Does Prostate-Specific Antigen Screening Influence the Results of Studies of Tomatoes, Lycopene, and Prostate Cancer Risk?

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In this issue of the Journal, Kavanaugh et al. (1) describe how the U. S. Food and Drug Administration (FDA) evaluated the scientific evidence for proposed qualified health claims for tomatoes and lycopene with respect to the risks of prostate cancer and other types of cancers. After the authors qualitatively reviewed the studies, they concluded that there was “a very low level of comfort that a relationship exists between the consumption of tomatoes and/or tomato sauce and prostate cancer risk.” This conclusion is disappointing given that some initial studies of tomato product intake or circulating lycopene levels suggested an association with a reduced risk of prostate cancer, providing some hope for prostate cancer prevention (2–6). However, a number of recent studies, including some (7–9) too recent to be included in the review by Kavanaugh et al. (1), have not supported this association or have been equivocal. Should we now conclude that tomatoes or lycopene are unlikely to have any role in prostate carcinogenesis? Before we do, we should consider a potentially complicating factor, which is that most of the recent studies have been conducted in populations in which most prostate cancers are identified through prostate-specific antigen (PSA) screening. In interpreting the evidence for a risk factor in relation to prostate cancer risk, two major considerations are how PSA screening influences the diagnosis and epidemiology of prostate cancer and when during prostate carcinogenesis that risk factor is operative.

PSA screening became highly prevalent in the United States in the early 1990s and profoundly influenced prostate cancer epidemiology because it changed 1) which prostate cancers are diagnosed, 2) the stage of the prostate cancers that are diagnosed, and 3) how they are diagnosed. These factors have enormous implications for interpreting results of studies of risk factors for prostate cancer. Before the widespread use of PSA screening, most prostate cancers that were diagnosed had progressed to a relatively advanced stage. In the PSA era, many more cancers are being diagnosed, including a pool of biologically indolent cancers, which usually were not detected in the pre-PSA era because they are latent and asymptomatic. Furthermore, prostate cancers get diagnosed in the PSA era much earlier in their natural history than those that were diagnosed in the pre-PSA era. In a population with no or minimal PSA screening, a diagnosis of prostate cancer signifies an “event” that follows some period of tumor growth that was presumably stimulated by some internal or external factor. In a population with widespread PSA screening, a diagnosis of prostate cancer signifies, in most cases, that a man happened to have a PSA test at that time. Many prostate cancers that are diagnosed on the basis of a PSA screening result would have never attracted clinical attention, including those that would progress if untreated because they are typically diagnosed before they develop manifestations of advanced disease, such as metastasis.

The second consideration is the stage at which risk factors for fatal prostate carcinogenesis are operative. A recent analysis of the Health Professionals Follow-up Study (HPFS) cohort reported that risk factors that were associated with an increased risk of prostate cancer mortality were associated with either 1) an increased incidence of prostate cancer, 2) an increased likelihood of poor prostate tumor differentiation (demonstrated by a high Gleason score), 3) a preferential increase in the promotion or progression of highly differentiated prostate cancers, or 4) an increased prostate cancer death rate independent of incidence, stage at diagnosis, or grade (10). At least in the HPFS cohort, almost all of the dietary and lifestyle factors that were associated with increased prostate cancer mortality were also associated with an increase in tumor progression or promotion or with an increase in the fatality rate, rather than with an increase in incidence. Certainly, poor tumor differentiation is a strong predictor of which cancers are likely to progress, but most risk factors assessed did not appear to act by preferentially increasing the pool of poorly differentiated cancer.

Before we exclude tomatoes and lycopene as relevant factors for the prevention of prostate carcinogenesis, we need to examine their associations with each of the four pathways leading to death described above. To date, most studies have focused on associations between tomatoes and lycopene and total incident prostate cancer. Although some of the earlier studies (2–6) seemed to support an association between tomatoes and lycopene and lower prostate cancer incidence, recent studies (7–9) have generally not been as supportive. One explanation could be that chance accounted for the results in the earlier studies and that no real association exists. However, another explanation may be that a true association is more difficult to demonstrate in the PSA era, which is when most of the recent studies that found no association were conducted. Supporting this latter explanation is the fact that essentially all of the supportive studies were conducted in the United States before PSA screening was widespread (2–4,6,11) or in other countries where PSA screening is not prevalent (5,12,13) and thus were not “contaminated” by PSA screening. Although the incident cancer endpoint used in the earlier studies was sensitive enough to show an association between tomatoes or lycopene and tumor progression, in fact, the association often appeared stronger for more advanced-stage lesions (2,4,11). However, given the deluge

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of early-onset, prevalent cancers in the PSA era, an “incident” cancer endpoint may not adequately reflect the actions of a promoting factor. This explanation is further supported by results from the HPFS, which is one of the few studies that straddled the PSA era. For example, initial analyses of the HPFS cohort for 1986–1992 found an inverse association between tomato sauce intake and total prostate cancer incidence; the association was stronger for advanced-stage cancer (2). In subsequent analyses of the HPFS cohort during the PSA era (1992–1998), the association was attenuated and weak, but a strong inverse association persisted for metastatic prostate cancer (combining the data from 1986 through 1998, the relative risk [RR] of metastatic prostate cancer for ≥2 servings per week of tomato sauce versus <1 serving per month = 0.34; 95% confidence interval [CI] = 0.19 to 0.90; \( P_{\text{trend}} = .01 \)) (14). Of note, the metastatic cases (n = 90) represented only about 4% of the total number of cases. In a further analysis of 2650 cases of organ-confined, largely PSA-detected prostate cancer from 1992 to 2002, no statistically significant association between tomato sauce intake and total prostate cancer incidence was observed (RR = 0.86; 95% CI = 0.70 to 1.04) (10). These findings indicate that studies conducted during the PSA era could easily miss important associations for risk factors associated with advanced-stage prostate cancer.

Some investigators appreciated the importance of distinguishing aggressive prostate and have examined high-grade disease as an endpoint for “aggressive” prostate cancer. Although some factors may act differentially on high-grade cancers [e.g., calcium intake (10)], most of the risk factors that have been considered, at least based on HPFS data, are not preferentially associated with high-grade prostate cancer. Moreover, because the majority of high-grade cancers detected in the PSA era are small and organ confined, they will not reflect risk factors associated with advanced-stage prostate cancer. Some studies (7–9) have examined associations between tomatoes or lycopene and advanced stage at prostate cancer diagnosis. Unfortunately, this endpoint is becoming less informative in the PSA era because so many prostate cancers are diagnosed at early stages. In the HPFS, only strict criteria of aggressive behavior, such as invasion into seminal vesicle or metastasis, appear to adequately detect risk factors that were associated with an increased risk of fatal prostate cancer (10). In the PSA era, the percentage of such cancers at the time of diagnosis is small. Less strict criteria of aggressive behavior, such as invasion into the capsule, are probably not adequate to detect associations; these cancers are probably not much different than the so-called “organ-confined” cancers (15).

A further complexity in using high-grade cancers as a surrogate of aggressive cancer would be if the risk factor of interest is associated with the progression of well-differentiated prostate cancers rather than with the progression of poorly differentiated lesions. This phenomenon is entirely plausible and, in fact, is likely to occur. For example, finasteride may be an agent that inhibits (or even regresses) growth in better differentiated lesions but not for poorly differentiated lesions (16). Furthermore, in the Physicians’ Health Study, high circulating levels of insulin-like growth factor 1 (IGF-1) were preferentially associated with an increased risk of low-grade and advanced-stage prostate cancers (17). A possible explanation for this observation is that growth in poorly differentiated cancers may be more autonomous because these cancers may have extensive mutations in the IGF-1 signaling pathway (18,19). By contrast, more highly differentiated cancers may have a relatively intact signaling pathway that remains responsive to circulating IGF-1 levels. It is interesting that in a recent analysis in the HPFS (10), higher intakes of tomato sauce were associated with an increased risk of low-grade, advanced prostate cancers (multivariable RR = 0.27, 95% CI = 0.10 to 0.96; \( P_{\text{trend}} = .02 \)). Although it may be purely coincidental that both low lycopene and high IGF-1 levels are associated with an increased risk of low-grade, advanced cancers, it is intriguing that some in vitro studies (20–22), animal studies (23,24), and preliminary human studies (25,26) suggest that lycopene reduces IGF-1 signaling by increasing the concentrations of IGF-binding proteins, possibly at the tissue level.

Finally, as discussed previously (14), it is important to consider the many additional methodologic factors that would tend to attenuate any real association between tomatoes or lycopene intake and prostate cancer risk. These factors include measurement error in assessing tomato or lycopene intake, the variability in bioavailability of lycopene from different sources, the range of lycopene levels or tomato intakes, and the use of a blood measure of lycopene at only a single time to estimate long-term lycopene levels. In the HPFS, lycopene intake was not associated with prostate cancer risk when intake was assessed with the use of a single questionnaire (RR for high versus low quintile of lycopene intake = 0.94, 95% CI = 0.83 to 1.08, \( P_{\text{trend}} = .39 \)) but was inversely associated with risk when multiple questionnaires were used to assess long-term intake (RR = 0.84, 95% CI = 0.73 to 0.96, \( P_{\text{trend}} = .003 \)) and when the bioavailability of lycopene was taken into account (RR = 0.76, 95% CI = 0.60 to 0.96, \( P_{\text{trend}} <.001 \)). In some of the studies that did not show an association with prostate cancer risk, the intakes of tomato products or sources of bioavailable lycopene were probably too low to demonstrate an association (27–29).

Given the complexities of studying the relationship between tomato or lycopene intake and prostate cancer risk, both in terms of the exposures and the outcome, one should not be too surprised that no firm conclusion of benefit would be made in the FDA review. The review was not designed to account for these issues, and the data addressing these issues are sparse. Although it may be premature to espouse increased consumption of tomato sauce or lycopene for prostate cancer prevention, this area of research remains promising. Studies of advanced prostate cancer conducted in populations with a wide variation in lycopene levels and in which the diagnosis of prostate cancer is not excessively influenced by PSA screening, such as in the European Prospective Investigation into Cancer and Nutrition study cohort (30), should prove informative. Furthermore, whether the relationship between lycopene level or intake and prostate cancer risk is modified by other antioxidants and genetic factors, as has been suggested recently (31,32), should be examined.

References
