that a miRNA signature has a higher sensitivity and specificity as a biomarker for colorectal cancer. To validate miRNA, the impact of tumor location and the different subtypes of colorectal cancer, such as MIN (microsatellite instability), CIN (chromosomal instability), and CIMP (CpG island methylator phenotype) on miR-21 serum levels need to be tested. For clinicians, it would be of further interest to understand the advantage of using miR-21 as a serum biomarker in the diagnosis and treatment monitoring of CRC in comparison to clinically used protein-based markers such as carcinoembryonic antigen (15). The clinical need to identify patients at high risk for recurrence in stage II disease and to monitor tumor response in stage IV disease should be addressed.

MiR-21 may not be “just another brick in the wall” but rather may be the keystone leading to a molecularly justified, miRNA-based, biomarker era in colorectal cancer.

References

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Good News for “Alice”: Height and Sex Differences in Cancer Risk
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In Lewis Carroll's Alice's Adventures in Wonderland, the eponymous heroine falls down a rabbit hole and finds a flask labeled “Drink Me” (1). Following this instruction, Alice shrinks to a size small enough to fit through the door to the mysterious world of Wonderland (Figure 1).

Let us imagine another, less fanciful Alice: a woman of less-than-average height, who if she is both sensible and lucky is a never-smoker, drinks alcohol only in moderation, and is able to maintain a healthy weight through diet and exercise. We do not fully understand why, but the good news for our Alice is that as a shorter woman with a healthy lifestyle she has a lower risk of cancer than most of her taller and/or male peers. In this issue of the Journal, Walter and colleagues (2) bring together these two mysteries of cancer epidemiology: a greater incidence among men than women of cancer at shared anatomic sites, and the association of greater height with increased risks for many cancer sites in both sexes.

Some of the reasons why Alice and other women have a lower incidence of cancer than men are already understood. Leaving aside cancers that are sex-specific due to anatomical differences between women and men, known environmental risk factors including alcohol intake, smoking, and occupational exposures to carcinogens are
likely to contribute to sex differences in cancer risk at several shared sites (3). For example, in most populations the prevalence of smoking has been lower in women than men, and therefore women have had a lower rate of smoking-related cancers such as lung cancer. As smoking patterns of men and women have become more similar in developed countries, the disparity between the sexes in lung cancer risk has largely disappeared (3–5). However, cancer incidence at several other sites is greater among men than women by 50% or more, a finding that is consistent across countries at different stages of economic development but which cannot easily be explained by known risk factors (3).

Even less is known about why our Alice’s height should be associated with her risk of cancer. Overall cancer risk increases by 10% to 15% per 10 cm (4 in) of height in both men and women, again consistent across different countries (6). Adult height can be measured accurately in middle age, but it is a marker of developmental processes and exposures that occur in early life and has been linked to a very large number of genetic (7) and environmental (8) factors. It is unknown whether a relatively small number of early-life factors might be conspiring to produce the height–cancer association through multiple mechanisms, or if instead the large number of genetic and environmental determinants of height might influence cancer risk through a single, intermediate mechanism. For example, there has been considerable interest in insulin-like growth factor 1 (IGF-1), a correlate of growth in childhood and of risk for some cancers (9). But taller people may simply have more cells, or it may be that many determinants of growth during normal development (perhaps including IGF-1) also have general effects on tumor growth (8).

Given the obvious relationship between height and sex, it is surprising that height and sex differences in cancer risk seem not to have been investigated together before. Walter et al. looked at whether height could statistically account for sex differences in cancer risk in the Vitamins and Lifestyle (VITAL) Study, a cohort of approximately 33,000 women and 32,000 men (2). They found that differences in height might account for a third to a half of the excess risk in men of cancers at shared anatomic sites. As with most previous studies, power was limited for specific cancer sites, but the cancers for which height accounted for a large proportion of the sex differences in risk (kidney cancer, melanoma, and hematologically malignant cancers) have previously been found to be associated with height (6).

There are several acknowledged limitations of Walter et al.’s analysis, including the use of self-reported height and that their statistical methods cannot conclusively attribute sex differences in cancer risk to height differences between the sexes. Differences in baseline risks between women and men could create sex differences that are not mediated by height, despite a common multiplicative association of height with cancer risk. However, the lack of alternative explanations for sex differences, and the consistency of sex differences across populations (3), speak in favor of mediation by height for those cancers where height appears to account for a substantial proportion of the sex differences in risk.

The etiologies of the associations of sex and height with cancer risk remain some of the most complex and enduring mysteries of cancer epidemiology. The study by Walter and colleagues makes an important contribution by showing that one of these mysteries might help to explain the other, but progress has been slow in understanding the underlying biological mechanisms. One problem is the practical difficulty of constructing large-scale studies with detailed data both on childhood exposures and on potentially confounding adult lifestyle and environmental factors.

In *Alice’s Adventures in Wonderland*, the Mad Hatter asks, “Why is a raven like a writing-desk?” Giving up on finding the solution, Carroll’s Alice retorts that it is a waste of time, “... asking riddles that have no answers” (1). Are epidemiologists Mad Hatters, then, wasting time with studies of sex differences or height? We believe not. Epidemiologic studies might never lead to a “Drink Me” potion to eliminate the height and sex differences in cancer risk. But these associations are clinically important, are observed across many cancer sites, and are consistent across populations—and such general relationships demand explanation.

**References**

In this issue of the Journal, Walter and colleagues (1) note three phenomena—1) men are at higher risk than women for developing many shared anatomic site cancers; 2) on average, men are taller than women; and 3) taller height is associated with higher risk for some cancers in both sexes—and question whether men might be at higher risk for some cancers because they are taller. The authors investigate the hypothesis that height mediates the relationships between sex and some cancers by applying a series of mediation analyses to data from the Vitamins and Lifestyle (VITAL) Study (2). The authors evaluate 10 specific anatomical sites and four combined sites via Cox proportional hazard models using time to cancer diagnosis as the outcome (with and without a large number of potential control variables). This editorial will focus on statistical and methodological issues in Walker et al’s assessments of mediation relations. Although we will point out some limitations, we applaud the application of mediation analysis to better understand the mechanisms by which sex and some cancers may be related. We hope that future research will 1) continue to investigate the role height may play in mediating relationships between sex or other explanatory variables and cancers and 2) use mediation analysis to better understand mechanisms that relate to other associated variables in cancer research.

The authors transform the height variable, using a quadratic parameterization (height and height squared), to reflect the mechanism by which height is hypothesized to transmit the effect from sex to cancer: an increased number of cells at risk “proportional to a two-dimensional surface area” (1). However, we question whether this quadratic version of height effectively captures the hypothesized two-dimensional surface area rather than simply assessing whether the relationship between height and cancer differs at varying levels of height (ie, a curvilinear relationship). Ideally, the authors would also assess a simpler model of unparameterized height, which, if found to be an adequate explanatory variable, could stimulate thinking about alternative height-related mechanisms.

Tests for mediation assess whether some third variable, M, mediates the relationship between X and Y, such that X has a causal effect on M, which in turn has a causal effect on Y. A mediating variable is statistically equivalent to the conceptually distinct confounder variable (3). The distinctive conceptual difference is that a mediator is part of a causal sequence of events. Consequently, researchers should have theoretical support for the mediation model and include potentially important confounders to maximize the ability to make causal inferences (4). Given that sex or height can never be randomly assigned, conclusions about causation must be made with extreme caution. In fact, many methodologists have argued that causal inference cannot be inferred for variables that could not possibly be observed under counterfactual conditions (eg, sex) (5,6). Regardless, we feel that with careful methodology, valuable information can be obtained regarding the potential for causal inference with sex. To help address this issue, the authors include a large set of covariates known to be associated with cancer to minimize the threat of missing confounders, but there may be other variables affecting the relationship between both sex and cancers (eg, the authors rightfully acknowledge the absence of occupational exposures as a potential confounder). Even though the inclusion of the full set of measured potential confounders was the more justifiable approach, the manuscript highlights results from the analyses without these covariates. For analyses that included all measured potential confounders, only melanoma provides evidence of a mediational relationship. An important potential confounder for melanoma, sun exposure, is included, but the measure is only assessed with a single “yes/no” question regarding the experience of three or more serious sunburns. It is possible that a more nuanced measure of sun exposure could account for sex differences in melanoma. And although the known important confounders were generally included, it is possible that there are still confounders missing. Further exploration of the data could consider sensitivity analyses (7) to assess the potential importance of omitted confounders or use propensity score methods (8,9) to help address omitted variable

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