

CORRESPONDENCE

Re: Micrometastatic Breast Cancer Cells in Bone Marrow at Primary Surgery: Prognostic Value in Comparison With Nodal Status

Early occult spread of tumor cells must be regarded as a major cause for the development of metastatic disease in patients with completely resected breast cancer. Immunocytochemical assays with monoclonal antibodies directed against epithelial differentiation antigens have allowed the detection of micrometastatic carcinoma cells in bone marrow. Most of the studies were performed with monoclonal antibodies either against cytokeratin (a major constituent of the cytoskeleton in epithelial cells) or against membrane-bound mucins (e.g., epithelial membrane antigen, human milk fat globule, and tumor-associated glycoprotein-12 [TAG12]).

Results from a recent study on more than 700 breast cancer patients (1) suggested that the presence of TAG12-positive cells in bone marrow, as detected with monoclonal antibody 2E11, could be used as an independent prognostic indicator of a clinical relapse (1). We were, therefore, interested in investigating in more detail the nature of the

TAG12-positive cells. Thus, we analyzed bone marrow samples from 165 control patients without carcinoma with the use of monoclonal antibody 2E11 and simultaneously with the use of monoclonal antibody A45-B/B3 directed against a common epitope present on several cytokeratin peptides, including heterodimers of cytokeratin polypeptides 8 and 18 as well as 8 and 19 (2).

As described previously (3,4), the antibody reaction was developed with the alkaline phosphatase anti-alkaline phosphatase technique, and we examined 2×10^6 mononucleated cells separated by Ficoll density centrifugation (900g for 20 minutes at room temperature) from each aspirate. As shown in Table 1, staining of bone marrow from these 165 control donors with antibody A45-B/B3 identified as positive two control cases only in which one and three positive cells, respectively, were found. In one case, these aspirates had been taken from a woman with acute exacerbation of a chronic mastitis; chronic inflammations are known to induce aberrant cytokeratin expression in hematopoietic cells (5). In contrast, antibody 2E11 stained bone marrow cells in 66 (62.9%) of 105 control aspirates (Table 1); 30 of these specimens (28.6%) presented with five or more TAG12-positive cells. To exclude the increased sensitivity of our assay as the cause of the difference between our findings and those of the previous study (1), we followed the published protocol even more closely. Sixty aspirates were analyzed with the described avidin-biotin-alkaline phosphatase complex technique (1); 35 of these

specimens (58.3%) turned out to contain stained cells (Table 1).

The reactivity of antibody 2E11 with autochthonous bone marrow cells was further investigated by simultaneous double labeling of 60 aspirates from control patients without carcinoma by use of antibodies A45-B/B3 and 2E11 in parallel. To avoid interference of the two labeling systems, we used direct antibody conjugates consisting of fluorescein isothiocyanate or cyanine-2 bound to Fab fragments of antibody A45-B/B3. These conjugates lack the Fc portion of the A45-B/B3 antibody and therefore do not carry the risk of nonspecific binding to the abundant Fc receptor-expressing cells (e.g., monocytes). In 35 (58.3%) of these samples, all of the detectable TAG12-positive cells were negative for A45-B/B3 antibody staining, suggesting that the TAG12-positive cells lacked the epithelial cytoskeleton (data not shown). Some of the immunostained cells could be clearly identified as erythroblasts, while others could not be easily distinguished from tumor cells by morphologic criteria. Moreover, the double labeling of bone marrow from 11 breast cancer patients revealed the consistent presence of TAG12-positive cells co-expressing the common leukocyte antigen CD45.

In previous studies (3,4), the CK2 antibody directed against cytokeratin 18 had been shown to be a specific probe for bone marrow micrometastases that were detected in patients with adenocarcinomas of various origins. Recently, however, isolated down-regulation of cytokeratin 18 has been observed in some breast cancer cells (3,6); therefore,

Table 1. Specificity and sensitivity of monoclonal antibodies applied for detection of bone marrow micrometastases in breast cancer patients*

Patients	Monoclonal antibody	Antigen	Staining technique	No. of patients	Fraction of BM samples with ≥ 1 immunoreactive cells (% of total)	Fraction of BM samples with ≥ 5 immunoreactive cells (% of total)
Control	A45-B/B3	CKs	APAAP	165	2 (1.2)†	0 (0.0)†
	CK2‡	CK18	APAAP	215	6 (2.8)†	0 (0.0)†
	2E11	TAG12	APAAP	105	66 (62.9)	30 (28.6)
	2E11	TAG12	ABC	60	35 (58.3)	8 (13.3)
Breast cancer	CK2	CK18	APAAP	185	60 (32.4)	16 (8.6)
	A45-B/B3	CKs	APAAP	185	86 (46.5)§	37 (20.0)

*Abbreviations used: BM, bone marrow; TAG12, tumor-associated glycoprotein-12; CKs, heterodimers of cytokeratin peptides 8 and 18 and 8 and 19; APAAP, alkaline phosphatase anti-alkaline phosphatase; ABC, avidin-biotin-alkaline phosphatase complex.

† $P < .0001$ compared with immunostaining with monoclonal antibody 2E11 (two-sided chi-squared test).

‡Data taken from (4).

§ $P = .0056$ compared with immunostaining with the CK2 antibody (two-sided chi-squared test).

|| $P = .0018$ compared with immunostaining with the CK2 antibody (two-sided chi-squared test).

false-negative results may be obtained with immunoassays based on this particular peptide alone. To compare the rate of tumor cells detected with the A45-B/B3 antibody or the CK2 antibody, we simultaneously analyzed bone marrow samples from 185 breast cancer patients (Table 1), with the majority (94.1%) showing no clinical signs of metastasis [stage M0 according to tumor-node-metastasis (TNM) classification (7)]. Antibody 2E11 was excluded from this analysis because of its low specificity. We found that a statistically significant correlation existed between the results obtained with both anti-cytokeratin antibodies (Spearman's correlation coefficient $r = .918$; 95% confidence interval = .892-.938). The inclination of the regression line ($y = 0.697x$), together with the strong correlation coefficient, however, indicated an increased sensitivity of the pan-cytokeratin A45-B/B3 over the mono-specific CK2 antibody ($P < .0001$; z test). This assumption is supported by the considerable shift toward higher numbers of positive cells that were detected with antibody A45-B/B3 compared with antibody CK2 (Table 1).

In conclusion, the specificity of the antibody used for tumor cell identification is one of the most critical variables for the reliable detection of micrometastases in bone marrow. Thus, the development of standardized protocols deserves the highest priority, while meta-analysis of extremely heterogeneous and thus incomparable sets of data (8) appears to be rather premature at present. Moreover, a cautionary note for too early interpretation of prognostic factors appears to be appropriate, since occult metastatic cells may disclose their influence on survival at 10 years or later.

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Notes

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Response

In their letter Braun et al. argue that the monoclonal antibody 2E11 used by our group (1,2) has a low specificity and that it is therefore not suitable for the analysis of tumor cell detection in bone marrow of breast cancer patients. Their results, however, address only the speci-

ficity of the antibody, without trying to test its sensitivity in breast cancer patients. We think that the data presented by Braun et al. provide additional information to a method (i.e., false-positive results in bone marrow of patients without carcinoma). Since they have slightly modified the staining method, the direct comparison of the data is difficult. Until 1995, we have used bone marrow smears; we started to use cytospin preparations in 1996. For that reason, our staining protocol has changed over time. Currently, we are comparing the two staining protocols to find out the reasons for the discrepancies in the results between our group and the Munich group. Moreover, we are comparing anti-cytokeratin antibodies with mucin-specific antibodies and are trying to improve the specificity and sensitivity of the detection system.

The discussion on sensitivity versus specificity reminds us of the debate about some serum tumor markers such as human chorionic gonadotropin (HCG). It is well known that HCG is not specific for gestational trophoblastic disease, since healthy pregnant individuals and patients with some lung cancers also have elevated HCG values. Nevertheless, once gestational trophoblastic disease has occurred, the sensitivity of HCG is near to 100%.

At present in Germany there are five other groups who are testing the 2E11 antibody in breast cancer. Their detection rate is in the range of 35%-45%, which is in concordance with our data. We have also encouraged other groups to use our detection system to confirm our clinical findings. But any statistical analysis requires a considerable number of breast cancer patients, and no group has yet investigated an appropriate number of patients to be able to compare it with our cohort of more than 1300 patients. To our knowledge, there is only one other group that has tested tumor cell detection in more than 200 breast cancer patients with long-term follow-up [using anti-epithelial membrane antigen-antibody; (3)].

An improvement in sensitivity can lead to a loss of specificity. However, as long as Braun and his group could not demonstrate that their tested sensitivity with 2E11 is at the same level

(35%–45%) or not, technical reasons cannot be ruled out for the different results in specificity and cross-reactivity.

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More About: Biology of Cachexia

This is in response to the correspondence in regard to hydrazine sulfate (1), which appeared in the April 15, 1998, issue of the Journal. In that letter, Dr. Wheeler stated that on the basis of “three randomized [National Cancer Institute-sponsored] trials” and a review of one—the CALGB (Cancer and Leukemia Group B)—of these trials by the U.S. General Accounting Office, hydrazine sulfate was found to be “no better” than a placebo.

In the CALGB trial (2), the authors essentially denied the use of tranquilizers, indicating that “virtually no patients received phenothiazine-type tranquilizers, with the exception of [short-term] prochlorperazine (Compazine)”; no mention was made of any use of the benzodiazepine tranquilizers. Yet, what

Wheeler does not point out, the CALGB authors in their succeeding article published in the same journal (3) admit to the widespread use of phenothiazine tranquilizers, benzodiazepine tranquilizers, or both—in 94% of all 266 study patients. Of these patients, only 120 received these tranquilizers “less than 48 hours,” some receiving them on an “as needed” or “continual” basis (4).

Before the commencement of the three National Cancer Institute (NCI)-sponsored studies, the NCI had been provided with published and unpublished animal data indicating that hydrazine sulfate was a potent monoamine oxidase (MAO) inhibitor and that tranquilizers—known to be incompatible with MAO inhibitors—could not be used with it. Specifically it was pointed out that, in tumor-bearing murine models, hydrazine sulfate and benzodiazepine tranquilizers used separately produced no morbidity or mortality, whereas when used together—in the same dosages—they produced comatose animals throughout the experiments, accompanied by a 50%–60% mortality, depending on which benzodiazepine tranquilizer was used. It was emphasized to the NCI that, if tranquilizers were used, negative studies and increased patient morbidity would result.

The fact remains that every single informed-consent, controlled clinical trial of hydrazine sulfate—with the exception of the NCI-sponsored studies, confounded by long-term (>48 hours) use of agents known to be incompatible with MAO inhibitors—has demonstrated efficacy and safety of the drug (5–10).

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Response

I appreciate the opportunity to respond to Dr. Gold's letter about the use of hydrazine sulfate in cancer patients. He correctly quotes the CALGB article (1) and the letter (2), both of which were referenced in my original letter. However, he does not mention that, of the 120 patients who received tranquilizers for less than 48 hours, there was still no difference in survival or response rate and quality of life remained worse in patients treated with hydrazine. Furthermore, in the two articles from the North Central Cancer Treatment Group (3,4), patients who had “planned use of tranquilizers” were excluded from participating in the study. In both of these studies, no benefit was demonstrated for hydrazine sulfate. Finally, the medications of concern were drugs such as tranquilizers and anti-nauseants given to try to help patients through both their illness and side effects of treatment. To omit these medications in our patients

would, by itself, potentially seriously decrease the quality of their lives.

Although Dr. Gold suggests that "every single informed-consent, controlled clinical trial of hydrazine sulfate—with the exception of the NCI-sponsored studies . . .—has demonstrated efficacy and safety," this is simply not true. In the study by Chlebowski et al. (5), the overall treatment effect for hydrazine was not statistically significant. Only subset analysis revealed that patients with favorable performance status showed improvement in survival. However, the editorial (6) accompanying the article by Chlebowski et al. (5) discussed the fact that the trial had too few patients to be meaningful. This is why the much larger trials were performed that did not show any benefit. The Russian study (7) reported 740 patients who had advanced cancer of various types and had received hydrazine in a phase II fashion. They noted objective responses by standard definition in only 4% of patients with lung cancer but a "subjective response" in 47%. Symptomatic improvement was poorly defined, and the influence of hydrazine on weight loss, nutritional status, and overall survival was not evaluated. In other clinical trials in which objective response rates were used as criteria for benefit, none have shown a significant response rate to hydrazine (8–10). Some uncontrolled trials have shown subjective improvement in 65%–70% of patients (11,12). However, as far as appetite improvement alone, 36%–55% of patients receiving placebos on two prospective double-blind clinical trials noted improvement (3,13). Thus, it should be no surprise that a fairly high percentage of patients do report subjective improvement when taking hydrazine. Unless hydrazine-treated patients are compared with a placebo-treated group, no valid assessment can be made of its true efficacy.

Proponents of alternative medical therapies need to realize that benefit from their treatment needs to be objectively determined in the same manner as that from mainstream treatment. All of us are looking for a magic bullet. However, stating that a treatment works without data to back it up simply gives false hope to cancer patients. Internet websites are full of this type of "information." Only careful clinical trials can

determine the true efficacy and ultimate importance of new therapies. Although cancer treatment today remains less than optimal, hydrazine sulfate is not the answer.

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Age- and Sex-Specific Seroprevalence of Human Herpesvirus 8 in Jamaica

A recent communication by Whitby et al. (1) in the *Journal* reported that the seroprevalence of human herpesvirus 8 (HHV-8) varies geographically in Italy, an area with an incidence of Kaposi's sarcoma ranging from 0.5 to 1.5 per 100 000 population.

We evaluated the seroprevalence of HHV-8 in Jamaica, an area with a low incidence of Kaposi's sarcoma (2), and showed that the seroprevalence of HHV-8 among the population varied predominantly by age and sex. HHV-8 has been linked etiologically to classic and acquired immune deficiency syndrome-related Kaposi's sarcoma, primary effusion lymphomas, and multicentric Castleman's disease by serologic and molecular evaluations (3). Although Jamaica has a low incidence of Kaposi's sarcoma, several cases of multicentric Castleman's disease, a lymphoproliferative disorder, have been reported (4,5).

We analyzed HHV-8 seroprevalence among two populations in Jamaica, 250 normal blood donors from the National Transfusion Service, Kingston, Jamaica, and 146 women visiting gynecology clinics affiliated with the University Hospital of the West Indies in Kingston. The median age among the blood donors was 41 years (range, 18–64 years), and 50% of them were female. The median age of the gynecology clinic patients was 33 years (range, 19–78 years). Sera were tested by use of whole virus (purified on a sucrose gradient) in an enzyme-linked immunoassay (Advanced Biotechnologies Inc. [ABI], Columbia, MD) and an immunofluorescence assay to detect lytic and latent proteins (ABI or Science Applications International

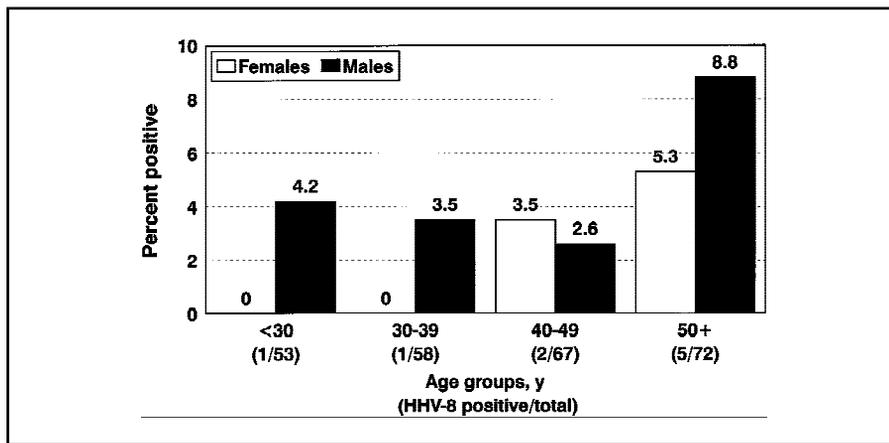


Fig. 1. Prevalence, expressed as percent seropositivity, of human herpesvirus 8 (HHV-8) in Jamaican blood donors—by age and sex. To yield a positive result, serum samples were required to test positive both to whole virus by use of an enzyme-linked immunoassay and to lytic and latent proteins of HHV-8 by use of an immunofluorescence assay.

Corp., Frederick, MD) (6). Serum samples were interpreted as seropositive if both immunoassays yielded positive results.

The overall seroprevalence among the blood donors tested was 3.6% (9/250). Among the normal blood donors, 5.0% of men (6/119) and 2.4% of women (3/122) had detectable levels of HHV-8 antibodies. Men were two times more likely to be seropositive than women (odds ratio = 2.1; 95% confidence interval = 0.43–12.9). Blood donors over the age of 40 years had a 2.9-fold greater likelihood of HHV-8 seropositivity (odds ratio = 2.89; 95% confidence interval = 0.53–29). The highest number of seropositives (6.9%) among both sexes was detected in individuals over the age of 50 years (Fig. 1). Among the women attending the gynecology clinics, only 0.68% (1/146) were seropositive, and that one seropositive patient was 44 years old. Thus, in the evaluation of HHV-8 seroepidemiology data among different subject populations, both age and sex of the individuals need to be considered.

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Response

Manns et al. investigated the seroprevalence of human herpesvirus 8 (HHV-8) in blood donors and gynecologic patients from Jamaica. The overall prevalence in the blood donor population was low, 3.6%, which confirms our finding that the seroprevalence of HHV-8 mirrors the incidence of Kaposi's sarcoma (1), with the exception of findings in West Africa (2). The observed male-to-female ratio reported by Manns et al. (2.0:1) is similar to the ratio of 1.7:1 reported by us for the Italian population (1), although another study of HHV-8 distribution in blood donors in Italy indicated that HHV-8 antibodies were distributed equally between men and women (3). It is more interesting that Mann et al. also documented higher HHV-8 seroprevalence rates in older people. Because the prevalence of HHV-8 in Jamaica is low, the number of seropositives analyzed was small.

In a series of 184 blood donors (1) and 63 children from Apulia, southern Italy, an endemic area for classic Kaposi's sarcoma, we observed that HHV-8 seroprevalence rates steadily increased with age, from 3.2% (2/63) in children under 18 years to 33% (8/24) in persons 50 years of age or older (Fig. 1). Similar findings have been reported by others (3). The striking differences in HHV-8 seroprevalence observed between regions with low and high incidences of Kaposi's sarcoma are greatest in older age groups. However, in the San Francisco Men's Health Study, Martin et al. (4) did not observe a correlation between HHV-8 seroprevalence rates and age in homosexual men infected with human immunodeficiency virus (HIV). It is possible, therefore, that the differences observed by Manns et al. in Jamaica, by us in Italy (1), and Calabro et al. in Italy (3) may be due to a cohort effect or to a difference in the pattern and route of transmission of HHV-8 between HIV-infected homosexual men and within other populations at risk for Kaposi's sarcoma. The data on HHV-8 antibodies in children in southern Italy presented here and also reported previously by Calabro et al. suggest that non-sexual routes of transmission occur in

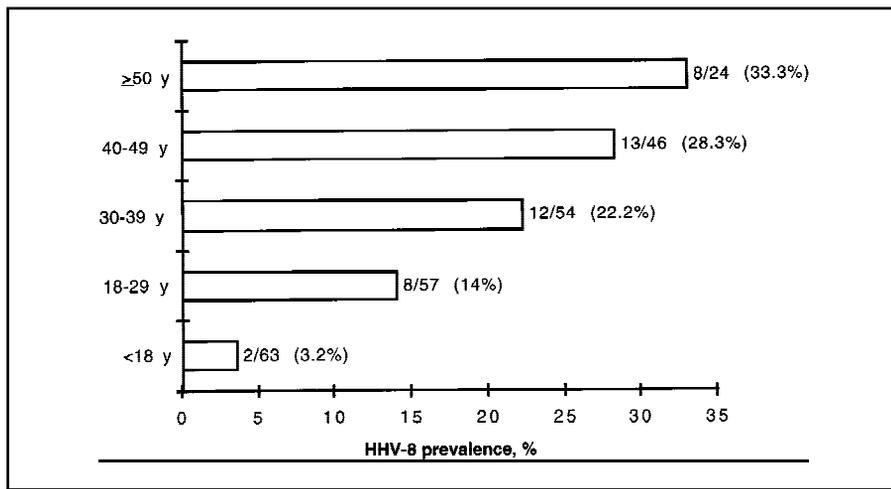


Fig. 1. Prevalence of antibodies to human herpesvirus 8 (HHV-8) in 184 adult blood donors and 63 children from Apulia, southern Italy, analyzed by age in five groups: <18 years of age (2/63, 3.2%), 18–29 years of age (8/57, 14%), 30–39 years of age (12/54, 22.2%), 40–49 years of age (13/46, 28.3%), and 50 years of age or older (8/24, 33%). HHV-8 serologic detection was performed by use of an LNA-1 immunofluorescence assay as previously described (1).

this population, as is also the case in Africa (5–7).

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More About: Saturated Fat Intake and Lung Cancer Risk Among Nonsmoking Women in Missouri

Swanson et al. (1) report that the results regarding lung cancer risk related to saturated fat intake, reported in full previously (2), were substantially affected by the method of analysis used. In essence, the method of energy adjust-

ment was found to attenuate the estimated risk increase associated with saturated fat intake.

Two obvious additional issues arise. First, it is noted by Swanson et al. that only two previous observational studies of fat and lung cancer have used any method of energy adjustment at all and also that both the rationale and the appropriate methods of energy adjustment remain controversial. Therefore, for the sake of comparison, it would be interesting to see what results would be obtained in the data of Swanson et al. from an analysis with no energy adjustment. Second, not only the final fat-intake analytic model of Swanson et al. is subject to potential influence by the method of energy adjustment. In their original report, the whole analytic strategy used the same method of energy adjustment, and the selection of nutrients and food groups for final models was based on results from energy-adjusted models with only one nutrient or food group at a time [Tables 3 and 4 in Alavanja et al., 1993 (2)]. Since their study is the largest case-control study of diet and lung cancer in nonsmokers to date, it would be of great interest to know how these first steps of their analysis are affected by the method of energy adjustment. In particular, one wonders how the estimates and significance levels for various other nutrients and food groups in Tables 3 and 4 in Alavanja et al. (2) are affected by different or no energy adjustment and how this might affect the conclusions to be drawn from their study.

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Response

We thank Dr. Nyberg for his interest in our recent correspondence to the *Journal* (1). In 1993, we reported a pronounced effect of saturated fat intake on risk of lung cancer (2). In that analysis, we entered both saturated fat and total calories as categoric variables in a standard multivariate model. Subsequently, we were persuaded that the standard multivariate model exaggerates the true variation in fat intake. Either the nutrient residual or the nutrient density approach provides a better estimate of the true variation in fat intake when data are modeled as quantile-categoric variables (3,4). Nyberg has asked us to address two questions. Was energy adjustment necessary for dietary constituents other than saturated fat? If we had not adjusted for total calories or used a different method of adjustment, would we have arrived at different conclusions?

Nyberg suggested that we examine risk estimates unadjusted for energy for a variety of dietary variables presented in two tables. The data are provided in Table 1 for selected dietary constituents. First, we examined energy-providing nutrients, all of which were highly correlated with total calories (Spearman correlations between .8 and .9). Unadjusted for total calories, both fats and carbohydrate were directly related to risk of lung cancer. When we examined fat and carbohydrate as a percent of total calories consumed, the fat and saturated fat associations persisted, but carbohydrate was now inversely associated with risk of the disease (odds ratios across increasing quintiles 1.0, 1.19, 0.87, 0.80, 0.75; two-sided *P* for trend .09), sug-

gesting that these macronutrients should be energy adjusted. By use of the standard multivariate approach, risk associated with fat was increased, whereas risk associated with intake of carbohydrate disappeared (2). Two food group variables—1) beans and peas and 2) citrus fruit and juice—were independently associated with risk of the disease; neither was affected by energy adjustment. Spearman correlations with total calories were .2 for beans and peas and .3 for citrus fruit and juice. In the present study, we also included yellow and green leafy vegetables, because the protective effect of this food group is well established for lung cancer. We saw no clear benefit of frequent consumption of these foods either with or without energy adjustment. Similarly, β -carotene was not protective or affected by method of energy adjustment.

In our original report (2), the analytic strategy was to identify dietary constituents (nutrients and food groups) independently associated with lung cancer risk. Since we had used the standard multivariate approach for energy adjustment, Nyberg was interested to know if we would have arrived at the same final model had we used different methods of energy adjustment. Saturated fat, beans and peas, and citrus fruit and juice were independently associated with risk, regardless of the method of energy adjustment (data not shown). The strength of the associations was not materially altered, and the test for trend remained statistically significant.

The issue of energy adjustment remains controversial. In our experience, the nutrient residual approach and the nutrient density approach provide com-

parable results. However, it is not clear whether energy adjustment is needed for all dietary constituents or whether one method is necessarily superior.

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Long-Term Follow-up of Untreated Stage T_{1a} Prostate Cancer

Stage T_{1a} prostate cancer is defined as incidental adenocarcinoma detected at the time of the transurethral resection of the prostate (TURP), involving 5% or less of the resected prostatic tissue (1). It is estimated that 6.5% of men undergoing TURP will have stage T_{1a} adenocarcinoma of the prostate (2). The biologic potential of stage T_{1a} adenocarcinoma is uncertain (2). Some studies (3,4) have suggested that a significant proportion of patients (16%–26%) with stage T_{1a} carcinoma will have clinically aggressive disease. However, our knowledge is limited with regard to the long-term outcome for untreated patients with stage

Table 1. Odds ratios* of lung cancer according to intake of selected dietary constituents: nonsmoking Missouri women

Dietary constituent	Odds ratio by quintile of intake					Two-sided <i>P</i> for trend
	1 (low)	2	3	4	5 (high)	
Fat	1.0	1.35	1.21	1.45	1.74	.04
Saturated fat	1.0	1.37	1.33	1.32	2.19	.004
Protein	1.0	0.87	1.17	1.29	1.06	.30
Carbohydrate	1.0	1.69	1.26	1.41	1.78	.35
Beans and peas	1.0	0.68	0.74	0.53	0.63	.02
Citrus fruit and juice	1.0	1.09	1.04	1.30	1.71	.02
Yellow and green leafy vegetables	1.0	0.77	0.73	0.84	0.88	.69
β -Carotene	1.0	0.63	0.74	0.86	0.93	.57

*Adjusted for age (continuous), smoking history (never smoked = 0; former smoker = 1), previous lung disease (no = 0; yes = 1), and interview type (direct = 0; proxy = 1).

Table 1. Characteristics of 14 patients with progression*

Patient No.	Age, y	Weight of TURP, g	Gleason score	No. of cancer foci	Cancer volume, cm ³ †	Disease progression	Time to disease progression, y	Follow-up, y	Current status
1	64	11	2 + 3 = 5	2	0.16	Gleason 4 + 3 = 7 cancer on needle biopsies‡ Involving 20% of specimens	12	13	Died of renal failure
2	69	22	3 + 2 = 5	1	0.04	Gleason 4 + 4 = 8 cancer on needle biopsies‡ Involving 20% of specimens	13	21	Died of unknown causes
3	72	25	2 + 2 = 4	4	0.16	Gleason 5 + 5 = 10 cancer on TURP Involving 90% of specimens	3	3	Died of acute renal failure
4	69	7	3 + 2 = 5	2	0.05	Gleason 3 + 4 = 7 cancer on needle biopsies‡ Involving 30% of specimens	5	9	Unknown
5	70	15	3 + 3 = 6	2	0.05	Gleason 4 + 3 = 7 cancer on needle biopsies‡ Involving 60% of specimens	8	11	Unknown
6	76	20	2 + 3 = 5	1	0.09	Gleason 5 + 4 = 9 cancer on TURP Involving 40% of specimens	1	5	Died of thrombocytopenic purpura
7	73	14	3 + 2 = 5	1	0.01	Gleason 3 + 3 = 6 cancer on needle biopsies‡ Involving 30% of specimens	2	10	Died of cardiac failure
8	70	10	3 + 2 = 5	2	0.17	Gleason 5 + 4 = 9 cancer on needle biopsies‡ Involving 80% of specimens	3	7	Died of myocardial infarction
9	64	8	1 + 2 = 3	1	0.03	Recurrent cancer on TURP Slides not available for review	8	16	Unknown
10	73	14	3 + 2 = 5	3	0.10	Distant metastasis	2	6	Died of congestive heart failure
11	73	40	3 + 3 = 6	2	0.08	Died of prostate cancer	23	23	Died of prostate cancer
12	59	12	3 + 3 = 6	1	0.01	Died of prostate cancer	2	3	Died of prostate cancer
13	73	9	3 + 3 = 6	1	0.02	Died of prostate cancer	8	9	Died of prostate cancer
14	68	26	3 + 3 = 6	1	0.02	Died of prostate cancer	12	12	Died of prostate cancer

*TURP = transurethral resection specimens.

†Cancer volume was measured by the grid method.

‡Needle biopsies were directed against clinically palpable nodules.

T_{1a} cancer. A recent study (5) indicated that 8% of men with untreated, clinically occult, and incidental cancer have metastatic progression with up to 15 years' follow-up.

In this study, we sought to determine the natural history of untreated stage T_{1a} prostate cancer after long-term follow-up.

The study group consisted of 102 consecutive case subjects who were diagnosed with stage T_{1a} prostate cancer at Mayo Clinic during the period from 1960 through 1970. None of these men were treated until there was evidence of disease progression. The ages of the case subjects at diagnosis ranged from 48 to 91 years (mean, 69 years). All histologic slides were reviewed by two pathologists (L. Cheng and D. G. Bostwick) and fulfilled the American Joint Committee on Cancer criteria for stage T_{1a} cancer (1). The weight of resected prostatic tissue ranged from 3 g to 115 g (mean, 24 g). Cancer volume, de-

termined by the grid method, ranged from 0.01 cm³ to 0.22 cm³ (mean, 0.06 cm³). The mean Gleason score was 5 (range, 2–7), and the mean number of cancer foci was 1.6 (range, 1–5).

The mean follow-up after initial diagnosis was 9.5 years (range, 0.3–31 years). One case subject was alive without evidence of disease. Fifty-five case subjects died of intercurrent diseases, four case subjects died of prostate cancer, and 14 died of unknown causes. Twenty-eight subjects were lost to follow-up. During the follow-up of 9.5 years, 14 men (14%) developed clinical progression (Table 1). The interval from diagnosis to clinical progression ranged from 1.0 to 23 years (mean, 7.3 years). Five case subjects had systemic progression, including four who died of prostate cancer. Six case subjects developed palpable prostatic nodules with subsequent biopsy-proven prostate cancer. Gleason grade was higher in recurrent cancer than

in initial TURP specimens in all cases (Table 1), suggesting the possibility of dedifferentiation during cancer progression. Of the 54 men who were followed for more than 8 years, eight (15%) developed clinical progression of disease.

In summary, men with untreated stage T_{1a} prostate cancer are at risk of clinical progression of cancer.

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Outcome Research After Radical Retropubic Prostatectomy for Prostate Cancer

Recent reports (1,2) describing outcome research after nerve-sparing radical retropubic prostatectomy showed only about 40% of men totally continent of urine and only about 30% of men potent without penile injections or penile prostheses.

Additional outcome research after nerve-sparing radical retropubic prostatectomy showed organ-confined disease (pT1-2) in 51% (4339 of 8477) of the surgical specimens (3). That report by Garnick and Fair was a summary

of six series of patients who had undergone a nerve-sparing radical prostatectomy procedure at one of six different academic medical centers; the number of patients in each series ranged from 415 to 3170.

Outcome research from The Johns Hopkins Medical Center, Baltimore, MD (4), where the nerve-sparing radical prostatectomy procedure was initially developed, showed that, of 586 patients who had undergone a nerve-sparing radical prostatectomy procedure and from whom pathology specimens were obtained, 328 (56%) had organ-confined disease (pT1-2), 123 (21%) had specimen-confined disease (pT3), and 135 (23%) had non-specimen-confined disease (pT4). With a median follow-up of 4 years, there were prostate-specific antigen (PSA) failures (detectable PSA) in 20 (6%), 32 (26%), and 107 (79%) patients with pT1-2, pT3, and pT4 disease, respectively. At a median follow-up of 4 years, there were clinical failures in 10 (3%), 12 (10%), and 51 (38%) patients with disease at stages pT1-2, pT3, and pT4, respectively.

Outcome research at the Mayo Clinic, Rochester, MN (5), showed that, after standard radical retropubic prostatectomy with maximal surgical margins, clinical recurrence was seen in 20% (52 of 261) of the patients with organ-confined disease (pT1-2) who were followed for a median of 9.4 years. These recurrences were local in 12% (31 of 261) of the patients and systemic in 12% (31 of 261) of the patients.

The biology of prostate cancer and the anatomy of the prostate gland dictate

these surgical outcomes—50% organ-confined disease (pT1-2) (3), 40% urinary continence (1,2), 30% potency (1,2), and 20% clinically recurrent cancer in patients with organ-confined disease (pT1-2) with a median follow-up of 9.4 years (5). Any apparent “cure” of prostate cancer by surgery will happen despite the surgery and be the result of the biology of the cancer and/or lead time bias.

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