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BRCA Mutations in Young Breast Cancer Patients Without a Family History Influence Histologic Features of the Tumors

ABSTRACT & COMMENTARY

Source: Armes JE, et al. *Cancer* 1998;83:2335-2345.

It is now understood that breast tumors that develop in women with germline mutations in cancer susceptibility genes (particularly BRCA1 and BRCA2) have distinct histologic phenotypes.[1,2] However, the majority of the current data is derived from affected individuals from cancer families, but mutations are also observed in women without such a family history. In fact, the majority of women with breast carcinoma who carry a BRCA1 or BRCA2 mutation do not have any family history of breast or ovarian cancer. The current study was designed to determine whether the histologic phenotypes recognized for tumors in BRCA1/2 mutation carriers from cancer prone families apply to breast carcinoma occurring in young women with germline BRCA1/2 mutations but no family history of breast cancer.

The study undertook a histologic assessment of breast carcinomas diagnosed before age 40 years identified from a population-based study. Samples were derived from the Australian Breast Cancer Family Study (ABCFS). Of 467 breast cancer cases diagnosed between 1992 and 1995 in this age group, blood samples were available from 388 cases. BRCA mutations were detected by the protein truncation test and were confirmed by manual cycle sequencing.

For the morphologic study, tumors from 10 cases with germline BRCA1 mutations and nine cases with BRCA2 mutations were compared with tumors from 21 control patients (younger than 40 years old, without BRCA mutations).

Breast cancer in BRCA1 mutation carriers was associated with distinct histologic appearance. The tumors were higher grade with greater mitotic counts, a syncytial growth pattern, pushing margins and confluent necrosis. Furthermore, atypical medullary carcinoma was observed to a greater extent in this group. In contrast, all low-

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grade tumors and tumors with low mitotic rates were found in the control groups (those without germline BRCA1/2 mutations). Those with germline BRCA2 mutations were more likely to have pleomorphic histology exhibiting extensive intraductal growth.

Thus, there appears to be distinct histologic correlates of mutations in the BRCA genes. The authors suggest that such histologic patterns observed in young patients may be useful in predicting those for whom more extensive genetic testing may be fruitful.

COMMENTARY

Screening for BRCA mutations is a cumbersome and expensive task. This is primarily because these are large genes and numerous evenly distributed mutation sites have been observed. Accordingly, widespread screening is currently not feasible. The criteria used to determine which patients or families should be screened have yet to be established. The current report may be helpful in this regard. Young women with atypical medullary or pleomorphic medullary carcinomas that have histologic features of syncytial growth or prominent pushing margins are more likely to have mutations in BRCA genes.

This may well be the first demonstration, on a population basis, of a phenotypic-genotypic correlation with regard to BRCA mutation. Prior kindred studies[3,4] also demonstrated similar histologic features, but in this report individuals were not selected for family history. The fact that such findings were clearly distinct in a small study such as this indicates just how powerful the association is.

High-grade tumors with similar histologic patterns have been identified with breast cancer in younger women in general.[5] From the current analysis of 40 patients, it could be predicted that those histologic correlates of more aggressive tumors (seen more commonly in young patients) might well relate, in part, to BRCA mutations. Genetic screening for the families of these patients would seem appropriate. ❖

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Which of the following statements about BRCA gene mutations in breast cancer is true?

a. BRCA mutations are found more commonly in elderly patients with breast cancer.
b. BRCA mutations are found to correlate with aggressive histologic patterns, but only in those individuals with "familial" breast cancer.
c. BRCA mutations are found to correlate with aggressive histological patterns in breast cancer patients with or without a family history of breast cancer.
d. BRCA mutations do not correlate with histological patterns.
e. BRCA mutations are associated with less aggressive histological patterns in patients with a family history of breast cancer.

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Ductal Carcinoma In Situ: When is Conservative Surgery Alone Sufficient?

ABSTRACTS & COMMENTARY

Synopsis: *Ductal carcinoma in situ is highly curable by mastectomy. More conservative surgical approaches have become commonly employed, but local recurrences are considerably more frequent (approximately 20%). The addition of radiation therapy effectively reduces local recurrence by about 50%. Yet, it is still unclear which patients are likely to benefit from more radical surgery or additional radiation. Two recent reports have*

addressed this issue. On the basis of these studies, patients best suited for conservative therapy alone (outside of a clinical trial) are those with low grade, small lesions with no necrosis and clear surgical margins.

Sources: Hetelekidis S, et al. *Cancer*1999;85:427-431; Boyages J, et al. *Cancer* 1999;85:616-628.

The management of ductal carcinoma in situ (DCIS) involves initial treatment decisions that are difficult. The difficulty emerges because mastectomy is nearly 100% curative[1] but is more aggressive treatment than is given to patients with invasive cancer and is perhaps more therapy than most patients need. Indeed, conservative surgical approaches have provided excellent results with low local recurrence rates and more satisfactory cosmetic and psychological outcomes.[2,3] When radiation therapy is added to a conservative surgical procedure, local recurrence rates approximate those observed after mastectomy in some series.

Recently, two papers published in *Cancer* provide useful data for clinicians advising patients in this decision-making process. In the first report, Hetelekidis and collegues from Harvard examined outcomes in 59 patients with DCIS who presented from 1985 to 1990 and were treated with excision alone. Study pathologists examined histologic slides and all had negative margins at the time of initial review. The median age at diagnosis was 54 years and the median follow-up time was 95.5 months. All but two presented with mammographic findings only and all of the patients who recurred had reexcision.

One factor considered important in predicting the chance for local recurrence has been the lesion size.[4,5] However, size has been difficult to assess because DCIS is usually not grossly apparent. Thus, histologic specimens have been used to assess size, and these methods have proven imprecise.[6] In this series, a novel approach was developed. The number of low power fields (40X) in which DCIS was identified were summed and used as a surrogate measure of overall size.

Similarly, margin status has proven to be a difficult assessment, primarily because DCIS lesions can have gaps of several millimeters separating them, suggesting that margins of just a few millimeters may be inadequate to assure total excision. In this series, patients with involved margins were not included. Those with margins of 1 mm or less were considered "close," whereas those with margins greater than1mm were considered "negative."

Although local recurrence developed in 10 of the 59 patients, no patients developed metastatic disease or died of breast cancer. The actuarial five-year local recurrence rate with a conservative surgical procedure alone was 10%. Four of the 10 recurrences were invasive carcinomas and six were DCIS. All recurrences occurred in close proximity to the originally resected lesion.

In this series, the single most important factor that predicted the development of local recurrence was lesion size. Those with low power field (LPF) scores of greater than 5 had 17% actuarial five-year local recurrence rates compared to 3% five-year local recurrence rates for those with smaller (<5 LPF) lesions. In fact, size was the only factor that reached a level of statistical significance in univariate analysis. Although patients with nuclear Grade 3 lesions had a higher local recurrence rate than those with nuclear Grade 1 and 2 lesions (18% vs 6% and 5% respectively), and patients with close margins (< 1mm) had a higher local recurrence rate than those with negative margins (> 1mm 25% vs 8%), these differences did not reach statistical significance. Yet, Hetelekidis et al point out, of the 19 cases with margins of less than 1 mm, lesion size of less than 5LPF and nuclear grade of 1 or 2, there were no local recurrences; by contrast, the remaining 40 patients had a five-year actuarial local recurrence rate of 15%.

Thus, in this single series, it appears that lesion size, nuclear grade,and margin status were prognostic factors that would help predict local recurrence and, thereby, be useful in advising patients regarding the use of adjunctive radiation therapy or mastectomy. Interestingly, in this series, factors such as patient age, family history, predominant architectural pattern (comedo type or other), or the presence of necrosis did not offer additional predictive value.

In the second report by Boyages and collegues, a meta-analysis of the patient, tumor, and treatment factors relevant to local recurrence after DCIS resection was undertaken. Boyages et al included the effects of such factors as patient age, presence or absence of family history, DCIS subtype, presence or absence of necrosis, and margin status (among others) to calculate risks of local recurrence for each treatment approach (mastectomy or conservative surgery plus radiation). The overall local recurrence rate was 22.5% for studies examining conservative surgical procedures alone, 8.9% for conservative surgery plus radiation therapy, and 1.4% for studies involving mastectomy alone. These summary figures are not exactly comparable because of the greater likelihood that those with smaller lesions and clear margins would be treated by conservative surgical procedures. Nonetheless, the patients with risk factors of presence of necrosis, high grade cytological features, or comedo subtype were found to derive the greatest improvement when radiation

therapy was added to a conservative surgical procedure.

Local recurrence among patients treated with conservative surgery alone was about 20% and radiation therapy would appear to reduce this risk by half. The differences in local recurrence rates between conservative surgery alone and conservative surgery plus radiation therapy were found to be most apparent for those patients with high grade tumors, DCIS with necrosis, or of the comedo subtype, and for those with close or positive surgical margins.

COMMENTARY

DCIS now accounts for about half of the malignancies detected by mammography. Although DCIS can present as a palpable tumor, or as a nipple discharge, or as Paget's disease of the nipple, most cases are found on mammography. There are several histologic patterns that DCIS can take; they are mainly divided into comedo and noncomedo forms. The latter include cribriform, micropapillary, solid, and clinging histologic patterns. The comedo form is more likely to be comprised of cells with greater cellular atypia, a higher proliferative rate, and greater expression of oncogenes such as HER-2/neu and mutant p53. The comedo and noncomedo forms can often be distinguished on the basis of the mammographic appearance: comedo forms are associated with coarse granular microcalcifications and noncomedo types are more often associated with fine granular microcalcifications.

Initial decisions in the management of DCIS are complex and involve a range of individual patient preferences. For some, conservative surgery is favored and it has been proposed that this approach may be equivalent in outcome to mastectomy, especially if adjunctive radiation therapy is included. However, many questions remain and are the subject of ongoing, randomized clinical trials (such as NSABP B17).[7] Until the completion of these trials, the clinical series by Hetelekidis et al and the meta-analysis by Boyages et al highlighted here provide useful insights.

The data from both reports would suggest that radiation therapy be added to conservative surgery in those patients with increased likelihood of local recurrence. Included among these patients who should receive radiation therapy would be those with larger lesions, although this is difficult to assess with quantitative certainty. The size of comedo lesions can be corroborated by amplified views of the mammogram in many cases; the mammographic appearance of the noncomedo forms is less reliable as a gauge of lesion size. Other factors that would favor the addition of radiation therapy include the absence of a reasonably wide surgical margin (optimally 10 mm), the presence of necrosis, comedo subtype, and, high cytological grade. Of course, for patients who seek the lowest risk for recurrence, the meta-analysis confirms that mastectomy reduces the risk of recurrence to close to 1%. As the Harvard series indicated, recurrences were local, and cures after recurrence remain likely.

Until more data is available, it would be inappropriate to be dogmatic in this decision-making process. Instead, it seems prudent to review those recurrence risk factors on a case-by-case basis and allow the patient to incorporate her own preferences for initial treatment. Women with small noncomedo lesions with an adequate margin around the resected tumor specimen have a low risk of recurrence with surgery alone. Most of the remaining patients may be cured with a combination of resection of the lesion and radiation therapy to the breast. ❖

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When considering treatment options for ductal carcinoma in situ (DCIS), which of the following statements is true?

a. Factors that would favor the addition of radiation therapy after conservative surgery include larger lesion size, narrow margins, and high cytologic grade.
b. The presence of a family history of breast cancer would favor the addition of radiation therapy after conservative surgery.
c. Conservative surgery followed by radiation therapy is associated with less local recurrence than mastectomy.
d. Recurrent breast cancer after conservative surgery (with or without radiation therapy) is more likely found in axillary nodes or bone than breast cancer occurring after mastectomy.

Edatrexate Plus Paclitaxel in Metastatic Breast Cancer

ABSTRACT & COMMENTARY

Synopsis: *Based on preclinical data suggesting synergistic activity, edatrexate was combined with a 3-h paclitaxel infusion in patients with advanced metastatic breast cancer in a phase I study involving escalating doses of edatrexate. A maximum tolerated dose for edatrexate in the combination was determined to be 350 mg/m^2. In addition to myelosuppression, diarrhea, stomatitis, nausea and vomiting,*

and myalgias were the major toxicities. In 23 patients, four complete and seven partial responses were noted (overall response rate 48%). This combination is active even in patients who have previously received methotrexate.

Source: D'Andrea G, et al. *Clin Cancer Res* 1999; 5:275-279.

In recent years, a number of important studies have identified the features of methotrexate action that make it effective as an antitumor agent. These studies have led to the development of methotrexate congeners that appear to be more effective than methotrexate. For example, edatrexate (10-ethyl-10-deaza-aminopterin) has a higher affinity for the one-carbon-reduced folate transporter than does methotrexate and is more readily polyglutamated by the folylpolyglutamate sythetase in tumors than is methotrexate. Therefore, greater concentrations of edatrexate polyglutamates accumulate in tumors and lower levels of these polyglutamates accumulate in normal proliferative cells than do methotrexate polyglutamates and the result is a higher therapeutic index.[1]

Paclitaxel is known to be highly active in the treatment of breast cancer and a number of other malignancies.[2] Investigation of potential interactions between paclitaxel and edatrexate in preclinical models suggested impressive synergy when edatrexate was administered before paclitaxel but antagonism if the order of administration was reversed[3]. Therefore, D'Andrea and colleagues at Memorial Sloan-Kettering Cancer Center undertook a phase I dose-escalation study in patients with metastatic breast cancer.

Thirty-five women were entered into the study. All had metastatic breast cancer with only one prior regimen for the treatment of their metastatic breast cancer with no history of prior taxane use. Prior methotrexate exposure as a component of adjuvant therapy was permitted. Patients were treated as outpatients every three weeks. Edatrexate was given as a one hour infusion on day 1 and paclitaxel was given at 175 mg/m^2 by three-hour infusion on day 2. The edatrexate doses were escalated from 180 mg/m^2 to 210, 240, 270, 300, 350, and 400 mg/m^2 in separate cohorts.

All 35 patients were assessable for toxicity and 23 patients had measureable disease and were assessable for tumor response. The median number of cycles of therapy given was four (range 2-33). The maximum tolerated dose of edatrexate was 350 mg/m^2 when given on this schedule with 175 mg/m2 of paclitaxel. At the maximum tolerated dose, one patient experienced grade 3 diarrhea, but no other grade 3 nonhematologic toxicities were encountered. By contrast, two patients at the 400 mg/m2 dose level experienced grade 4 stomatitis. Thus, gastrointestinal tract toxicity is dose-limiting for this combination. Other toxicities included myalgias and neurosensory complaints.

Encouraging antitumor efficacy was noted. Of the 23 patients evaluable for response, four (17%) achieved a complete response and seven (30%) achieved a partial response. None of these eleven responders had prior therapy for metastatic disease; two had only hormonal therapy for their metastatic disease and nine had received adjuvant chemotherapy, including six who had taken methotrexate.

COMMENTARY

Resistance to methotrexate is usually mediated by mechanisms involving reduced folate transport or intracellular metabolism. These mechanisms usually do not affect sensitivity to tubulin-binding agents such as paclitaxel. Similarly, paclitaxel resistance mechanisms, while not completely defined, generally do not lead to methotrexate resistance. Thus, the combination of the two agents could be effective clinically.

This phase I study of paclitaxel with the supermethotrexate edatrexate provides substantial encouragement based upon the modest toxicity and high level of activity (48% response rate) in metastatic breast cancer. The responders were mainly patients with minimal prior treatment; nevertheless, it is clear that additional exploration of the combination in phase II and possibly phase III studies is warranted.

It is difficult to understand why the activity of this combination would be sequence-dependent. It remains to be determined whether this in vitro sequence dependence will be clinically apparent and if so, whether the mechanism can be defined and used to predict other synergistic interactions. ❖

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Which of the following statements about edatrexate is *false*?

a. It is more readily taken up by cells than methotrexate.
b. It is more readily polyglutamated in tumors than methotrexate.
c. When exposed to tumor cells following paclitaxel, it has synergistic antitumor effects.
d. When exposed to tumor cells before paclitaxel, it has synergistic antitumor effects.

Conformal Radiation Therapy Lowers the Risk of Radiation-Induced Proctitis Compared to Conventional Prostate Radiation Therapy

ABSTRACT & COMMENTARY

Synopsis: *Late toxic effects of radiation therapy on normal tissues limit the amount of radiation therapy that can be safely administered. The development of novel methods employing multileaf collimators, three-dimensional simulation, and specially shaped blocks is called conformal radiation therapy and has the potential to more accurately deliver radiation to the tumor volume. Men were randomly assigned to receive 64 Gy in daily 2 Gy fractions to treat prostate cancer by either conventional treatment planning or conformal techniques. Those receiving conformal radiation therapy had similar disease control but significantly lower rates of radiation-induced proctitis and bleeding.*

Source: Dearnaley DP, et al. *Lancet* 1999;353:267-272.

A major factor that limits the efficacy of radiation therapy is the limit of normal tissue tolerance to external beam radiation therapy. Thus, administration of more than 60 Gy to pelvic organs can produce a serious risk of radiation-induced proctitis, rectal bleeding, and urinary bladder problems. Some data suggest that the ability to augment the dose of prostate radiation therapy to 75 Gy might result in significantly better local tumor control than 60 Gy.[1] Preliminary single-arm clinical trials suggest that the use of three-dimensional treatment planning with computed tomography, together with multileaf collimators to shape the beam and specially shaped blocks to restrict the radiation to the tumor bed, is capable of permitting the delivery of higher and more effective doses of radiation therapy and improving treatment outcome.[2,3]

Researchers at the Royal Marsden Hospital in the United Kingdom conducted a prospective randomized study in 225 men with prostate cancer. One-hundred-fourteen men were assigned to receive conformal radiation therapy and one-hundred-eleven were assigned to receive conventional radiation therapy. All patients had prostate cancer without lymph node involvement and had a projected life expectancy of 5-10 years. Median follow-up was 3.6 years. Patients were treated with a three field technique, anterior and lateral, or posterior oblique fields.

Those receiving conventional radiation therapy had routine treatment planning; those receiving conformal therapy had special blocks designed to shield normal tissue with a margin around the tumor field of 6 mm. Six to 10 MeV photons were the source of radiation therapy and treatment was given in 2 Gy fractions to a total dose of 60-64 Gy. By using conformal techniques, it had previously been projected that 48% less rectum and 38% less bladder would be treated to the 90% isodose.[4]

Baseline characteristics of the two groups were similar. Proctitis of grade 1 severity or higher occurred in 56% of patients receiving conventional radiation therapy and in 37% of those receiving conformal radiation therapy ($P = 0.004$). Rectal bleeding occurred in 12% of patients receiving conventional radiation therapy and in 3% of those receiving conformal radiation therapy. After five years, the actuarial probability of remaining free of grade 2 or higher proctitis was 82% in the group treated with conventional radiation therapy and 92% in the group treated with conformal radiation therapy ($P = 0.002$). By contrast, there were no differences between the groups in urinary symptoms.

Although the lower volume of tissue treated with radiation therapy in the group receiving conformal radiation therapy resulted in less rectal toxicity, the local tumor control rates were similar with the two approaches. Local control at two years (97% for conformal, 96% for conventional) and at five years (78% for conformal,

83% for conventional) was similar in the two groups and overall survival at five years was 66% for those on the conformal arm and 64% on the conventional arm.

Using prostate-specific antigen levels as a measure of disease control, patients on the conformal arm appeared to have somewhat better biochemical cancer control (39% at 5 years vs 31% at 5 years). However, these apparent differences did not translate into better survival.

COMMENTARY

The treatment of prostate cancer is controversial. Not only is it not clear that all prostate cancers require treatment, there is no consensus on the best treatment approach to those that do require treatment. Radical prostatectomy is generally considered to be the treatment of choice, but a large fraction of patients become impotent as a consequence of the treatment and a small, but significant, fraction of patients become incontinent as well. Radiation therapy has generally been felt to be inferior to surgery because it is also associated with serious toxicities to the bladder and rectum, serum prostate-specific antigen levels did not fall as quickly or as far as one would like to see, and some studies suggest a higher relapse rate.

The evidence is reasonably strong that the ability to safely deliver higher doses of radiation therapy to the primary tumor might improve the treatment results from radiation therapy. Using conformal techniques, it may be possible to increase the radiation doses to 78-81 Gy. Large studies are currently in progress to compare conventional treatment planning that delivers 64 Gy with conformal treatment planning that delivers 74 Gy or more. It will be of interest to know whether these higher doses of radiation therapy are capable of improving local disease control at an acceptable risk of toxicity. Ongoing randomized studies are addressing this question.

It is somewhat disappointing that the conformal treatment planning appears to be ineffectual at altering the risk of bladder toxicity. It is conceivable that the bladder could be protected by instilling a radioprotective agent into the bladder during treatment. It is also possible that brachytherapy could be designed to deliver a higher and more effective dose of radiation to the tumor. ❖

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Which of the following statements is true about conformal radiation therapy treatment planning?

a. While conformal planning results in the treatment of a smaller tumor volume, the incidence of serious bladder and rectal toxicities is unaffected.
b. Conformal planning results in the treatment of a smaller tumor volume which lowers the risk of rectal toxicities, though bladder toxicity was not significantly changed.
c. Conformal planning lowers the risk of toxicity but is associated with a higher relapse rate.
d. Conformal planning has been shown to permit the safe delivery of higher and more effective doses of radiation therapy in prospective randomized trials.
e. The use of conformal treatment planning improves survival in patients with prostate cancer.

Potential Clinical Value of p53 Analysis in Colorectal Cancer

ABSTRACT & COMMENTARY

Synopsis: *In patients with colorectal carcinomas, examination of tumor cells for p53 gene expression by immunohistochemical techniques employing antibodies has been proposed to offer prognostic value. In the current report, sequence analysis of the complete coding region of tumor cell p53 genes was completed in 190 samples from 189 Swedish patients that were treated between the years 1988 and 1992. In this series, the presence of p53 mutations correlated well with cancer-specific survival, whereas the immunohistochemistry results did not. Thus, this technically more laborious method may prove to be of greater clinical value, particularly if new methods are developed to simplify the technique and reduce the expense.*

Source: Kressner U, et al. *J Clin Oncol* 1999; 17:593-599.

The importance of mutations in certain genes to the development and progression of colorectal carcinomas has been established.[1] The suppressor gene *p53*, located on the short arm of chromosome 17, encodes a 53-kd nuclear phophoprotein that regulates the cell cycle.[2] Mutations in this gene have been associated with about half of all human malignancies including colorectal carcinoma.[1] Other studies have demonstrated that overexpression of *p53*, detected by immunohistochemical methods, is found in a large portion of

cases (from 30-70%) and this overexpression has been interpreted as a surrogate marker for *p53* mutation because the half-life of the nonmutated physiologic protein is short and it is usually not detectable. In several,[3,4] but not all[5] studies, overexpression of *p53* has correlated with poorer prognosis in patients with colorectal cancer.

In the report by Kressner and collegues, sequencing of the entire coding region of the *p53* gene was undertaken in 191 frozen tumor samples from 189 patients obtained nearly a decade ago in Sweden. To do this, RNA was extracted from the frozen samples and synthesized into cDNA by reverse transcription. *p53* was amplified by the polymerase chain reaction and sequenced using an automated laser fluorescence sequencer. From the same tissue samples, p53 overexpression was evaluated by immunohistochemistry using a monoclonal antibody to the *p53* protein (DO-7).

Mutations were detected in 99 samples from the 189 patients (52%). Survival time was clearly shorter for patients who had *p53* mutations when compared to those that did not. Mutations outside the evolutionarily conserved regions of the gene were associated with an even worse prognosis. Multivariate analysis indicated that the presence of a *p53* mutation was an independent prognostic factor. In contrast, there was no significant relationship between overexpression of *p53* protein (by immunohistochemistry) and cancer-specific survival.

COMMENTARY

There has been some controversy about the value of determining abnormalities of *p53* gene expression in samples of colon tumors. Although some have demonstrated a correlation with survival,[3,4] others have not.[5] An explanation for these conflicting data may be found in this report. Not all *p53* mutations will result in overexpression of the *p53* protein. In this series, of the 188 cases in which the comparison was possible, there was a concordance of immunohistochemistry and presence or absence of mutations in 74% of the subjects. Twenty-eight of the tumors that were positive by cDNA sequencing were negative by immunohistochemistry. This relates to the fact that certain mutations resulted in "stop" codons, and others in deletions that resulted in decreased expression. Interestingly, 20 (22%) of the tumors that displayed the wild-type gene on cDNA sequencing were positive by immunohistochemistry. This would suggest that in some cases, *p53* gene expression was influenced by factors other than mutations in the coding regions.

The important finding was the correlation of mutations and survival in a series in which the immunohistochemistry failed to demonstrate the same. This would suggest that immunohistochemistry, although technically much easier and less expensive, is not as good a marker of *p53* mutation as hoped. Certainly the techniques used by Kressner et al would be problematic and currently not feasible in the typical clinical setting. However, new techniques for mutation detection are being developed and these may ultimately be applied to simplify the search for *p53* mutations in clinical samples from colon cancer patients.

Other than offering prognostic information, *p53* analysis may offer important treatment guidance. Fluorouracil, commonly used to treat patients with colorectal cancer, inhibits DNA synthesis by inhibition of thymidylate synthase and also fragments DNA directly. Damaged DNA may result in the tumor cell arresting in G1 or it may stimulate cell death by apoptosis. This response may rely on a normal *p53* protein. Thus, drug-induced cytotoxicity may not occur in tumors with dysfunctional *p53*. Certainly, this concern could be tested by examining chemotherapy-induced responses in patients for whom the presence or absence of tumor cell *p53* mutation is established. Inasmuch as a large portion (30-70%) of colorectal cancer patients has tumor cells with these mutations, chemotherapy that relies on a functional *p53* gene to produce cytotoxicity could be avoided. ❖

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13. Which of the following statements about *p53* gene expression in patients with colorectal cancer is true?

a. Patients with tumor cells with increased *p53*, as detected by immunohistochemistry, have slower growth patterns and longer survival than those without increased *p53* protein.
b. Patients with tumor cells that lack demonstratable *p53* mutations are more likely to have greater survival time than those with demonstrable mutations in this gene.
c. Increased *p53* protein detected by immunohistochemistry correlates 100% with *p53* gene mutation.
d. Mutation of *p53*genes and the increased expression of *p53* protein in tumor cells may be important in individual cases, but occur in only a small percentage (5%) of cases.

In Future Issues:

Survival Comparison Between Sporadic, Familial Polyposis, and Nonpolyposis Colon Cancer