

Cancer Culture: Epidemics, Human Behavior, and the Dubious Search for New Risk Factors

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Epidemics appear, and often disappear without traces, when a new culture period has started; thus with leprosy, and the English sweat. The history of epidemics is therefore the history of disturbances of human culture.

Rudolph L. K. Virchow^{1(p1)}

To paraphrase Virchow, the rise of melanoma and the almost complete decline of stomach cancer clearly reflect disturbances of our human culture during the 20th century. Recent declines in lung cancer in the United States among men, first for younger age groups and then for older age groups successively over time, and among women aged 40 to 59 reflect changes in cigarette smoking.² The decline in melanoma mortality in Australia for those born after 1950 also attests to the success of population-wide prevention strategies.³ These successes support the contention that it is time to stop searching for new risk factors. Instead, we should channel far greater effort and resources into implementing our existing knowledge regarding the role of lifestyle factors that cause cancer and other major chronic diseases of the industrial and postindustrial world.

Although both genes and environment must be considered, studies of migrants clearly show that environmental factors play a dominant role in the epidemiology of melanoma, breast and colon cancer, and many other malignancies.⁴⁻⁷ Furthermore, while we can identify some new genetic markers of risk, we can classify known risk factors into those that are modifiable and those that are not (see the Web site <http://www.yourcancerrisk.harvard.edu>). Further insight into nonmodifiable risk factors (such as genes) will not necessarily translate

into public health prevention strategies.⁸ Modifiable risk factors such as smoking, diet, physical activity, weight gain, sexual practice, and use of postmenopausal hormones can be readily translated into ways to reduce the population burden of cancer.⁹ Clear strategies have been delineated for such population-wide interventions. It is time to implement them further.

Population Burden of Disease

Much of the discussion regarding population-level changes in the risk of chronic conditions is based on the understanding that disease classification uses arbitrary cutpoints, or stages, for conditions that in fact reflect a continuum. We should therefore consider, as a prevention strategy, shifting the population distribution of risk factors and the prevalence of these stages in the underlying distribution of disease.

In the case of colon cancer—its cutpoints are precancerous polyps, early invasive disease, late invasive disease, and death—estimates from the Health Professionals Follow-Up Study indicate that most men have multiple modifiable risk factors.¹⁰ In that study, only 3% of middle-aged and older men had no modifiable risk factors for colon cancer. With population-wide increases in levels of physical activity and folate intake, and with reductions in alcohol intake, adult weight gain and obesity, red meat consumption, and smoking, up to 70% of colon cancer could be avoided. For example, if the entire US population increased its level of physical activity through walking for an additional 30 minutes per week, we would reduce the burden of colon cancer by

15%.¹¹ Of course, screening offers additional cost-effective strategies for early detection of cancer and removal of precursor polyps.^{12,13} Colon cancer, the second-leading cause of cancer mortality, is highly preventable, with numerous population-wide strategies already available to reduce its incidence.

The fundamental object of epidemiology is to estimate the population average risk of disease. Risk is a population measure, not an individual measure. Epidemiology does not estimate individual levels of risk, nor does it perfectly predict individual likelihood of disease. As noted by Rose, epidemiology does not describe why an individual case of cancer arises in the population but rather the population burden of cancer.¹⁴ In his article in this issue of the Journal, Begg ignores this principle and uses the term “risk” as an individual-level variable.¹⁵ Begg’s focus on the occurrence of second primary cancers to approximate the coefficient of risk variation in the population illustrates his consideration of risk as an individual-level quantity, rather than as the aggregate-level measure that epidemiologic risk models, including those containing genetic variables, show it to be.

This high-risk approach to prevention aims to identify those most at risk of disease

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and avoid the apparent wastefulness of mass prevention strategies which are characterized by large societal benefits but little individual gain. As already noted, given that disease is a continuum, population-level changes shift the underlying risk. The melanoma prevention efforts in Australia, where incidence of the disease is the highest in the world, illustrate the benefits of this approach: there, population-wide strategies to reduce sun exposure have succeeded in reducing sunburn among youths.¹⁶ Exposure to solar radiation is accepted as the major environmental cause of melanoma^{17,18}; family history is an independent risk factor, with a typical relative risk of 2 compared with no family history.¹⁹ High risk as defined by Begg might include genetic characteristics that predispose to melanoma; however, family history is independent of the phenotypic markers of risk, which include hair, eye, and skin color, number of childhood sunburns, and mole count, and may account for less than 5% of melanoma.¹⁹ As already mentioned, studies of migrants show that age at migration to high-risk countries has a strong impact on the risk of this malignancy.¹⁷ It is clear that melanoma risk is a function of genetic and environmental factors.

Does knowledge of phenotypic risk factors change prevention messages? For melanoma, can we recommend that only a subset of the population avoid excess sun exposure? Begg infers that this is the likely answer, but the public health application is absent from his argument. Estimates by English and colleagues based on Australian data suggest that 54% of melanoma occurs in 16% of the population,²⁰ which might therefore be suitable for more intensive surveillance. However, to exclude the “low-risk” segment of the population from prevention messages or strategies would be to miss the potential for preventing 46% of cases.

In the Nurses’ Health Study, some 75% of cases arise from the 58% of the population with at least one identifiable risk factor for melanoma (more than 3 moles, red or blond hair, childhood sensitivity to sun, 10 or more serious sunburns, and first-degree family history of melanoma) (data not shown). If we limited the population for “preventive intervention” to, say, those with 3 or more risk factors, we would intervene on 9% of the population. Given that only 24% of cases arise from this group, we would have little impact on the population burden of melanoma. These estimates of the proportion of disease arising from those with epidemiologic risk factors is consistent with recent work by Wald et al. showing that risk factors are poor markers for identifying subpopulations for prevention.²¹ Hence, as Rose noted, prevention strategies must be widespread.

Compared with the high-risk approach that is tailored to each malignancy, one at a

time, population-wide strategies with benefits across multiple chronic conditions will have far greater effects on the public’s health.²² For example, increasing physical activity will also reduce the burden of type 2 diabetes, coronary heart disease, and stroke.

Population Attributable Risk

Population attributable risk (PAR) is used in numerous reports to quantify the proportion of cancer that might be avoided if the lifestyle factors contributing to cancer were removed from society. Alternative measures such as years of life lost have also been proposed, but such measures fail to quantify the potential for prevention. The PAR is not a means to understand causal mechanisms, but it can still be useful in estimating how much of disease can be avoided. It is well known that the PAR does not add up to 100%, nor should it be expected to.²³ To infer that subtracting the PAR from 100% might give the contribution of some unmeasured or yet-to-be-identified risk factor is inappropriate and wrong. The PAR can be considered the upper estimate for preventability through eliminating a given risk factor, because it does not consider the time course of disease and the interval over which the benefit will accrue once lifestyle changes are implemented. Further, the estimates that up to 5% of breast, colon, prostate, and other malignancies are due to genetic factors come from individual studies.²⁴

Begg fails to point out an important limitation of the PAR in summarizing etiologic knowledge about a disease: for many chronic diseases, the PAR can be made high only if exposure is defined such that almost the entire population is labeled as being exposed or at elevated risk. That is, the magnitude of a PAR may say far more about arbitrary exposure cut-points than about the state of etiology. This point, again, proves Rose’s argument that susceptibility to any disease is rarely confined to a high-risk minority within a population. All of these issues show that caution must be exercised in the interpretation of PARs as a summary of the state of etiology. As already mentioned, however, PARs often have implications for preventive strategies. It is time we used PARs correctly.

Limits of Individual Risk Prediction

Begg questions whether individual risk predictions are accurate on a person-by-person basis. Individual risk of cancer (or other major chronic illness) is either 1, you get it, or 0, you live free of it to 80 years. Risk predictions that fall between these 2 limits do little to help identify those who will or will not develop the dis-

ease. Between 0 and 1, risk is a population parameter. Epidemiologic models do poorly at predicting individual disease.¹⁴

As Rockhill et al. recently reported, 60% of breast cancer cases over a 5-year period in the Nurses’ Health Study arose among the majority of the population that was below the 5-year risk cutpoint of 1.67%,²⁵ which the Food and Drug Administration has used to define “high-risk” women suitable for chemoprevention with tamoxifen. Of note, almost all risk predictions were below 5%. What then does a 30% predicted risk mean if it ever arises, and how can it be accurate? Certainly it does not apply at the individual level. Begg’s article does not clarify such issues.

Will we ever have such precise deterministic data that epidemiology can predict perfect occurrence of disease at the individual level? This seems far beyond the realm of any present or future genetic discoveries, but if it were available, it would likely fit a medical model of interventions through some clinic-based estimation of future health. The complex pathophysiology and redundancy within the human body, together with the time-varying accumulation of exposures over life, suggest that the prediction of disease at the individual level is meaningless in the short term and probably will never be applicable for widespread population use.

To eliminate large portions of the burden of cancer, we do not need this level of understanding. Recommendations to stop smoking were made long before the molecular pathways from tobacco to lung cancer were described. On the basis of the evidence from 7 prospective studies available in 1964, Surgeon General Luther Terry concluded that smoking causes lung cancer in men, and he recommended that men stop smoking. Subsequent to the 1964 surgeon general’s report, there have been widespread changes in patterns of smoking and, ultimately, changes in lung cancer incidence. The incidence of lung cancer is now falling, and evidence from California attests to the ability of aggressive tobacco control programs to reduce deaths from coronary heart disease.²⁶ One might well ask, “How will refined understanding of molecular pathways to malignancy help reduce the population burden of lung cancer?” Perhaps it won’t, but it may lead to strategies for treatment. Perhaps greater effort should be placed on understanding and interrupting the pathway from marketing, modifying social norms, the uptake of smoking, and addiction.

Begg argues that many major genes remain to be identified that will explain much of the variation in cancer risk. Meanwhile, we already know that smoking causes numerous cancers, including those of the lung, upper airways, stomach, pancreas, colon, kidney, and

bladder, and, likely, acute leukemia and cancer of the cervix. Are we to avoid the public health strategy of prevention (smoking cessation) and search for genetic pathways for the development (or not) of these numerous cancers? Perhaps such work will lead to more effective therapies, but surely it will not speed prevention strategies in the near term.

Broad campaigns can be effective, as the melanoma prevention program in Australia has demonstrated, and recent data from California attest to the impact of increases in tobacco taxes and antitobacco education campaigns in preventing smoking.²⁶ Arguing that high-risk approaches may be more effective and that most risk is concentrated in a small subset of the population appears to deny the mounting evidence from cardiovascular disease and cancer that most cases arise from the average risk portion of the population.²⁷ Shifting the whole population distribution will have a greater impact on cancer burden than trying to identify a subset of susceptible individuals who are at sufficiently high risk (yet are a large enough subset of the population) to account for a substantial portion of the disease burden. The decline of stomach cancer over the past 100 years, and the rise and now recent decline in lung cancer, reflect the aggregate burden.

Conclusion

Begg offers no practical strategies for reducing the burden of cancer, unlike the reports from the Harvard Center for Cancer Prevention and other estimates of population-level cancer prevention. For example, the American Cancer Society quantifies the proportion of cancer that can be prevented²⁸ and sets time-dependent goals, which are now used to set priorities and to bring into focus efforts to make prevention of colon cancer the leading priority. These targets for the year 2015 have thus been translated into short-term goals to advance the prevention of cancer. In contrast, Begg's academic arguments further a research agenda and ignore the enormous potential for disease prevention that has already been identified through decades of public health research.

It is time to implement existing cancer prevention strategies through providers, regulatory changes, and programs focused on individuals: programs to encourage smoking cessation and counter trends in youth smoking

initiation as well as programs that encourage people to eat a healthy diet, avoid weight gain, be physically active, drink in moderation if at all, practice safe sex, and avoid sunburns and excessive sun exposure. It is also time to stop chasing after new risk factors. □

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