Invited Commentary: Screening and the Elusive Etiology of Prostate Cancer

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The role of lifestyle risk factors in prostate cancer risk remains elusive despite a large number of epidemiologic studies. In a pooled analysis of data from South and East Asian countries published in this issue, Fowke et al. (Am J Epidemiol. 2015;182(5):381–389) found no evidence for an association between prostate cancer mortality and obesity, alcohol, or smoking. Prostate cancer screening is very uncommon in these countries, and previous evidence for associations with lifestyle factors comes primarily from studies carried out in North America, where screening is very common. Fowke et al. concluded that screening biases are likely to explain the differences in study results. In this commentary, we discuss the potential influence of population-based cancer screening programs in estimates of association from epidemiologic studies. This highlights the importance of carefully considering the impact of screening in the analysis and interpretation of results, in order to advance our understanding of the etiology of cancers that can be detected by screening.

alcohol drinking; Asia; mortality; obesity; prostate cancer; prostate-specific antigen; smoking

Abbreviation: PSA, prostate-specific antigen.

The chances of receiving a diagnosis of prostate cancer increase sharply with age and vary widely depending on where men live (1, 2). On average, 1 in 1,000 men are diagnosed with prostate cancer every year in North America, and the diagnosis is likely to be of a nonaggressive cancer detected by screening. In contrast, 1 in 10,000 men living in eastern Asia will be diagnosed with prostate cancer every year, and the diagnosis will likely be of an aggressive cancer diagnosed after the onset of symptoms. Adoption of a westernized lifestyle has been proposed as an explanation for geographical differences and temporal trends; however, prostate cancer screening is likely to be a major contributing factor (3, 4).

Despite a wealth of epidemiologic studies of this common cancer in Western countries, the role of lifestyle factors in prostate cancer risk has remained elusive (1). It has been suggested that some of the inconsistencies in the literature could be explained by lifestyle factors’ having differing associations with the incidence and progression of prostate cancer (5). For instance, meta-analyses of prospective studies have shown a lower risk of nonaggressive prostate cancer in obese men compared with leaner men but an elevated risk of being diagnosed with an aggressive cancer (2, 6, 7) or of dying from this disease (3, 4, 8). Several biological mechanisms have been proposed to explain this differential association of obesity with non-aggressive and aggressive prostate cancer (1, 7, 9); however, there is no definite evidence. Similarly, cigarette smoking has been related to an increased risk of aggressive prostate cancer and mortality from this disease (5, 10, 11). The evidence for alcohol is even less clear (12–14). In contrast, most genetic susceptibility loci for prostate cancer identified to date have shown similar associations for aggressive and nonaggressive disease (15, 16), bringing into question whether this classification reflects etiologically distinct tumors.

An alternative explanation for the observed stage-specific associations and the lack of progress in determining the major causes of prostate cancer is screening bias. This would be most notable in North American studies, where prostate cancer screening by digital rectal examination and prostate-specific antigen (PSA) testing is very common. Indeed, in a recently published meta-analysis on weight gain and prostate cancer, Keum et al. (17) suggested that screening could be an explanation for the observed stronger protective association in US
studies than in studies from Europe, where PSA screening is less common. Similarly, in another recent meta-analysis, Bagnardi et al. (14) found a significant increase in prostate cancer risk with increasing alcohol consumption in North American studies but not in European or Asian studies.

Fowke et al. (18), whose study appears in this issue of the Journal, attempted to address this potential screening bias by evaluating the associations of obesity, smoking, and alcohol intake with the risk of fatal prostate cancer in studies conducted in South and East Asian countries, where prostate cancer screening is still very uncommon (19). They conducted a pooled analysis of data from 18 prospective cohort studies with a total of 522,736 men, 634 of whom died of prostate cancer during follow-up. They found no evidence of an association between prostate cancer mortality and obesity, alcohol, or smoking. They concluded that the most likely explanation for the differing results obtained in previous meta-analyses is screening biases in studies of Western populations. However, other population differences, such as the prevalence or timing of lifestyle exposures (5), could also contribute to explaining the observed differences across studies. In addition, as the authors pointed out, in spite of combining data from multiple cohorts, the study had low statistical power to detect small-to-moderate associations with mortality. Therefore, further studies are still needed to directly evaluate the impact of screening on associations between lifestyle factors and prostate cancer incidence and mortality. Indeed, it might be very difficult to disentangle potential screening bias from a differential association of exposures with incidence and disease progression, because the two are intrinsically linked. Less aggressive disease is more likely to be detected by screening. This problem generalizes to other cancers for which screening is more or less effective at detecting certain disease subtypes.

Two commentaries previously published in the Journal over 10 years ago discussed the potential biases introduced by population-based screening programs in epidemiologic studies of cancer. Weiss (20) highlighted the need to measure and account for cancer screening to be able to adequately interpret study results; however, this is still a rare practice in epidemiology, presumably because of the difficulty of collecting high-quality information on screening. Self-reports can be particularly problematic (21). Two approaches to addressing this are either to aim for unscreened populations, as in the current study by Fowke et al. (18), or to use studies conducted in settings with electronic screening records for the entire population (as in the United Kingdom or Sweden) or in managed-care settings such as a health maintenance organization (in the United States). A consideration when studying unscreened populations is that there can be a large pool of subclinical prostate cancers within apparently healthy men serving as controls.

In order for screening bias to occur, screening needs to be related to both the probability of being diagnosed with cancer and the exposure of interest. The former can occur when screening identifies cancers that would never have become symptomatic and therefore would not have been diagnosed in the absence of screening (22). Thus, conditions with a high prevalence of subclinical disease such as prostate cancer (23) would be particularly susceptible to screening biases. Exposures can be related to screening in a number of ways. The most widely recognized is the situation where the exposure of interest is related to screening attendance. A less commonly recognized problem is where the exposure affects the sensitivity of the screening test. Fowke et al. (18) suggest that the latter could be one of the problems with PSA and the lifestyle factors they investigated. Screening could also mediate or modify the relationship with the exposure of interest. Each of these possibilities is described below and illustrated with examples.

As Weiss discussed (20), screening history can introduce confounding bias, since the probability of being screened or the frequency of screening is often related to exposures that are used to determine whether someone should go for screening. For instance, women at higher risk of breast cancer because of their family history or other risk factors are likely to start mammography screening earlier or to be screened more frequently. Indeed, most risk factors for breast cancer have been found to be associated with mammography utilization in the Nurses’ Health Study (25). If having a mammogram were also related to the probability that a woman with subclinical breast cancer would be diagnosed with breast cancer during the study period, screening would confound the association between factors related to screening history and breast cancer risk. This bias can be accounted for in the analysis through adjustment, as with any type of confounding bias; however, this requires collection of information on screening history, which (as noted above) is difficult. Adjustment for screening history in the Nurses’ Health Study had a small impact on relative risk estimates for most risk factors; however, it fully accounted for an association between current smoking and a lower breast cancer risk observed in that study before adjustment (25). As indicated in Joffe’s commentary (21), controlling for time since last screening would be preferable to controlling for having had screening or not, since the effect of screening depends on whether the screen occurred during the detectable preclinical phase of the disease, which is hard to define. Screening bias can also occur when the exposure of interest is related to the performance of screening, so that the probability of cancer detection varies by exposure. This potential bias is of particular concern when detection of cancers that would not have been clinically relevant (i.e., “overdiagnosis”) by screening is substantial, as in the case of PSA screening for prostate cancer.

A relationship between exposure and screening sensitivity could also lead to apparent effect modification by stage at diagnosis, as described above for obesity and prostate cancer. Indeed, obese men have lower PSA levels and larger prostate glands, both factors leading to a lower sensitivity of screening by either PSA or digital rectal examination, respectively (26). Therefore, in screened populations, prostate cancer in obese men would be more likely to progress and to be diagnosed at an aggressive stage (9). This would lead to the observed dual association of obesity with nonaggressive and aggressive prostate cancer and is one of the explanations posed by Fowke et al. (18) for the discrepant findings between their studies and US studies for smoking, obesity, and alcohol. Another example is the potential influence of mammography screening on the observed associations between breast cancer and obesity, particularly after menopause, when screening is more common. Obese women have lower mammographic breast...
density than leaner women, which results in an increased sensitivity of mammographic screening and thus a higher probability of being diagnosed with a less aggressive, screen-detected type of breast cancer than a more aggressive interval cancer, as was recently shown in a Swedish study (27). In contrast to obesity, menopausal hormone therapy increases breast density, resulting in decreases in the sensitivity of mammography. Menopausal hormone therapy has also been more strongly related to the risk of lobular tumors than the risk of ductal tumors (28), which are harder to detect by mammographic screening because of their scattered growth pattern. This could explain a stronger association between menopausal hormone therapy and interval breast cancers as compared with screen-detected breast cancers (28, 29). In the presence of effect modification by mode of detection, the overall association will vary across populations, depending on how common screening is in the population. Therefore, analyses accounting for screening and mode of detection are critical to investigate this potential bias. This again requires detailed information on screening.

Screening can act as an intermediate variable between exposure and disease. For instance, the increased sensitivity of mammographic screening in obese women caused by a lower breast density can be thought as a mediator of the relationship between obesity and breast cancer risk in postmenopausal women. The decreased sensitivity of breast palpation for tumor detection in obese women with larger breasts could also mediate the lower risk of breast cancer in premenopausal obese women. As Joffe discussed (21), the “overall” effect of the exposure, including both “indirect” (i.e., mediated by screening) and “direct” (i.e., mediated by biological mechanisms) effects, as well as the indirect and direct effects themselves, could be of interest. For instance, for public health purposes the overall effect of exposure could be the best measure of the impact of an exposure on disease burden in a particular population with a given screening pattern (21). On the other hand, estimation of direct effects would be of interest in order to evaluate the biological effects of an exposure on disease. Separating direct and indirect effects is difficult, however, and needs to be approached with caution (30, 31).

In summary, cancer screening can have multiple strong influences on the estimates of association in epidemiologic studies, as well as on studies of the potential impact of public health interventions. The intractability of the etiology of certain cancers, including prostate and thyroid cancer, may be related to screening. It is critical, therefore, that investigators conducting epidemiologic studies of cancers with population-based screening programs or widespread screening consider carefully the impact of screening in the analysis and interpretation of results. This requires epidemiologists to collect high-quality data on screening practices and modes of detection if screening occurs in the study population. Studies of primarily or fully unscreened populations, such as those of Fowke et al. (18), can be useful to estimate the direct effects of exposures on disease that are not mediated or confounded by screening. Studies of populations without widespread screening that nevertheless collect high-quality information on screening histories might be the best design for advancing our understanding of the etiology of cancers that can be detected by screening.

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REFERENCES


