
Letter

Curcumin is emerging as a very interesting and complex compound. Some of the complexities are not addressed in the above study, however, leaving the impression that curcumin is useless, or even dangerous, as a chemotherapy adjuvant.

Contrary to the findings of the present study, curcumin has been shown to augment the cytotoxic effects of chemotherapeutic drugs, including doxorubicin (1), tamoxifen (2), cisplatin and camptothecin (3), daunorubicin, vincristine, and melphalan (4). Navis et al. (5) reports that curcumin normalizes elevations in tumor-related enzymes when combined with cisplatin, leading to the inference that it will be a good adjuvant for this drug as well. There appear to be methodological problems with the present study that cause results that conflict with these and other published studies.

The dose of curcumin used in the study may be insufficient for the purpose it’s intended. It is well established that curcumin has distinct dose-related behavior. For example, treatment of mice with 250 mg/kg/day produces a 1.8 fold increase in activity of glutathione S-transferase (6), whereas treatment with 1 g/kg produces a 20% decrease in glutathione S-transferase activity (7, 8). Curcumin can act as an antioxidant or prooxidant, depending on dose. At 10 μM (the maximum dose used in the present study), curcumin is a documented antioxidant (9). At 50 μM, it generates superoxide radicals and induces apoptosis (10). Reactive oxygen species may be necessary for curcumin’s apoptotic effect (10).

Reactive oxygen species are also thought to be a factor in the effectiveness of cancer drugs. As such, it would seem counterproductive to use an antioxidant dose of curcumin in a study designed to assess chemotherapy adjuvant potential. Goel et al. (11) document maximum cytotoxicity for HT-29 cells at 75 μM. This is in agreement with Hanif et al. (12). The amount used in the present study, 10 μM, had no effect in those studies. It is unclear why Somasundaram et al. would evaluate a chemopreventive dose rather than a cytotoxic dose.

Time is another critical factor in determining curcumin’s cytotoxic effect. The maximum time point in the present study is 15 h; however, curcumin’s cytotoxic effects may not occur for at least 48 h (12). Maximal growth inhibition in Goel et al. (11), was observed at 72 h, and little or no effect was observed by Goel et al. (11) and Hanif et al. (12) at 15 h, the maximum incubation time in the present study. Chuang et al. (13) report a biphasic effect when combined with chemotherapeutic drugs, which may have relevance.

Somasundaram et al. adopt the premise that because the activation of NFκB1 is critical to the cytotoxicity of some chemotherapeutic drugs and because curcumin suppresses this signal transduction pathway, the compound will interfere with the effectiveness of such drugs. The exact opposite view is held by other investigators, who have been able to demonstrate that curcumin’s suppression of NFκB enhances some NFκB-activating chemotherapies and that such activation creates resistance that can be overcome with curcumin and other NFκB-suppressing compounds [see, e.g., Wang et al. (14)]. The beneficial effect of curcumin in combination with NFκB-activating drugs has been demonstrated for doxorubicin, 5-fluorouracil, cisplatin, vincristine and paclitaxel, among others (3, 4, 13).

The present study demonstrates that curcumin reverses the camptothecin and mechloethamine activation of activator protein-1, and similarly argues that this interferes with a critical cytotoxic mechanism of these drugs. Jarvis et al. (15) show, however, that curcumin has no effect on the toxicity of etoposide, daunorubicin, and idarubicin, which activate apoptosis through this pathway. In a study on isothiocyanates, Xu and Thornalley (16) showed that inhibition of JNK only delayed apoptosis, not prevented it. The assertion that curcumin’s suppression of signal transduction pathways interferes with the effectiveness of some chemotherapeutic drugs is not supported by published research.

The authors of the present study mention curcumin chemoprevention trials several times and warn that people undergoing chemotherapy should not be enrolled in such trials. Curcumin doses for parts of the study were apparently based on such trials, but the authors seem to be confusing prevention with treatment. People undergoing chemotherapy are not likely to be enrolled in prevention trials, and the dose of curcumin optimal for treatment is not likely to be the same as for prevention. It is not clear why the issue of chemoprevention was even brought up in this report.

Finally, the authors infer that it is equivocal whether curcumin has any effect on HT-29 cells (first part of the “Discussion”) by citing two studies, one of which they state “found no effect.” However, the “no effect” study they cite (12) in fact reports a 96% decrease in cellular proliferation, an effect so impressive the authors were compelled to write that it is “very significant.” Although it is true that Hanif et al. (12) did not detect apoptosis, the authors qualify it by saying that the fact they did not detect it does not mean that it did not occur and might be detected by different means. Since that study was published, it has been reported that curcumin induces an atypical apoptosis that may not be detectable by usual techniques (17, 18). To suggest, as the present authors do, that there are two studies on the issue, one pro and one con, is disingenuous. All published studies on curcumin and HT-29 cells that I found show that curcumin, by itself, induces cytotoxicity regardless of whether apoptosis is detected [see, e.g., Jiang et al. (19) and Goel et al. (11)]. Studies on other types of colon and gastric cancer cells showed the same thing (20). The Somasundaram study itself appears to confirm the cytotoxicity of curcumin on breast cancer xenografts; it therefore is not clear why the authors would question whether curcumin can induce apoptosis in cancer cells.

In light of the foregoing, it seems to me that the reviewers should have questioned why a compound that has been proven to be a powerful cytotoxic agent and to augment the effects of some types of chemotherapy would suddenly, in one study, become so dangerous as to warrant the admonition that people undergoing chemotherapy should not even consume it as a spice. If they had, I think they would have questioned the methodology of the study that undermines its validity.

The issue of whether curcumin should be consumed by people undergoing chemotherapy is not answered by the present study. It is, however, a very intriguing and important question to pursue given studies published to date that suggest that curcumin may be a good chemotherapy adjuvant. It appears that this will depend on several factors, including the type of cancer and the type of drug. It has recently been demonstrated that a significant synergistic effect occurs in both PC-3 and DU145 prostate cancer cells treated with doxorubicin, 5-fluorouracil or paclitaxel when curcumin is given at a particular time relative to chemotherapy (21). This points up the danger of making negative assumptions about the potential therapeutic use of adequate curcumin as chemotherapy adjuvant before research is done.

Received 10/04/02; accepted 6/17/03.

1 The abbreviation used is: NFκB, nuclear factor-κB.

Terri M. Mitchell
Ocean Springs, MS 39564
LETTER TO THE EDITOR

In his letter about our recent publication in Cancer Research (1), Terri Mitchell notes that curcumin is an interesting and complex compound, a conclusion with which we heartily agree. He then proceeds to take issue with several aspects of our work, however, and begins by implying that our study contradicts the body of literature in this area and is the only one that has shown curcumin inhibits apoptosis. This ignores the references discussed in our “Introduction” that reported the ability of curcumin to inhibit programmed cell death induced by several stimuli, including bleomycin, doxorubicin, dexamethasone, and radiation. Mitchell himself advances references that he feels show curcumin has the opposite effect we described. However, Harbottle et al. (2) evaluated cytotoxicity, Verma et al. (3) studied cell growth inhibition, Navis et al. (4), which Mitchell references as “Sriganth,” followed serum tumor markers, and the work described in the abstract of Dr. Michaels looked at tumor growth delay. In a similar vein, Mitchell later reports that we inferred in our “Discussion” that curcumin had equivocal cytotoxic effects on HT-29 cells. This statement is a misrepresentation of our text, however, in that we again wrote specifically about apoptosis. He himself admits that Hanif et al. (5), whose results he uses to refute our discussion, “...did not detect apoptosis.” Although these various investigators have reported noteworthy findings about the activity of curcumin, they all used different model systems from ours, different cell death stimuli, and are not strictly comparable with ours because none evaluated apoptosis, which we used as our end point. Mitchell inappropriate equates the results of assays of apoptosis with those of growth inhibition, cellular cytotoxicity, and even surrogate tumor marker levels. In addition, because Wang et al. (6) did not use curcumin in their studies, this reference is not applicable. Finally, Mitchell seems to contend that apoptosis is not an appropriate end point because Piwocka et al. (7) and Bush et al. (8) have reported curcumin induces atypical forms of apoptosis. In doing so, he ignores the publications of investigators who have noted activation of classical forms of programmed cell death by curcumin, which are too many in number to reference in this forum. Furthermore, Bush et al. reported that curcumin indeed induced apoptosis through a caspase-3-dependent pathway, and in our work, we showed that curcumin inhibited activation of caspase-3. There is ample support in the literature for the study of curcumin’s effects on apoptosis using the assays that we used, which, in addition to caspase-3 activity, included DNA fragmentation and mitochondrial release of cytochrome c.

Mitchell’s letter proceeds to say that the effects of curcumin can differ depending on the dose and incubation time that is used, an assertion which we accept. He then questions our choice of experimental conditions, suggesting that higher doses of curcumin with longer exposures would have yielded different results and saying that we should have used cytotoxic doses of curcumin, rather than chemopreventive ones. Because we did not perform our studies under the conditions Mitchell favors, it is possible that he is right about the outcome of these hypothetical experiments, and we would be interested to see data from his own investigations in this regard. Simply speculating that our results would have been different had we changed the most critical parameters of the experiment does not seem to be sufficient cause on which to impugn our data, however. The rationale for our choice of conditions was clearly stated in our manuscript and based on the first controlled human clinical trials that have been performed with curcumin to date, which did study chemopreventive applications. Cheng et al. (9) found that dosing of curcumin at the highest level of intake they tested, 8000 mg daily, produced peak serum curcumin levels of 1.77 ± 0.87 μM, supporting our use of curcumin concentrations in the 1–10 μM range. Presumably, Mitchell would like for us to have used curcumin at 50–75 μM, two of the concentrations he quotes. To our knowledge, however, there is no evidence supporting the possibility that such massive levels are attainable systemically in vivo. We invite him to provide references demonstrating otherwise, which he does not, yet he makes conclusions about the adjuvant properties of curcumin under these nonphysiological conditions.

In a subsequent paragraph, Mitchell claims that we have adopted the hypothesis that the ability of curcumin to suppress activation of

References

Received 1/29/03; revised 4/5/03; accepted 5/23/03.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked advertisement in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.
been taking 1800 to 3600 mg a day of curcumin. Interestingly, in this piece note is made that, process Mitchell notes that Jarvis et al. (12) found no effect of curcumin on apoptosis. However, he does not mention that Jarvis et al. used curcumin at 500 nm, a concentration we did not study, and in a different model system. The former omission is an especially interesting one given that the concentration dependence of curcumin’s actions is a major point in Mitchell’s critique of our work. In addition, he does not report the fact that Jarvis et al. did see inhibition of ceramide- and sphingosine-induced apoptosis by curcumin. As further proof that the c-Jun-NH2-terminal kinase pathway is not part of curcumin’s antiapoptotic activity, he refers to the work of Xu and Thornalley (13), but these investigators studied the effects of isothiocyanates and did not use curcumin in their work, so it is not clear how their findings could be used to refute ours.

Later, Mitchell suggests the reviewers should have considered why in our study curcumin became “… so dangerous as to warrant the admonition that people undergoing chemotherapy shouldn’t even consume it as a spice.” In this he distorts our conclusions, which are much more rational and circumspect, e.g., in the “Abstract,” we state only that our work “… suggest(s) that additional studies are needed to determine whether breast cancer patients undergoing chemotherapy should avoid curcumin supplementation and possibly even limit their exposure to curcumin-containing foods.” Nowhere do we use the kind of language that Mitchell attributes to us, nor do we anywhere suggest that curcumin is a dangerous agent.

Lastly, Mitchell states that the publication of our work represents an example of the breakdown of the peer-review process. Despite making this claim, he himself does not submit any data for peer review that controverts our results, nor does he make reference to any directly comparable studies. We invite Mitchell to substantiate his complaints about our work in a scientific fashion and also to submit some of his writings on the subject of curcumin to a scientific peer-review process, e.g., in the July 2002 issue of the online Life Extension Magazine, he extols curcumin as “… a natural substance so smart it can tell the difference between a cancer cell and a normal cell; so powerful it can stop chemicals in their tracks; and so strong it can enable DNA to walk away from lethal doses of radiation virtually unscathed.” Interestingly, in this piece note is made that, “Most cancer patients have been taking 1800 to 3600 mg a day of curcumin. …” On the basis of the work of Cheng et al. (9), this dosing would result in even lower systemic levels of curcumin than the ones tested in our studies, which Mitchell criticized as being too low. Later in Mitchell’s article, a recommendation is made that, “Since curcumin has not been adequately tested with other chemotherapy drugs, it might be safe to wait until chemotherapy is completed before initiating curcumin.” In that Mitchell seems to echo our own conclusions in his article, it is his critique of our work in his letter that seems disingenuous to us. We welcome a spirited academic debate into the merits of our work on the fascinating compound curcumin. In publishing our original manuscript, we intended to report interesting findings, by which we continue to stand. In addition, we wished to sound a cautionary note that agents such as curcumin may have many beneficial but also potentially detrimental applications under some circumstances. These products need to be studied in more detail before being promoted in the fashion affected by Mitchell’s writings.

Robert Z. Orloski
Sivaguruunathan Somasundaram
Department of Medicine
Division of Hematology/Oncology
Chapel Hill, North Carolina 27599

References


Letter

We read the recent study of Rosin et al. in Cancer Research (1) with great interest. The authors used LOH analysis to assess the risk that

Received 1/15/03; accepted 3/6/03.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked advertisement in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

1 The abbreviation used is: LOH, loss of heterozygosity.
precursor lesions in patients after being treated for their primary p.o.
tumor develop into new second p.o. malignancies. Although we fully
acknowledge the importance of the question addressed in this study,
we would like to emphasize that a critical issue is not included in the
experimental design with possible consequences for the interpretation
of the results and thereby the implications of the findings.

The definition of second p.o. malignancy needs further description.
It is well known that patients with p.o. cancers have a high risk for
developing local recurrences even when the resection margins were
found to be tumor free after thorough histopathological examination.
In relation to the index tumor, a recurrent tumor is defined to be <2
cm away and occur within a time interval of 3 years, according to
current clinical criteria (2, 3). In addition, these patients are also at risk
for developing second primary tumors (>2 cm away or >3-year interval)
in the same or adjacent anatomical area. Although the authors
have recognized this distinction, they prefer only to “second oral
malignancy,” because there is no difference in the proportion of cases
with LOH at 3p and/or 9p that developed into second p.o. malignancy
before and after 3 years (see “Materials and Methods”). We agree with
the notion that second primary tumors arise from precursor lesions
after therapy, as has clearly been described in previous studies (4–8).
However, and this should be stressed, we do not agree with the
assumption that local recurrences exclusively originate from precursor
lesions. Local recurrences might also originate from remaining tumor
cells as we and others (3, 7, 9) discussed in previous publications.
In fact, we recently determined that ~60% of the local recurrences
originate from tumor cells left behind in patients with histologically
malignant resection margins. Apparently, we are dealing in significant
proportion of patients with nonresected tumor cells that can only be
detected with sensitive molecular methods. The percentage of
tumor-derived recurrences might even be higher in patients selected
on the basis of “treatment with curative intent,” as was used as criterion
in the present study. The authors touched on this problem by
stating that they did not find differences in risk profiles in the cases
that developed a second p.o. malignancy within and after 3 years.
In our view, this is not sufficient. The question is whether the authors
have performed a detailed molecular analysis of both the tumor and
local recurrence to check whether they have included local recurrences
that originate from nonresected tumor cells. This is the only way to establish the value of different LOH patterns for risk assessment
in post-treatment p.o. precursor lesions. It may even be that after correction for the proportion of tumor-derived recurrences, different
and even higher risk factors will be obtained.

Although we do not question the importance of the presented
findings, the current study may tell only a part of the story of the
development of recurrent or second p.o. malignancies.

Boudewijn J. M. Braakhuis
C. Renee Leemans,
Ruud H. Brakenhoff
Department of Otolaryngology/Head and Neck Surgery
Vrije Universiteit Medical Center
1007 MB Amsterdam
the Netherlands

References
1. Rosin, M. P., Lam, W. L., Poh, C., Le, M. D., Li, R. J., Zeng, T., and Priddy, R. 3p14
and 9p21 loss is a simple tool for predicting second oral malignancy at previously
and Brakenhoff, R. H. Second primary tumors and field cancerization in oral and
oropharyngeal cancer: molecular techniques provide new insights and definitions.
Teo-To-Seela, F., and Langdon, J. D. Detection of minimal residual cancer to inves-
5. Forastiere, A., Koch, W., Trotti, A., and Sidransky, D. Medical progress—head and
7. van Houten, V. M. M., Tabor, M. P., van den Brekel, M. W. M., Kummer, J. A.,
Denkers, F., Dijkstra, J., Leemans, C. R., Van der Waal, I., Snow, G. B.,
and Brakenhoff, R. H. Mutated P53 as molecular marker for the diagnosis of head and
8. Tabor, M. P., Braakhuis, R. H., Ruitter-Schippers, H. J., Van Der Waal, I., Snow, G. B.,
Leemans, C. R., and Braakhuis, B. J. M. Multiple head and neck tumors
Goodman, S. N., and Sidransky, D. Molecular assessment of histopathological staging

Reply
The term “second oral malignancy” (SOM) (1), as used in Rosin et al.
(2), refers to second tumors in the oral cavity, regardless of origin. This
includes recurrent tumors developing from residual tumor cells, SPTs
developing from independently altered mucosal cells, local metastasis,
and/or SFTs. The latter term (second field tumor) has been recently
proposed by Braakhuis et al. (3, 4) for tumors derived from the same
genetically altered mucosal field as that of the primary tumors, sharing
some but not all genetic markers, and possibly representing lesions that
were originally related but diverged at a later stage.

We share the view that molecular investigation of the origin of
SOMs promises to improve classification, because current clinico-
pathological criteria have limited value in delineating the origin of
SOM. However, even molecular tools, such as LOH and p53 mutation
analyses, used to investigate the source of SOMs (5–7) may not always differentiate among these tumors with complete confidence.
The complexity of clonal evolution and resulting heterogeneity of
subpopulations within a tumor can complicate interpretation. SOMs
developing at the same (or adjacent) anatomical site with the same
molecular alterations as the primary squamous cell carcinoma are
most likely recurrent tumors. Conversely, SOMs with distinctly dif-
ferent patterns of genetic alterations are likely to be clonally independent and hence “true” SPTs. Unfortunately, absolute concordance
(or discordance) between a primary tumor and an SOM is uncommon
and, in most cases, primary tumors and SOMs will share some but not all alterations.

Currently no consensus exists on how the latter SOMs should be
classified. Lesions that share an identical novel microsatellite shift or
a signature gene-specific mutation are likely to be clonally related.
However, establishing a relationship based on more common genetic
markers, and possibly representing lesions that were originally related but diverged at a later stage.

We share the view that molecular investigation of the origin of
SOMs promises to improve classification, because current clinico-
pathological criteria have limited value in delineating the origin of
SOM. However, even molecular tools, such as LOH and p53 mutation
analyses, used to investigate the source of SOMs (5–7) may not always differentiate among these tumors with complete confidence.
The complexity of clonal evolution and resulting heterogeneity of
subpopulations within a tumor can complicate interpretation. SOMs
developing at the same (or adjacent) anatomical site with the same
molecular alterations as the primary squamous cell carcinoma are
most likely recurrent tumors. Conversely, SOMs with distinctly dif-
ferent patterns of genetic alterations are likely to be clonally independent and hence “true” SPTs. Unfortunately, absolute concordance
(or discordance) between a primary tumor and an SOM is uncommon
and, in most cases, primary tumors and SOMs will share some but not all alterations.

Currently no consensus exists on how the latter SOMs should be
classified. Lesions that share an identical novel microsatellite shift or
a signature gene-specific mutation are likely to be clonally related.
However, establishing a relationship based on more common genetic
events, such as LOH at microsatellite markers, can be less distinctive.

1 Supported by NIH Grant R02 DE13124 from the National Institute of Dental and
Craniofacial Research.
2 The abbreviations used are: SOM, second oral malignancy; SPT, second primary
tumor; SFT, second field tumor; LOH, loss of heterozygosity.

LETTER TO THE EDITOR

C. Renee Leemans,
Ruud H. Brakenhoff
Department of Otolaryngology/Head and Neck Surgery
Vrije Universiteit Medical Center
1007 MB Amsterdam
the Netherlands

Supported by NIH Grant R02 DE13124 from the National Institute of Dental and
Craniofacial Research.

5168

Downloaded from cancerres.aacrjournals.org on August 30, 2017. © 2003 American Association for Cancer Research.
One approach is to stratify markers into early and late events, and then compare these patterns in the index and SOM. Presumably, recurrence and SFT would share the same early events with the index tumor (e.g., 3p or 9p loss) but differ in late events, with recurrence more closely resembling the index tumor. However, even in recurrent tumors, the degree of similarity is affected by clonal evolution or heterogeneity. Furthermore, even greater difficulty is encountered when this approach is used to differentiate SFTs from SPTs. SFTs and index tumors are presumed to harbor the same early events, but SFTs do not. However, because such events are found in high frequency in all tumors, similarity can occur by chance alone. Extensive allelotyping with multiple markers for each chromosome arm may be necessary to improve such classification (5). Even then, some level of discordance attributable to clonal evolution is expected. Classification is based on proportional similarities or dissimilarities in the markers using arbitrary (subjective) cutoffs with the presumption that true recurrence will share most markers with the index tumors, whereas SFT will share some and SPT will share few or no markers.

Because of this lack of a reliable method in differentiating among SOMs, we feel it may be premature to subclassify the SOMs in our sample set (2) until we have a better method of delineation. Comparing multiple oral samples from the same patients might be an effective approach to delineation of clonal relatedness. Jang et al. (5) established the clonal relationship by stringent criteria that involved an assessment of the probability of two lesions exhibiting the same allelotypes by chance alone. Remarkably, a sequence of genetic events on three arms was reconstructed using 33 biopsies in four patients, revealing multiple lineages of related clones. These data point to the value of repeated sampling within a high-risk field to facilitate the delineation of clones and to establish criteria for molecular subclassification of SOMs.

Meanwhile, the issue at hand is to reduce SOM through the development of tools that assist the clinician during patient follow-up. We propose broadening studies in oral cancer patients from the focus on subclassification of SOM to risk prediction through temporal analysis of clinicopathological and molecular patterns in high-risk mucosal fields. At present, despite aggressive monitoring and the awareness of the high rate of SOM, little improvement in prognosis has occurred. A major problem is that early changes leading to SOM may not be clinically apparent or, if present, not readily differentiated from reactive changes induced by treatment. In either case, a biopsy may not be available for either histological or molecular analysis. Improvement in our ability to detect tissue that requires biopsy is a pressing issue. Similarly, even when a lesion is biopsied, the risk prediction is still limited when pronounced dysplasia is absent. The Rosin et al. article (2) was intended to test whether a set of microsatellite markers previously shown to be predictive of progression for oral premalignant lesions would also predict development of SOM for leukoplakia developing at the former cancer site. (We did not set out to distinguish the two classes; the leukoplakia could contain residual tumor cells or premalignant clones developing at the former cancer site.) Loss of 3p14 and 9p21 was shown in our study to be a simple tool for predicting second oral malignancy at previously treated oral cancer sites. Cancer Res., 62: 6647–6450, 2002.

We think that using a combination of clinicopathological and molecular alterations to assess the tissue left behind after cancer treatment may be a practical approach to risk assessment. To this end, we have established a prospective study of 200 oral cancer patients that are being followed using both traditional and experimental diagnostic procedures (toluidine blue, fluorescence imaging) in parallel with molecular analyses of brushings and biopsies of this field to develop a risk model for clinical management of patients. Early studies from this laboratory have already established that LOH at 3p and 9p can be identified in exfoliated cells collected from clinically normal mucosa at previous cancer sites months before the appearance of leukoplakia and the subsequent development of SOM (8, 9). This noninvasive approach allows the repeated monitoring of cancer sites even when the lesion is innocuous or not apparent clinically. We and others have also shown that toluidine blue staining localizes to sites containing high-risk molecular clones and, hence, can be used to target the site of exfoliated cell scrapes or biopsies (1, 10).

In conclusion, both subclassification and the development of cancer risk markers of SOM are critical to the improvement of prognosis for oral cancer patients. We advocate temporal analysis and echo the call of Braakhuis et al. (4) and others for longitudinal studies to establish clinical and molecular patterns in high-risk mucosal fields.

Lewei Zhang
Faculty of Dentistry
University of British Columbia
2199 Wesbrook Mall
Vancouver, British Columbia
V6T 1Z3 Canada

Wan L. Lam
British Columbia Cancer Research Centre
601 West 10th Avenue
Vancouver, British Columbia
V5Z 1L3 Canada

Miriam P. Rosin
British Columbia Cancer Research Centre
601 West 10th Avenue
Vancouver, British Columbia
V5Z 1L3 Canada

References

To whom requests for reprints should be addressed, at Faculty of Dentistry, the University of British Columbia, 2199 Wesbrook Mall, Vancouver, BC, V6T 1Z3 Canada. Phone: 604-877-6123; Fax: 604-877-1868; E-mail: Lewei@shaw.ca.

Boudewijn J. M. Braakhuis, C. René Leemans and Ruud H. Brakenhoff


Updated version
Access the most recent version of this article at:
http://cancerres.aacrjournals.org/content/63/16/5167

Cited articles
This article cites 16 articles, 5 of which you can access for free at:
http://cancerres.aacrjournals.org/content/63/16/5167.full#ref-list-1

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.