REPORTS

Relationship Between Sunlight Exposure and a Key Genetic Alteration in Basal Cell Carcinoma

Mae R. Gailani, David J. Leffell, AnneMarie Ziegler, Earl G. Gross, Douglas E. Brash, Allen E. Bale*

Background: Basal cell carcinoma (BCC) of the skin is the most common cancer in humans. Epidemiologic studies implicate sunlight exposure as one risk factor, but the limited association between BCCs and UVB radiation (i.e., UV radiation of a wavelength of 280-320 nm) suggests that additional factors must be involved. At the molecular level, not much is known about the role of specific environmental agents in the pathogenesis of BCCs. Point mutations of the types produced by UVB radiation are seen in the p53 gene (also known as TP53; chromosome 17p) of 40%-56% of BCCs. Loss of heterozygosity (LOH) on chromosome 9q22, however, is the most frequent genetic alteration in these tumors, and its causative agent is unknown. Purpose: We investigated whether the genetic alteration in chromosome 9 is common to all clinical subtypes of BCCs and whether inactivation of this putative tumor suppressor is related to sunlight exposure. The presence of UVB radiation-related point mutations in the p53 gene was used as an internal control for sunlight exposure to the precursor cells. Methods: Tumor and blood samples were obtained from skin cancer patients by a surgeon who used Mohs' micrographic surgical technique. Clinical information on each tumor included location, size, histologic subtype, and whether it was primary or recurrent and sporadic or hereditary. Sixty BCCs from 58 patients were evaluated for LOH with 12 polymorphic markers that span chromosome 9. A subset of 18 tumors was evaluated for point mutations in exons 2-11 of the p53 gene, and a subset of 26 tumors was evaluated for LOH by use of a polymorphism in exon 4 of the p53 gene. Associations between tumor characteristics and molecular alterations were tested by a two-tailed chi-squared analysis or a two-tailed Fisher's exact test, depending on sample size. Results: In a clinically diverse series of 47 informative tumors, 32 (68%) showed LOH for chromosome 9q markers, irrespective of histologic characteristics or clinical behavior. Forty-four (94%) of the 47 tumors were from sun-exposed areas of the body, defined as the head and neck in both sexes, shoulders or chest in males, and legs in females. No association was found between chromosome 9q LOH and sunlight exposure, as assessed by either the location of tumors on the body or the presence of UVB radiation-related p53 mutations. Of note, there was a striking difference between the frequency of LOH on chromosome 17p (two [12.5%] of 16 informative tumors) and on chromosome 9q (32 [68%] of 47 informative tumors; P<.001). Conclusions: Inactivation of a gene on chromosome 9q22 may be a necessary event for basal cell carcinogenesis. The pathogenesis of mutations in this gene may involve factors other than sunlight in a large proportion of tumors. Implications: The limited association between sunlight exposure and BCC incidence may reflect an etiologic contribution of additional environmental agents. [J Natl Cancer Inst 1996;88: 349-54]

Basal cell carcinoma (BCC) of the skin is the most common type of cancer in humans (/). BCCs are slow-growing tumors that rarely metastasize or cause death, but they can result in extensive morbidity through local invasion and tissue destruction. The cell of origin is probably an epidermal pluripotential stem cell, and there is a range of histologic subtypes, including the well-circumscribed nodular (45%-60%), superficial (15%-35%), pigmented (1%-2%), and aggressive growth or infiltrative (4%-17%) (2). Although there is no formal grading system, the infiltrative subtype is considered more aggressive than the nodular and superficial subtypes and is more likely to recur because of noncontiguous growth and difficulty in defining surgical margins (/). Epidemiologic studies show some association between sunlight exposure and BCCs. More than 80% of tumors occur on the head and neck, the areas of greatest sun exposure; moreover, BCCs affect Caucasians almost exclusively, especially those who sunburn easily (3). Factors other than sunlight, however, are also involved. UVB radiation (i.e., UV radiation of a wavelength of 280-320 nm) is generally considered to be the carcinogenic component of sunlight (4). In contrast to the incidence of squamous cell carcinoma of the skin, which is strongly associated with cumulative UVB radiation exposure in humans, the incidence of BCC of the skin shows only a modest association with total UVB radiation exposure (35).

Furthermore, the distribution of squa-
mous cell carcinoma on the head and neck is closely associated with areas on the body of greatest sun exposure, but up to 33% of BCCs occur in areas with minimal sun exposure (6,7).

Despite the frequency of BCCs, little is known about their molecular pathogenesis. Moreover, there is only limited molecular evidence implicating a specific environmental agent in basal cell carcinogenesis. For some tumors, particular agents have been associated with specific genetic alterations; e.g., aflatoxin B1 appears to lead to mutation in codon 249 of the p53 gene (also known as TP53) in hepatocellular carcinoma (6,9). UV radiation can cause several types of genetic damage, including formation of photodimers that most commonly result in a G-C to T-A transition opposite a di-nucleotide site, as well as single-strand breaks (primarily UVA radiation exposure, i.e., UV radiation of a wavelength of 320-400 nm) (10-12). UVB radiation-related point mutations have been found in the p53 gene of 45%-56% of BCCs (13-15). Two tumors occur at “hotspots” that are unique to nonmelanoma skin cancers and that are not common mutation sites in internal cancers (14,16). In addition, mutations in the ras family of proto-oncogenes, detected in 2%-14% of BCCs, are often of the type caused by UVB radiation (17,18).

Analysis of allelic loss in BCCs has implicated inactivation of a putative tumor suppressor gene on chromosome 9q22 as a frequent step in carcinogenesis (15,19-21). The gene for Gorlin’s syndrome, an autosomal dominant disorder predisposing to BCCs, maps to this exact location (19,20,22,23) and is presumed to be the tumor suppressor inactivated at this site.

In this study, we have investigated the association of allelic loss in chromosome 9 with occurrence of BCCs. In addition, we have examined the relationship between this genetic alteration and sunlight exposure.

**Patients and Methods**

**Clinical Material**

Tumor tissue was removed by Mohs’ micrographic surgery, during which the central tumor mass was first debulked, and then the tumor margins were excised by examining serial frozen sections under the microscope. The debulked material, which should contain minimal contaminating normal tissue, was shown by histologic examination to contain greater than 50% tumor cells. Tumor tissue was snap-frozen in liquid nitrogen and stored at -80°C. Blood samples (10 mL) were obtained from each patient as a source of constitutional DNA. Clinical information on each tumor included location, size, histologic subtype, and whether the tumor was primary or recurrent and sporadic or hereditary.

The study was approved by the Yale University School of Medicine Human Investigation Committee. Informed verbal consent was obtained from each patient for blood drawing and the use of excess tumor tissue for research.

**Pathology**

Hematoxylin-eosin-stained tumor specimens were evaluated for histologic characteristics, including features associated with “aggressive” BCCs (epithelial islands separated by increased stroma; poorly defined, peripheral palisading; epithelial spikes; and infiltrative behavior) (24). All slides were reviewed and categorized by the Mohs surgeon.

**Isolation of DNA**

Tumor tissue was pulverized in liquid nitrogen, then resuspended in 5 mL of TNE buffer (i.e., 10 mM Tris [pH 8.0], 100 mM NaCl, and 25 mM EDTA) with 1 mg/mL protease K (Boehringer Mannheim GmbH, Mannheim, Federal Republic of Germany) and 1% sodium dodecyl sulfate (SDS), and incubated at 37°C for at least 2 hours. After two phenol-chloroform extractions, DNA was precipitated with the addition of one-tenth volume of 3 M sodium acetate (pH 5.2) and two volumes of 100% ethanol and resuspended in TE buffer (i.e., 10 mM Tris [pH 8.0] and 1 mMEDTA).

Blood samples were suspended in a red blood cell lysis buffer (1.6 M NH4Cl, 0.1 M KHCO3, and 1 mM EDTA, pH 7.5) and centrifuged at 500g for 5 minutes at 4°C. DNA was extracted from the leukocyte pellet by the guanidine-hydrochloride method (25).

**Chromosome 9 Analysis**

**Southern blot.** DNA samples (5 µg) were digested to completion with various restriction enzymes according to conditions recommended by the manufacturer, size fractionated by electrophoresis in a 1% agarose gel in TNE buffer, denatured in 0.4 N NaOH, and transferred to a nylon membrane (Gene Screen Plus; Du Pont NEN. Boston, MA) according to the manufacturer’s instructions. Chromosome 9 probes (50 ng DNA) were labeled to a specific activity of 1 x 10^6 cpm/µg DNA with [32P]deoxyctydine triphosphatase (dTTP) (Amersham Life Science Inc., Arlington Heights, IL) by use of a random primed labeling kit (Boehringer Mannheim GmbH). Hybridization was carried out for 15 hours at 65°C in 0.5 M NaHPO4 (pH 7.2), 7% SDS, 1% bovine serum albumin, 1 mM EDTA, and 200 µg/mL, forming sperm DNA. Blots were washed once at room temperature for 20 minutes in 2x SSC and 0.1% SDS and once at 65°C for 20 minutes in 0.1x SSC and 1% SDS and then placed on film for 1-3 days at -80°C. Autoradiography was used as a means of visualization of chromosome bands either by visual inspection or by densitometry. Chromosome 9 probes were obtained from the American Type Culture Collection. Rockville, MD (pDH20 [DS18], pEKNZ130 [DS959], pLAMPP2 [DS959], pMC012 [DS938], pAIL2 [ABL], pMCT [DS10], and pEDF126.3 [DS871]) (Table 1).

**Microsatellites.** Samples were typed for five microsatellite markers (DS912, DS9159, DS9180, DS9127, and DS9109) on chromosome 9q22-31 by the polymerase chain reaction (PCR) (Table 1). Genomic DNA (100 ng) was amplified by use of an Ericipom Twin Block system thermocycler (Ercornp, San Diego, CA). The 50±L reactions included 200 µM each of deoxyguanosine triphosphate (dGTP; Boehringer Mannheim, Indianapolis, IN), deoxythymidine triphosphate (dTTP; Boehringer Mannheim), dCTP, and deoxyadenosine triphosphate (dATP; Boehringer Mannheim); 1 U [3P]dCTP; 100 pmol primer: 0.25 µM spemidine (Sigma Chemical Co., St. Louis, MO); 2.5 U Taq polymerase (Promega Corp., Madison, WI); and buffer supplied by Promega Corp. Cycles parameters were 94°C for 1 minute, 55°C for 1 minute, and 72°C for 2 minutes for 25-30 cycles with a 10-minute extension at 72°C at the end of the amplification process. PCR products were boiled for 2 minutes, placed on ice, and size fractionated in a 6% denaturing (8 M urea) polyacrylamide gel (Sequagel: National Diagnostics, Atlanta, GA).

**p53 Analysis**

Tumors were evaluated for point mutations in exons 2-11 of the p53 gene by direct DNA sequencing of both strands of the PCR products, as previously described (14). Sequencing of each product was performed twice. Loss of heterozygosity (LOH) in p53 was detected with a polymorphism from the fourth exon (26). DNA from blood-tumor pairs was amplified by PCR and then digested with Acc II. Fragments were separated by electrophoresis through a 2% agarose gel in TNE buffer, and LOH was read as loss of one of the bands in tumor DNA in informative pairs.

**Statistical Analysis**

Associations between tumor characteristics and molecular alterations were tested by a chi-squared analysis or Fisher’s exact test, depending on sample size. Because there were no prior hypotheses about specific associations between molecular and clinical characteristics of tumors, two-tailed significance limits were used in all calculations (37).

**Results**

Fifty-five sporadic BCCs from 54 patients and five BCCs from four patients with Gorlin’s syndrome were evaluated for allelic loss in chromosome 9. Thirteen sporadic tumors, which were similar in clinical characteristics to the remaining 47 tumors, were excluded from further study because they were uninformative.
for all markers tested. Many of the tumors were large, aggressive, and recurrent, as expected at a referral center for Mohs' surgery (38); however, a wide range of tumor characteristics was represented in the sample (Table 2). Histologic typing of the sporadic and hereditary BCCs (n = 47) showed that 32 (68%) were infiltrative, 11 (23%) were nodular, and four (9%) were superficial. Classified by size, 14 (30%) were less than 1 cm in diameter, 10 (21%) were 1-2 cm in diameter, nine (19%) were 2-5 cm in diameter, and 14 (30%) were greater than 5 cm in diameter. Of the 47 informative tumors, 44 (94%) were from sun-exposed areas and four (9%) were superficial. Classified by size, 14 (30%) were less than 1 cm in diameter, 10 (21%) were 1-2 cm in diameter, nine (19%) were 2-5 cm in diameter, and 14 (30%) were greater than 5 cm in diameter. Of the 47 informative tumors, 44 (94%) were from sun-exposed areas of the body, defined as the head and neck in both sexes, shoulders or chest in males, and legs in females (3).

Molecular analysis revealed LOH for 9q markers in 32 (68%) of 47 tumors (Fig. 1). Most tumors retained some markers on chromosome 9, but the region of allelic loss always included 9q22 (data not shown), where the Gorlin's syndrome gene maps. LOH occurred in 28 (67%) of 42 sporadic tumors and in four (80%) of five hereditary tumors (P = 1.0, difference not significant).

Although the majority of tumors in this study were relatively large, even the smallest tumors had a high frequency of allelic loss (tumors <1 cm compared with tumors ≥1 cm; P = .83, not significant). There was no trend toward a greater frequency of allelic loss in the more aggressive, infiltrative tumors compared with the superficial and nodular tumors (P = .89, not significant). Recurrent tumors were neither more likely nor less likely to show LOH for markers on chromosome 9 (P = .54, not significant). Tumors from non-sun-exposed areas on the body appeared to be as likely to have chromosome 9 allelic loss as tumors from sun-exposed areas (P = 1.0, not significant), but the power of the study to detect a difference was very limited because only three tumors from non-sun-exposed areas were evaluated. Of tumors from the nose, a site highly exposed to sun, 10 (56%) of 18 had LOH, compared with 22 (76%) of 29 for all other areas on the body combined (P = .15, not significant).

In a subset of 18 tumors (all from sun-exposed areas) evaluated for p53 mutations, 11 (61%) had alterations. All mutations were opposite a dipyrimidine site, and most were C→T or CC→TT transitions (a finding consistent with UVB radiation damage). All were putative null mutations (14). In six tumors, mutation led to a premature stop codon presumed to generate an inactive product. Four tumors had mutations identical to those found in the germline of Li-Fraumeni patients or in families with a history of osteosarcoma. These mutated p53 products are unable to suppress the growth of cells in vitro (39). The remaining tumor had a mutation in codon 281 of the p53 gene, which results in a reduced ability of the mutant p53 protein product to cooperate with the Ras oncoprotein in transformation (40). Four of the 11 tumors had point mutations in both p53 alleles, and one tumor had LOH accounting for inactivation of the second allele. No inactivating mutation of the second allele was identified in six tumors (14). No trends were identified suggesting a relationship between p53 mutation and tumor size, histology, or recurrence, although the sample was small (data not shown). There was no association between LOH in chromosome 9 and UVB radiation-induced mutation in the p53 gene (P = 1.0, not significant) (Table 3).

Of note, there was a striking difference between the frequency of LOH in chromosome 17p (two [12.5%] of 16 informative tumors) and chromosome 9q (32 [68%] of 47 informative tumors; P<.001).

### Discussion

Neoplasia is believed to result from a series of genetic alterations leading to a progressive disorder of the normal mechanisms of growth control and cell-cell interactions. Tumor suppressor genes play an important role in carcinogenesis in many tissue types. These genes normally exert a negative control on cell growth, and inactivation of both homologues ("two hits") is required for a growth-promoting effect. One hit is almost invariably a point mutation. Frequently, the other homologue is lost through a gross chromosomal rearrangement such as deletion or nondisjunction, which is manifested as LOH for polymorphisms surrounding the gene. Germline mutation of one copy of a tumor suppressor can cause autosomal, dominant cancer predisposition because the remaining homologue is likely to be lost in a proportion of susceptible cells through random or environmentally induced somatic events (41).

Previous studies (15,19-21) suggested that the gene for Gorlin’s syndrome on chromosome 9q22 is a tumor suppressor important in BCCs. The current analysis of sporadic and hereditary BCCs indicates that inactivation of the Gorlin’s syndrome gene may be a necessary event for carcinogenesis. In this large series of tumors, 68% had LOH for markers in chromosome 9. The results almost certainly underestimate the true incidence of

---

**Table 1. Chromosome 9 probes used for studies of loss of heterozygosity**

<table>
<thead>
<tr>
<th>Probe</th>
<th>Locus</th>
<th>Location</th>
<th>Enzyme</th>
<th>Probe size, kb</th>
<th>Allele size, kb</th>
<th>Reference No.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Single-copy polymorphic probes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pHHH20</td>
<td>D9S18</td>
<td>9p</td>
<td>Taq1</td>
<td>3.6</td>
<td>2.3/3.0</td>
<td>(26)</td>
</tr>
<tr>
<td>pEKZ130</td>
<td>D9S9</td>
<td>9q21</td>
<td>Msp1</td>
<td>2.8</td>
<td>4.5/6.2</td>
<td>(27)</td>
</tr>
<tr>
<td>pLAMP92</td>
<td>D9S29</td>
<td>9q31</td>
<td>Taq1</td>
<td>4.0</td>
<td>7.6/14.0</td>
<td>(30)</td>
</tr>
<tr>
<td>pMCOA12</td>
<td>D9S28</td>
<td>9q34</td>
<td>Msp1</td>
<td>3.0</td>
<td>2.5/10.0</td>
<td>(28)</td>
</tr>
<tr>
<td>pablK2</td>
<td>ABL</td>
<td>9q34</td>
<td>Pst1</td>
<td>1.5</td>
<td>6.8/11.0</td>
<td>(26)</td>
</tr>
<tr>
<td>pMCT</td>
<td>D9S10</td>
<td>9q34</td>
<td>Pst1</td>
<td>2.2</td>
<td>2.0/2.2</td>
<td>(30)</td>
</tr>
<tr>
<td>pEFD126.3</td>
<td>D9S7</td>
<td>9q34</td>
<td>Taq1</td>
<td>4.2</td>
<td>1.5/2.0</td>
<td>(31)</td>
</tr>
</tbody>
</table>

*kb = kilobase; bp = base pair.*
Table 2. Clinical and molecular characteristics of basal cell carcinomas (n = 47)

<table>
<thead>
<tr>
<th>Tumor No.</th>
<th>Age, y</th>
<th>Sex</th>
<th>Location</th>
<th>Size</th>
<th>Histology†</th>
<th>Type‡</th>
<th>Recurrence§</th>
<th>LOH 9</th>
<th>p53§</th>
<th>Codon</th>
<th>Base change</th>
<th>Amino acid change</th>
<th>LOH 17#</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>67</td>
<td>Male</td>
<td>Jaw</td>
<td>L</td>
<td>N</td>
<td>S</td>
<td>P</td>
<td>+</td>
<td>ND</td>
<td></td>
<td></td>
<td>Arg-Stop</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>44</td>
<td>Female</td>
<td>Nose</td>
<td>L</td>
<td>Inf</td>
<td>S</td>
<td>R</td>
<td>-</td>
<td>ND</td>
<td></td>
<td></td>
<td>Arg-Stop</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>48</td>
<td>Male</td>
<td>Cheek</td>
<td>Inf</td>
<td>S</td>
<td>R</td>
<td>+</td>
<td>-</td>
<td>ND</td>
<td></td>
<td></td>
<td>Arg-Stop</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>45</td>
<td>Male</td>
<td>Cheek</td>
<td>Inf</td>
<td>S</td>
<td>R</td>
<td>+</td>
<td>-</td>
<td>ND</td>
<td></td>
<td></td>
<td>Arg-Stop</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>61</td>
<td>Male</td>
<td>Leg</td>
<td>Inf</td>
<td>S</td>
<td>R</td>
<td>+</td>
<td>-</td>
<td>ND</td>
<td></td>
<td></td>
<td>Arg-Stop</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>48</td>
<td>Male</td>
<td>Nose</td>
<td>Inf</td>
<td>S</td>
<td>R</td>
<td>+</td>
<td>-</td>
<td>ND</td>
<td></td>
<td></td>
<td>Arg-Stop</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>82</td>
<td>Male</td>
<td>Cheek</td>
<td>Inf</td>
<td>S</td>
<td>R</td>
<td>+</td>
<td>-</td>
<td>ND</td>
<td></td>
<td></td>
<td>Arg-Stop</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>79</td>
<td>Male</td>
<td>Shoulder</td>
<td>Inf</td>
<td>S</td>
<td>R</td>
<td>+</td>
<td>-</td>
<td>ND</td>
<td></td>
<td></td>
<td>Arg-Stop</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>56</td>
<td>Male</td>
<td>Shoulder</td>
<td>Inf</td>
<td>S</td>
<td>R</td>
<td>+</td>
<td>-</td>
<td>ND</td>
<td></td>
<td></td>
<td>Arg-Stop</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>73</td>
<td>Male</td>
<td>Temple</td>
<td>Inf</td>
<td>S</td>
<td>R</td>
<td>+</td>
<td>-</td>
<td>ND</td>
<td></td>
<td></td>
<td>Arg-Stop</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>81</td>
<td>Female</td>
<td>Nose</td>
<td>Inf</td>
<td>S</td>
<td>R</td>
<td>+</td>
<td>-</td>
<td>ND</td>
<td></td>
<td></td>
<td>Arg-Stop</td>
<td></td>
</tr>
</tbody>
</table>

*Ś = small (<1 cm in diameter); 1 = intermediate (1-2 cm); L = large (2-5 cm); XL = extra-large (>5 cm).
†N = nodular; Inf = infiltrative; S = superficial.
§P = Primary tumor; R = recurrent tumor.
| IlLOH 9 | loss of heterozygosity on chromosome 9. + = LOH; – = no LOH.
| $p+$ = presence of mutation; – = absence of mutation; ND = not done.
| #Four additional tumors were tested for loss of heterozygosity (LOH) on chromosome 17p (LOH 17) (n = 26, 16 informative tumors). All four showed no LOH. + = LOH; – = no LOH; NI = not informative; ND = not done.

inactivation of this gene, since some tumors probably have point mutations of both homologues, not detectable as LOH. In retinoblastoma, for example, only 50% of tumors show LOH in the region surrounding the retinoblastoma gene, although the gene is inactivated in all tumors of this type (42).

Our study and other studies (20,21) showed that minute BCCs are as likely as large tumors to have chromosome 9 allelic loss, suggesting that this genetic alteration is an early step in carcinogenesis. That all histologic subtypes, whether primary or recurrent, have a high frequency of LOH in chromosome 9 indicates a unity at some stage in the molecular pathogenesis of BCCs, regardless of the clinical characteristics of the tumors. Other molecular changes may also be necessary for tumor formation or to enhance aggressiveness of BCCs.

The role of UV radiation in the pathogenesis of the genetic alteration on
show allelic loss, although the power of the study was very limited because of the small number of tumors from non-sun-exposed regions. UVB radiation-induced mutations in p53 almost certainly reflect sunlight exposure to the precursor cells of the tumors. With the assumption that these mutations can serve as a molecular dosimeter, there was no suggestion of an association between sun exposure and chromosome 9 allelic loss; i.e., UVB radiation-related point mutations in p53 were independent of LOH in chromosome 9. Data on the spectrum of p53 mutations in non-sun-exposed tumors are lacking, and the use of UVB radiation-related p53 mutations as a marker for sun exposure needs further validation.

Other factors in addition to UVB radiation exposure may play a synergistic role in many BCCs. Besides UVB radiation, arslenicals, polyaromatic hydrocarbons, and ionizing radiation have been linked to an increased risk of nonmelanoma skin cancer (3). In addition, UVA radiation, the major component of UV radiation in sunlight, can produce single-strand breaks in DNA that could lead to LOH (11).

**References**


Notes

Supported in part by Public Health Service grants K11CA60199 (M. R. Gailani) and R01CA57605 (A. E. Bale) from the National Cancer Institute, National Institutes of Health, Department of Health and Human Services; by The Argyll and Anna G. Hull Cancer Center Award (M. R. Gailani); and by a Brain Tumor Society research grant (A. E. Bale). Manuscripts received July 21, 1995; revised November 21, 1995; accepted November 30, 1995.

If you're looking for some good reading, you've just found it. The free Consumer Information Catalog.

The Catalog lists about 200 federal publications, many of them free. They can help you eat right, manage your money, stay healthy, plan your child's education, learn about federal benefits and more.

So sharpen your pencil. Write for the free Consumer Information Catalog. And get reading worth writing for.