site</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Axial</td>
<td>132 (58.1)</td>
<td>38 (40.9)</td>
<td>94 (70.1)</td>
</tr>
<tr>
<td>Extremity</td>
<td>95 (41.9)</td>
<td>55 (59.1)</td>
<td>40 (29.9)</td>
</tr>
<tr>
<td>Ulceration</td>
<td>34 (15.0)</td>
<td>12 (12.9)</td>
<td>22 (16.4)</td>
</tr>
<tr>
<td>Recurrence</td>
<td>14 (6.2)</td>
<td>5 (5.4)</td>
<td>9 (6.7)</td>
</tr>
</tbody>
</table>

NOTE: Unknown values are not included in the table.
*Other* comprises desmoplastic, lentigo maligna and acral lentiginous, as well as those melanomas that did not fit into one histologic category.

melanoma patients were studied. Ninety-eight percent of patients were Caucasian. The gender distribution of these patients (59% men and 41% women) is nearly identical to the gender distribution of melanoma patients in the United States (1). The median age at melanoma diagnosis was 58 years, similar to the national median of 59 years. The distribution of melanomas by stage was 75.3% stage I, 16.7% stage II, 7.9% stage III, and 0% stage IV. No differences were found between men and women with respect to personal or family history of melanoma, histologic type, median tumor thickness, ulceration, or recurrence. However, the anatomic site of melanoma did differ significantly between men and women (P < 0.001, Fisher’s exact test). This observation is in accordance with published epidemiologic data (35). In addition, 98% of patients in the study were Caucasian, as is typical for the incidence of melanoma in the U.S. population.

MDM2 SNP309 and p53 Arg72Pro genotypes in patient germline DNA. As an initial analysis, we compared the PCR-restriction fragment length polymorphism genotyping methodology with routine sequencing of DNA extracted from 11 melanoma cell lines available in the lab. We found complete concordance between these methods, and used the PCR-restriction fragment length polymorphism method for the patient samples. An example of the genotyping results is shown in Fig. 1. Among the cell lines, the distribution of MDM2 SNP309 genotypes was TT 18.2%, TG 54.5%, and GG 27.3%. The distribution of p53 Arg72Pro genotypes was RR 72.7%, RP 0%, and PP 27.3%. Supplemental Table S1 shows the SNP309 and Arg72Pro genotypes for each melanoma cell line. We subsequently examined MDM2 SNP309 and p53 Arg72Pro genotypes in the cohort of melanoma patients described above. We successfully amplified DNA from 216 of 227 (95.2%) patients for MDM2 SNP309, and from 213 of 227 (93.8%) patients for p53 Arg72Pro. MDM2 SNP309 genotype frequencies were TT 31.5%, TG 44.4%, and GG 24.1%; p53 Arg72Pro genotype frequencies were RR 57.7%, RP 35.2%, and PP 7.0%.

Analysis of SNP309 and p53 Arg72Pro genotypes and clinicopathologic variables. We analyzed the histopathologic features of each patient’s tumor specimen for association with the MDM2 and p53 genotypes. There were no associations between the polymorphisms and histopathologic subtype, tumor thickness, anatomic site, and tumor ulceration (Table 2A and B). In addition we did not find any association between these genetic polymorphisms and patient recurrence or overall survival (data not shown).

Association between SNP309 genotype, patient gender, and age at melanoma diagnosis. Figure 2 presents boxplots that summarize the distribution of age at diagnosis for MDM2 SNP309 and p53 Arg72Pro genotypes by gender. Overall, the median age at diagnosis in men was 58.5 years compared with...
57 years in women. Among women, age at diagnosis ranged from 19 to 97 years of age, and was 13 years earlier among women with the MDM2 SNP309 GG genotype (median, 46 years; IQR, 31) as compared with women with TG+TT genotypes (median, 59 years; IQR, 19; \( P = 0.19 \), Mann-Whitney). Among men, age at diagnosis ranged from 25 to 92 years of age, and was approximately equal between men with the MDM2 SNP309 GG genotype (median, 60 years; IQR, 21.5) and men with TG+TT genotypes (median, 58 years; IQR, 19.5; \( P = 0.48 \), Mann-Whitney).

The distributions of MDM2 SNP309 genotypes among patients in the 10-year age-at-diagnosis groups are shown in Table 3. Comparing women with the GG genotype to women with either TT or TG phenotypes, we observed that by the age of 50 years, 11 of 21 (52.4%) of women with a GG genotype were diagnosed with melanoma, compared with 15 of 68 (22.1%) of women with TG+TT genotypes (median, 58 years; IQR, 19; \( P = 0.19 \), Mann-Whitney).
women with either a TT or TG genotype ($P = 0.0126$, Fisher’s exact test). Among women with the GG genotype, the highest proportion, 8 of 21 (38.1%), were diagnosed between the ages of 30 and 39 years. Among women with TG and TT genotypes, only 6 of 68 (8.8%) were diagnosed in the 30- to 39-year-old age group ($P = 0.0034$, Fisher’s exact test). These differences were not observed in men.

Table 4 shows the odds ratios for initial diagnosis of melanoma below a specified age (with age dichotomized at 10-year intervals) for patients with the SNP309 GG genotype as compared with patients with SNP309 TG+TT genotypes. This is shown separately for men and women. At age cutpoints below 50 years of age, women with the SNP309 GG genotype are more likely to be diagnosed with melanoma in the younger age category as compared with women with TG+TT genotypes; at age cutpoints of ≥60 years, the association is weak. Women with the MDM2 SNP309 GG genotype had a 3.89 times greater chance of being diagnosed at <50 years of age as compared with women with TG+TT genotypes (95% confidence interval, 1.22-12.31; $P = 0.01$). Note that the odds ratio was 4.62 (95% confidence interval, 1.23-16.86; $P = 0.02$) when an age of <40 years was used as a cut point, although there was considerable overlap between the confidence intervals for the odds ratios when age was cut at 40 and at 50 years. These associations were not seen among men. p53 Arg72Pro genotypes were not associated with melanoma risk in women or men.

Discussion

Our study identified an important association among age at melanoma diagnosis, female gender, and the GG genotype for MDM2 SNP309. Although overall MDM2 SNP309 genotype frequencies did not differ between genders, women diagnosed at younger ages were more likely to have an MDM2 SNP309 GG genotype as compared with older women. The greatest odds ratio for the diagnosis of melanoma among women with a SNP309 GG genotype was for those <40 years of age and the association remained significant as age increased to 50 years. The association was weak for ≥50 years of age. The decrease in the odds ratio from 4.62 to 3.89 as the age cutpoint increased from age 40 to age 50 years may reflect the fact that it is not uncommon for women to undergo menopause prior to the age of 50, but it is rare for this to occur prior to the age of 40 years (2, 3). These findings, combined with the SEER epidemiologic observation that prior to the age of 40 years melanoma is more common among women than men (but not after the age of 50 years), support the hypothesis that active estrogen signaling in combination with the GG genotype may contribute to melanoma onset in women. Nevertheless, this pilot study was limited by not having information regarding the menopausal status of our patients at the time of their melanoma diagnosis. A follow-up replication study will include these data to more precisely characterize the association between the SNP309 genotype and menopausal status at the time of melanoma diagnosis.

The role of estrogen in the development of melanoma remains controversial. The debate began in the 1970s when two initial observations were made: (a) young women taking oral contraceptives seemed to be at increased risk for melanoma (36), and (b) pregnancy-related skin pigmentation changes were linked to the accelerated synthesis of melanin by estrogen (37). Although some follow-up studies found associations among oral contraceptives, hormonal replacement, pregnancy, and melanoma (38–41), others did not (42–46). In addition, immunohistochemical studies in melanoma showed little or no staining for what is now recognized as estrogen receptor α (47–50), but type-II, low-affinity estrogen binding sites were detected in melanoma (51). Interestingly, estrogen receptor β, a subsequently discovered isoform of the estrogen receptor (52), was recently found to be expressed in 100% of 94 melanocytic lesions, whereas only 7.5% of these lesions expressed estrogen.
receptor α (53). A meta-analysis of clinical trials using tamoxifen, a selective estrogen receptor modulator, in patients with metastatic melanoma showed that tamoxifen did not improve response or survival when administered with combined chemotherapy regimens (54); however, recent breast cancer studies have shown that estrogen receptor β may affect tumor resistance to tamoxifen (55–57), so it is conceivable that the failure of tamoxifen to improve outcomes in melanoma patients is related to the greater expression of estrogen receptor β versus estrogen receptor α in melanoma.

Limitations of the current study include the lack of a group of patients unaffected by melanoma, and lack of patient ancestry data. Regarding nonmelanoma controls, MDM2 SNP309 genotypes have been analyzed in over 2,000 control subjects worldwide (4, 6–8, 12, 26, 28, 58–63). The GG genotype frequency in these control individuals ranged from 10% to 25%, with no substantial variation between men and women. Variation in allele frequencies has been observed among ethnic populations and could potentially bias our results if the two cohorts may be related to differences in ancestry among the patients enrolled. Alternatively, it may be related to patient age at diagnosis. We found a high GG frequency (42%) in women diagnosed at <50 years of age, and a much lower frequency (14%) in women diagnosed at ≥50 years of age. The mean age of melanoma diagnoses in our cohort was 63.4 years versus 57 years for both the mean and median of women in our cohort. Therefore, it is possible that the lower GG genotype frequency in our cohort is related to the higher mean age of their patients compared with our patients.

Studies in other cancers have reported a combined effect of both MDM2 and p53 polymorphisms on cancer risk and survival (26–28). The effect of p53 Arg72Pro on melanoma remains controversial, with some studies reporting associations between melanoma and the PP genotype (31–33) and others reporting associations between melanoma and the RR genotype (34). In our study, the distribution of p53 Arg72Pro genotypes did not vary by age or gender, and there was no evidence suggesting a strong association between the p53 Arg72Pro genotypes and melanoma risk, including a possible combined effect of both MDM2 SNP309 and p53 Arg72Pro genotypes on melanoma risk.

Several studies have examined the effect of MDM2 SNP309 on cancer survival. Studies on gastric and renal cell carcinomas have shown that MDM2 SNP309 associates with decreased

---

**Table 3. MDM2 SNP309 genotype distribution in 10-year age-at-diagnosis groups**

<table>
<thead>
<tr>
<th>Age at diagnosis (y)</th>
<th>TT+TG Total</th>
<th>GG Total</th>
<th>n (%)</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>19-29</td>
<td>2 (2.9)</td>
<td>0 (0)</td>
<td>2 (2.2)</td>
<td></td>
</tr>
<tr>
<td>30-39</td>
<td>6 (8.8)</td>
<td>8 (38.1)</td>
<td>14 (15.7)</td>
<td></td>
</tr>
<tr>
<td>40-49</td>
<td>7 (10.3)</td>
<td>3 (14.3)</td>
<td>10 (11.2)</td>
<td></td>
</tr>
<tr>
<td>50-59</td>
<td>19 (27.9)</td>
<td>1 (4.8)</td>
<td>20 (22.5)</td>
<td></td>
</tr>
<tr>
<td>60-69</td>
<td>16 (23.5)</td>
<td>4 (19.0)</td>
<td>20 (22.5)</td>
<td></td>
</tr>
<tr>
<td>70-79</td>
<td>11 (16.2)</td>
<td>3 (14.3)</td>
<td>14 (15.7)</td>
<td></td>
</tr>
<tr>
<td>80-89</td>
<td>6 (8.8)</td>
<td>0 (0)</td>
<td>6 (6.7)</td>
<td></td>
</tr>
<tr>
<td>90-99</td>
<td>1 (1.5)</td>
<td>2 (9.5)</td>
<td>3 (3.4)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>68 (100)</td>
<td>21 (100)</td>
<td>89 (100)</td>
<td></td>
</tr>
</tbody>
</table>

P = 0.0098 (χ²)

**Men**

<table>
<thead>
<tr>
<th>Age at diagnosis (y)</th>
<th>TT+TG Total</th>
<th>GG Total</th>
<th>n (%)</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>19-29</td>
<td>2 (2.1)</td>
<td>4 (12.9)</td>
<td>6 (4.7)</td>
<td></td>
</tr>
<tr>
<td>30-39</td>
<td>6 (6.3)</td>
<td>2 (6.5)</td>
<td>8 (6.3)</td>
<td></td>
</tr>
<tr>
<td>40-49</td>
<td>19 (19.8)</td>
<td>2 (6.5)</td>
<td>21 (16.5)</td>
<td></td>
</tr>
<tr>
<td>50-59</td>
<td>26 (27.1)</td>
<td>7 (22.6)</td>
<td>33 (26.0)</td>
<td></td>
</tr>
<tr>
<td>60-69</td>
<td>26 (27.1)</td>
<td>7 (22.6)</td>
<td>33 (26.0)</td>
<td></td>
</tr>
<tr>
<td>70-79</td>
<td>14 (14.6)</td>
<td>7 (22.6)</td>
<td>21 (16.5)</td>
<td></td>
</tr>
<tr>
<td>80-89</td>
<td>2 (2.1)</td>
<td>2 (6.5)</td>
<td>4 (3.1)</td>
<td></td>
</tr>
<tr>
<td>90-99</td>
<td>1 (1.0)</td>
<td>0 (0)</td>
<td>1 (0.8)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>96 (100)</td>
<td>31 (100)</td>
<td>127 (100)</td>
<td></td>
</tr>
</tbody>
</table>

P = 0.12 (χ²)

NOTE: Percentages displayed are column percentages, representing percents within genotypes.

---

**Table 4. Odds ratios and exact 95% confidence intervals for initial diagnosis of melanoma at ages less than the age shown below, for the MDM2 SNP309 GG genotype compared to other MDM2 SNP309 genotypes**

<table>
<thead>
<tr>
<th>Age cutpoint (y)</th>
<th>Women (n = 89)</th>
<th>Men (n = 127)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td>&lt;40 vs ≥40</td>
<td>4.62 (1.23, 16.86)</td>
<td>2.64 (0.68, 9.55)</td>
</tr>
<tr>
<td>&lt;50 vs ≥50</td>
<td>3.89 (1.22, 12.31)</td>
<td>0.89 (0.31, 2.39)</td>
</tr>
<tr>
<td>&lt;60 vs ≥60</td>
<td>1.33 (0.44, 4.08)</td>
<td>0.76 (0.31, 1.96)</td>
</tr>
<tr>
<td>&lt;70 vs ≥70</td>
<td>1.15 (0.34, 4.60)</td>
<td>0.53 (0.19, 1.54)</td>
</tr>
<tr>
<td>&lt;80 vs ≥80</td>
<td>1.09 (0.19, 11.61)</td>
<td>0.47 (0.05, 5.89)</td>
</tr>
</tbody>
</table>

Abbreviations: OR, odds ratio; 95% CI, 95% confidence interval.
survival (28, 60); however, a recent study on ovarian cancer has shown that MDM2 SNP309 associates with improved survival (14). Data from our group and others have shown that accumulation of MDM2 protein in primary melanoma is an independent predictor of improved survival (20, 21). It is possible that the increased expression of MDM2 in these patients was due to the presence of a SNP309 GG genotype. Unfortunately, germline DNA from the patients in our previous study is not available for analysis. In the current study, mean follow-up time was not sufficient to analyze the effects of MDM2 SNP309 on survival. Future studies will be conducted to address this question.

In conclusion, our pilot study suggests that MDM2 may play an important role in the development of melanoma in women. The MDM2 SNP309 genotype may help identify women at risk of developing melanoma at a young age. Also, these data suggest that it may be worthwhile to revisit the effects of estrogen on melanoma in the context of the appropriate MDM2 SNP309 genotype.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Acknowledgments

We acknowledge Weiming Gai and Adam Litterman for assistance with laboratory methods, and Jessie Yu for help with collecting clinicopathologic data.

References

44. Osterlind A, Tucker MA, Stone B, Jensen OM. The
Association of \textit{MDM2} SNP309, Age of Onset, and Gender in Cutaneous Melanoma

Elnaz F. Firoz, Melanie Warycha, Jan Zakrzewski, et al.


Updated version

Access the most recent version of this article at:
http://clincancerres.aacrjournals.org/content/15/7/2573

Supplementary Material

Access the most recent supplemental material at:
http://clincancerres.aacrjournals.org/content/suppl/2009/03/24/1078-0432.CCR-08-2678.DC1

Cited articles

This article cites 63 articles, 24 of which you can access for free at:
http://clincancerres.aacrjournals.org/content/15/7/2573.full#ref-list-1

Citing articles

This article has been cited by 4 HighWire-hosted articles. Access the articles at:
http://clincancerres.aacrjournals.org/content/15/7/2573.full#related-urls

E-mail alerts

Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions

To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions

To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.