Evidence accumulated over decades of research using a variety of different study designs clearly indicates that, beyond the obvious example of smoking, many preventable causes of cancer relate to lifestyle (1). Experience and evidence has shown that it is possible to reduce lifestyle-related cancer risks, and favorable lifestyle alterations can complement therapy of cancer. Successful interventions, regardless of whether they are developed and applied for preventive or therapeutic purposes, typically rely on behavioral change (e.g., cessation of tobacco use; increasing physical activity; reducing alcohol intake; initiating broad nutritional modifications; limiting adverse recreational exposures, such as solar radiation; and avoiding hazardous occupational exposures). A related class of interventions embeds an assistive agent or device within a program of behavioral change. Examples include vitamins and other isolated nutritional supplements, nicotine replacement, and acupuncture.

But there is a great need for additional effective interventions to further mitigate the still-great health burden of cancer. To our knowledge, structured “developmental pathways” (2) have not previously been used in lifestyle alteration research. The lifestyle alteration pathway (Fig. 1) can provide a shared framework for understanding the challenges facing research involving lifestyle alterations, and for developing policies and initiatives to address them more effectively.

General Considerations in Assessing the Efficacy of Lifestyle Alterations

A key challenge of lifestyle alteration research is the difficulty or impossibility of conducting a double-blinded, randomized, controlled trial (RCT) to generate definitive evidence of efficacy for every promising approach.

First, it may be ethically impermissible, in humans, to design a RCT in which the intervention would be reasonably expected to be harmful (e.g., smoking or excessive eating). In situations involving a substantial imbalance between probable risks and benefits, researchers and public health policy makers generally feel confident issuing recommendations to avoid a particular behavior, activity, or environment without definitive evidence of harm.

Second, many interventions involving lifestyle alterations address behaviors or exposures that are highly complex and difficult to understand, define, or control compared with intervention with a defined pharmacologic agent, which is produced according to Good Manufacturing Practice standards and applied following a specific regimen (i.e., dose, route, frequency, and duration to a defined population). Large-scale dietary intervention trials illustrate the point well: it can be extremely difficult to adequately control for variations in the purity/strength of myriad ingredients, the metabolic variations of subjects, multiple mechanisms of action by various components (some of which may not necessarily be under study),

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and adherence to the intervention and data collection procedures.

Third, experiments involving behavioral choice cannot always be structured with a convincing control group because of the complexity of the variables that may be involved. In addition, trials of this nature are often susceptible to "drop-in" effects (when "control" participants begin using the intervention before its usefulness has been proven) because of the ease of adoption of the intervention, as well as "drop-out" effects (participants randomized to the "active" agent stopping the intervention on their own), which are common in all intervention trials.

Fourth, logistical, environmental, and financial barriers can be forbidding. Many effects derived from lifestyle alterations are relatively subtle (e.g., 10-20% differences are common) compared with those of a pharmacologic agent, which are often much more dramatic. The number of subjects required to power such a study may run into the thousands, and reductions in risk (and especially in mortality) are commonly not evident for years. In addition, lifestyle alterations may be dependent on, or heavily influenced by, environmental factors that are difficult to change quickly, such as elimination of secondhand smoke exposure in public places or buildings or creation of communities that support physical activity.

Finally, intervention trials are often a decade in the planning, recruiting, and follow-up, during which time new epidemiologic and animal research may reveal information that affects the relevance and value of the lifestyle alteration, as tested (3).

These challenges and barriers to RCTs in the lifestyle alteration arena can discourage funders and policy makers from undertaking such studies. In the zero-sum game of publicly funded biomedical research, it can be more appealing to invest in the search for the next important drug, especially when it eventually comes with definitive RCT evidence of efficacy and can be vetted with Food and Drug Administration approval. At the same time, there is typically little or no commercial incentive for the development of lifestyle alterations. On the other hand, as 40 years of data on tobacco exposures show, at least some forms of cancer are preventable, and the potentially enormous real-world effect of lifestyle alterations can be observed in the recent decreases in U.S. cancer mortality, due in large measure to the declining prevalence of smoking (4).

**Weight of Evidence Approach**

Where RCTs are infeasible, scientists and public health policy makers apply standard criteria to observational associations between risks and disease in an attempt to clarify which may be truly causal, as opposed to merely correlative, in nature. These criteria include several measures such as "strength of association," the "precautionary principle," and "coherence" (e.g., dose response, biological plausibility, and epidemiologic sense) to draw conclusions about associations between lifestyle factors and specific cancers, and to offer recommendations based on the "weight of evidence" (5). Weight of evidence has been used as a metaphor for at least 50 years in the scientific literature but continues to be elucidated and systematized. Although the RCT remains the cornerstone of evidence-based medicine for good reason, it too has limitations, most notably in the area of generalizability to usual practice settings. Thus, all evidence advanced to support a proposed intervention must be evaluated critically for relevance to practice.

The limitations of non-RCT data are a reason for great care in decision making and for critical evaluation of the real-world effects of interventions, but they are certainly not a justification for total paralysis in areas of potentially enormous public health effect. As Sir Bradford-Hill noted more than 40 years ago in his classic treatise on the criteria of association versus causation, "In asking for very strong evidence I would, however, repeat emphatically that this does not imply crossing every 't' and swords with every critic, before we act. All scientific work is incomplete—whether it be observational or experimental. All scientific work is liable to be upset or modified by advancing knowledge. That does not confer upon us a freedom to ignore the knowledge we already have, or to postpone the action that it appears to demand at a given time" (6).
Thus, for example, despite the lack of definitive RCTs showing harm, scientists are confident in their recommendation to avoid tobacco. Tobacco harbors a variety of proven carcinogens, and avoiding them is highly unlikely to entail hidden benefits that could outweigh the risks. There is ample justification for wide dissemination of information on the risks of tobacco, and on approaches to cessation of its use.

Steps in the Lifestyle Alteration Pathway

**Discovery.** Epidemiology is the foundation for the assessment of human risks associated with lifestyle factors, and very often is the source of discoveries about correlations between an exposure or a behavior, and a disease. For example, (a) studies of migrants who move from countries with low incidence rates of cancer to countries with higher rates consistently show an important role for nongenetic factors; (b) case-control studies compare rates of exposures or behaviors between subjects with cancer and subjects without; and (c) cohort studies measure exposures of interest among a population at risk of cancer, and then follow the population to record the occurrence of disease.

Classic epidemiology is now supplemented by molecular epidemiology, which seeks to identify associations between lifestyle choices and cancer by investigating exposures/lifestyle choices, outcomes, or both at a molecular level in either germline or somatic biospecimens. Historically, laboratory studies have served primarily to validate associations initially observed in epidemiologic studies. With the advent of molecular epidemiology, however, the process and possibilities have become much more complex and insightful, as bench work allows us to dissect exposures, lifestyle choices, and outcomes into their molecular components, thereby identifying novel "observables" and improving our mechanistic understanding of observed associations.

**Credentialing.** Credentialing entails a consensus of indicative findings within and across known studies. Generally speaking, this means satisfying the classic "Bradford-Hill criteria," which provide a guide to evaluate whether emerging evidence of an association may reasonably be construed as supportive of an underlying causal relationship. In brief, associations lie somewhere along the spectrum from merely correlative to strictly causal. According to the Advisory Committee to the Surgeon General of the Public Health Service that wrestled with data on tobacco and health effects in 1964, as well as Sir Bradford-Hill's subsequent synthesis, an association is more likely to be causal when it is temporally related (i.e., the likely cause precedes effect); reasonably strong within various studies, study designs, and populations; reasonably consistent across studies, study designs, and populations; reflective of a dose-response relationship; biologically plausible; unlikely to be explained by alternative associations; demonstrable through experimentation; adequately specific; and coherent (i.e., consistent with existing knowledge and theory; refs. 6, 7).

A key question is whether a feasible and practical intervention can be developed from insights about correlations with risk. Fortunately, for any given insight about risk, there is usually a way to formulate an intervention that reduces that risk and, thus, in principle, could be an ethical basis for an interventional study. However, most lifestyle alterations rely on behavior change. The rich research literature on conditioning and other basic principles of psychology suggests many possible approaches, but achieving any substantial and durable behavioral change in the real world remains a difficult challenge with few, if any, sure solutions.

**Supporting tools.** In the post-genomic era, powerful new research tools are being developed and refined to further elucidate the mechanisms of carcinogenesis. A current promising area involving lifestyle alterations is the effect of calorie restriction not only on cancer but also on aging more broadly. Target- and pathway-specific work on calorie restriction agents and strategies can be integrated with diet and lifestyle variables. Such a synthesis points to a major goal of contemporary nutrition research: learning how to incorporate the known anticancer effects of calorie restriction into an intervention that could be successful in humans.

Rapid advances in genomics may also be able to identify cohorts to which specific lifestyle alterations can be targeted, in at least two ways: (a) presence of an overexpressed molecular target or pathway revealed through gene or protein expression, which could supplement more evident biological markers such as body mass index, or adenomas in the case of colorectal cancer; and (b) presence of a "risk phenotype" whose behavioral tendencies may be detected before individuals make choices exposing them to greater risk or exposure. For example, there has already been considerable research on the genetics of nicotine dependence.

**Creation of modality.** Once a concept is judged worth pursuing, any number of researchers might have a role in "assembling" an intervention that would eventually move into human testing. The development of a suggested lifestyle alteration can be exceptionally challenging because success may depend on specific details that go far beyond the level of detail available in the "discovery data set." For example, an apparent protective association, between fruit/vegetable intake and colon cancer, would probably require substantial extrapolations about the type(s) of fruits/vegetables to be recommended or tested, as well as specification of the site of origin, amounts, frequency, duration, and other aspects of the planned fruit/vegetable consumption. Increased cross-disciplinary collaboration in the identification and refinement of promising approaches may pay dividends in this key step.

**Preclinical development.** Animal models are a main pillar of translational research in some of the other developmental pathways (2), providing crucial data on biological plausibility, pharmacodynamics, pharmacokinetics, and gene and protein expression. The question is whether animals have a similar role in lifestyle alteration research, given that many aspects of human lifestyles (e.g., dietary components, preparation methods, and patterns including the nonseasonality of food choices; tobacco use; occupational exposures; relative paucity of physical activity relative to caloric intake; and built environments) are relatively, if not absolutely, unique. In addition, human behaviors and behavior change are sometimes seen as unique and complex compared with the behaviors and
experiences of animals. The answer, of course, is that no animal-based experiment is ever a perfect model of human biology, but they can be useful despite their limitations. Another part of the answer lies in the evolutionary heritage of mammalian biology and its reflection in mammalian behaviors. For example, reinforcement is highly conserved across species, as are many of the biological underpinnings of nutrition. The antiaging effects of calorie restriction, for example, have been shown in the mouse, rat, hamster, guinea pig, dog, and cow, as well as in phylogenetically “lower” organisms, including protozoa and yeast. Work looks promising in nonhuman primates as well, so it would be very surprising if the phenomena were not also conserved in humans. The entire area of energy balance and cancer has been very actively modeled in animals (8). There has been notable work as well on animal models for nicotine dependence, although the available models are sometimes questioned as insufficiently realistic for translational research (9, 10).

Because animal models that perfectly mirror both the human disease and the response to intervention do not exist, effects of candidate interventions are likely to be addressed using data from several different models that converge to show the biological plausibility of the presumed mechanism. Researchers gain confidence in moving a finding forward along the pathway when comparable and reproducible results—on targets, pathways, gene and protein expression, pharmacokinetics, and pharmacodynamics data—begin to emerge from multiple model systems. This practice is generally consistent with the weight of evidence approach described earlier in reference to observational data.

In some situations, the work extends not only across model systems but also across cancer sites. Transgenic mice are sometimes created to mimic special subpopulations, such as a widely used estrogen receptor–positive mammary model used to model estrogen receptor–positive breast cancer, or mouse models harboring adenomatous polyposis coli mutations to reflect patients with familial adenomatous polyposis. In the same vein, models without a functioning estrogen system are sometimes created to mimic special subpopulations, such as a widely used estrogen receptor–negative breast cancer. Research on energy balance is of growing interest as well; previous work in this area has identified a panel of inflammatory and hormonal markers in the mouse that respond very much like the human; failure to respond in the in vivo model pretty much ends the inquiry.

In sum, animal models may have a very significant role in lifestyle alteration research on cancer. Yet, there is often an insufficient appreciation of these vital strategic in vivo data, which is reflected by underfunding of such research and by poor communication with other lines of inquiry that would benefit from progress in this area.

Clinical trials. At some point, the proposed lifestyle alteration is ready for preliminary human studies. Strictly speaking, these are not phase I and II studies as those concepts have been advanced in a drug development context, yet they may be designed to develop similar preliminary information on the safety and efficacy of the approach, or they could still be focused on biological mechanisms and physiology to validate the animal results. Another goal could be to identify biomarkers as proxies for the ultimate desired effects. Yet, another is a kind of “test drive” to provide insight for refinement of the intervention and/or study design. A recent example is the measurement of a variety of cellular and molecular markers in the colon in men and women who participated in a year-long daily exercise intervention (11–13).

Biomarkers may play an important role for several reasons. In principle, physiologic indicators could be used to measure not only the effect of an intervention but also the consistency of adherence to it. A now-classic example is the use of cotinine to validate self-reports of smoking status by clinical trial participants (14, 15). Cotinine is a metabolite of nicotine that can be measured in either urine or saliva for several days following tobacco use/exposure. Several tests are now Food and Drug Administration approved and marketed to detect cotinine, as a measure of recent tobacco use or abstinence. Development of these tests provided an example of a developmental effort along the biospecimen-based risk assessment pathway (2) that is directly relevant to the development of tobacco cessation as a lifestyle intervention.

By contrast, a full-scale human intervention trial may take 5 to 10 years or longer and require thousands of participants; protocols where biomarkers can be identified as intermediate end points provide researchers more insight into the mechanisms of an intervention as well as enhanced opportunities to monitor the progress of the trial, and they may help reduce the “noise” that is inevitable in any such large study that involves behavioral choice and self-reporting.

Larger studies of effectiveness. In other Translational Research Working Group (TRWG) developmental pathways, the final step involves the hand off for large-scale, definitive phase III testing, usually with one or more RCTs. The relevance and

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Fig. 1. Lifestyle Alteration Developmental Pathway. The pathway is depicted as a flowchart, a schematic process representation widely used in engineering. The rounded rectangle at the top indicates the origin of the process. Square-cornered rectangles indicate activity steps. Conditional tests, or decision steps, are represented as diamonds. Unidirectional arrows indicate the direction of the activity sequence, and the direction of transfer of supporting tools from their parallel development paths to the main path of modality development. The initial steps of the pathway (blue) are required to proceed through the pathway, with the blue diamonds representing the credentialing steps of scientific validation, clinical need, and feasibility. The pathway includes three parallel paths, representing development of the modality itself (green) as well as development of two different classes of supporting tools (red): tools for characterizing and evaluating the effects of the modality and tools for defining the cohort for which the modality is appropriate. Parallel paths have been made explicit to acknowledge that some of the required tools may not exist and their parallel or codevelopment may be a prerequisite for the viability of the new modality. Some of the supporting tools are assessment modalities represented by either the biospecimen-based or imaging-based assessment modality pathways. Subsequent steps include preclinical development (purple) and early-stage clinical trials (yellow). For each activity, decision point, parallel path, or feedback loop, it is understood that there are many more variations that can occur, and that not all steps may occur in each instance. The pathway does not address the ways in which insights gained from late-stage clinical trials can influence the development process, although they certainly may. Lifestyle interventions may be used for treatment or for primary, secondary, or tertiary prevention. The pathways are conceived not as comprehensive descriptions of the corresponding real-world processes but as tools designed to serve specific purposes, including research program and project management, coordination of research efforts, and professional and lay education and communication.
viability of conducting such trials in the area of lifestyle alterations has been discussed above—in some cases, they are feasible and required, in others, either impossible or unnecessary. Both pilot and definitive lifestyle alteration trial designs present researchers with unique challenges because of the inherent nature of the undertaking; researchers are often trying to recapitulate an outcome that was originally detected by observational or epidemiologic studies. The controlled conditions they impose for the intervention trial are rarely as transparent as they may seem, as they try to account for the difficult variables of human choice/behavior and idiosyncratic individual phenotypic variations. The significant pieces that must be assembled are identical to those in other developmental pathways that move to definitive clinical trials: (a) defining a plausible or relevant cohort, (b) tailoring the intervention, and (c) selecting valid, clinically relevant end points, which may often be intermediate in nature.

Cohort issues:
- Which risk group is most likely to benefit and least likely to be harmed by the proposed intervention? Is it possible to operationalize eligibility criteria based on this definition?
- Within the relevant risk group, is it possible to recruit a representative sample willing to participate in the study and to adhere to the interventional regimen?

Intervention issues:
- How much of a “dose,” or amount of intervention, is needed to see an effect? For example, with regard to tobacco use, how much of a reduction is necessary to observe a beneficial effect—complete abstinence, a 40% reduction in the number of cigarettes, etc.?
- When, how frequently, and for how long must the dose be applied (i.e., what is the “regimen”)?
- How should one balance the intensity or dose of the intervention (and hence likelihood of showing an effect within the study) against the generalizability of the intervention to broader populations if a beneficial effect is shown?
- What are the effects of combining lifestyle alterations (e.g., both calorie restriction and exercise)?

Intermediate end points are intended to provide insight into the study results as early and as effectively as feasible, consistent with the size of the effect and the number of participants. Yet, our limited understanding of the relevant mechanisms underlying the potential efficacy of some lifestyle alterations may make it difficult to specify robust proxy indicators for decreased risk.

Researchers must cope with several challenges that are inherent either to the behavioral aspects of a proposed lifestyle alteration or to the fact that a RCT cannot be done on the study question. These interventions require careful trial design, especially if they are likely to have broad, but possibly subtle, short-term effects. Relative to the original hypothesis, researchers are trying to guard against confounding and/or effect modification, which is all the more difficult where there can be multiple mechanisms of action that might still be incompletely or imprecisely characterized, and/or relatively weak. Because trial recruits have chosen to participate, and their personal stake in the trial outcome may be less than in a drug trial, study designers must estimate and plan for the potential effect of “drop-ins” and “drop-outs.”

Examples of the Use of the Lifestyle Alteration Pathway

Many current lifestyle recommendations intended to modify cancer risks have been derived from “weight of the evidence” inferences based on observational associations that were deemed to be both compelling and consistent across studies, time, and populations. For example, the American Cancer Society’s dietary and physical activity guidelines for cancer prevention7 are largely based on consistent observations suggesting that a “healthy” diet lowers the risk of several cancers and promotes overall well being. Similarly, recommendations for tobacco cessation have not been based on controlled trials of smokers randomized to cessation versus continuation, which would have been difficult if not impossible to conduct for ethical reasons, but from a variety of studies suggesting profound personal (and possibly, communal) health benefits of smoking cessation.8

In other cases, suggested lifestyle alterations have followed the proposed lifestyle alteration pathway reasonably closely. The development of evidence suggesting that exercise and diet can reduce the risk of breast cancer recurrence provides a partial example, although it has not yet been taken all the way through definitive phase III trials.

In terms of the initial scientific discovery, several observational studies indicated that excess weight and obesity were associated with a poorer prognosis and survival for breast cancer patients. Credentialing of the observation was provided by investigators at the Fred Hutchinson Cancer Research Center, who followed 1,185 breast cancer cases for 10 years and noted that women who were physically active both before and after diagnosis had a lower recurrence rate, suggesting that physical activity could potentially improve prognosis (16). However, because weight, diet, and physical activity are highly correlated, it was difficult to assess their independent contributions to breast cancer prognosis from such observational studies alone. A pilot diet-exercise intervention trial in nine overweight, sedentary breast cancer patients was done to define a reasonable level of intervention (i.e., the “creation of the modality” step) and test the feasibility of developing a more definitive trial (17). The results indicated that recruitment and compliance were very high, and that significant reductions in weight, body fat, blood pressure, and pulse were achievable. Hormone levels were identified as a potential intermediate

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Randomized controlled studies, as a supporting tool. Randomized controlled studies, representing the final clinical trials step of the pathway before testing the intervention for its utility against breast cancer recurrence, examined the effect of a 1-year, moderate-intensity exercise program on hormone levels of ~170 sedentary, overweight postmenopausal women. This trial showed reductions in serum estrogen, testosterone, and insulin, which may explain the observed association of exercise with reductions in breast cancer recurrence (18–20).

**Conclusion**

Lifestyle alteration research addresses the interplay of complex biological, psychosocial, and environmental influences on cancer incidence and progression. This interplay creates unique challenges that require extensive, cross-disciplinary collaboration, but it also offers important opportunities to benefit public health on a broad scale. The TRWG developmental pathway can provide a framework to facilitate communication and collaboration across disciplinary boundaries, and a context for progress on field-wide issues, such as standardization of study designs and tools, the definitions of regimens, wording and administration of survey instruments, and definition and use of proxy or intermediate end points.

**Disclosure of Potential Conflicts of Interest**

No potential conflicts of interest were disclosed.

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