

Commentary

Smoking, The Missing Drug Interaction in Clinical Trials: Ignoring the Obvious

Ellen R. Gritz,¹ Carolyn Dresler,² and Linda Sarna³

Department of Behavioral Science, The University of Texas M.D. Anderson Cancer Center, Houston, Texas; ²Tobacco and Cancer Group, IARC, Lyon, France; and ³School of Nursing, University of California-Los Angeles, Los Angeles, California

Abstract

Tobacco use is universally recognized as the foremost preventable cause of cancer in the United States and globally and is responsible for 30% of all cancer-related deaths in the United States. Tobacco use, including exposure to secondhand smoke has been implicated as a causal or contributory agent in an ever-expanding list of cancers, including lung, oral cavity and pharynx, pancreas, liver, kidney, ureter, urinary bladder, uterine cervix, and myeloid leukemia. In addition to and independent of the etiologic effects of tobacco carcinogens in numerous cancers, there is a growing literature on the direct and indirect effects of smoking on treatment efficacy (short-term and long-term outcomes), toxicity and morbidity, quality of life (QOL), recurrence, second primary tumors (SPT), and survival time as summarized below. Oncology health professionals have called for increased advocacy for tobacco control. Despite the critical relevance of smoking to cancer outcomes, most oncology clinical trials do not collect data on smoking history and status unless the malignancy is widely acknowledged as smoking related (e.g., lung or head and neck cancer). Usually, these data are collected only at trial registration. Changes in smoking status during treatment or follow-up are monitored in very few trials and are infrequently reported in sample descriptions or

included in analysis plans as a potential moderator of outcomes. Based on mounting evidence that tobacco use affects cancer treatment outcomes and survival, we recommend that smoking history and status be systematically collected as core data in all oncology clinical trials: at diagnosis, at trial registration, and throughout treatment and follow-up to long-term survival or death. We feel that the inclusion and analysis of such data in clinical trials will add important information to the interpretation of outcomes and the development of scientific knowledge in this area. Smoking status has been called another "vital sign" because of its relevance to a patient's immediate medical condition. We explain the critical value of knowing the smoking status of every patient with cancer at every visit by providing a brief overview of the following research findings: (a) the effects of tobacco use on cancer treatment and outcome; (b) recent findings on the role of nicotine in malignant processes; (c) some unexpected results concerning tobacco status, treatment, and disease outcome; and (d) identifying key questions that remain to be addressed. We provide a suggested set of items for inclusion in clinical trial data sets that also are useful in clinical practice. (Cancer Epidemiol Biomarkers Prev 2005;14(10):2287-93)

Introduction

Tobacco use is universally recognized as the foremost preventable cause of cancer in the United States and globally and is responsible for 30% of all cancer-related deaths in the United States. Tobacco use, including exposure to secondhand smoke, has been implicated as a causal or contributory agent in an ever-expanding list of cancers, including lung, oral cavity and pharynx, pancreas, liver, kidney, ureter, urinary bladder, uterine cervix, and myeloid leukemia (1). In addition to and independent of the etiologic effects of tobacco carcinogens in numerous cancers, there is a growing literature on the direct and indirect effects of smoking on increased risk of disease. This includes increased second primary tumors (SPT), decreased survival time, decreased treatment efficacy (short-term and long-term outcomes), increased toxicity and morbidity, and diminished quality of life (QOL) as summarized below. Many of these negative outcomes may be expected after long-term tobacco use, including increased prevalence of tobacco-related comorbidities, such as cardiovascular and respiratory

diseases. There also may be unanticipated consequences in which cancer and cancer treatment outcomes for current and former smokers may differ from nonsmokers.

Despite the critical relevance of smoking to cancer outcomes, most oncology clinical trials do not collect data on smoking history and status unless the malignancy is widely acknowledged as smoking related (e.g., lung or head and neck cancer). Usually, these data are collected only at trial registration. Changes in smoking status during treatment or follow-up are monitored in very few trials and are infrequently reported in sample descriptions or included in analysis plans as a potential moderator of outcomes.

Based on mounting evidence that tobacco use affects cancer treatment outcomes and survival, we recommend that smoking history and status be systematically collected as core data in all oncology clinical trials: at diagnosis, at trial registration, and throughout treatment and follow-up to long-term survival or death. We feel that the inclusion and analysis of such data in clinical trials will add important information to the interpretation of outcomes and the development of scientific knowledge in this area. Smoking status has been called another "vital sign" because of its relevance to a patient's immediate medical condition (2). We explain the critical value of knowing the smoking status of every patient with cancer at every visit by providing a brief overview of the following research findings: (a) the adverse effects of tobacco use on cancer

Received 3/31/05; revised 7/8/05; accepted 8/9/05.

Requests for reprints: Ellen R. Gritz, Department of Behavioral Science, The University of Texas M.D. Anderson Cancer Center, Unit 1330, 1515 Holcombe Boulevard, Houston, TX 77030. Phone: 713-745-3187; Fax: 713-794-4730. E-mail: egritz@mdanderson.org

Copyright © 2005 American Association for Cancer Research.

doi:10.1158/1055-9965.EPI-05-0224

treatment and outcome; (b) some unexpected results concerning smoking status, treatment, and disease outcome; (c) recent findings about the biological interactions of tobacco-related carcinogens in malignant processes; and (d) the questions that remain to be addressed. Finally, we provide some recommendations on what smoking data to include in clinical trials; these may be important in clinical practice more generally. These issues are not unique to oncology clinical trials conducted by cooperative groups (the focus in this article) but are relevant for investigator-initiated studies and for other diseases, particularly cardiovascular and respiratory drug trials.

Effects of Smoking on Cancer Treatment and Outcome

The list of direct and indirect adverse health consequences of tobacco use on health status continues to expand, affecting nearly every organ in the body, including heart disease, chronic obstructive pulmonary disease, osteoporosis, cataracts, etc. (3). Thus, before the diagnosis of cancer, both current and former smokers might be expected to have an increased number and severity of tobacco-related comorbid conditions that would adversely affect their general health status, symptom experience, and QOL. A growing number of reports in the medical literature describe the effects of smoking cigarettes on cancer treatment and outcome, both short and long-term (4, 5). The long-term effects of smoking in patients with cancer are uniformly negative, although risks decline with time since cessation. The risk of SPTs is significantly increased in smokers (6-13). This elevated risk applies to malignancies that are related to smoking and those that are not; as an example, individuals treated with radiation therapy to the chest (e.g., for breast cancer) are at increased risk of lung SPTs if they smoke (14, 15). Stopping smoking, even at diagnosis, significantly reduces the risk of SPTs (refs. 9, 16, 17; cf. refs. 6, 18). Overall survival is also poorer in smokers either as a direct result of malignancy or as a consequence of other smoking-related diseases (19-24). In one study, men who had undergone curative external beam radiation therapy for localized prostate cancer and who were current smokers had more aggressive cancers, were at increased risk of relapse, and had higher overall mortality (25). In another study, patients with early-stage lung cancer had poorer survival if they were current smokers at the start of definitive radiation or chemoradiation therapy (26). Furthermore, smoking has been reported as a predictor of shorter survival in patients with lung cancer independent of expected tobacco-related comorbid conditions (27).

Multiple studies have supported the deleterious consequences of tobacco use during cancer treatment. For example, smokers can develop severe pulmonary complications following surgery (28, 29). Thus, many surgeons insist that patients stop smoking for at least 2 weeks before an operation (30), and some recommend a minimum of 2 months of abstinence if timing permits (31). Major pulmonary complications resulting in increased death rates have been reported in patients following pneumonectomy who continued to smoke up to 1 month before surgery compared with those who had quit earlier (32). Furthermore, wound healing is compromised by smoking as a function of the vasoconstrictive actions of nicotine, an effect that has been shown dramatically in breast reconstruction after mastectomy and in surgery for smoking-related tumors (33, 34). Smoking also increases complications of radiation therapy. Patients with head and neck cancer, who continued to smoke during radiation therapy, experienced reduced treatment efficacy and increased toxicity and side effects (21). In a study of women who underwent pelvic radiation therapy for stage I or II carcinoma of the cervix, smoking one or more packs of cigarettes per day was the

strongest predictor of small bowel complications (35). In addition, smoking history was a major risk factor for radiation pneumonitis after therapy for lung cancer (36).

The effects of smoking during chemotherapy have been explored the least, probably because of the failure to assess and record smoking status and dose during treatment. However, some potential sequelae of smoking include exacerbation of drug toxicity and side effects, further impairment of immune function, and increased incidence of infection (37-41). Treatment-related weight loss and cachexia would also be expected to be exacerbated by smoking because smoking suppresses appetite and weight gain (42-44). Nicotine alters the basal metabolic rate; thus, smokers have increased energy expenditures that might exacerbate cancer-related cachexia (45, 46) albeit via a different mechanism. Furthermore, via the induction of hepatic enzymes, nicotine increases the metabolism of many pharmaceutical agents, thus potentially decreasing their efficacy (30, 47). This observation needs to be explored further in relation to chemotherapeutic agents.

Smoking puts patients at risk for comorbid diseases that adversely affect QOL and can confound QOL results for cancer clinical trials, a factor rarely considered in the analysis of these outcomes (48). Such comorbidities are especially relevant for those diagnosed with early-stage disease who are likely to become long-term survivors. For example, women who are postmenopausal cancer survivors are at risk of osteoporosis, and smoking may further elevate this risk (3). This may also be true for those treated with steroids and with premature menopause induced by cancer treatment. Limited evidence is available about the effect of continued smoking on QOL during the course of cancer treatment and survivorship. Poorer QOL at up to 3 years of follow-up has also been reported among survivors with lung cancer who continued to smoke after diagnosis (49). In comparison with never smokers, persistent smokers reported significantly higher symptom distress scores and former smokers had intermediate scores.

Additionally, exposure to secondhand smoke, which is rarely assessed, is carcinogenic and is associated with significant comorbidity; therefore, it is relevant to both smokers and nonsmokers, especially women (e.g., nonsmoking wives exposed to active smoking by their husbands; refs. 1, 50-52). In a study of lung cancer survivors, exposure to secondhand smoke was an independent predictor of poor health status (53).

Biological Interactions of Tobacco-Related Carcinogens in Malignant Processes

Although tobacco and environmental tobacco smoke are recognized to contain numerous carcinogens (1, 50) the role of these substances is unexplored in patients already diagnosed with cancer [e.g., determining the potential effects of benzo[*a*]pyrene and its up-regulatory effects on CYP1A1 (54) or its ability to mutate p53 (55)].

Nicotine is safe when used in nicotine replacement products for tobacco cessation (56), and there are no specific contraindications in the oncology setting. However, the *in vivo* effects of long-term nicotine exposure could affect persistent cellular proliferation, inhibition of apoptosis, and stimulation of vascular endothelial growth factor, which can result in increased microvessel density within the tumor. In 1994, nicotine was found to reverse opioid-induced growth inhibition in lung cancer cells by activating protein kinase C through receptors on the cancer cells (57). Since then, nicotine has been found to have multiple effects on several proteins within the intracellular signal transduction pathways *in vitro*. For example, in lung cancer cells, nicotine activates the mitogen-activated protein kinase pathway, resulting in inhibition of apoptosis (58).

Nicotine and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone have been shown to activate the Akt pathway in human airway epithelial cells, resulting in induction of downstream substrates that promote cell cycle progression and inhibition of apoptosis (59). The authors made a significant effort to identify the responsible nicotinic acetylcholine receptors and found that both α_7 (nicotine) and α_3 (4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone) subunits were involved.

Various research groups are currently studying nicotinic acetylcholine receptors and their functions (60). Such functions could include intracellular communication downstream from the epidermal growth factor receptor, thus modifying the effect of oncologic drugs (61, 62). In a mouse lung cancer model, nicotine increased vascular endothelial growth factor levels, resulting in increased microvessel density and increased tumor growth (63), compared with levels in animals not exposed to nicotine (64). Nicotine also has been shown to induce extracellular signal-regulated protein kinase with resultant activation of cyclooxygenase-2 and increased vascular endothelial growth factor expression (65). Trials of cyclooxygenase-2 inhibitors should investigate the influence of smoking on treatment efficacy. A recent laboratory study showed that exposure to tobacco smoke resulted in an increase in cyclooxygenase-2 expression due to stimulation of epidermal growth factor receptor (66). With the plethora of potential effects that nicotine alone could exert on cancer cells and the number of times per day that nicotine or known carcinogens are inhaled, it is critical that these effects be assessed (67), as such differences between smokers and nonsmokers may confound trial results.

Unexpected Trial Outcomes Related to Smoking

Although the existing knowledge about the disease effects of smoking support expected differences between smokers and nonsmokers (e.g., in specific diseases and in poorer general health status), there might be some unanticipated outcomes as well. Smoking status has been shown to have an unexpected effect in several clinical trials.

β -carotene (68), a micronutrient that as a dietary component has been found to be strongly associated with reduced cancer risk in epidemiologic studies, and β -carotene plus vitamin A (69, 70) actually increased lung cancer incidence and deaths among current smokers in the treatment arms of two large-scale, randomized, controlled chemoprevention trials. In a randomized, controlled chemoprevention trial comparing isotretinoin and placebo in patients with stage I non-small cell lung cancer, there were no between-group differences in the rates of SPTs (primary end point) or recurrence or death (secondary end points; ref. 20). However, in the isotretinoin arm, in multivariate analyses, recurrence and mortality rates were significantly increased among those who were current smokers at entry compared with never smokers.

Lynch et al. (71) recently showed that never smokers are the most likely to experience a response to a chemotherapeutic agent that interacts with a tyrosine kinase. In a therapeutic trial combining erlotinib or placebo with paclitaxel and carboplatin chemotherapy in patients with stage IIIB or IV non-small cell lung cancer, there was no difference in the primary end point: survival time between the two arms. However, never smokers in the erlotinib arm survived twice as long (22.5 months) as those in the placebo arm (10.01 months); neither current nor former smokers experienced any survival benefit (72). Recent work has suggested that a history of cigarette smoking interacts with mutations in the tyrosine kinase inhibitors and that such mutations are more likely to occur in never smokers (71). Thus, epidermal growth factor receptor-tyrosine kinase inhibitors, alone or combined

with chemotherapy, might plausibly specifically benefit never smokers who express epidermal growth factor receptor mutations; this hypothesis awaits testing in a prospective trial (66, 72).

Effects such as these also may be occurring in other studies but are unknown because relevant data on smoking are missing or, if collected, are not included in the analysis. Thus, it is not possible to determine the effects of smoking alone on clinical trial outcomes or of the interaction between smoking history and status and therapy. In addition, because of smokers' increased risk of comorbid disease, especially cardiovascular and respiratory, they may be less likely to meet the physical and functional status criteria for entry into clinical trials.

Unexplored Topics

We list five unexplored topics here but expect that others can identify additional, equally important areas. Our top five include the following:

1. The effects of smoking on the efficacy of chemotherapy, radiation therapy, immunotherapy, vaccine therapy, and new anticancer pharmaceutical agents currently under development. Three subtopics include the following:
 - (a) The effects and interactions of smoking and therapy may differ for different smoking-related cancer sites, such as lung versus head and neck (20).
 - (b) The conflicting data in several studies showing no effect versus a positive effect of cessation on prognosis may reflect a lack of adequate data (18, 19, 21, 27, 73); and
 - (c) The effects of smoking on treatment outcomes in non-smoking-related tumors are unexplored.
2. The effect of smoking history and status on sex differences in survival and unwanted effects of cancer treatment. For example, women with lung cancer tend to survive longer than do men, perhaps due to their consistently shorter tobacco exposure history (74, 75).
3. The effect of smoking on symptom experiences and QOL. QOL reports rarely include smoking (ref. 48; cf. refs. 76, 77), but smoking may serve as an indicator of distress (e.g., smoking and psychiatric comorbidity), requiring tailoring of other psychosocial interventions. Nicotine withdrawal symptoms may mimic emotional distress. As mentioned earlier, smoking is also a marker for comorbidities that affect QOL and may increase symptom distress.
4. The most effective tobacco cessation strategies after a diagnosis of cancer (4, 5, 33). Relatively few studies have been conducted in cancer patient populations compared with healthy adults and persons with other chronic diseases.
5. The effect of exposure to secondhand smoke on treatment outcomes and health status.

Recommendations: Including Smoking Data in Clinical Trials

Measurement of Smoking History and Behavior. Changes in smoking status and behavior (e.g., cessation or relapse) during and after cancer treatment are extremely important to assess and account for in analyses of trial outcomes. For decades, the epidemiologic convention of summarizing smoking history and dose in terms of pack-years (number of packs smoked per day multiplied by number of years smoked) has dominated the epidemiologic and clinical descriptions of smoking. However, this variable does not provide the relevant detailed information about smoking behavior.

Peto (78) suggested that duration of smoking (i.e., years smoked) is a much stronger factor than dose (i.e., cigarettes smoked per day) for lung cancer risk and that the two are independent variables. When asked, in the clinical setting, how long they have smoked, patients often respond "20 to 30 years." However, if the average age at diagnosis of lung cancer is ~65 years and the average age at smoking initiation is ~15 years, the 20- to 30-year figure may be a serious underestimate. Asking the age at which a patient started to smoke and then calculating the duration by subtracting the age of smoking initiation from the patient's current age is more accurate. Thus, using data on smoking from medical records may obscure analytic findings because of lack of precision. For example, Toh et al. (79) did not find a statistically significant difference in survival among patients with non-small cell lung cancer who were smokers and those who were nonsmokers; however, the data on smoking history and current smoking status were assessed from physician case records and were limited.

Nicotine dependence is a good indicator for the clinician of the intensity of cessation treatment required and serves as a guide for pharmacologic treatment with nicotine replacement or bupropion. Nicotine dependence can be assessed by whether a patient smokes during the first 30 minutes after waking (80). Measures of readiness to quit smoking (81) and secondhand smoke exposure are also useful for advice and referral purposes (see Assessment and Analytic Issues).

As summarized above, trial outcomes, QOL, prognosis, and survival can be adversely affected by smoking status. Thus, it is critical to assess smoking status (current, former, or never smoker) at each patient visit, including all post-treatment follow-up visits. Gritz et al. (82) assessed patterns of smoking and cessation over time in patients with stage I non-small cell lung cancer participating in Lung Cancer Study Group trials. Most current smokers at registration attempted to quit within the first year (83.2% point prevalence, with 53.0% sustained abstinence), but only 59.6% were abstinent 2 years later (with 47.0% sustained abstinence). Smoking status fluctuated over the follow-up period; 43.4% of current smokers at registration had multiple periods of smoking and abstinence during follow-up. Garces et al. (49) reported that 30% of 5-year lung cancer survivors who were smoking at baseline continued to smoke at a follow-up assessment. Sarna et al. reported 13% current smoking among long-term survivors of lung cancer (83). High rates of sustained abstinence were reported in a smoking cessation trial conducted among patients with newly diagnosed squamous cell carcinomas of the head and neck. When the health care team (physician and dentist) delivered smoking cessation advice and treatment, 70.2% of all patients were continuously abstinent at 1 year of follow-up (84). In this same study population, QOL was poorer in patients who were still smoking at 1 year of follow-up than those who had quit (85).

Assessment of tobacco use may serve as an intervention, prompting patients to quit (2, 56). However, some clinicians may fear that continually assessing patients' smoking "blames" the patient. For example, a qualitative study of 45 patients with lung cancer in the United Kingdom revealed that many reported stigma and blame associated with lung cancer because of the link to smoking (86). This was felt by some participants to impair their interactions with health care professionals and their access to care. However, if continuing to smoke exacerbates unwanted effects and shortens survival, the patient and family should be informed in an empathic and nonjudgmental manner and offered assistance with cessation as well as symptom management. In a similar vein, one item on the Functional Assessment of Cancer Therapy-Lung survey (76) asks whether current smokers regret their smoking. It

would be interesting to perform an analysis of this item in relation to QOL and distress scores and later changes in smoking status. Regret could be construed in a self-blaming manner, similar to guilt, but it may also serve to motivate change, particularly at the time of diagnosis.

Because most patients are aware that smoking is the cause of their malignancies and is harmful to their health overall, they may be reluctant to admit that they continue to smoke or began smoking again during or after treatment. In a study by Gritz et al. (84), the validation rate of self-reported nonsmoking status, as measured by urinary cotinine, was consistently between 85.6% and 91.3% during the 1 year of follow-up, representing a low rate of misreporting. However, in the Head and Neck Retinoid Chemoprevention Trial (13), 39.1% of patients who had quit smoking within the year before trial enrollment (recent former smokers) and 7.9% of patients who had quit for >1 year before (long-term former smokers) had serum cotinine levels consistent with smoking. This finding reflects both the unreliability of self-reported quitting around the time of cancer diagnosis and patients' potential reluctance to reveal continued smoking (see also refs. 18, 83). In addition, there are reports of inconsistencies between self-reported smoking status and biochemically verified smoking status in patients with cancer that are sometimes associated with serious treatment consequences (33, 83). The case is frequently made that self-reports of smoking status are accurate in many settings, but "high demand" medical situations may put a patient more in conflict about honest reporting. Inexpensive and rapid verification of self-reports by breath carbon monoxide or salivary or urinary cotinine dipstick determination should be built into research trials (87) and into clinical practice.

Assessment of Smoking by Oncology Cooperative Groups. An informal assessment of the current practices of major U.S. medical, radiation, and surgical oncology cooperative groups revealed that none routinely collect data on smoking history and status at registration for all studies. For example, the American College of Surgeons Oncology Group does not collect data on smoking status routinely or in trials involving smoking-related tumors. However, in several cooperative groups, studies involving smoking-related cancers (particularly aerodigestive), smoking data are usually collected at registration but are not regularly reassessed subsequently. The reason for this failure is that many researchers and/or cooperative groups stipulate that an outcome effect on smoking must be included in the research objectives to justify collecting such data. Furthermore, cooperative groups lack adequate support for the collection and storage of all desired, but not specifically required, information. This is true of the Cancer and Leukemia Group B, Southwest Oncology Group, Eastern Cooperative Oncology Group, Gynecologic Oncology Group, and Radiation Therapy Oncology Group.

The Radiation Therapy Oncology Group has a voluntary patient-completed demographic form that includes an assessment of smoking history and status (including current smoking status according to the National Health Interview Survey definitions, age at initiation, number of years smoked, average number of cigarettes smoked per day, and, for former smokers, age at cessation). In addition, Radiation Therapy Oncology Group protocol 9801, a randomized phase III trial of amifostine as a radioprotective agent in non-small cell lung cancer therapy, has a pretreatment, patient-completed assessment form that also includes subcategories for former smokers (within 1 year versus >1 year), an assessment of nicotine dependence, and current use of nicotine replacement therapy. In the Prostate Cancer Prevention Trial (Southwest Oncology Group protocol 9217), smoking history, smoking status according to the National Health Interview Survey definitions,

Table 1. Assessment of smoking history, current smoking status, and related behaviors

{Each question block is a separate module that can be combined with other modules, and the items can be renumbered.}

- Initial Assessment
- Have you smoked at least 100 cigarettes in your entire life? (5 packs = 100 cigarettes)
 - Yes
 - No (If no, this is the end of section) (Code as: *Never Smoker*)
 - Don't know/Not sure
 - Do you NOW smoke cigarettes?
 - Everyday (Skip to item 5)
 - Some days (Skip to item 5) {a and b—Code as: *Current Smoker*}
 - Not at all (Code as: *Former Smoker*)
 - For how many years did you smoke regularly? ____ {Duration—Former Smoker}
 - If you do not currently smoke cigarettes but did in the past, how long has it been since you last smoked regularly (i.e., everyday or some days)?
 - Within the past month (0-1 month ago)
 - Within the past 3 months (1-3 months ago)
 - Within the past 6 months (3-6 months ago)
 - Within the past year (6-12 months ago)
 - a-d—Code as: *Recent Former Smoker*
 - Within the past 5 years (1-5 years ago)
 - Within the past 15 years (5-15 years ago)
 - More than 15 or more ago
 - e-g—Code as: *Long-term Former Smoker*
 - Don't know/Not sure
 - Never smoked regularly
 - On average, about how many cigarettes a day do (or did) you smoke? (1 pack = 20 cigarettes) ____ cigarettes {Dose}
 - At what age did you begin smoking regularly? ____ {Age at Initiation}*

*{To calculate duration for current smokers, subtract age at initiation from current age.}

- Follow-up Assessment
- Do you NOW smoke cigarettes?
 - Everyday
 - Some days {a and b—Code as: *Current Smoker*}
 - Not at all {If you do not smoke cigarettes at all, this is the end of section.} (Code as: *Quit*)
 - On average, about how many cigarettes a day do you smoke? (1 pack = 20 cigarettes) ____ cigarettes {Dose}

- Nicotine Dependence
- How soon after you wake up do you smoke your first cigarette?
 - After 30 minutes
 - Within 30 minutes (Code as: *Highly Dependent*)

- Readiness to Stop Smoking
- How many times in the last 12 months have you tried to quit smoking cigarettes and stayed off for at least 24 hours? ____
 - Are you seriously thinking about quitting in the next month?
 - Yes (If yes, this is the end of section) (Code as: *Preparation Stage* if >1 quit in item 1 or *Contemplation Stage* if 0 quits in item 1)
 - No
 - Are you seriously thinking about quitting smoking in the next 6 months?
 - Yes (Code as: *Contemplation Stage*)
 - No (Code as: *Precontemplation Stage*)

- Other Forms of Tobacco
- Have you ever used other forms of tobacco?
 - Yes
 - No (If no, this is the end of section)
 - What other forms of tobacco do (did) you use?
 - Pipe
 - Cigar
 - Chewing tobacco
 - Snuff
 - Other, specify ____
 - Do you use other forms of tobacco everyday, some days, or not at all?
 - Everyday (This is the end of section)
 - Some days (This is the end of section)
 - Not at all
 - If you do not currently use other forms of tobacco but did in the past, how long has it been since you last used other forms of tobacco regularly (i.e., daily)?

Table 1. Assessment of smoking history, current smoking status, and related behaviors (Cont'd)

- Within the past month (0-1 month ago)
 - Within the past 3 months (1-3 months ago)
 - Within the past 6 months (3-6 months ago)
 - Within the past year (6-12 months ago)
 - Within the past 5 years (1-5 years ago)
 - Within the past 15 years (5-15 years ago)
 - More than 15 years ago
 - Don't know/Not sure
 - Never smoked regularly
- Exposure to Secondhand Smoke
- Do people in your household smoke in the home?
 - Yes (If yes, how many? ____)
 - No
 - Is smoking allowed in your workplace?
 - Yes
 - No

and use of other tobacco products were assessed at registration. An interesting finding was that pack-years of smoking was a significant predictor of some level of self-reported sexual problems at baseline (88).

Serving as strong examples, several trials that we have cited in this article (13, 18, 20, 21, 71, 72)⁴ and others have made detailed assessments of smoking at registration and throughout treatment, including some into follow-up. This brief review is intended to be exemplary rather than exhaustive and to suggest future "best practices." Support for collecting these critical data is needed from the clinical and scientific community, from the financial sponsors, including the National Cancer Institute, and from the cooperative groups themselves.

Assessment of Smoking and Analytic Issues. Table 1 contains a suggested list of standardized items for clinical trial core-data items drawn from national survey data (89) or used in many smoking cessation research studies. The minimum core set of items for initial assessment includes numbers 1 to 6 assessing smoking history, current smoking status, and dose at initial assessment and numbers 1 and 2 for follow-up assessments. Patients might be reluctant to admit persistent smoking with a diagnosis of a malignancy, especially if the malignancy is a tobacco-related cancer. Therefore, it is highly desirable to perform biochemical verification of their smoking status with serum, urine, or salivary cotinine, or exhaled carbon monoxide (87). As supported by recommendations in the *Treating Tobacco Use and Dependence. Clinical Practice Guideline* (56), additional items that should be assessed for a more complete description of smoking behavior and exposure and to guide clinical advice for quitting and relapse prevention include nicotine dependence (80), readiness to stop smoking (81), other forms of tobacco use, and secondhand smoke exposure (see ref. 50).

The classification of smoking status for assessment and analytic purposes is not standardized across oncology clinical trials in the same manner that it is in most behavioral smoking research studies. It is critical to use standardized definitions, such as those found in the National Health Interview Survey and Behavioral Risk Factor Surveillance System (89), in assessing smoking status, and it is equally critical to follow such standards when proposing analytic strategies. One of the challenges to any classification scheme

⁴ R. Komaki, M.D. Anderson Cancer Center, personal communication, January 5, 2005.

is the "former smoker" category. Some clinical trials classify patients who have stopped smoking within the last year (recent quitters) as current smokers. Reasons include the following: patients may have only recently stopped smoking because of cancer-related symptoms; they have high rates of relapse; and they may resemble, biologically, current smokers more than former smokers who stopped smoking >1 year previously (6, 13, 18). In such studies, former smokers include only those individuals who quit smoking >1 year ago.

Several studies have found treatment-by-smoking interactions in which current smoking is associated with a harmful effect, but benefit is seen in never smokers (20, 71, 72). The repeated assessment of smoking status throughout treatment and follow-up is also critical to monitoring these interactions and the long-term influences of continued smoking versus stopping (18). Thus, it is increasingly important to accurately classify smoking status in analysis, and we argue strongly against merging recent quitters with current smokers. We suggest four strata in analysis: never smoker, current smoker, recent former smoker, and long-term former smoker (see Table 1, Initial Assessments, for items and coding).

In smaller trials, there may be sample size issues that affect whether an analysis has sufficient power to detect significant differences among strata. Treatment-by-smoking interactions are statistically complex, and analyses may sometimes need to be secondary rather than primary. Further, adverse reactions may differ markedly by smoking status; thus, small sample size alone should not preclude collection of this information.

We recommend incorporating specific smoking hypotheses to be prospectively tested in large phase III trials and that a data bank of clinical trials be created to investigate the important questions raised in this article.

Conclusions

We can no longer ignore the obvious: smoking is a critical variable that affects cancer treatment and outcome and has been shown to vitiate or interact with the effects of some therapeutic agents and chemopreventive agents. Measurement of smoking history and status in clinical trials of cancer therapy will increase our knowledge of the adverse effects of the constituents of tobacco smoke, including nicotine, and of drug interactions.

Oncology health professionals have called for increased advocacy for tobacco control (90-92). Furthermore, the routine inclusion of smoking status and cessation need to become a standard of care for all patients (56, 93). The inclusion of smoking data in oncology clinical trials will also provide clinicians with improved means of delivering individualized advice to patients with cancer that may be critical in motivating their cessation efforts and sustained abstinence. Scientific, financial, and clinical support is critical to this goal.

The failure to date to assess, analyze, and report smoking status has limited our ability to investigate the effect of smoking on treatment efficacy and outcome. The time has come to integrate data about the single most important lifestyle risk factor in cancer prevention into cancer treatment and survivorship trials.

References

- IARC. IARC Monographs on the evaluation of the carcinogenic risk of chemicals to humans. Vol. 83. Tobacco smoke and involuntary smoking. Lyon: IARC Press; 2004.
- Fiore MC, Jorenby DE, Schensky AE, Smith SS, Bauer RR, Baker TB. Smoking status as the new vital sign: effect on assessment and intervention in patients who smoke. *Mayo Clin Proc* 1995;70:209-13.
- USPHS. The health consequences of smoking. A report of the Surgeon General Report 2004. Atlanta (GA): Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and

Health; 2004. Available from: http://www.cdc.gov/tobacco/sgr/sgr_2004/index.htm.

- Gritz ER, Vidrine DJ, Lazev AB. Smoking cessation in cancer patients: never too late to quit. In: Green CW, Given B, Champion VL, Kozachik S, Devoss DN, editors. Evidence-based cancer care and prevention: behavioral interventions. New York: Springer Publishing Co.; 2003. p. 107-40.
- Sanderson Cox L, African NL, Tercyak KP, Taylor KL. Nicotine dependence treatment for patients with cancer: review and recommendations. *Cancer* 2003;98:632-44.
- Do KA, Johnson MM, Doherty DA, et al. Second primary tumors in patients with upper aerodigestive tract cancers: joint effects of smoking and alcohol (United States). *Cancer Causes Control* 2003;14:131-8.
- Johnson BE. Second lung cancers in patients after treatment for an initial lung cancer. *J Natl Cancer Inst* 1998;90:1335-45.
- Richardson GE, Tucker MA, Venzon DJ, et al. Smoking cessation after successful treatment of small-cell lung cancer is associated with fewer smoking-related second primary cancers. *Ann Intern Med* 1993;119:383-90.
- Tucker MA, Murray N, Shaw EG, et al. Second primary cancers related to smoking and treatment of small-cell lung cancer. *Lung Cancer Working Cadre. J Natl Cancer Inst* 1997;89:1782-8.
- Day GL, Blot WJ, Shore RE, et al. Second cancers following oral and pharyngeal cancers: role of tobacco and alcohol. *J Natl Cancer Inst* 1994; 86:131-7.
- Fleshner N, Garland J, Moadel A, et al. Influence of smoking status on the disease-related outcomes of patients with tobacco-associated superficial transitional cell carcinoma of the bladder. *Cancer* 1999;86:2337-45.
- Rice D, Kim HW, Sabichi A, et al. The risk of second primary tumors after resection of stage I non-small cell lung cancer. *Ann Thorac Surg* 2003;76:1001-8.
- Khuri FR, Kim ES, Lee JJ, et al. The impact of smoking status, disease stage, and index tumor site on second primary tumor incidence and tumor recurrence in the Head and Neck Retinoid Chemoprevention Trial. *Cancer Epidemiol Biomarkers Prev* 2001;10:823-9.
- Ford MB, Sigurdson AJ, Petrusis ES, et al. Effects of smoking and radiotherapy on lung carcinoma in breast carcinoma survivors. *Cancer* 2003;98:1457-64.
- Neugut AI, Murray T, Santos J, et al. Increased risk of lung cancer after breast cancer radiation therapy in cigarette smokers. *Cancer* 1994;73: 1615-20.
- Obedian E, Fischer DB, Haffty BG. Second malignancies after treatment of early-stage breast cancer: lumpectomy and radiation therapy versus mastectomy. *J Clin Oncol* 2000;18:2406-12.
- Kawahara M, Ushijima S, Kamimori T, et al. Second primary tumours in more than 2-year disease-free survivors of small-cell lung cancer in Japan: the role of smoking cessation. *Br J Cancer* 1998;78:409-12.
- Do KA, Johnson MM, Lee JJ, et al. Longitudinal study of smoking patterns in relation to the development of smoking-related secondary primary tumors in patients with upper aerodigestive tract malignancies. *Cancer* 2004;101: 2837-42.
- Fujisawa T, Iizasa T, Saitoh Y, et al. Smoking before surgery predicts poor long-term survival in patients with stage I non-small-cell lung carcinomas. *J Clin Oncol* 1999;17:2086-91.
- Lippman SM, Lee JJ, Karp DD, et al. Randomized phase III intergroup trial of isotretinoin to prevent second primary tumors in stage I non-small-cell lung cancer. *J Natl Cancer Inst* 2001;93:605-18.
- Browman GP, Wong G, Hodson I, et al. Influence of cigarette smoking on the efficacy of radiation therapy in head and neck cancer. *N Engl J Med* 1993;328:159-63.
- Johnston-Early A, Cohen MH, Minna JD, et al. Smoking abstinence and small cell lung cancer survival: an association. *JAMA* 1980;244:2175-9.
- Bako G, Dewar R, Hanson J, Hill G. Factors influencing the survival of patients with cancer of the prostate. *Can Med Assoc J* 1982;127:727-9.
- Kucera H, Enzelsberger H, Eppel W, Weghaupt K. The influence of nicotine abuse and diabetes mellitus on the results of primary irradiation in the treatment of carcinoma of the cervix. *Cancer* 1987;60:1-4.
- Pickles T, Liu M, Berthelet E, Kim-Sing C, Kwan W, Tyldesley S. The effect of smoking on outcome following external radiation for localized prostate cancer. *J Urol* 2004;171:1543-6.
- Fox JL, Rosenzweig KE, Ostroff JS. The effect of smoking status on survival following radiation therapy for non-small cell lung cancer. *Lung Cancer* 2004;44:287-93.
- Tammemagi CM, Neslund-Dudas C, Simoff M, Kvale P. Smoking and lung cancer survival: the role of comorbidity and treatment. *Chest* 2004;125:27-37.
- Thawley SE, Panje WR, editors. Comprehensive management and head and neck tumors. Philadelphia: W.B. Saunders; 1987.
- Moller AM, Pedersen T, Villebro N, Schnaberich A, Haas M, Tonnesen R. A study of the impact of long-term tobacco smoking on postoperative intensive care admission. *Anaesthesia* 2003;58:55-9.
- Dresler CM, Gritz ER. Smoking, smoking cessation and the oncologist. *Lung Cancer* 2001;34:315-23.
- Warner MA, Offord KP, Warner ME, Lennon RL, Conover MA, Jansson-Schumacher U. Role of preoperative cessation of smoking and other factors in postoperative pulmonary complications: a blinded prospective study of coronary artery bypass patients. *Mayo Clin Proc* 1989;64:609-16.
- Vaporciyan AA, Merriman KW, Ece F, et al. Incidence of major pulmonary morbidity after pneumonectomy: association with timing of smoking cessation. *Ann Thorac Surg* 2002;73:420-5; discussion 425-6.

33. Gritz ER, Fingeret MC, Vidrine D. Success and failures of the teachable moment: smoking cessation in cancer patients. *Cancer*, in press.
34. Chang DW, Reece GP, Wang B, et al. Effect of smoking on complications in patients undergoing free TRAM flap breast reconstruction. *Plast Reconstr Surg* 2000;105:2374–80.
35. Eifel PJ, Jhingran A, Bodurka DC, Levenback C, Thames H. Correlation of smoking history and other patient characteristics with major complications of pelvic radiation therapy for cervical cancer. *J Clin Oncol* 2002;20:3651–7.
36. Monson JM, Stark P, Reilly JJ, et al. Clinical radiation pneumonitis and radiographic changes after thoracic radiation therapy for lung carcinoma. *Cancer* 1998;82:842–50.
37. Ferson M, Edwards A, Lind A, Milton GW, Hersey P. Low natural killer-cell activity and immunoglobulin levels associated with smoking in human subjects. *Int J Cancer* 1979;23:603–9.
38. Geng Y, Savage SM, Razani-Boroujerdi S, Sopori ML. Effects of nicotine on the immune response. II. Chronic nicotine treatment induces T cell anergy. *J Immunol* 1996;156:2384–90.
39. Tollerud DJ, Clark JW, Brown LM, et al. Association of cigarette smoking with decreased numbers of circulating natural killer cells. *Am Rev Respir Dis* 1989;139:194–8.
40. Smith JB, Fenske NA. Cutaneous manifestations and consequences of smoking. *J Am Acad Dermatol* 1996;34:717–32; quiz 733–4.
41. Arcavi L, Benowitz NL. Cigarette smoking and infection. *Arch Intern Med* 2004;164:2206–16.
42. Gritz ER, Klesges RC, Meyers AW. The smoking and body weight relationship: implications for intervention and post cessation weight control. *Ann Behav Med* 1989;11:144–53.
43. Gritz ER. Smoking and smoking cessation in cancer patients. *Br J Addict* 1991;86:549–54.
44. Brown JK. Gender, age, usual weight, and tobacco use as predictors of weight loss in patients with lung cancer. *Oncol Nurs Forum* 1993;20:466–72.
45. Hofstetter A, Schutzy Y, Jequier E, Wahren J. Increased 24-hour energy expenditure in cigarette smokers. *N Engl J Med* 1986;314:79–82.
46. Moffatt RJ, Owens SG. Cessation from cigarette smoking: changes in body weight, body composition, resting metabolism, and energy consumption. *Metabolism* 1991;40:465–70.
47. Lippman AG. How smoking interferes with drug therapy. *Mod Med* 1985;8:141–2.
48. Sarna L, Riedinger MS. Assessment of quality of life and symptom improvement in lung cancer clinical trials. *Semin Oncol* 2004;31:1–10.
49. Garces YL, Yang P, Parkinson J, et al. The relationship between cigarette smoking and quality of life after lung cancer diagnosis. *Chest* 2004;126:1733–41.
50. California Environmental Protection Agency. Proposed identification of environmental tobacco smoke as a toxic air contaminant—June 2005. California Environmental Protection Agency, California Air Resources Board, Office of Environmental Health Hazard Assessment; 2005. Available from: <http://www.arb.ca.gov/toxics/ets/dreport/dreport.htm>.
51. U.S. Department of Health and Human Services. Women and smoking: a report of the Surgeon General—2001. Rockville (MD): U.S. Department of Health and Human Services, Public Health Service, Office of the Surgeon General; 2001. Available from: <http://www.surgeongeneral.gov/library>.
52. Sarna L, Evangelista L, Tashkin D, et al. Impact of respiratory symptoms and pulmonary function on quality of life of long-term survivors of non-small cell lung cancer. *Chest* 2004;125:439–45.
53. Evangelista LS, Sarna L, Brecht ML, Padilla G, Chen J. Health perceptions and risk behaviors of lung cancer survivors. *Heart Lung* 2003;32:131–9.
54. Vaury C, Laine R, Noguez P, et al. Human glutathione S-transferase M1 null genotype is associated with a high inducibility of cytochrome P450 1A1 gene transcription. *Cancer Res* 1995;55:5520–3.
55. Smith LE, Denisenko MF, Bennett WP, et al. Targeting of lung cancer mutational hotspots by polycyclic aromatic hydrocarbons. *J Natl Cancer Inst* 2000;92:803–11.
56. Fiore MC, Bailey WC, Cohen SJ, et al. Treating tobacco use and dependence. Clinical practice guideline. Rockville (MD): U.S. Department of Health and Human Services, Public Health Service; 2000.
57. Maneckjee R, Minna JD. Opioids induce while nicotine suppresses apoptosis in human lung cancer cells. *Cell Growth Differ* 1994;5:1033–40.
58. Heusch WL, Maneckjee R. Signaling pathways involved in nicotine regulation of apoptosis of human lung cancer cells. *Carcinogenesis* 1998;19:551–6.
59. West KA, Brognard J, Clark AS, et al. Rapid Akt activation by nicotine and a tobacco carcinogen modulates the phenotype of normal human airway epithelial cells. *J Clin Invest* 2003;111:81–90.
60. Wang K, Hackett JT, Cox ME, Van Hoek M, Lindstrom JM, Parsons SJ. Regulation of the neuronal nicotinic acetylcholine receptor by SRC family tyrosine kinases. *J Biol Chem* 2004;279:8779–86.
61. Ye YN, Liu ES, Shin VY, Wu WK, Luo JC, Cho CH. Nicotine promoted colon cancer growth via epidermal growth factor receptor, c-Src, and 5-lipoxygenase-mediated signal pathway. *J Pharmacol Exp Ther* 2004;308:66–72.
62. Gazdar AF, Shigematsu H, Herz J, Minna JD. Mutations and addition to EGFR: the Achilles “heal” of lung cancers? *Trends Mol Med* 2004;10:481–6.
63. Cooke JP, Bitterman H. Nicotine and angiogenesis: a new paradigm for tobacco-related diseases. *Ann Med* 2004;36:33–40.
64. Heeschen C, Jang JJ, Weis M, et al. Nicotine stimulates angiogenesis and promotes tumor growth and atherosclerosis. *Nat Med* 2001;7:833–9.
65. Shin VY, Wu WK, Ye YN, et al. Nicotine promotes gastric tumor growth and neovascularization by activating extracellular signal-regulated kinase and cyclooxygenase-2. *Carcinogenesis* 2004;25:2487–95.
66. Moraitis D, Du B, De Lorenzo MS, et al. Levels of cyclooxygenase-2 are increased in the oral mucosa of smokers: evidence for the role of epidermal growth factor receptor and its ligands. *Cancer Res* 2005;65:664–70.
67. Minna JD. Nicotine exposure and bronchial epithelial cell nicotinic acetylcholine receptor expression in the pathogenesis of lung cancer. *J Clin Invest* 2003;111:31–3.
68. The α -Tocopherol BCCPSG. The effect of vitamin E and β carotene on the incidence of lung cancer and other cancers in male smokers. *N Engl J Med* 1994;330:1029–35.
69. Omenn GS, Goodman GE, Thornquist MD, et al. Risk factors for lung cancer and for intervention effects in CARET, the β -Carotene and Retinol Efficacy Trial. *J Natl Cancer Inst* 1996;88:1550–9.
70. Omenn GS, Goodman GE, Thornquist MD, et al. Effects of a combination of β carotene and vitamin A on lung cancer and cardiovascular disease. *N Engl J Med* 1996;334:1150–5.
71. Lynch TJ, Bell DW, Sordella R, et al. Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. *N Engl J Med* 2004;350:129–39.
72. Herbst RS, Prager D, Hermann R, et al. Tribute—a phase III trial of erlotinib HCl (OSI-774) combined with carboplatin and paclitaxel chemotherapy in advanced non-small cell lung cancer. *Proc Am Soc Clin Oncol* 2004;23:617.
73. Browman GP, Mohide EA, Willan A, et al. Association between smoking during radiotherapy and prognosis in head and neck cancer: a follow-up study. *Head Neck* 2002;24:1031–7.
74. Batevik R, Grong K, Segadal L, Stangeland L. The female gender has a positive effect on survival independent of background life expectancy following surgical resection of primary non-small cell lung cancer: a study of absolute and relative survival over 15 years. *Lung Cancer* 2005;47:173–81.
75. Ebbett JO, Williams BA, Sun Z, et al. Duration of smoking abstinence as a predictor for non-small-cell lung cancer survival in women. *Lung Cancer* 2005;47:165–72.
76. Cella DF, Bonomi AE, Lloyd SR, Tulsky DS, Kaplan E, Bonomi P. Reliability and validity of the Functional Assessment of Cancer Therapy-Lung (FACT-L) quality of life instrument. *Lung Cancer* 1995;12:199–220.
77. List MA, D’Antonio LL, Cella DF, et al. The performance status scale for head and neck cancer patients and the Functional Assessment of Cancer Therapy-Head and Neck Scale. A study of utility and validity. *Cancer* 1996;77:2294–301.
78. Peto R. Influence of dose and duration of smoking on lung cancer rates. *IARC Sci Publ* 1986;74:23–33.
79. Toh CK, Wong EH, Lim W-T, et al. The impact of smoking status on the behavior and survival outcome of patients with advanced non-small cell lung cancer. *Chest* 2004;126:1750–6.
80. Fagerstrom KO, Schneider NG. Measuring nicotine dependence: a review of the Fagerstrom tolerance questionnaire. *J Behav Med* 1989;12:159–82.
81. Prochaska JO, DiClemente CC, Norcross JC. In search of how people change. Applications to addictive behaviors. *Am Psychol* 1992;47:1102–14.
82. Gritz ER, Nisenbaum R, Elashoff R, Holmes ECfL. Smoking behavior following diagnosis in patients with stage I non-small cell lung cancer. *Cancer Causes Control* 1991;2:105–12.
83. Sarna L, Padilla G, Holmes C, Tashkin D, Brecht ML, Evangelista L. Quality of life of long-term survivors of non-small-cell lung cancer. *J Clin Oncol* 2002;20:2920–9.
84. Gritz ER, Carr CR, Rapkin D, et al. Predictors of long-term smoking cessation in head and neck cancer patients. *Cancer Epidemiol Biomarkers Prev* 1993;2:261–70.
85. Gritz ER, Carmack C, de Moor C, et al. First year after head and neck cancer: quality of life. *J Clin Oncol* 1999;17:352–60.
86. Chapple A, Ziebland S, McPherson A. Stigma, shame, and blame experienced by patients with lung cancer: qualitative study. *BMJ* 2004;328:1470–4.
87. Hughes JR, Keely JP, Niaura RS, Ossip-Klein DJ, Richmond RL, Swan GE. Measures of abstinence in clinical trials: issues and recommendations. *Nicotine Tob Res* 2003;5:13–25.
88. Moynour CM, Darke AK, Pauler DK. Determining predictors of men’s report of sexual problems: advantages of a two-part model for zero scores. Vol. 12. 10th Annual Conference of the International Society for Quality of Life Research; 2003 Nov 12–15. Prague (Czech Republic): Kluwer Academic Publishers.
89. Centers for Disease Control and Prevention. Behavioral risk factor surveillance system survey questionnaire. Atlanta (GA): U.S. Department of Health and Human Services; 2000.
90. Mazzone PJ, Arroliga AC. How many ways can we say that cigarette smoking is bad for you? *Chest* 2004;126:1717–8.
91. American Society of Clinical Oncology. ASCO policy statement update: tobacco control-reducing cancer incidence and saving lives. *J Clin Oncol* 2003;15:2777–86.
92. Sarna L, Bialous SA. Tobacco control policies of oncology nursing organizations. *Semin Oncol Nurs* 2004;20:101–10.
93. Joint Commission of American Hospital Organizations. Specification manual for national implementation of hospital core measures. Version 2.0. Implementation to begin with July 2004 discharges; 2005. Available from: <http://www.jcaho.org/pms/core+measures/information+on+final+specifications.htm>.

Smoking, The Missing Drug Interaction in Clinical Trials: Ignoring the Obvious

Ellen R. Gritz, Carolyn Dresler and Linda Sarna

Cancer Epidemiol Biomarkers Prev 2005;14:2287-2293.

Updated version Access the most recent version of this article at:
<http://cebp.aacrjournals.org/content/14/10/2287>

Cited articles This article cites 80 articles, 15 of which you can access for free at:
<http://cebp.aacrjournals.org/content/14/10/2287.full#ref-list-1>

Citing articles This article has been cited by 34 HighWire-hosted articles. Access the articles at:
<http://cebp.aacrjournals.org/content/14/10/2287.full#related-urls>

E-mail alerts [Sign up to receive free email-alerts](#) related to this article or journal.

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

Permissions To request permission to re-use all or part of this article, use this link
<http://cebp.aacrjournals.org/content/14/10/2287>.
Click on "Request Permissions" which will take you to the Copyright Clearance Center's (CCC) Rightslink site.