Cancer Progress and Priorities: Prostate Cancer

Kevin H. Kensler and Timothy R. Rebbeck

Background
Prostate cancer is the second most common cancer globally among men, although incidence and mortality rates vary greatly between countries and there are large disparities in prostate cancer incidence and mortality within countries. Despite the high burden of this disease, epidemiologic studies have identified few consensus risk factors for total prostate cancer: age, race, family history, and genetic risk loci. High-grade prostatic intraepithelial neoplasia (HGPIN) is likely a precursor lesion associated with invasive prostate cancer, although the relationship of HGPIN to prostate cancer is complex and remains incompletely understood (1). However, increasing focus on prostate cancer subtypes in epidemiologic research could yield additional insights into prostate cancer etiology and progression that may lead to identification of further consensus risk factors.

Descriptive Epidemiology
An estimated 1.3 million cases of prostate cancer were diagnosed in 2018 making prostate cancer the second most common cancer among men globally (2). There is approximately 25-fold variability in incidence rates, with the highest incidence in western and northern Europe, North America, and Australia/New Zealand, intermediate incidence in eastern Europe, South America, southern Africa, and western Asia, and the lowest incidence in southern and eastern Asia, and the rest of Africa (Fig. 1). Some of this heterogeneity can be attributed to variable use of prostate-specific antigen (PSA) testing across countries. Patterns of prostate cancer mortality differ greatly from those for incidence, with the highest mortality rates observed in sub-Saharan Africa, the Caribbean, and South America. Mortality rates are intermediate in Europe, North and Central America, and Australia/New Zealand, and lowest in Asia (Fig. 2). Estimated lifetime risk is estimated to be 6% globally, but ranges from 2% in countries with a low/intermediate sociodemographic index to 14% in countries with a high sociodemographic index (3).

Prostate cancer is the most commonly diagnosed cancer among men in the United States (excluding non-melanoma skin cancer) with an annual age-standardized incidence rate of 112.6 per 100,000, as estimated by the Surveillance, Epidemiology, and End Results Program (SEER) between 2011 and 2015 (4). Lifetime risk of prostate cancer is estimated to be 11.2% for U.S. males. Prostate cancer is rarely diagnosed before age 45, although incidence steadily rises from age 45 through age 70, and then declines after age 70 (Fig. 3). The median age of diagnosis is 66 years in the United States. As shown in Fig. 4, incidence rates in the United States approximately doubled from the late 1980s into the early 1990s with the introduction of PSA testing, before stabilizing between 1995 and 2005, and falling since that time.

The estimated age-standardized prostate cancer mortality rate is 19.5 per 100,000 in the United States. In part, due to the effects of widespread PSA testing, 5-year survival for prostate cancer is 98% overall, although varies substantially by tumor stage, with 100% 5-year survival for localized (78% of cases) and regional (12%) staged cancers, and 30% 5-year survival for metastatic cancers (5%). Mortality rates steadily grew through the mid-1990s but have declined by 3% to 4% annually since then (Fig. 4), likely driven, in part, by both early detection and advances in treatment (5, 6). Five-year survival has increased from 66% in 1975 to its current level.

Following the U.S. Preventive Services Task Force (USPSTF) Grade D recommendation against PSA testing in 2012, there was a reduction in PSA testing across age groups and decrease in the incidence of early-stage prostate cancer (7–10). However, rates of advanced and metastatic disease appear to be increasing following this recommendation (10, 11). The USPSTF recommendation for men ages 55 to 69 was reclassified to Grade C (recommendation to selectively offer testing) in 2018, and it is too early to tell what the long-term effects of changes in PSA testing patterns will have on prostate cancer mortality in the United States.

Disparities
There are substantial differences in prostate cancer rates across racial/ethnic groups in the United States that represent important disparities in prostate cancer risk and outcomes (12). At almost every point along the prostate cancer continuum and for most every age group, prostate cancer is more common in African American men than White men. Autopsy studies reveal higher prevalence of latent HGPIN and prostate tumors among African American men relative to White and Asian men (13, 14). The disparity is apparent even in latent prostate cancer, which is detected in autopsies in 50% of men of Asian descent ages 90 to 99, 50% of men of European descent ages 80 to 89, and 50% of men of African descent men ages 60 to 69 (14).

There is a similar disparity in the prevalence of cancers detected upon initial screening: The rate of prostate cancer detection in African American men is consistently higher than in White men in the United States (15–19). In addition, the prevalence of screen-detected cancers in Ghanaian men is higher than that reported in any African American population, suggesting the rates of prostate cancer in Africa may equal or exceed those in African Americans (20), and that elevated prostate cancer rates are a phenomenon of men of African ancestry throughout the African diaspora.

It is also well known that population-based prostate cancer incidence and mortality vary substantially by race/ethnicity. SEER 18 data from 2011 to 2015 estimated that age-adjusted prostate cancer incidence in African Americans (178.3 per 100,000 men) is substantially greater than in non-Hispanic Whites (105.7 per 100,000 men). This represents 69% greater incidence in African American versus non-Hispanic White men. Prostate cancer mortality statistics show even

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Cancer Epidemiol Biomarkers Prev 2020;29:267-77
doi: 10.1158/1055-9965.EPI-19-0412
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greater disparities: Mortality in African American men is 39.9 per 100,000 compared with 18.2 per 100,000 in non-Hispanic Whites, a 2.2-fold higher rate. This is the largest African American:White disparity in cancer mortality of any tumor site in U.S. men or women. Despite the magnitude of these prostate cancer racial disparities, they represent an improvement from the disparities that existed only a few years ago. As shown in Fig. 4, the disparity in prostate cancer mortality grew during the period from the mid-1980s to approximately 2005, during which PSA testing became widespread. Since 2010, the absolute disparity in mortality rates between African American and non-Hispanic Whites has declined, though a significant disparity persists. The disparity in prostate cancer mortality is age-dependent, with greatest disparities in prostate cancer mortality occurring in men under age 75.

Figure 1.

Figure 2.
These data suggest that the disparity may have a biological component, as the disparity is evident even before cancer is usually clinically detected. However, the African American:White disparity increases in magnitude in clinically detected disease and mortality, suggesting that factors related to exposure, behavior, or access to care are also important factors in prostate cancer disparities. While it is clear that there is substantial disparity at all phases of the prostate cancer continuum, data suggest that there is racial/ethnic disparity in certain prostate cancer-related parameters but not others. A meta-analysis by Evans and colleagues (2008) reported no disparity in overall survival by race, but did find evidence for a difference in prostate cancer-specific survival and biochemical (PSA) failure that persisted after adjustment for comorbidities, PSA testing, or access to free health care (21). Similarly, it has been suggested that racial differences in prostate cancer mortality diminish or disappear in certain patient subgroups or if treatment is equalized among all patients (22, 23). Studies within the supposedly equal-access Veterans Affairs (VA) healthcare system have found no differences in prostate cancer outcomes or even better outcomes for African American veterans (24–27). However, not all studies have been clearly able to demonstrate that equal access and treatment leads to equal outcome. An analysis of SEER-Medicare data from patients with clinically localized prostate cancer found that mortality rates varied within screening, treatment, and racial groups (28). The data available to date do not completely resolve the question whether racial disparities could be eliminated if treatment were equalized among all cases.

Finally, most studies of prostate cancer disparities are based on self-identified race or ethnicity classifications. However, genomically determined ancestry is also finding a place in the study of disparities. The use of genomic ancestry may be able to define groups differently than self-identified race or ethnicity and thus may be a useful adjunct in our understanding of the biological and social determinants of prostate cancer risk, outcomes, and disparities.

**Etiologic Heterogeneity**

Prostate cancer is clinically heterogeneous, and while a fraction of tumors is phenotypically aggressive, the majority are indolent. Advanced cancers are variably defined and can refer to higher grade or stage, metastatic, or lethal prostate cancer. Several potential prostate cancer risk factors, such as height, demonstrate stronger associations with the incidence of aggressive disease, while others are solely associated with this phenotype, such as obesity (29, 30).

Genomic profiling of prostate tumors in The Cancer Genome Atlas revealed seven molecular subtypes of cancers defined by the presence of ETS fusions or mutations in SPOP, FOXA1, and IDH1 (31). To date, this taxonomy of prostate cancer has had limited application in etiologic epidemiologic research. A notable exception is the prostate...
cancer subtype defined by presence of the TMPRSS2-ERG fusion, a somatic gene fusion in which the ERG oncogene becomes androgen-regulated (32, 33). Select risk factors, including obesity and height, among others, have been found to be associated with the incidence of TMPRSS2-ERG–positive disease (34–38). There is substantial intratumoral genomic heterogeneity within multifocal prostate tumors, representing an important consideration when evaluating molecular classifications of prostate cancers (39–41).

## Risk Factors

The proportion of prostate cancer that can be explained by known risk factors is one of the lowest of all common cancers (42). The heritability of prostate cancer is among the highest across cancer sites—estimates from twin studies range from 42% to 57% (43, 44). However, migrant studies support a substantial role of lifestyle and environmental factors in prostate cancer etiology (45–47). As summarized in Table 1, the only clear and consistent risk factors identified to date for total prostate cancer are age, race, and family history, with height as a probable risk factor. There is a dearth of modifiable risk factors with convincing evidence for an association with prostate cancer risk (48). Some factors, including obesity, have probable associations with prostate cancer subtypes, such as advanced prostate cancer (often defined as high grade or stage) or lethal prostate cancer. The effects of widespread PSA testing further complicate the identification of risk factors for total or aggressive prostate cancer.

### Table 1. Summary of factors with strong evidence for association with total or advanced prostate cancer risk.

<table>
<thead>
<tr>
<th>Factor</th>
<th>Est. RR</th>
<th>Comments</th>
<th>Refs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total prostate cancer</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>1.11</td>
<td>Lifetime risk among U.S. males</td>
<td>4</td>
</tr>
<tr>
<td>African descent</td>
<td>1.7</td>
<td>RR relative to non-Hispanic Whites; Asian/Pacific Islanders have lower risk</td>
<td>4</td>
</tr>
<tr>
<td>Family history</td>
<td>2.0</td>
<td>RR for first-degree relative</td>
<td>117–119</td>
</tr>
<tr>
<td>Height</td>
<td>1.04</td>
<td>RR per 5-cm increase</td>
<td>53, 63</td>
</tr>
<tr>
<td>Advanced prostate cancer</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Obesity</td>
<td>1.08</td>
<td>RR per 5-kg/m² increase in body mass index</td>
<td>53–57</td>
</tr>
</tbody>
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Abbreviation: RR, relative risk.
PSA-based screening can lead to overdiagnosis of otherwise indolent tumors, and can confer a 3- to 10-year lead time for detection of aggressive tumors, influencing the age and stage at their diagnosis (49). Moreover, undergoing PSA testing is correlated with engaging in healthful behaviors and healthcare utilization, and is a strong predictor of prostate cancer incidence; thus, it is a major potential source of bias in epidemiologic studies of prostate cancer risk (50–52). Further understanding of prostate cancer heterogeneity and consideration of detection biases may yield additional insights into prostate cancer etiology and progression.

**Obesity**

Body fatness is not associated with total prostate cancer, although the totality of evidence suggests that increased body fatness is associated with a higher risk of advanced prostate cancer. The 2014 World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) Continuing Update Project (CUP) meta-analysis reported an 8% increase in risk of advanced disease per 5-kg/m² increase in body mass index [BMI; relative risk (RR) = 1.08, 95% confidence interval (CI), 1.04–1.12; ref. 53], in line with findings from other recent meta-analyses (54–56). An umbrella review of adiposity and cancer characterized the evidence for an association between BMI and risk of advanced prostate cancer as weak (57). Alternative measures of adiposity including waist circumference and waist-to-hip ratio are also associated with risk of advanced disease (53). Multiple mechanisms have been proposed for how obesity may contribute to the incidence of advanced prostate cancer, including increased levels of circulating growth factors, induction of chronic inflammation, and reduction of circulating androgen levels (58–60). The association with adiposity is further complicated by potential detection biases, as obese men tend to have lower PSA levels, which may delay diagnosis or make them less likely to undergo biopsy (61, 62).

**Adult height**

Epidemiologic evidence generally supports an association between greater adult height and higher risk of prostate cancer. The 2014 WCRF/AICR meta-analysis found that each 5-cm increase in adult attained height was associated with a 4% increase in total prostate cancer risk (RR = 1.04; 95% CI, 1.03–1.05; ref. 53) This finding was consistent when examining risk of nonadvanced, advanced, and lethal prostate cancer. Adult height is a product of early life growth rate, which is influenced by levels of hormones and growth factors, including IGF (63–65).

**Alcohol**

A 2016 meta-analysis of 27 studies found an 18% increase in prostate cancer morbidty and mortality comparing higher volume drinkers (65+ g/day) to abstainers (RR = 1.18; 95% CI, 1.10–1.27), with a significant dose–response relationship (66). However, prior meta-analyses found no significant association and the WCRF/AICR found no conclusive evidence for an association (53, 67, 68). In addition, several prospective studies have reported inverse associations between alcohol consumption and the risk of advanced or lethal prostate cancer (69–71).

**Smoking**

While smoking has not been linked to prostate cancer incidence, there is suggestive evidence that smoking is associated with higher prostate cancer mortality, with an estimated 15% to 25% higher rate of prostate cancer–related death among current smokers (72–74). Add-
circulating lycopene levels and aggressive, advanced, and lethal prostate cancer (92).

There is no evidence for an association between beta-carotene consumption or supplementation and total or advanced prostate cancer risk (53).

Consumption of 6 cups of coffee per day (versus no consumption) was associated with 60% lower risk of lethal prostate cancer in the Health Professionals Follow-Up Study (94). A subsequent meta-analysis supported this finding, concluding that coffee consumption is associated with approximately 10% decrease (per each 3 cups/day) in the incidence of high-grade and fatal prostate cancer, while there is no evidence for an association with total disease (95).

**Statins**

There is growing evidence that use of statins, a class of lipid-lowering medications, may be associated with lower prostate cancer risk, particularly for advanced disease. A 2012 meta-analysis of 27 observational studies reported relative risks of 0.93 (95% CI, 0.87–0.99) and 0.80 (95% CI, 0.70–0.90) for total and advanced prostate cancer, respectively (96). However, a subsequent meta-analysis did not observe significant associations within any particular type of statin (97). Statin use postdiagnosis is also potentially associated with better survival (98, 99).

**Diabetes mellitus**

A 2015 meta-analysis of 56 studies found that men with type II diabetes experienced 12% lower risk of total prostate cancer (RR = 0.88; 95% CI, 0.82–0.93), with mixed findings reported in subsequent large studies (100–102). The evidence remains inconclusive for this association, however, as there is no clear association between glycemic biomarkers and prostate cancer risk (103–106), and metformin use is not associated with prostate cancer risk (107, 108). The evidence also does not support an association between diabetes and risk of advanced or aggressive prostate cancer (102, 109, 110). Preexisting diabetes was associated with 29% higher prostate cancer mortality in a recent meta-analysis (111).

**Other hypothesized risk factors**

The body of evidence is inconclusive for potential associations between vasectomy (112), ejaculation frequency (113), exposure to Agent Orange (114), sexually transmitted infections including Trichomonas vaginalis (115), or prostatitis (116) and prostate cancer risk.

**Familial and genetic factors**

In contrast to the limited or inconsistent evidence for epidemiologic risk factors, there is strong evidence that prostate cancer etiology, aggressiveness, and progression are influenced by genetics. Family history of prostate cancer in a father or brother is associated with approximately 2-fold higher risk of prostate cancer (117–119). Prostate cancer has the highest heritability of any common cancer. However, few hereditary prostate cancer syndromes have been reported, and the genes that may explain these have not been confirmed. Family-based linkage studies of hereditary prostate cancer have identified high penetrance genes including HPC1 (1q24–25; refs. 120–122), PCA3 (1q42–43; refs. 122–124), HPCX (Xq27–28; ref. 125), CAPB (1q36; refs. 122, 124), HPC20 (20q13; ref. 126), HOXB13 (127, 128), and others (122, 127). However, these have not been translated into clinical practice either because the responsible gene or pathogenic mutations have not been identified, or the associations have not been validated to warrant application in prostate cancer risk assessment (129). In contrast, inherited mutations in BRCA2 are being used in risk assessment (129). Presence of a BRCA2 mutation may also be used in prostate cancer screening decision-making as well as in both early-stage and advanced/metastatic disease management. In addition, HOXB13 and DNA mismatch repair gene mutations identified in Lynch syndrome are clearly associated with prostate cancer and represent candidates for clinical genetic testing and risk assessment (129). Importantly, the availability of PARP inhibitors in patients with BRCA2 mutations and pembrolizumab in patients with mismatch repair mutations provide novel therapeutic opportunities and a strong motivation for genetic testing in certain men with prostate cancer (130, 131).

A large number of low to moderate penetrance loci have been associated with prostate cancer in genome-wide association studies. At least 170 common variants associated with prostate cancer have been reported (132) explaining about 32% of familial relative risk for prostate cancer. Examples of candidate genes that have been identified using large gene panels or GWAS include the androgen receptor (AR; ref. 133), kalikrein genes (e.g., KLK3, that encodes prostate specific antigen; refs. 134–136), telomere-related genes (TERT, TET; refs. 133, 137), and loci containing carcinogen metabolism (UGT1A8, CYP21A2; ref. 138), miRNAs (138), or matrix metalloproteinase genes (138). Despite the very high risk and unfavorable prostate cancer outcomes in African American men, most associations reported in European or Asian descent populations have not been replicated in African descent populations (139), and few novel GWAS loci have been identified in African American or African populations (140). Multiple independent genomic associations at 8q24 have been validated as prostate cancer susceptibility loci in multiple races, including African Americans (141). Although no gene has been designated to be responsible for this cancer risk, regulation of the downstream gene MYC or regulation by IncRNAs has been reported (142). Although polygenic risk scores (PRS) have been developed that include these low penetrance variants as well as other clinical variables, the additional predictive value of these PRS add to existing clinical risk predictors is small, particularly for predicting aggressive prostate cancer (143, 144). Thus, the clinical value of these tests has not led to clearly actionable preventive or therapeutic strategies that have changed clinical practice (129). Nonetheless, the information included in PRS is being implemented in some clinical settings for risk assessment and clinical management strategies. Additional research will be needed to fully understand the optimal application of this information and its clinical impact in optimizing early detection and treatment.

**Risk Prediction Models**

Numerous models for prediction of prostate cancer risk have been developed, including models developed in the Prostate Cancer Prevention Trial (PCPT) and European Randomized Study of Screening for Prostate Cancer (ERSPC), although none are currently widely implemented (145–150). These models primarily are used to predict the presence of prostate cancer among men referred for biopsy and have AUCs ranging from 0.69 to 0.77. Given the dearth of strong prostate cancer risk factors, these models predominantly include age, race, family history, PSA levels and velocity, result of digital rectal exam, and prior biopsy.

**Future Trends**

Projections of prostate cancer incidence rates suggest a 0% to 2% annual percent decrease through 2030 in the United States (151, 152). However, despite the stability of risk factor profiles in the United States, the development of new risk prediction models and the refinement of existing ones is necessary to keep pace with the changing nature of prostate cancer risk factors.
States, with population aging, counts of prostate cancer diagnoses are projected to increase, with the greatest growth among African American men (153). Incidence of metastatic disease is expected to increase by 1% annually with greater increases for men under age 70 (11). Mortality rates are anticipated to decrease by approximately 3% annually (151, 152).

Prevention
Primary prevention efforts for prostate cancer have principally focused on diet and lifestyle modification, although three large prostate cancer prevention trials have been conducted. The SELECT trial found that vitamin E supplementation alone increased prostate cancer risk by 17% among 35,333 U.S. males, but selenium did not affect risk (153). Two addition randomized trials evaluated prostate cancer prevention through treatment with 5α-reductase inhibitors. In the initial report of the PCPT, finasteride treatment reduced total prostate cancer incidence by 25%, but there was 27% relative increase in the incidence of high-grade disease in the finasteride group (154). The REDUCE trial yielded similar results with dutasteride treatment reducing total prostate cancer incidence by 23%, but associated with a small suggestive increase in the incidence of high-grade disease (155). In light of these results, the FDA added a warning to 5α-reductase inhibitor labels. The effect of finasteride on high-grade prostate cancer incidence attenuated in extended follow-up of the PCPT (RR = 1.17; 95% CI, 1.00–1.37; ref. 156). In addition, there was no increase in the risk of prostate cancer mortality, nor worse survival following a diagnosis of prostate cancer in the finasteride arm, suggesting that the observed higher incidence of high-grade disease was likely an artifact, potentially arising from detection biases resulting from the drug's effects on prostate gland volume (156–159).

Screening
Serum PSA testing has been commonly used for the early detection of prostate cancer since the late 1980s, although its widespread use is fraught with controversy (160). Applying a cutoff of 4.0 ng/mL, an American Cancer Society systematic review found that the sensitivity of the PSA test was 22% (51% for high-grade tumors), while the specificity was 91% among men at average prostate cancer risk (161). Hence, widespread prostate cancer screening using PSA can lead to overdiagnosis and overtreatment while still failing to detect many advanced tumors. Accordingly, the United States Preventive Services Task Force (USPSTF) currently recommends shared decision-making regarding testing between men ages 55 to 69 and their physician, while PSA testing is not recommended for men ages 70 or above (162). The USPSTF did not give specific recommendations but suggested that screening at younger ages may be beneficial for African American men and men with a family history of prostate cancer. Three large randomized clinical trials have been conducted to evaluate the efficacy of PSA testing on the reduction of prostate cancer mortality: the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial (163), the ERSPC (164), and the Cluster Randomized Trial of PSA Testing for Prostate Cancer (CAP; ref. 165). Combined, in primary analyses, these trials show that PSA testing leads to a higher incidence of prostate cancer, but the trials had variable findings regarding prostate cancer mortality; ERSPC found a significant 21% reduction in mortality, but no mortality benefit was observed in PLCO nor in early reports from CAP (162, 166). However, PLCO was limited by contamination of the control arm, there was low adherence in the CAP intervention, and there was substantial heterogeneity in findings across study sites in ERSPC. Microsimulation models show that upon adjustment for differences in trial implementation, design, adherence, and practice settings, results from PLCO and ERSPC were both compatible with a 25% to 30% reduction in prostate cancer mortality (167). Prostate cancer screening may be improved through implementation of baseline PSA-stratified screening regimens, incorporation of other serum kallikrein markers such as free PSA, the 4k Score, and the Prostate Health Index, or use of urinary markers such as PCA3 or TMPRSS2: ERG (168–170). The increasing use of active surveillance for management of low-risk prostate cancers may reduce the potential for overtreatment associated with PSA-based screening (171). A major need in the early detection of prostate cancer is to identify risk-stratified approaches that can be implemented in specific groups of men and to identify appropriate actions based on a positive screening test to avoid overtreatment and undertreatment. New technologies such as Prostate-Specific Membrane Antigen Positron Emission Tomography (PSMA-PET) may aid in the staging of localized, advanced, and metastatic disease, and guide the selection of therapeutic intervention, while multiparametric magnetic resonance imaging (mpMRI) could improve diagnosis of prostate cancer (172, 173).

Future Directions
A critical challenge in prostate cancer research will be to further our understanding of tumor heterogeneity. Epidemiologic research should focus on the stratification of indolent and aggressive tumors, and further elucidate the etiology of the latter. Consideration of tumor molecular subtypes may lead to enhanced risk stratification as well as provide clearer evidence surrounding potential prostate cancer risk factors. In addition, careful consideration of detection biases in the study design and conduct of epidemiologic studies will be crucial for strengthening evidence about potential drivers of prostate cancer incidence and progression. Finally, further study of the social, environmental, and biologic drivers of prostate cancer disparities will be vital to ameliorate the higher burden of prostate cancer among African American men.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

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Writing, review, and/or revision of the manuscript: K.H. Kensler, T.R. Rebbeck
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): K.H. Kensler, T.R. Rebbeck
Study supervision: K.H. Kensler, T.R. Rebbeck

Acknowledgments
This work was supported in part by NIH grants P20CA233255 (to T.R. Rebbeck), U01CA184374 (to T.R. Rebbeck), and F32CA243285 (to K.H. Kensler).

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Received April 12, 2019; revised June 10, 2019; accepted December 3, 2019, published first February 5, 2020.
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