Time Course of Risk Factors in Cancer Etiology and Progression

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ABSTRACT

Patients with cancer increasingly ask what they can do to change their lifestyles and improve outcomes. Risk factors for onset of cancer may differ substantially from those that modify survival with implications for counseling. This review focuses on recent data derived from population-based studies of causes of cancer and of patients with cancer to contrast risk factors for etiology with those that impact survival. For different cancer sites, the level of information to inform the timing of lifestyle exposures and risk of disease onset or progression after diagnosis is often limited. For breast cancer, timing of some exposures, such as radiation, is particularly important. For other exposures, such as physical activity, higher levels may prevent onset and also improve survival. For colon cancer, study of precursor polyps has provided additional insight to timing. Extensive data indicate that physical activity reduces risk of colon cancer, and more limited data suggest that exposure after diagnosis improves survival. Dietary factors including folate and calcium may also reduce risk of onset. More limited data on prostate cancer point to obesity increasing risk of aggressive or advanced disease. Timing of change in lifestyle for change in risk of onset and for survival is important but understudied among patients with cancer. Counseling patients with cancer to increase physical activity and avoid weight gain may improve outcomes. Advice to family members on lifestyle may become increasingly important for breast and other cancers where family history is a strong risk factor.

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INTRODUCTION

Models of disease can be used to predict future risk of developing disease and to shed light on the mechanism and timing of causal agents in the pathway from normal tissue to preinvasive and invasive cancer.¹ Understanding risk and the role of lifestyle factors in etiology or survival can inform clinical practice and counseling for risk reduction. Given that breast, colon, prostate, and lung cancers are well studied both for etiology and survival and account for approximately 50% of all new cases diagnosed, we focus primarily on these malignancies.

Risk or the accumulation of genetic changes on the pathway to cancer increases with age. For example, the early modeling of cancer mortality data by Doll and Armitage² revealed that the log of mortality increased 6 units for each one unit increase in the log of age. This association was consistent across 17 cancer sites, and for breast, ovary, and cervix the observed drop off in mid life reflected a reduction of one of the later changes in the process of carcinogenesis (promoter). The number of changes needed to transform from normal cells to malignant appeared constant across many cancers and supported a multistage model of carcinogenesis. For

lung, Doll and Peto³ estimated this power function to be a factor of 5, consistent with the multistage model of carcinogenesis⁴⁻⁵ and for colon cancer mortality the factor of 6 is now reflected in more detailed modeling of genetic mutations.⁶ Thus, if the natural history of risk accumulation is fully understood, we can use causal and protective factors and the timing of exposures in the life course to guide prevention counseling. Likewise understanding when change after diagnosis can modify survival can guide practice. To date, however, the underlying models for survival have less richness for lifestyle than do models for incidence.

BREAST CANCER

The impact of age on breast cancer risk is such that risk rises at approximately 8.5% per year from menarche to menopause and at only 2.5% per year after menopause.⁷ This suggests that the impact of risk factors may vary among pre- and postmenopausal women. Thus, breast cancer incidence can serve as a model for numerous insights to timing of exposure and risk. For example, the strongest data on radiation and risk from the follow-up of women with

exposure to the atomic bomb shows that dose and age at exposure have important impact on breast cancer risk (eg, exposure during childhood and adolescence shows strong increase in risk, but exposure after age 30 [presumably after first pregnancy when the breast undergoes final development in preparation for lactation] has far less impact on risk).⁸ Radiation is then used therapeutically after diagnosis. Obesity also has markedly different impact on risk across the life course. Childhood and adolescent obesity are inversely related to premenopausal incidence,⁹ as is obesity through early adult years¹⁰ but obesity after menopause is a cause of breast cancer¹¹ and after diagnosis it contributes to poor survival.¹² The contrasting relation for obesity may reflect the relation of adiposity to regularity of menstrual cycles among premenopausal women and directly to circulating hormone levels among postmenopausal women.¹³ The other component of energy balance is physical activity. Unlike obesity, it has quite consistent relations with incidence and survival showing an inverse relation to breast cancer incidence with higher physical activity through premenopausal years¹⁴ and among postmenopausal women.¹⁵ Higher physical activity levels after diagnosis are also related to reduced risk of breast cancer recurrence.¹⁶

Diet and breast cancer adds further to the evidence on the importance of timing of exposure. Many studies of dietary fat intake and risk of breast cancer have, over time, come to show little overall association with incidence,¹⁷ and reduction in fat intake after menopause is not related to lower risk in the Women's Health Initiative dietary intervention.¹⁸ Nor is fat or fiber intake after diagnosis related to survival.¹⁹ In contrast, the WINS trial of fat reduction after diagnosis achieved significant reductions in energy from fat and showed that, in addition to weight loss, the women in the intervention arm had reduced recurrence of breast cancer.²⁰ Randomized controlled trial data from the Women's Healthy Eating and Living trial, an intervention to increase fruit and vegetable consumption, shows that despite large increases in vegetables, fruit, and fiber intake, there is a convincing lack of association between diet and prognosis.²¹ Observational data do, however, suggest that timing of intake of soy products is important for prevention of breast cancer.²² Interest in soy and cancer risk is motivated in part by historically low breast risk among Asians. A detailed review by Wu et al²² shows that at high intakes typical of Asian diets soy intake is significantly related to reduced risk for breast cancer, and the effect may be strongest for intake in childhood and adolescence. A meta-analysis found that intake of high amounts of soy (20 mg per day of isoflavone) in Asian women was associated with a decreased risk for breast cancer, compared with Asian women consuming lower amounts (5 mg daily). However, even the lowest intake of soy isoflavones in the Asian population was more than fivefold the high intake (0.8 mg per day) of women in Western countries, where studies have not shown a protective effect for soy. Furthermore, intake in childhood and adolescence may be the most protective against breast cancer.²³ Although some additional benefit may be observed with adult intake, separating adult from childhood diet remains difficult. Promising evidence on higher intake after diagnosis among women living in China where intakes of 9 or more grams of soy protein per day are consumed by approximately half of women, suggests that soy intake may reduce risk of recurrence and death.²⁴

Alcohol has been studied in relation to precursor or premalignant breast lesions, such as proliferative benign breast disease, showing a strong relation to incidence of breast cancer.²⁵ Feeding studies suggest hormone changes may provide a pathway for alcohol to cause

breast cancer.²⁶ Combined data from prospective cohort studies,²⁷ the more recent Million Women Study,²⁸ and several meta-analyses show a consistent monotonic increase in risk with higher alcohol intake, risk rising approximately 7% per 10 g of alcohol per day.²⁹ The adverse effect of alcohol on incidence may, however, be offset by higher folate intake^{30,31} though not all studies confirm this potential protection.³² Alcohol intake after diagnosis is not related to survival outcomes,³³ but intake before diagnosis is associated with reduced mortality in some studies.³⁴⁻³⁵ Thus, across several lifestyle factors and breast cancer, we see a range of associations that highlight differing impact according to age and timing in relation to onset or survival.

COLON CANCER

From colon cancer, we have additional precision in understanding the action of causal and protective factors through the study of an intermediate marker, colon polyps, which have a likely range of 10 to 20 years of growth to become invasive. Thus, we can evaluate risk factors for polyps, for invasive cancer, and for mortality.

Compelling evidence is unfolding that suggests folate, for example, may influence colorectal cancer risk differentially by timing of exposure. Epidemiologic evidence evaluating the role of dietary folate supports an inverse association between dietary folate, or multivitamins containing folate, and the risk of colorectal cancer and adenoma.³⁶ However, more recent animal³⁷ and epidemiologic studies, have reported null or positive associations between folic acid supplementation and adenoma recurrence.^{38,39} Of particular interest, the Aspirin/Folate Polyp Prevention Trial reported a 67% increased risk of advanced lesions with high malignant potential, and a less than two-fold increased risk of having at least three adenoma among the folic acid supplementation group. Additional analyses of this trial support the hypothesis that adequate folate is beneficial, but only up to a threshold level, beyond which there is no additional benefit.⁴⁰ These apparent contradictions can be understood in terms of the dual role of folate in DNA pathways. In the setting of normal mucosa, folate deficiency can lead to DNA instability, and uracil misincorporation,⁴¹ thus dietary folate sufficiency will reduce the risk of early transformative stages of colorectal carcinogenesis. However, in the setting of a preneoplastic lesion, which is undergoing accelerated cell divisions, folate deficiency can act as it does in chemotherapy—rendering DNA synthesis less effective and suppressing the promotion of small adenoma toward carcinoma.⁴² For preneoplastic or neoplastic tissue, folate sufficiency or supplementation provides the substrates for tumor replication and growth, increasing the likelihood that a small lesion would progress. Once carcinoma has developed, chemotherapy treatments such as fluorouracil rely on antifolate activity to suppress the growth of the colorectal tumor. The effect of folate status on prognosis of colorectal cancer has been less studied, but in one large prospective analysis, prediagnostic plasma folate levels did increase or predict later mortality.⁴³ Thus, from normal mucosa to cancer prognosis and mortality, folate has a complex and at times, contradictory effect.

Smoking provides another example of differential effects during the time course of colorectal carcinogenesis. Early studies on smoking and colorectal cancer were largely null, however, when colorectal

Fig 1. Nonparametric regression curve for the relationship between total calcium intake and colorectal cancer. We excluded participants in the top 1% of total calcium intake in each study to avoid excessive influence of extreme intake and treated the studies as a single data set.⁴⁹

adenoma was subsequently examined as the end point, the associations were strong and consistent.⁴⁴ These results support the hypothesis that cigarette smoking is involved in the initiation of colorectal adenoma from normal mucosa and once a sufficient lag-time has been accounted for, the increased risk of colorectal cancer associated with smoking becomes apparent. A recent meta-analysis supports this mechanism showing that current smokers have a higher risk of colorectal cancer than former smokers, suggesting that smoking may cause early-stage damage to normal, healthy colorectal mucosa that is irreversible.⁴⁵ The impact of cigarette smoking on survival has been addressed among patients with stage III colon cancer and evidence indicates that smoking history before diagnosis may be important prognostic factor.⁴⁶

Other dietary factors exemplify the importance of evaluating the role of an individual risk factor in terms of the time course of disease. For example, clinical trials of calcium supplementation support an inverse association between calcium supplementation (1,200 to 2,000 mg/d) and the recurrence of colorectal adenoma,⁴⁷ the protective effects of which remains for several years after supplementation has ceased.⁴⁸ Combined dietary intake data from 10 prospective cohort studies shows a steady decline in risk of colon cancer with increasing calcium intake at baseline for intakes up to approximately 1,000 mg/d and little further reduction in risk with additional intake (Fig 1).⁴⁹ The effects of calcium intake on survival are unstudied.

One example of a factor that appears to reduce risk at each level of colon carcinogenesis is vitamin D. Although not strictly a dietary factor, vitamin D status (measured by dietary intake or plasma levels) has been associated with a reduced risk of colorectal adenoma,⁵⁰ colorectal cancer,⁵¹⁻⁵² and colorectal cancer survival.⁵³⁻⁵⁴ Similarly, higher levels of physical activity have been consistently associated with a reduced risk of colon adenoma⁵⁵ and colon cancer.⁵⁶ Recent evidence suggests that postdiagnostic physical activity can also improve survival.^{57,58} Other energy balance-related factors, such as obesity, have been associated with the progression of adenoma and colorectal cancer⁵⁹ but have not been associated with recurrence or death in patients with stage III colon cancer (Cancer and Leukemia Group B).⁶⁰

LUNG CANCER

Smoking and lung cancer has been modeled to show strong effects for age at starting to smoke (initiation) and duration of smoking—implying both an initiation and an additional later promoter effect.⁶¹ Genetic events that underlie the transition from normal epithelium to hyperplasia, squamous metaplasia, dysplasia, carcinoma in situ, and to invasive carcinoma in the lung are well-documented.⁶² The rapid drop in incidence after cessation from smoking adds further evidence on the importance of a late promoter effect of current smoking among middle aged and older adults.⁶³ Smoking after diagnosis has further adverse effects among patients with lung cancer increasing risk of second cancers and poor survival.⁶⁴ Head and neck cancer clearly show etiologic impact for smoking and also the impact of smoking after diagnosis. After a diagnosis of oral cancer, continuing to smoke is associated with increased risk of oral cavity, pharynx, esophagus, and lung cancers; risk of second cancer was significantly reduced five or more years after cessation,⁶⁵ and quitters are more likely to survive through 18 months.⁶⁶ These data highlight the importance of cessation services for all smokers treated for cancer.

PROSTATE CANCER

Evidence for an association between obesity and prostate cancer has been largely equivocal. However, more recent analyses have suggested this may result from a failure to separate low grade from aggressive and metastatic tumors.⁶⁷ Obese men tend to have lower levels of testosterone, which may decrease their risk of developing lower-grade tumors. However, tumors that develop in this low testosterone environment may be more aggressive.⁶⁸ A recent meta-analysis reported that obesity was only associated with risk of advanced disease when the tumors were examined separately.⁶⁹ This finding was supported in subsequent studies, which also found an inverse association of obesity and low-grade tumors.⁷⁰⁻⁷¹

In contrast, data suggests that lycopene may benefit both prostate cancer prevention and recurrence. However, the evidence is quite limited. As with obesity, evidence increasingly suggests differential associations by tumor grade. A recent qualitative review suggested that the low-grade tumors largely detected during PSA screening are not associated with lycopene, but lycopene is protective against advanced and metastatic disease.⁷² For example, the Health Professionals Follow-Up Study found tomato sauce intake was inversely associated with total prostate cancer incidence, although these tumors largely arose in the pre-PSA era, and was stronger for advanced-stage tumors.⁷³ However, a later analysis, which included more PSA-detected tumors, found the association for total incidence was significantly attenuated, but a strong inverse association was found for metastatic prostate cancer.⁷⁴ A randomized trial found lycopene supplementation reduced PSA doubling time in men treated with orchiectomy for metastatic prostate cancer.⁷⁵

SPARSE DATA: THE CHALLENGE OF PROGNOSIS

Defining when a factor impacts progression among those with a specific cancer diagnosis will inform interventions to complement standard therapy among cancer survivors. However, while numerous models have been developed relating lifestyle factors, family history

Table 1. Timing of Exposure in Pathway to Incidence and Mortality: Links Between Lifestyle Factors and Premalignant Lesions, Invasive Cancer, and Cancer Survival

Exposure	Premalignant Lesion	Invasive Cancer	Survival
Colon			
Smoking	Increases risk	Increases risk (after lag)	Worsens
Folate, higher levels	Increases risk of progression from small to large	Reduces risk	—
Vitamin B6, deficiency	Increases risk	Increases risk	—
Regular physical activity and weight control	Reduces risk	Reduces risk	Improves
Vitamin D			
Deficiency	Increases risk (particularly progression)	Increases risk	
Higher levels			Improves
Breast			
Radiation	Increases risk (after lag)	Increases risk (after lag)	Improves (as treatment)
Obesity	Reduces risk	Premenopausal - Reduces risk Postmenopausal - Increases risk	Worsens
Regular physical activity	Reduces risk	Reduces risk	Improves
Prostate			
Obesity		Increases advanced disease	—
Lycopene, higher levels		Reduces advanced disease	—
Lung			
Smoking	Increases risk	Increases risk	Worsens

NOTE. — indicates no known association.

and screening cancer incidence,^{69,76} models predicting survival are largely limited to tumor characteristics and therapy.⁷⁷ As indicated in the summaries for specific cancers (Table 1), new studies are emerging to address lifestyle after diagnosis and risk of recurrence and overall survival.

Obesity is assessed in many clinical studies and serves as the most consistently evaluated lifestyle factor, although body fat distribution and other refinements beyond BMI have yet to be thoroughly evaluated. It is related to survival after postmenopausal breast cancer, but evidence that weight loss among postmenopausal women reduces incidence is far stronger⁷⁸ than the limited evidence that weight loss after diagnosis reduces risk of recurrence.⁷⁹ The role of obesity in colon and prostate cancer survival is also being studied, though data are fewer than for breast cancer.

Physical activity, in contrast, appears to reduce incidence of breast cancer (among both pre- and postmenopausal women),^{11,14} and after diagnosis higher activity levels are associated with significant reduction in disease-specific and total mortality.¹⁶ For colon cancer, similar patterns are observed with reductions in incidence⁵⁶ and improved survival⁵⁸ among men and women with higher levels of physical activity. Recent evidence suggests that higher physical activity levels may reduce overall mortality among patients with prostate cancer.⁸⁰ Few studies have addressed diet patterns and survival for any of the leading cancers, but evidence does not appear to support an important role for diet.¹⁹

Recommendations for increased physical activity for breast and colon cancer survivors is well-justified. Furthermore, evidence from randomized controlled trials shows that provider-delivered messages translate to change in behavior, not just for smoking, but also for physical activity.⁸¹

Not all risk factors relate to survival as we have summarized. Some, like radiation, may operate uniquely as initiating agents in the pathway. In etiology, time course matters for several reasons. First, it provides insight to when a risk factor operates on the development of the carcinogenic process. This then informs both when preventive interventions must be focused and when the subsequent benefit from intervention will be observable in terms of cancer incidence. Additional key issues to be addressed when framing prevention efforts include the time course from behavior change to reduction in risk of onset or recurrence and the magnitude of change necessary to obtain health benefits. Additional insight from early life exposures, including physical activity and prevention of breast cancer, suggests a growing role for oncologists in advising strategies for family members to reduce risk in offspring.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

SUMMARY

If a risk factor operates differently for those at different ages, or for incidence and mortality from a specific cancer, then prevention messages must be appropriately framed. For example, rigorous implementation of smoking cessation for patients with head and neck cancer is necessary given the high risk of second cancers and mortality among survivors who continue to smoke. Likewise rec-

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