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Prevention Trials: Their Place in How We Understand the Value of Prevention Strategies

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Abstract

Several key factors bear on the interpretation of prevention trials and observational studies that inform prevention strategies. These factors include the underlying disease process and aspects of the intervention: sustainability of behavior change, the time course of the intervention within the disease process, dose and duration of exposure needed to effect risk reduction, durability of the impact of intervention, and methodological problems in implementing and interpreting randomized trials and observational studies to evaluate prevention strategies. The question asked through an intent-to-treat analysis of a randomized controlled trial (RCT) differs from that in the observational setting. Furthermore, the long duration necessary to conduct prevention trials and the resulting lack of adherence to therapy can bias results toward the null. A broader range of approaches to evaluate prevention interventions and programs with improved knowledge synthesis and translation to public health practice will speed our progress toward achieving public health and prevention of chronic diseases.

Keywords

durability; adherence; bias; behavior modification; drugs; intention-to-treat

INTRODUCTION

Fifty to sixty percent of cancer deaths can be prevented (20), and lifestyle modification could prevent the majority of coronary heart disease and diabetes (41, 71), major contributors to premature mortality in western countries. The level and sources of evidence supporting change in exposure to reduce disease risk, or to prevent chronic illnesses, vary substantially across both lifestyle exposures and diseases that are a focus of prevention. In this review, we consider several key factors that bear on the interpretation of prevention trials and observational studies that may inform prevention strategies. These factors include the underlying disease process and aspects of the intervention: sustainability of behavior change, the time course of the intervention within the disease process, the dose and duration of exposure needed to effect risk reduction, the durability of the impact of intervention, as well as methodological issues in implementing and interpreting randomized trials and observational studies to evaluate components of prevention strategies.

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Sources of Evidence Supporting Prevention of Chronic Diseases

When considering diabetes prevention, for example, many studies show reduction in weight and increase in exercise both lead to rapid changes in glucose metabolism (56). An accepted intermediate end point in the disease process aids in the study of behavior change and prevention. Furthermore, lifestyle changes that are maintained over a two-year interval can reduce onset of diabetes (24). Thus a well-understood biomarker and an accepted "predisease" facilitate the use of randomized trials to quantify the potential for prevention of diabetes. However, the etiology of cancer spans decades, with few premalignant conditions that are useful as end points for intervention studies. Hence estimates for the proportion of cancer that can be prevented traditionally draw largely on international variation in cancer incidence and mortality. Changes in risk observed in studies of migrants and reduction in risk of smoking-related cancers after stopping smoking add to this body of evidence (17; 25). Recently, a small number of randomized trials of primary prevention strategies including diet, hormones, and vaccination have added to the evidence base for specific malignancies. Most cancers can be prevented with changes in lifestyle, although the time frame for risk reduction after change in diet is not well undestood (25). Thus public health authorities, health care providers, and individuals have responded by adopting prevention targets and strategies that include implementation of regulations to enforce health-related protections; global public health campaigns to impact personal, community, and corporate decisions that improve lifestyle; and a decrease in environmental and occupational exposures to carcinogens (20).

Ideally, one would like to see randomized trials of documented change in exposure leading to significant reduction in chronic disease incidence. As noted above, this occurrence may be observed for diabetes, but evidence for cancer is extremely limited. When randomized trial data are not available, we rely on epidemiologic evidence. Risk reduction following cessation from smoking offers one such example that has been evaluated in many epidemiologic studies. The 1990 report of the Surgeon General (72) summarized this extensive body of evidence and concluded that the evidence clearly indicates that smoking cessation has major and immediate health benefits for men and women of all ages. Subsequent additional epidemiologic studies contributed to further reports. Smoking cessation has been the subject of detailed assessment because of smoking's addictive properties and the lack of alternative sources of exposures for the products of cigarette combustion. Behavior change strategies have been extensively studied in short- and medium-term randomized trials using behavior (cessation from smoking) as the outcome.

Underlying the prevention trial as a model for evidence, one expects to observe a reduction in incidence in the relatively short time frame, say five or ten years, of the randomized trial. For example, with strong evidence for Cox2 inhibitors reducing genetic changes in the progression of normal colonic epithelium to adenomatous polyp and to colon cancer, trials would need to accommodate the duration of time needed to interrupt this process and then observe a reduction in the incidence of cancer. The design considerations for such a trial, with polyps or invasive colon cancer as the end point, must reflect the temporal relation between exposure and onset of disease. This and other issues in disease course underlying prevention strategies are discussed in detail below in the context of cancer, which makes several of these considerations more pertinent.

PREVENTIVE INTERVENTIONS

One useful schema to help interpret the potential for prevention of various interventions is to classify interventions by their approach or type, including behavior modification, antimicrobials and vaccines, drugs, nutritional agents, and screening.

Behavior Modification

Numerous lifestyle factors including cigarette smoking, weight gain and obesity, lack of physical activity, and excess alcohol consumption relate to risk of many chronic diseases and, in particular, account for a substantial portion of preventable cancers. Given the wealth of evidence on smoking and disease and the documented benefits of cessation from smoking (72), many interventions have used sustained cessation from smoking as an end point with clear implications for long-term reduction in risk of chronic disease. Randomized controlled trials (RCTs) addressing individual- and community-level changes to support reduction in smoking have been effective in guiding policy and practice (22, 70). Changes in diet, including fruit and vegetable consumption, meat intake, and use of vitamins, can be documented through RCTs (28), but the time course for a range of long-term health benefits is less well understood. Additionally there is a relative lack of knowledge on how behavioral modification interacts with environmental and policy approaches.

RCT: randomized controlled trial—Obesity is estimated to have at least as great an impact on health as smoking has in the United States today. Yet we have limited data on the magnitude of risk reduction or the time course for reduction with successful weight loss. Weight-loss studies have documented health benefits in terms of intermediate end points (e.g., blood pressure, glucose metabolism) (56). One common approach to increase the efficiency of prevention trials is to recruit participants who are at increased risk of disease, thus adding to the power or reducing the size of the study. The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) followed this approach by choosing patients with impaired glucose tolerance, who were at increased risk of diabetes, to mount a prevention trial showing that lifestyle change resulted in a reduction in diabetes (24) Observational studies do not solve the challenge in quantifying the benefits of weight loss on health due to the strong national secular trend to increased weight (and body mass index) in the United States. Hence identifying a population with sustained weight loss, either in existing cohort studies or using other designs, has not informed the underlying time course of risk reduction caused by behavior change. Only after 28 years of follow-up did the Nurses' Health Study (NHS) have sufficient data on weight loss after menopause to show a significant correlation between lower risk of breast cancer and weight loss (27). A primary prevention trial would add further knowledge in this area, but the size and complexity of such a trial would likely be prohibitive. Assuming a 7% weight loss can be sustained for many years, and a baseline breast cancer incidence of 300 cases per 100,000 person years, a trial lasting 10 years would need ~12,000 participants in each arm to observe a significant 20% reduction in risk associated with a sustained 7% weight loss. Of course, no study has shown a sustained weight loss beyond two years, so the feasibility of such a primary prevention study is far from established.

Addressing physical activity and weight through diet and lifestyle interventions has brought on additional challenges such as the timing of a lifestyle factor as a preventive agent in the disease process and the range of exposure. Unlike smoking or screening tests, where the exposure is finite and can be completely stopped and started, diet, physical activity, and weight change cannot go to zero for prolonged periods and sustain life. The range of intake of nutrients is a major issue when enrolling participants into prevention trials and observational studies. Often more health-conscious volunteers are identified and screened as eligible for a trial (76). Consider the dietary component of the Women's Health Initiative as an example of this healthy participant effect.

The epidemiology of diet and colon cancer has been extensively studied. For example, a combined analysis of prospective dietary studies of calcium and vitamin D intake included 10 cohorts (14). The dose-response relation for calcium showed that the greatest benefit for

increasing calcium intake was for those with reported daily intake below 1000 mg/day. Bringing those with low intake to the level of 1000 mg/day would give a 20% reduction in risk. Beyond this level of intake, however, there was little further reduction in risk of colon cancer. In the Women's Health Initiative, at baseline, participants had a mean calcium intake of 1150 mg/day and increased this amount on average in the intervention arm to 2250 mg/day. This magnitude of increase was not related to risk in the trial and showed only a limited association in the combined prospective cohort studies (75). Similar findings apply to the interpretation of the vitamin D intervention in the Women's Health Initiative and highlight the role of dietary intake at randomization when evaluating diet through randomized trials. Thus the shape of the dose-response relation and the level of exposure at randomization are fundamental considerations when proposing studies or defining populations who can reduce risk through behavior changes.

Antimicrobials and Vaccines

The etiology of some 18% of cancers worldwide can be linked to chronic infections such as hepatitis B, human papillomavirus, and *Helicobactor pylori* (59). Interventions to modify the time course of infection and cancer provide added insight to the challenges of interpreting prevention trials. The U.S. Centers for Disease Control and Prevention (CDC) currently recommend administration of the HPV vaccination to women between ages 13 and 26 to reduce their risk of cervical cancer; the benefit of this prevention will be observed many years hence. Hepatitis vaccination programs in Africa and Asia further illustrate these points. In the Gambia, a program launched in 1986 aims to evaluate the effectiveness of childhood hepatitis B vaccination, and current estimates predict that the final outcome of reduced hepatocellular carcinoma in adults should be measurable from 2017 onward (74). In Asia, results after 10 years of nationwide hepatitis B vaccination, implemented in Taiwan in 1984, show significant reduction in hepatocellular carcinoma in children (11). The downside of childhood vaccinations to prevent cancer is that many years of follow-up are required to demonstrate protection of adults, although this outcome is implied by results to date. Similar concerns have been raised regarding timing of vaccination and duration of protection when considering use of Bacillus Calmette-Guerin (BCG) vaccine to prevent tuberculosis (16).

Drugs

Numerous drugs, particularly the widespread use of antihypertensive medication and lipid-lowering drugs for the prevention of cardiovascular diseases, contribute to the reduction in chronic disease burden. Despite the relatively low incidence of disease and the long duration of therapy required, cancer also provides informative examples of benefit from chemoprevention.

Aspirin has been extensively studied in observational epidemiologic settings that address duration of use, dose, and magnitude of risk reduction. The observational evidence is consistent with evidence from randomized primary prevention trials, which have shown that use of at least 300 mg of aspirin per day for at least 5 years is effective in preventing colon cancer, reducing risk by ~25% (31). A latency of ~10 years is observed. Like all chemoprevention strategies, risks and benefits must be balanced (35). To date, the risk-benefit considerations of cardiovascular disease, bleeding complications, stomach pain, and heart burn have precluded recommendations for aspirin use as a widespread prevention strategy (36).

Selective estrogen receptor modulators (SERMs) such as Tamoxifen and Raloxifene have been shown in randomized controlled prevention trials to reduce risk of preinvasive and invasive breast cancer (30, 49). The separation of incidence curves is dramatic and clear within two years of initiating therapy. Like aspirin, SERMs also raise the challenge of risks

and benefits of therapies as well as the limitation of randomized trials to quantify potential harms that are much less frequent than the primary trial end point. Tamoxifen increases risk of uterine cancer, a finding confirmed by epidemiologic studies; Raloxifene, which looks to have a safer profile, does not (12).

Difluormethylornithine (DFMO) plus Sulindac has been implemented Meyskins et al (52) as a newer model for chemoprevention using lower doses of multiple agents that act via different mechanistic pathways to prevent recurrent colon adenomas. DFMO is a potent inhibitor of colon carcinogenesis in animal models, and a low dose was chosen to reduce potential toxicity (hearing loss). Sulindac is a nonsteroidal antiinflammatory drug shown to be effective in previous clinical studies. Using the combination of these two agents, a substantially smaller sample size was required (375 patients), and the lower doses may have helped sustain adherence to therapy. After three years of follow-up, the recurrence rate for adenomas was reduced by 70% in the active drug group and side effects were not significantly different between active drug and placebo groups (52). Thus a combination of chemotherapeutic agents used at low doses produced added efficacy and reduced risk of side effects.

Nutritional Agents

A number of interventions containing micronutrients, have been evaluated in RCTs.. Again, the timeframe of the intervention in relation to the disease outcome is a critical consideration in design and interpretation of results. One model used for chemoprevention studies draws on poylp recurrence for an outcome. For several such studies, investigaotrs recruited men and women who had been diagnosed with a colonic polyp and randomized them to a nutritional agent, with follow-up for recurrence of a polyp as the trial end point. Understanding the design, the underlying disease processes, and issues of dose and duration of intervention, as noted above, are essential to interpretation of the study results.

Null results of prevention trials with wheat fiber (2) or fruit and vegetables (67), when polyp recurrence has been the end point under study, raise questions of the timeframe for prevention interventions. Has the set of genetic changes that can be prevented by components of diet already been established in the colonic mucosa of trial participants who were 40 to 80 years of age when randomized to these dietary changes? Other studies using this same disease model have shown that calcium supplementation significantly reduces risk of recurrent polyps (4, 37), as does aspirin (31).

Screening

As a prevention strategy, screening is more complex than some other interventions. The combination of early detection together with effective treatment underpins effective screening. Additional principles are summarized in Table 1.

The Hypertension Detection and Follow-up Program recruited participants from population-based screening of more than 150,000 adults 30–69 years of age. Some 10,940 participants with high blood pressure were randomized to a systematic antihypertensive treatment program (stepped care) or referred to community medical therapy. Five-year mortality from all causes was 17% lower for stepped care compared with referred care and confirmed the potential for screening and treatment of hypertension to reduce mortality substantially (1).

Although screening will typically not be a one-time event, as noted by Wilson & Jungner (65), the frequency of screening and age at beginning of screening will be informed by the natural history of disease. While randomized trials could evaluate these components of a screening program, in practice this is rarely done. Rather, as noted later, observational data often inform these decisions that impact the cost and effectiveness of a screening program.

Summary

Changes in level of exposure to causes of cancer, resulting in reductions in cancer incidence as summarized through examples of behavior change, antimicrobials and vaccines, drugs, nutritional agents, and screening, highlight some of the many issues that must be addressed when designing prevention trials. Among these methodological considerations are important aspects of the time course of prevention interventions. These are (*a*) the ability of interventions to change the exposure sufficiently, (*b*) the timing in the process of carcinogenesis, or the development of cancer, (*c*) adherence to behavior change over time (79), and the durability of the effect. Behavioral interventions have a rich history of evaluating short-term change in behavior through randomized trials (63). Sustainable behavior change, however, plagues randomized trials of screening and lifestyle changes (e.g., with diet, physical activity, or drugs) that use disease end points for the outcome. Adherence to the experimental and control interventions has not been high in longer-term primary prevention randomized trials (13, 23, 75). For example, ~40% of women stopped the intervention in the WOMEN'S HEALTH INITIATIVE, and many of the control women "dropped in," or began using the intervention agents (66). For interventions of calcium and vitamin D, the dose was not high enough, and too few of the women in the intervention arm had a low intake at enrollment to achieve the reductions in colon cancer incidence observed in epidemiologic studies and polyp prevention trials (48).

In sum, the time course to achieve reduction in cancer incidence through active primary prevention programs may vary substantially by exposure and cancer site. The timing of the intervention in the time course of carcinogenesis and the ability of individuals or populations to maintain the lifestyle changes necessary to reduce the cancer burden both contribute to the ultimate benefit of the active prevention intervention.

Whether observational data will be as informative as RCTs regarding change in risk after lifestyle changes will depend, in large part, on the range of exposures in the population at the beginning of follow-up, how well they are quantified, how much they change during follow-up, and if the changes are maintained over time. Longstanding use of migrant studies has highlighted how much cancer risk can change, and studies of specific cancers have reported the degree of change in diet and other cancer risk factors over generations (80). One nonmigrant population that shows how much reduction can be achieved through long-term adherence to a cancer-reducing lifestyle is the members of the Seventh Day Adventist church in the United States. This population avoids smoking, alcohol, and consumption of meat, being largely lacto-ovo-vegetarian, and shows an overall 27% lower cancer mortality among men than the U.S. population at large (54). Reductions in cancer mortality among women were less, in part because of the burden of breast and other reproductive cancers, which may be less responsive to changes in diet and smoking.

THE IMPACT OF STUDY DESIGN ON RESEARCH FINDINGS

The impact of study design on the results of medical research has long been an area of both substantial debate and a smaller body of empirical research. Examples come from many disciplines within clinical medicine and public health research. The hierarchy of design implemented in guidelines reflects efforts to address concerns of bias and internal validity (9, 73).

Among the early major contributions in the 1970s was work by Mosteller and colleagues who noted that innovations in surgery and anesthesia showed greater gains compared with standard therapy when non-RCTs were evaluated compared with the gains in RCTs (32). More recently we, and others, have evaluated the impact of design in medical and surgical research (15, 53) and concluded that the mean gain comparing new therapies to established

therapies was biased in favor of new therapies in nonrandom trials compared with RCTs. Benson & Hartz (6) conducted a literature-based study among publications after 1985 for therapies evaluated both in **RCT**s and in non-RCT studies. For each treatment, the magnitude of effect was estimated by meta-analysis of reported results in observational studies and then separately in randomized trials that evaluated the same treatment. On the basis of 136 reports of 19 diverse treatments, they concluded that in only 2 of the 19 analyses did the combined data from the observational studies lie outside the 95% confidence interval for the combined data from the randomized trials (6). A similar analysis drawing only on published study results reported from 1991 to 1995 showed results remarkably similar to when meta-analysis of observational studies was compared with meta-analysis of RCTs (21). These more recent data suggest that advancing study design and improved analytic methods may reduce bias in some nonrandomized evaluations of medical and public health interventions. Such methods apply not only to the original studies but also to the approaches taken to combine results quantitatively using meta-analytic approaches such as random effects meta-regression and Bayesian meta-analysis, among others (57). With attention to thorough data analysis, design issues can be understood, and their impact or bias can be estimated, on average, and then ideally accounted for when interpreting data.

Consider some more clearly delineated preventive exposures in which issues of study design have been addressed. Examples include research synthesis that combines results from randomized trials and contrasts these with combined results from observational studies in the evaluation of preventive interventions, such as BCG vaccination (16) and mammography screening (23). When interpreting apparent heterogeneity in results, it is important to step back and ask, “What is the relation being evaluated?” under these different study designs. For example, an RCT uses intention-to-treat analysis to preserve the merit of randomization. This approacch to analysis is based on the initial treatmentintent (or randomization) not on the treatmetn eventually administered (or compliance). Such an analysis is not evaluating the exposure disease relation but rather the impact of offering a new therapy versus an alternative therapy (regardless of adherence to the intervention, or control, or placebo). A case-control study or a prospective cohort study, however, evaluates the impact of the screening test among those who were actually screened as compared with those who were never screened by measuring actual screening service utilization. In prevention studies, the design must also address the fundamental issue of the timing of the exposure in the natural history of disease. In addition, adherence to therapy by healthy research volunteers is a key consideration in primary prevention trials. For some preventive interventions such as screening tests and chemoprevention, another issue is the duration of protection, or the interval from the beginning of therapy to the observation of a protective effect (lag effect).

Dose and Duration of Intervention

Dose and duration of intervention are typically informed a priori by observational data. Given the complexity of implementing a primary prevention RCT, the importance of choosing the correct dose is imperative. Determination of the proper dose requiresation of risks and benefits because adverse effects of most therapeutic interventions cannot be completely avoided. Screening tests offer a different set of issues where dose relates to the screening frequency and duration may include consideration of how long screening should continue.

Case-control studies of preventive interventions such a screening mammography, colon screening (68), and prospective population-based studies of pap smears have capitalized on the natural variation in time since last screen in the population at large to evaluate the protective interval for a screening test (412) (see Table 2). For example, data from an international study evaluating cervical screening programs in eight countries show that the

relative protection against cervical cancer is higher among women who have had two or more negative screening tests than in women with only one negative test. These data also inform the frequency of screening, showing that cumulative incidence of cervical cancer among women ages 35 to 64 is reduced by 93.5% with annual screening, 92.5% with screening every 2 years, and by 83.6% with screening every 5 years (42). Such data clearly inform preventive practices and policies (19).

In contrast, a trial must choose a level of exposure, say annual mammography or colon screening every 10 years with colonoscopy, regardless of evolving evidence on duration of protection after a negative screening test. Other examples, from the United Kingdom, in mammography attest to the value of observational data to complement the RCT data informing the duration of protection from screening (78), hence guiding population-wide screening recommendations and implementation.

Intention to Treat and Adherence to Randomized Intervention

Continuing the mammography example, Demisse and colleagues combined data from seven randomized trials and six case-control studies investigating the association between participation in breast cancer screening programs and breast cancer mortality (23). As seen in Table 3, the combined intention-to-treat efficacy estimate of the RCTs was 0.76 (95% CI 0.69–0.83) for women randomized to screening versus control, and the combined case-control protective effect was 0.44 (95% CI 0.38–0.50). Adherence was 50%--80% in the treatment groups in the RCTs. Assuming noncompliance with mammography screening (approaching 30%) and that 20% of the control group are screened (i.e., drop in), then with noncompliance random with respect to the underlying breast cancer risk among thoses who change from their allocated trial arm, the benefit of mammography in terms of reduced mortality is comparable in epidemiologic studies and RCTs (0.46 estimated true RR after adjustment) after adjusting RCTs for nonadherence (23). Thus, the different study designs are fundamentally measuring different constructs of the impact of screening. Clarifying the exposure being evaluated is essential to correctly interpreting prevention studies. The RCT is evaluating the offer of participating in a screening program while the case-control study is evaluating actually being screened.

Zelen considered the challenges of primary prevention trials in the 1980s and addressed both compliance and models of carcinogenesis as major impediments to the use of RCTs to evaluate cancer prevention strategies (79). It is important to contrast these issues in treatment trials and prevention trials. In treatment trials, we typically take recently diagnosed patients and offer them, often in a life-threatening situation, the option to participate in a trial of a new therapy compared with standard therapy or placebo. Compliance or adherence to therapy is usually very high among these highly motivated patients and outcomes are generally in a short to mid term time frame. In contrast, prevention trials recruit large numbers of healthy participants, offer them a therapy, and then follow them over many years, since the chronic diseases being prevented are relatively rare. With substantial nonadherence---often in the range of 20%--40% over the duration of the trial---an intention-to-treat analysis is no longer unbiased.

Time Frame of Disease Process

Returning to the time frame of exposure in the carcinogenic process, the null RCTs of fiber (2) and fruit and vegetables (67) for prevention of polyp recurrence amply illustrate Zelen's concerns about the timing of the preventive intervention in the disease process. Randomized trials of fiber and fruit and vegetables in the prevention of colon polyp recurrence have not shown any benefit from increased intake (2, 67); similarly, the Women's Health Initiative trial of reduced fat intake (along with increased fruit and vegetable intake) to prevent breast

cancer did not show a significant reduction in risk over 8.1 years (61). The level of adherence to the Women's Health Initiative diet in this long-term primary prevention study limited the likelihood of the RCT showing benefit. Furthermore, in prevention trials addressing recurrence of polyps, the extent of DNA damage accumulated across the colonic mucosa at the time the eligibility polyp is detected certainly is not limited to only the removed polyp. The protective findings noted earlier for drugs (aspirin) attest to the importance of the mechanistic timing of exposure to achieve risk reduction. Thus we must ask of RCTs, at what stage in the disease process may fiber play a role in protecting against colon cancer? Constraints of design in RCTs usually limit to a narrow time point and defined dose of exposure (and specific duration), which contrast with the richness of epidemiologic studies that can address exposure over the life course and relate such exposure to disease risk.

Other nutritional agents have also been tested in chemoprevention trials in the developed world and in China (39). Based on evidence documenting that people in Linxian, China, had low intakes of several nutrients, a randomized trial comparing combinations of retinol, zinc, riboflavin, niacin, vitamin C and molybdenum, beta-carotene, vitamin E, and selenium was undertaken (7). Significant reductions in mortality were observed for those who received the combination of beta-carotene, vitamin E, and selenium (factor D), and the reduction was greater for those who began the therapy at a younger age. These results again emphasize the importance of the timing of exposure in the disease process.

Stratification of the results by sex and age was planned a priori. There were no statistically significant interactions with sex. However, when stratified by age, factor D had a strong protective effect in individuals under age 55 but demonstrated almost no effect in subjects aged 55 years or older (62). This pattern was seen consistently for total mortality, total cancer mortality, gastric cancer mortality, and esophageal cancer mortality. Indeed, the effect of factor D on esophageal cancer was reversed by age, showing a protective effect for younger individuals but a harmful effect for older individuals. Further insight into the timing in the carcinogenic process is provided by a separate RCT in Linxian (47), which gave further support for a preventive effect of selenium in subjects with preexisting esophageal squamous dysplasia, the precursor lesion of esophageal squamous cell carcinoma. Compared with control subjects, those with mild dysplasia who received 10 months of daily supplementation with 200 μg of selenomethionine were more likely to have regression and less likely to have progression of their esophageal squamous dysplasia.

In contrast, studies have shown no benefit of beta-carotene in high-risk smokers (The Alpha-Tocopherol Beta-Carotene trial; reference 3), or in men at high risk because of smoking or asbestos exposure (CARET; reference 57). Similarly, no benefit was observed among average-risk populations (40). Together, these trials show strong evidence against the hypothesis that beta-carotene can substantially reduce risk of lung cancer (59). However, if dietary antioxidants such as beta-carotene act early in the carcinogenic process, say, delaying initiation of carcinogenesis among adolescent and young-adult smokers, trials such as these would not have detected any benefit. Further study of diet across the full time course of carcinogenesis is clearly necessary. To date, however, we have few studies and little likelihood that the randomized design will be applicable at all to childhood and adolescent exposures for risk reduction of adult chronic diseases.

Perhaps the best known example of exposure over the life course and disease risk is the radiation follow-up effects cohort in Japan. For each woman exposed to the effects of the atomic bomb, a radiation dose was estimated, and follow-up over 40 years showed a clear and strong relation to increased risk of breast cancer; higher exposure was reported among those exposed before age 20 (46). Few studies of lifestyle offer such a rich exposure

assessment over the life course to relate diet, physical activity, or excess adiposity in infancy, childhood, adolescence, and early and later adult life to disease risk. Although models of breast cancer confirm the evidence from radiation that early life exposure is likely most important for breast cancer (18), the observational evidence is limited and the likelihood of randomized prevention trials is exceedingly low, given the lack of accepted intermediate end points that can be effectively evaluated in such studies. One dietary intervention evaluating a low-fat diet in prepubertal girls is informative. Dorgan and colleagues added an ancillary study to the Diet Intervention Study in Children (DISC), a multicenter RCT to test the safety and efficacy of a dietary intervention to reduce serum low-density lipoprotein cholesterol in children with elevated levels (26). Using hormone levels as a marker of breast cancer risk, the investigators evaluated change in hormone levels over a five-year dietary intervention and observed reductions in estrogen and luteal-phase progesterone. Despite these significant changes in response to dietary modification, the long-term correlation of change in hormones during adolescence to change in risk of breast cancer decades later remains unknown. Other studies are evaluating other potential intermediate end points for breast cancer, including magnetic resonance to quantify breast water and fat content among 15- to 30-year-old women (8). However, like other developing intermediate markers, the long-term relations are yet to be defined, which limits the interpretation of data for prevention.

To fill in exposure over the life course, it is impractical to conduct randomized trials of childhood or adolescent behaviors and observe disease end points such as cancer and heart disease decades later. Rather, when using disease end points, we must use observational data to fill in these often important periods of risk accumulation. Prospective dietary data evaluated in relation to chronic diseases have been limited largely to adult dietary intake. As collected in numerous cohort studies that contribute to the pooled analysis of diet and chronic disease, this approach has the added potential to allow for consistent strategies for error correction across the participating cohorts (69). A further advantage of prospective cohort studies is the potential to obtain unbiased recall from participants free of disease to fill in dietary history from earlier in life. This approach, implemented within the Nurses' Health Studies, has allowed investigators to assess high-school diet, and validation studies show that such adult recall provides a reasonably valid measure of adolescent diet (50, 51). Such recall is necessary to evaluate dietary intake in early life in relation to cancer end points given the temporal constraints. Emerging data show that diet, adiposity in childhood, and physical activity in adolescence are significantly related to breast cancer risk.

Overall, prospective cohort studies offer several advantages for the study of diet disease relations, particularly when validation studies allow investigators to consider error correction (64, 65). With repeated measures, one can address the timing of exposure in the disease process to determine the mechanisms of disease and prevention. The dose of exposure varies according to current population practices, and change over time in diet can be related to disease risk, just as time since cessation from smoking can be related to disease mortality when one has repeated measures of cigarette smoking (43). Although trials for prevention of chronic disease have merit, interpretation of their results must consider individuals' levels of participation and the potential that investigators are addressing an intervention at the wrong point in the carcinogenic process, for example.

Durability of Prevention Effect

The additional insight on prevention gained from the precise knowledge of exposure recorded in the randomized trial includes the added understanding of the disease process after cessation of a precisely measured intervention. Continued follow-up of trial participants has shown the durability of the effect of a prevention agent. In the Linxian trial, factor D, which included selenium, vitamin E, and beta-carotene, statistically significantly

reduced total mortality, total cancer mortality, and mortality from gastric cancer (7). An important question remained, however: whether the preventive effects of factor D would last beyond the trial period. The results of the continued follow-up showed that hazard ratios (HRs), as indicated by moving HR curves, remained less than 1.0 for each of these end points for most of the follow-up period; 10 years after completion of the trial, the group that received factor D still showed a 5% reduction in total mortality and an 11% reduction in gastric cancer mortality (62).

Similar insight on the duration of protection has been provided from continued follow-up of three tamoxifen trials, which showed benefit after the conclusion of active therapy (29). The calcium polyp prevention trial also reported that the protection observed during the trial persisted for up to 5 years after supplementation ended and may, in fact, have been stronger after, rather than during, active intervention (37). With the exception of smoking cessation, cessation of exposure to occupational carcinogens, and termination of drug use, lifestyle factors (diet, energy balance, physical activity) rarely have a clearly demarcated cessation, thus limiting observational studies to provide insight on the durability of effects and lag from exposure to disease.

DESIGN FOR DISSEMINATION

Two major proof-of-principle prevention trials have received much attention. First, the Diabetes Prevention Program (DPP) was an intensive two-year intervention during which lifestyle modification performed better than drug therapy to reduce progression to diabetes (24). Second, Koutsky and colleagues' trial of the HPV vaccine, which prevents DNA damage from HPV (45), also informed our biologic understanding of the intervention. Neither intervention was determined to be ready for widespread application. Yet the reported benefit from these RCTs has led to a rush to implement prevention programs that are not yet evaluated for sustained public health impact. The gap between proof-of-principle prevention trials and design for dissemination (44) is substantial and should ideally be addressed in the design phase of interventions that have substantial potential for public health benefit. The importatnce and prioities among strategeis to increase design for dissemination have been identified by the National Cacnere Insitute (55) with an aim to speeding the improvement in population health. Of note metrics have ben propsed to move beyond decision making that is limited by consideration of only effeicacy inradndomized trials and add consideration of external validity and applicaability of research to inform transsaltion to practice (38). Glasgow and others have addressed this issue through the RE-AIM approach which employs a number of metrics including: Reach; Efficacy; Adoption; Implementation; and Maintenance (33, 34) (See reference 34 for a more detailed presentation on this framework). These dimensions provide a framework to evaluate prevention programs to determine their overall public health impact. Few randomized trials record and report on this spectrum of measures.

CONCLUSIONS AND FUTURE DIRECTIONS

This review of sources of evidence highlights numerous strengths and limitations of randomized trials and observational data to inform our understanding of the value of prevention strategies. The rigor of randomized trials may evaluate specific research questions in relation to prevention. Observational data will often inform issues of dose and duration of an intervention, which are necessary to achieve a preventive benefit. The design of RCTs, including size, duration, and number of exposures and outcomes evaluated, are invariably influenced and constrained by funding availability. The question asked through an intent-to-treat analysis of an **RCT** differs from that asked in the observational setting. Furthermore, the long duration necessary for prevention trials and the resulting lack of

adherence to therapy can bias results toward the null. Application of results from research studies documenting evidence-based strategies to reduce the burden of chronic disease often requires the balancing of an intervention's risks and benefits (35). These estimates at the individual and population level must synthesize data from trials and from observational studies.

For clearly delineated exposures (drugs, nutritional supplements, screening tests, and smoking cigarettes), duration of effect after an intervention can be documented. But for many prevention interventions, these data are far from clear, and yet they have major impact on the balance of risks and benefits, the duration of interventions, and the associated costs. Research to address these issues must be a high priority for prevention.

Although methodological rigor forces us to focus on design issues, many public health advances result from natural experiments that do not fit the designs discussed here. As Cameron and colleagues have noted, communities can move faster than researchers, developing and implementing untested interventions that impact public health (10). For example, with money from the tobacco settlement, Florida used a student-driven approach to smoking prevention and reduced statewide smoking rates among youths by 18% to 40% over 2 years (5). A broader range of approaches to evaluation of prevention interventions and programs with improved knowledge synthesis and translation to public health practice will speed our progress toward improved public health and prevention of chronic diseases. Improved methods and approaches to integrating data from diverse sources and study designs will be needed to achieve these goals.

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Table 1

Principles of screening. From Wilson & Jungner (77).

1. The condition sought should be an important health problem.
2. There should be an accepted treatment for patients with recognized disease.
3. Facilities for diagnosis and treatment should be available.
4. There should be a recognized latent or early symptomatic stage.
5. There should be a suitable test or examination.
6. The test should be acceptable to the population.
7. The natural history of the condition, including development from latent to declared disease, should be adequately understood.
8. There should be an agreed policy on whom to treat as patients.
9. The cost of case finding should be economically balanced in relation to the possible expenditure on medical care as a whole.
10. Case finding should be a continuing process and not a once-and-for-all project

Table 2

Pap smear screening frequency and protection against cervical cancer. From Reference 41.

Interval between screens	% reduction in cumulative incidence
1	93.5
2	92.5
3	90.8
5	83.6
10	64.1

Table 3

Observed and estimated true relative risk of screening mammography from randomized controlled trials. Adapted from Demissie (23).

Observed RR	Proportion complied with treatment	Proportion screened in control group	Estimated true RR
0.7	1.0	0.2	0.65
0.8	1.0	0.2	0.76
0.7	0.7	0	0.57
0.8	0.7	0	0.71
0.7	0.7	0.2	0.46
0.8	0.7	0.2	0.63
0.7	0.7	0.2	0.39
0.8	0.7	0.3	0.57