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Article *in* Cancer Causes and Control · February 1996

DOI: 10.1007/BF00115646 · Source: PubMed

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DOI: 10.1164/rccm.200712-1805ED

Nutrition and Lung Cancer

Lessons from the Differing Effects of Foods and Supplements

In this issue of the *Journal* (pp. 524–530), Slatore and coworkers report findings on the association between nutritional supplement use and lung cancer risk using information from a cohort of 77,721 adults in Washington State. Vitamin and mineral supplement use in the prior 10 years was largely unrelated to risk for incident lung cancer (1). There was no suggestion of any benefit from vitamin supplement use for any subgroups defined by histologic type of lung cancer or by smoking status. However, there was modestly increased lung cancer risk with the use of vitamin E supplements, which was particularly apparent for continuing smokers.

Vitamin pills are widely used with the idea that supplementing our diet with extra vitamins must be a good thing. However, almost every time we take a hard look at objective evidence regarding nutritional supplements, the balance tips away from benefit and toward harm (2). Over the past two decades, we have been repeatedly disappointed in the ability of vitamin supplements to reduce risk for cancers at several sites, including the stomach, colorectum, breast, and lung (2). Foods that are rich in vitamins seem to be associated with reduced risk of cancer, but vitamins packaged as pills clearly do not have the same effect.

On November 1, 2007, the World Cancer Research Fund (WCRF) issued a comprehensive report on the effects of foods and nutrients on the risk of cancer, based on systematic literature reviews commissioned from around the world, judged by 21 experts on nutrition and cancer (3). For lung cancer, the main conclusions were derived from 32 case-control studies, 25 cohort studies, and three randomized, controlled trials. After careful adjustment for tobacco use history, the WCRF concluded there was an approximate 20% increased risk for incident lung cancer among those in the lowest quintile of fruit intake. On the basis of unequivocal findings from randomized, controlled trials (4, 5), they also concluded that beta-carotene supplements increased lung cancer risk. These conclusions are consistent with the previously published conclusions of an expert panel convened by the American Cancer Society (ACS) (6).

On the basis of early observations that lung cancer risk seemed to be lower among smokers and former smokers who consumed more fruits and vegetables, trials were designed to test the idea that the pro–vitamin A antioxidant beta-carotene might reduce risk of lung cancer (4, 5). In those trials, the dosage of beta-carotene was determined as that just below which the skin turned noticeably orange. These trials of supernutritional levels of beta-carotene proved that such high levels could increase risk of lung cancer, beginning as soon as 2–3 years after the onset of supplementation. It is interesting to note that, in the control groups in these trials, low levels of fruit intake at baseline and low circulating levels of beta-carotene in the blood predicted increased lung cancer risk.

The conclusion drawn by Slatore and colleagues that high-dose vitamin E supplementation might have adverse effects on lung cancer risk is reminiscent of the findings from previous randomized controlled trials of beta-carotene (4, 5). How could a beneficial effect of consuming fruits be consistent with an adverse effect of a nutrient that is derived in large part from that same food group? The answer likely resides in the same conclusion that usually emerges from thoughtful analysis of any type of biologic study: the processes involved in biologic systems end up being far more complex than we had previously thought. Fruits contain not

only vitamins but also many hundreds of other phytochemical compounds whose functions are not well understood. Many of these compounds seem to have antiviral, antimicrobial, and antineoplastic properties that benefit the plant. It is humbling to realize that nearly two decades since the failed beta-carotene trials, we still do not know the mechanism for the adverse effect of beta-carotene. Interference with normal functioning of the retinoid receptor system, prooxidation at the cellular level, or some interference with other nutrients are all possibilities.

So what should we now say or do about nutrition and lung cancer? The WCRF and ACS recommendations to eat at least two servings of fruits each day would likely lead to reduced risk for lung cancer, as well as reduced risk for several other cancers and cardiovascular diseases (3, 6). Just how much of a public proclamation we should make in particular about a benefit to lung cancer risk is not obvious. Any benefit to the population of smokers from increasing fruit intake to reduce lung cancer risk by 20% would be more than offset if even a small proportion of smokers decided to continue tobacco use in favor of such a diet change. The high cost of conducting a randomized controlled trial to generate more conclusive evidence about this relationship hardly seems worth it. However, testing the effects of increasing fruit intake after the diagnosis of lung cancer may make more sense. There is no evidence to date about the effects of nutritional factors on lung cancer outcomes, but for many other cancers, nutritional factors that modify cancer risk seem also to affect cancer prognosis (3, 6). Perhaps we should consider a trial to test the effects of increasing fruit intake on outcomes after the diagnosis of lung cancer. Such a trial was recently performed among breast cancer survivors in which women were taught to double their intake of fruits and vegetables, accomplished mostly by adding blenderized foods to the diet (7). Although that intervention did not affect breast cancer recurrence (indeed there was little reason to suspect it should have as fruits and vegetables are not related to risk of breast cancer incidence [3]), the intervention worked quite well among those breast cancer survivors who were highly motivated. Adding calories by doubling or tripling fruit intake among lung cancer survivors using this same type of intervention might offer important extra benefits in maintaining body weight and improving well-being as the possible effects on lung cancer prognosis are being assessed.

***Conflict of Interest Statement*:** T. B. has no financial relationship with a commercial entity that has an interest in the subject of this manuscript.

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DOI: 10.1164/rccm.200711-1681ED

A Good Case for a Declining Role for Mediastinoscopy Just Got Better

The discovery of metastatic N2 or N3 disease has significant implications for the prognosis and optimal care of patients with lung cancer. Positron emission tomography (PET) and PET–computed tomography (PET-CT) scanning have advanced the accuracy of clinical staging over CT scan alone (1). However, when evaluated prospectively, the combination of CT and PET-CT still remains relatively unsatisfactory, and unsuspected N2 disease may be proven pathologically in up to 9% of patients with clinical stage I and 26% of patients with clinical stage II disease (2).

Mediastinoscopy has been the mainstay of prethoracotomy pathological staging for patients with lung cancer. However, it is not without its drawbacks, both in theory and in practice. Mediastinoscopy is a procedure that requires general anesthesia, and while its complication rate is around 1%, severe hemorrhage can occur in nearly 0.3% of cases, requiring emergent sternotomy or thoracotomy (3–5).

Mediastinoscopy can sample only a fraction of the mediastinal lymph node stations. Standard cervical mediastinoscopy can access the paratracheal and subcarinal lymph node stations (2R, 2L, 4R, 4L, 7), but not the paraesophageal, inferior pulmonary ligament, and aortopulmonary window lymph node (stations 8, 9 5, 6). In addition, the lower aspect of the subcarinal station may be inaccessible via mediastinoscopy. Not surprisingly, the vast number of N2 nodes missed with mediastinoscopic staging tend to be found in those latter stations (3, 4).

Similar to any operator-dependent procedure, there is variability in how effectively mediastinoscopy is actually performed. In a survey of practice patterns of 729 U.S. hospitals in which over 40,000 patients received surgical care for lung cancer in 2001, only 28% underwent mediastinoscopy prior to surgical resection (6). Keeping in mind that these data predate widespread usage of PET-CT scanning, the strikingly low proportion implies that a number of patients may have been understaged and thus did not receive optimal care. Even more concerning is the performance metric of nodal tissue obtained in the fraction of patients who underwent mediastinoscopy, as only 47% of these patients were found to have documentation of lymph node specimens submitted for pathological examination. Although the last two large (>2,000 patients each), single-institution series