

Our finding that treatment interruption increases risk for renal progression is supported by another recent investigation in SMART (1, 2). Stored samples were used to measure cystatin C, a marker of renal function, during the first year of the study but before the protocol change. Cystatin C levels increased significantly in the treatment interruption group compared with those in patients randomly assigned to receive continuous antiretroviral therapy (2).

Ultimately, we think that the risk and benefits of antiretroviral treatment are best assessed in a randomized trial of early therapy instead of a treatment interruption study, such as SMART. A trial called START (Strategic Timing of AntiRetroviral Therapy) is scheduled to begin next year and is designed to investigate the risks and benefits of early antiretroviral treatment on clinical outcomes, including renal disease, and other serious non-AIDS conditions, such as cardiovascular disease, liver disease, and malignant conditions.

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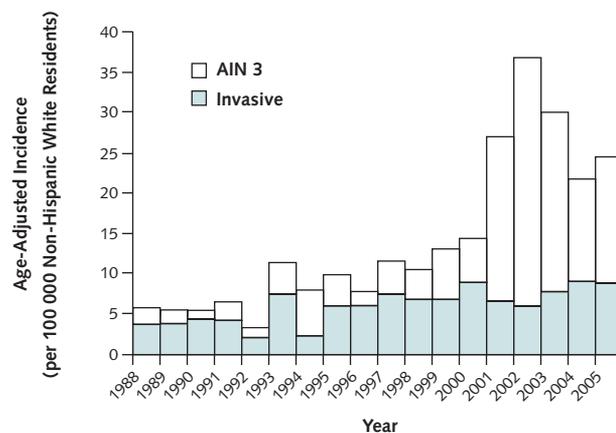
Is There a Proven Link Between Anal Cancer Screening and Reduced Morbidity or Mortality?

TO THE EDITOR: We read with interest the study by Chin-Hong and colleagues (1) comparing techniques to detect anal intraepithelial neoplasia (AIN) among men who have sex with men. A more pressing question is whether sufficient evidence of effectiveness, in terms of reducing anal cancer morbidity or mortality, exists to support anal cancer screening. It does not.

No prospective studies, including randomized, controlled trials, have assessed the effectiveness of anal cancer screening (2). Instead, screening proponents have cited indirect evidence, including analogy to cervical cancer screening, to advocate for routine screening among certain populations, such as men who have sex with men (2, 3). As screening proponents rightly note, randomized, controlled trials of Papanicolaou smears for cervical cancer prevention were never conducted; evidence of effectiveness is based on data correlating increased screening and decreased cancer incidence (2).

In San Francisco, anal cancer screening has been offered at health care provider practices since the late 1990s. Reporting of invasive anal cancer and AIN 3 (sometimes called *in situ carcinoma*) is legally mandated in California. We used data from the California Cancer Registry to examine trends in AIN 3 lesions and invasive anal squamous cell cancer reported among non-Hispanic white male residents of San Francisco County during 1988 to 2005 (4). As shown in the **Figure**, the age-adjusted incidence of invasive anal squamous cell carcinoma was

Figure. Age-adjusted incidence of AIN 3 and invasive squamous cell carcinoma of the anus* among non-Hispanic white male residents of San Francisco County, 1988–2005.



AIN 3 = anal intraepithelial neoplasia 3 (including *in situ carcinoma*).
* Anal cancer was defined by using International Classification of Diseases, Oncology, 3rd edition, site codes C210–C212 and C218; AIN 3 by histology code 8077; *in situ* squamous cell carcinoma by histology codes 8010, 8051–8078, 8081; and invasive squamous cell carcinoma by histology codes 8010, 8051–8076, and 8078.

stable from the mid-1990s, whereas the incidence of AIN 3 substantially increased during 2001 to 2005 compared with previous years. Anal cancer mortality rates are not reliable for this population because fewer than 5 deaths per year occur from anal cancer.

These data demonstrate that screening was associated with increased detection of AIN 3 lesions but not decreased incidence of invasive cancer. Biological or anatomical differences between the anal canal and the cervix might render anal cancer screening less effective than cervical cancer screening. Negative consequences of anal cancer screening, including anxiety, fear, and depression after receiving abnormal results, and procedural complications (5) might also affect the cost–benefit ratio unfavorably.

This ecological analysis does not prove that screening is ineffective. Invasive cancer incidence might have increased without screening; insufficient numbers or types of patients might have been screened; insufficient time might have elapsed to detect a reduction in incidence; or ecological analysis might lack sensitivity to detect incidence changes among specific populations at high risk. Only a randomized, controlled trial involving numerous participants can—and, we hope, ultimately will—provide conclusive effectiveness data (2). Meanwhile, given the costs and consequences of screening, sufficient evidence does not exist to support routine anal cancer screening for men who have sex with men.

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IN RESPONSE: We appreciate Dr. Katz and colleagues' comments and their efforts to draw attention to this important issue. They are correct: The incidence of anal cancer is not decreasing. Indeed, published data show that the incidence of invasive anal cancer is increasing in men and women worldwide. In a recent review of 39 population-based registries in the United States between 1998 and 2003, invasive anal cancer increased 2.6% per year on average (1). Using California Cancer Registry data, Cress and Holly (2) used age-adjusted incidence rates from 1973 to 1999 (beginning before the period analyzed by Dr. Katz and colleagues) to show that, among Hispanic and non-Hispanic white men in San Francisco County, age-adjusted rates of invasive anal cancer tripled from 1.5 per 100 000 persons in 1973 to 1978 to 4.5 per 100 000 persons in 1991 to 1995. Dr. Katz and colleagues' data are consistent with

Cress and Holly's data for the period they reviewed (beginning in 1988) and show a further increase in incidence of invasive anal cancer to almost 10 per 100 000 persons by 2004 to 2005.

The increase in anal cancer incidence is even more pronounced in high-risk populations, such as HIV-positive persons, despite the widespread use of highly active antiretroviral therapy (HAART). Matching data from the San Francisco AIDS registry and the California Cancer Registry, Hessol and colleagues (3) demonstrated that after adjustment for age at AIDS diagnosis, race, risk group, sex, calendar year, HAART use, and HAART era, the risk for anal cancer was significantly higher in the HAART era (relative hazard, 2.74). Given that HAART was not associated with a decline in the incidence of invasive anal cancer, even with the limited number of people screened and treated, it is possible—as Dr. Katz and colleagues postulate—that the rates of invasive anal cancer could have been even higher if there was no screening for and treatment of AIN 3 in this population.

However, this is speculative and, as Dr. Katz and colleagues state, “This ecological analysis does not prove that screening is ineffective.” One could use ecological data to show a population-level impact of screening on reducing cancer incidence, but this kind of analysis will be less sensitive to demonstrate a true effect if there really was one, unless screening is relatively common in the population at highest risk for disease. Unfortunately, this is not the case. In our community-based sample of men who have sex with men in San Francisco County, a population for which we have advocated systematic screening, only 7% previously underwent anal cancer screening.

Overall, the evidence points to an increase in invasive anal cancer in men and women in the general population. In the absence of widespread systematic anal cancer screening (even in San Francisco), it is difficult to use population-based cancer registry data to discount the benefit of anal cancer screening. We strongly agree that more studies are needed to determine the effect of screening on a population level, similar to what was done with cervical cancer screening. In this case, we would focus on the highest-risk group—those with HIV infection—to most quickly determine the impact of screening. Studies are also needed to determine the acceptability and tolerability of treatment of AIN. If the prophylactic quadrivalent human papillomavirus vaccine is approved for men by the U.S. Food and Drug Administration, additional studies will be needed to determine the effectiveness of the vaccine on anal cancer and associated precursor lesions. In the interim, given the high prevalence of anal human papillomavirus infection and potential anal cancer precursor lesions among men who have sex with men and among HIV-positive men and women, we believe that sufficient evidence already exists for screening populations at high risk for anal cancer. We believe that investment in capacity building is most needed, with continued training of personnel to provide education to patients and providers and to conduct high-resolution anoscopy and treatment.

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Is There a Connection Between High Educational Debt and Suicidal Ideation Among Medical Students?

TO THE EDITOR: We commend Dyrbye and colleagues (1) on their important work linking burnout to suicidal ideation among medical students. To assist educators in addressing this issue, we wondered if there were any observable differences between students who reported “chronic burnout” and those who “recovered from burnout.” For example, do more resilient students have marital support or lower educational debt? We also found it especially noteworthy that higher levels of educational debt were associated with increased suicidal ideation in this study (1). It is plausible that high educational debt may act as a chronic stressor, contributing to persistent burnout in certain students. In support of this hypothesis, another recent study observed an association between anticipated debt and perceived financial stress, suggesting that anxieties about future debt also contribute to student stress (2). This highlights the need to consider how to prepare students with higher debt to address this mental stressor.

In addition to these factors, it is also important to understand how much of recovery from burnout is a natural part of completing the stressful, and predominantly clinical, third year. Students in their third year had increased suicidal ideation compared with those in other years (1). In an insightful review (3), 3 of the authors of this study discuss the myriad causes leading to medical student moral distress. During the clinical years, however, moral or ethical distress may play an especially subtle but substantial role in student well-being (4). Using the cardiac stress test as an analogy, clinical clerkships may inadvertently act as an ethical stress test that risk-stratifies those students who are particularly susceptible to poor resilience, cynicism, and burnout as future resident physicians. Given the new accreditation requirement to “periodically assess the learning environment” at U.S. medical schools (5), the extent of burnout and resilience among students might serve as a useful proxy to “risk-stratify” even medical schools—particularly those schools with learning environments that are at high risk for eroding student well-being and promoting burnout.

This study therefore emphasizes the importance of further research on the specific contributions of financial and moral stress in promoting burnout. Through more work like this, medical educators will be better able to target students burdened with high educational debt or those showing poor resiliency from burnout. Early interventions are particularly important before high-risk students become burned-out residents responsible for patient care.

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IN RESPONSE: We thank Drs. Yoon and Arora for their thoughtful letter. We agree that debt is a substantial source of stress for today's medical student. As reported, students with more than \$100 000 of educational debt were 1.47 times more likely to have suicidal ideation during the previous year than students with less than \$50 000 in reported debt on univariate analysis. Despite this association, debt was not independently associated with suicidal ideation during the previous year on multivariate analysis. The amount of debt that students reported was associated with other factors, such as age, relationship status, parental status, year in school, and burnout (all $P < 0.02$). This observation suggests that the relationship between debt and suicidal ideation may be mediated through interactions between debt and burnout or other characteristics rather than directly. This possibility is worthy of further study. We also believe it is important to identify what personal and professional characteristics are associated with recovery from burnout. We hope this information can inform efforts to assist struggling students. We are in the process of performing a comprehensive formal analysis of this aspect, which will be the subject of a future article.

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Is Too Much Intervention Recommended in the ACP Osteoporosis Treatment Guidelines?

TO THE EDITOR: We reviewed the American College of Physicians (ACP) guidelines on the treatment of low bone density or osteoporosis to prevent fractures (1). Strengths of these guidelines include