本田財団レポート No.108
第２５回本田賞授与式　記念講演（２００４年１１月１７日）

「研究進捗レポート：最良の食生活を求めて」

ハーバード大学パブリックヘルス校
栄養部門主任教授

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The Search for Optimal Diets:
A Progress Report

Commemorative Lecture at the Twenty-Fifth Honda Prize
Awarding Ceremony on the 17th November 2004 in Tokyo

Walter C. Willett
Professor of Epidemiology and Nutrition,
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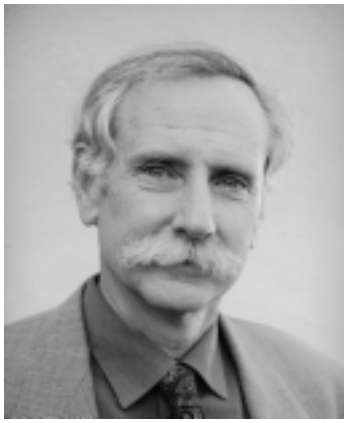


■略歴

1945 年	米国ミシガン州ハートで生まれる
1970 年	ミシガン大学医学部で医学博士号
1973 年	ハーバード大学公衆衛生大学院で修士号（公衆衛生）
1980 年	ハーバード大学公衆衛生大学院疫学科で博士号（公衆衛生）
1980～84 年	ハーバード大学公衆衛生大学院衛生学科 助教授
1984～87 年	ハーバード大学公衆衛生大学院衛生学科 準教授
1986～92 年	ハーバード大学医学部 講師
1987 年～	ハーバード大学公衆衛生大学院疫学 栄養学教授
1991 年～	ハーバード大学公衆衛生大学院栄養学科 学科長
1992 年～	ハーバード大学医学部 教授

■受賞歴（1990 年以降）

1994 年	全米ガン協会よりガン予防賞
1996 年	米国予防腫瘍学協会より功労賞
1997 年	近代栄養学国際賞
2001 年	ゼネラル・モーターズ・ガン研究基金よりチャールズ・S・モット賞
2003 年	国民薬学賞優秀賞（公衆衛生研究・交流）

執筆活動：

1998 年	「食事調査のすべて　栄養疫学　[第 2 版]」（第一出版）
2001 年	「太らない、病気にならない、おいしいダイエット」（光文社）

他に 900 以上の論文が出版されている

■Personal History

1945	Born in Hart, Michigan, USA
1970	M.D. University of Michigan Medical School
1973	M.P.H. Harvard School of Public Health
1980	Dr. P.H. Harvard School of Public Health, Epidemiology
1980-84	Assistant Professor of Epidemiology, Department of Epidemiology, Harvard School of Public Health
1984-87	Associate Professor of Epidemiology, Department of Epidemiology, Harvard School of Public Health
1986-92	Lecturer in Medicine, Harvard Medical School
1987-	Professor of Epidemiology and Nutrition, Harvard School of Public Health
1991-	Chairman, Department of Nutrition, Harvard School of Public Health
1992-	Professor of Medicine, Harvard Medical School

■Awards (from 1990 onward)

1994	American Cancer Society Cancer Prevention Award
1996	Distinguished Achievement Award, American Society for Preventive Oncology
1996	John Snow Award, APHA
1997	International Award for Modern Nutrition
2001	The Charles S. Mott Prize for most outstanding recent contribution related to the cause or prevention of cancer. General Motors Cancer Research Foundation
2003	People's Pharmacy Award for Excellence in Research and Communications for the public Health

Publications:

1998	“Nutritional Epidemiology”
2001	“Eat, Drink, and Be Healthy”

other over 900 articles has published.

このレポートは、平成 16 年（2004 年）11 月 17 日　ホテルオークラにおいて行われた第 25 回本田賞受賞記念講演の要旨をまとめたものです。

17 November, 2004

The Search for Optimal Diets: A Progress Report

Walter Willett, M.D., Dr.P.H.

Good evening ladies and gentlemen.

Being here this evening to receive an award from the Honda Foundation is a great honor, and I wish to thank all those who have made this possible. In particular I would like to thank the Honda Foundation for recognizing the efforts of those who work to improve our environment, and to Mr. Ishihara and Mr. Ban for their kind hospitality in making the arrangements for this visit. I am especially grateful that several of my colleagues from Japan are able to join us this evening.

Before beginning, I would like to acknowledge the work of many colleagues with whom I have worked to better understand the relation between diet and health. Dr. Frank Speizer started the Nurses' Health Study in 1976, which provided a launching pad for my research. Drs. Meir Stampfer, Graham Colditz, David Hunter, JoAnn Manson, Sue Hankinson, Eric Rimm, Ed Giovannucci, Frank Hu and many others have been an integral part of this work for many years. Many dozens of other colleagues, post doctoral fellows, and students have contributed to this work; I will mention a few of them specifically later. I am also grateful to Dr. Bruce Ames, a former Honda Foundation awardee, for nominating me. Dr. Ames has been an intellectual inspiration to me and countless others for many years.

Today I will describe our work on the development of the field of nutritional epidemiology. Like any aspect of science, progress is enhanced by the intellectual interactions of many individuals. I would in particular like to recognize the contributions of the late Dr. Tsuyoshi Hirayama, who envisioned that much could be learned from the study of dietary habits in large populations.

The Development of Nutritional Epidemiology

The foundation of modern epidemiology, which aims to understand the causes of human disease, largely rests on work of Sir Richard Doll and colleagues in England. Half a century

ago, Doll documented a clear relation between cigarette smoking and lung cancer, which established a paradigm for the identification of modifiable causes of disease. Nutritional epidemiology uses epidemiologic methods to understand the role of nutritional factors in the cause and prevention of disease. The development of this field was fueled by studies of rates of disease among different countries. Most importantly, the incidence rates of most major diseases were found to vary greatly among countries. For example, rates of breast cancer in most parts of Asia, Latin America, and Africa were less than one fifth the rates in northern Europe, and these rates were strongly correlated with per capita intake of fat. In the 1960's, for example, breast cancer rates in Japan were very low and so was fat intake, about 10% of calories (figure 1).

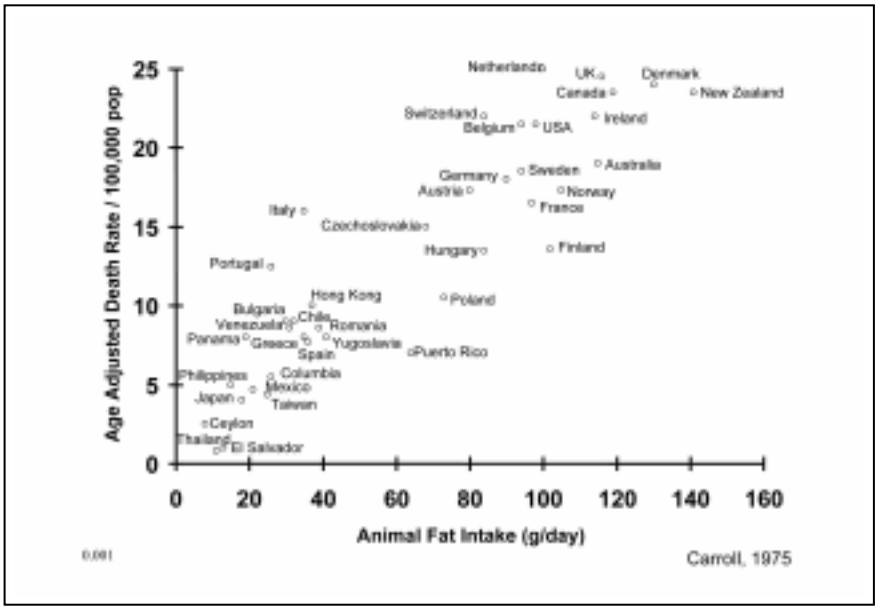


figure 1

Rates of colon cancer varied even more dramatically, and these were associated with intake of red meat; again fifty years ago Japan had among the world's lowest rates (figure 2).

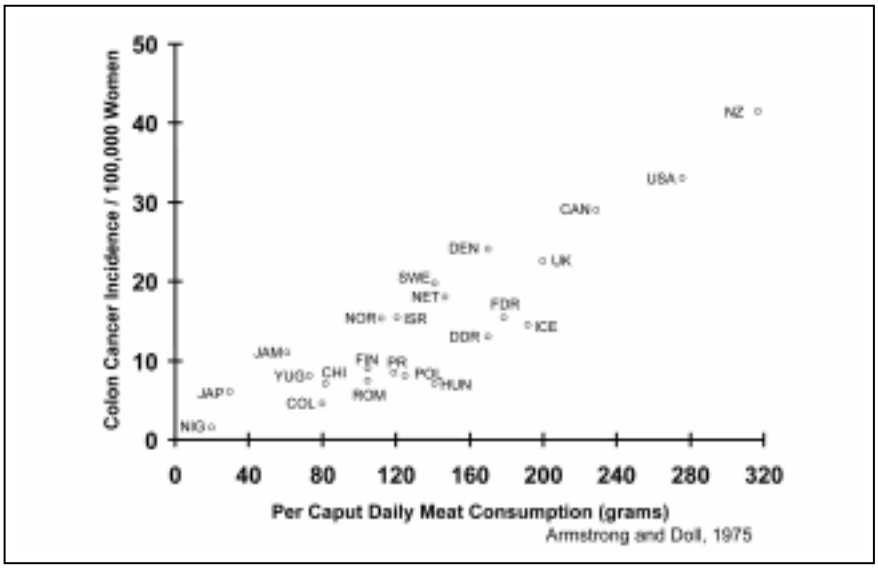


figure 2

Also, in an international study initiated by Dr. Ancel Keys, coronary heart disease mortality rates differed more than ten-fold among countries; rates were low in Japan and in the Mediterranean countries (figure 3) and were approximately ten-fold higher in Northern European countries and the U.S. Interestingly, total fat intake was high in both the lowest risk area, the Greek island of Crete, and in the highest risk area, northern Finland. However, the type of fat differed greatly as it was olive oil in Crete and butter in Finland.

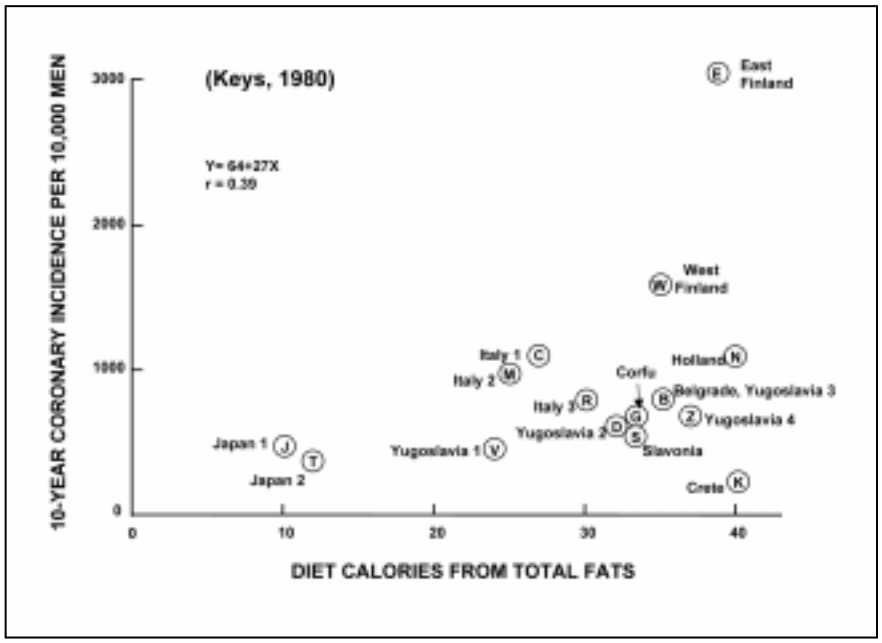


figure 3

The strong correlations among countries between aspects of diet and disease rates should be interpreted with great caution because many other aspects of diet and lifestyle, including physical activity and reproductive patterns, also differed between the traditional cultures in Asia, the Mediterranean, and Africa and those of Europe and North America. One possible explanation for the large differences in disease rates among countries could be variation in genetic factors. This possibility was addressed by examining populations that migrated from countries with low rates to countries with high rates. In almost every instance, the cancer and heart disease rates of migrating populations have become similar to those of the new home country. For example, among Japanese populations migrating to Hawaii, after two generations rates of breast cancer were similar to those of Caucasians in the U.S. (figure 4). Not all has been bad for migrants, though, because the rates of stomach cancer, which were extremely high in Japan, declined dramatically upon moving to Hawaii. These studies of migrants were fundamentally import because they clearly indicated that the high rates of specific cancers and of cardiovascular disease seen in some populations were not inevitable. This provided a strong incentive to identify the causal factors, with the expectation that most of these diseases could potentially be prevented if these factors were modified.

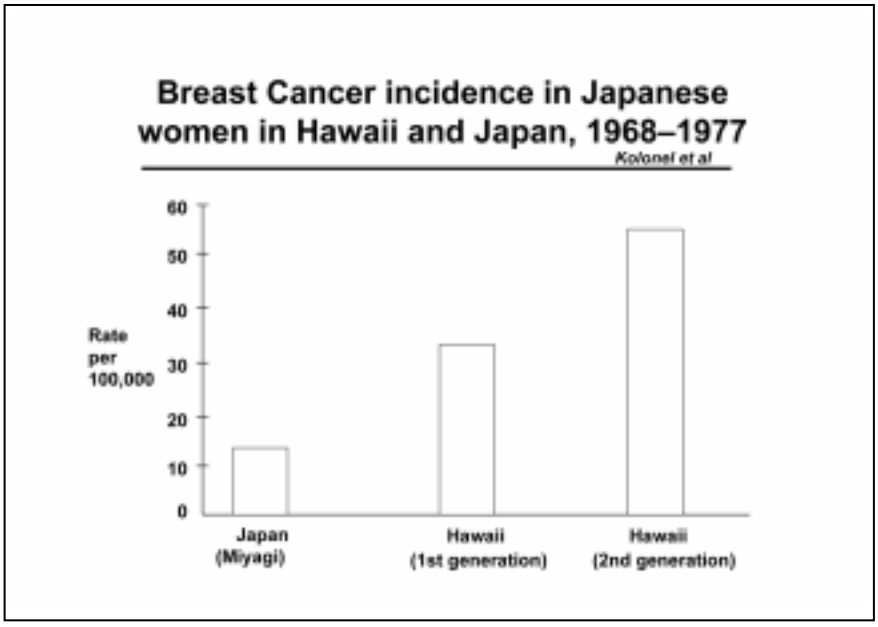


figure 4

As time has passed, we have also seen that disease rates within countries can change dramatically, for example, rates of colon cancer have been rising strikingly within Japan and have now even surpassed those of the U.S., the speed at which these disease patterns can change is truly remarkable. On the other hand rates of stomach cancer have declined sharply in the U.S. during the last eighty years, where it is now a rare cause of death, and more recently decreases are occurring in Japan. This provides further evidence that environmental and lifestyle factors, not genetics, are the primary determinants of disease rates.

Given this background, many epidemiologists have worked to identify the specific factors that influence risks of important chronic diseases. Our research group has established three large prospective studies (figure 5).

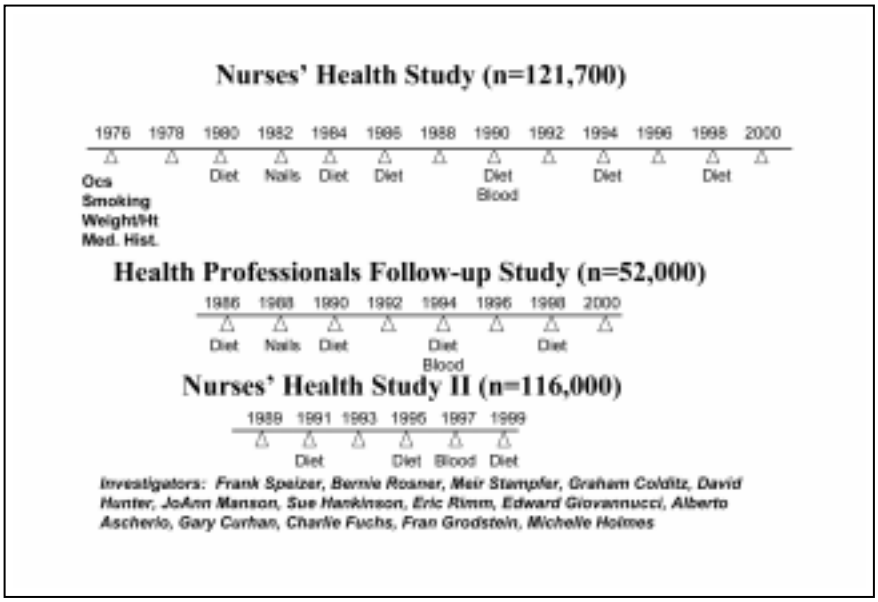


figure 5

The Nurses' Health Study began in 1976 under the leadership of Dr. Frank Speizer and enrolled 121,000 women, initially to study the long term effects of oral contraceptives. In 1989 we enrolled 52,000 men who were also health professionals, and in 1989 we enrolled another 116,000 younger women to study risk factors in early adult life. In each study, medical history, smoking, physical activity, and diet are collected every 2-4 years and the occurrence of major diseases is monitored. This allows us examine specific aspects of diet, and changes in diet over time, controlling for family history of specific diseases, smoking, and other behaviors. We have also collected toenail clippings, which are used to measure intake of trace minerals and heavy metals, and blood samples, which are used for hormonal and nutrient analyses and to determine genetic risk factors using DNA.

The central challenge in nutritional epidemiology has been to measure dietary intake of individuals in a way that was sufficiently inexpensive to study large populations, which is essential for studies of cancer and heart disease, and to be able to repeat the assessments of diet over time. Many thought that this was impossible. Almost every epidemiologist who has considered this challenge has concluded that some form of a food frequency questionnaire (FFQ) was the most reasonable method (figure 6).

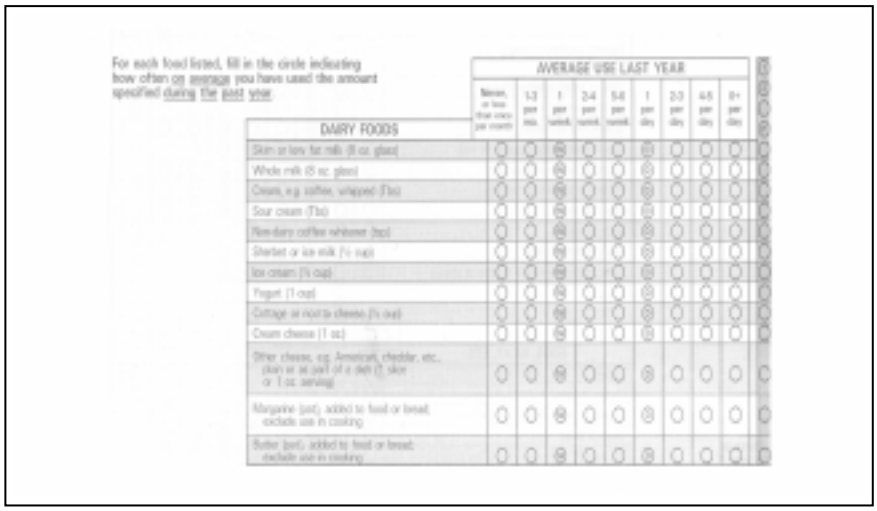
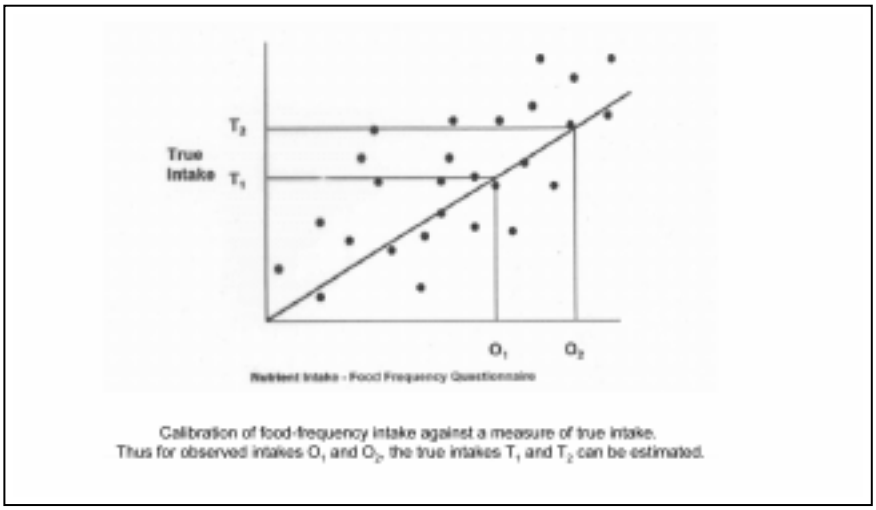


figure 6

Thus, using a series of pilot studies, we carefully selected the most important foods in the U.S. diet, approximately 130 items, and included them on our questionnaire. For each food we ask about the average use over the past year, not just in the past few days, because it will be longer term intake that is related to risk of cancer and cardiovascular disease. We also include a detailed assessment of nutritional supplement use on the questionnaires. Our forms are optically scannable, which greatly reduces the cost and time for processing. The data on food intake are then linked to a comprehensive food composition database that converts information on food consumption to intake of nutrients. Because of skepticism that the diets of free living individuals could be measured, we have examined the validity of this

information in many ways. For example, we studied in great detail several hundred participants who had completed our standardized dietary questionnaire; participants completed meal by meal records of everything they ate, using a scales to measure quantity, during four one-week periods over a year. When we compared nutrient intakes calculated from the food frequency questionnaire and from the diet records, good correlations were seen between methods. The data from this detailed study can also be used as a form of calibration in which the intakes assessed by the standardized questionnaires used in our large populations can be converted to more quantitative measures of intake (figure 7).



Calibration of food-frequency intake against a measure of true intake.
Thus for observed intakes O_1 and O_2, the true intakes T_1 and T_2 can be estimated.

figure 7

My colleagues and I have developed a series of statistical methods that use this data to correct for measurement errors when we assess the relation of dietary intake to risk of disease, but I won't go into these details here. Also, we examined the relation between dietary intakes and factors measured in blood known to be influenced by diet. For example, the food frequency questionnaire correctly predicted the relation between intake of folic acid and blood levels of homocysteine, a risk factor for cardiovascular disease (figure 8).

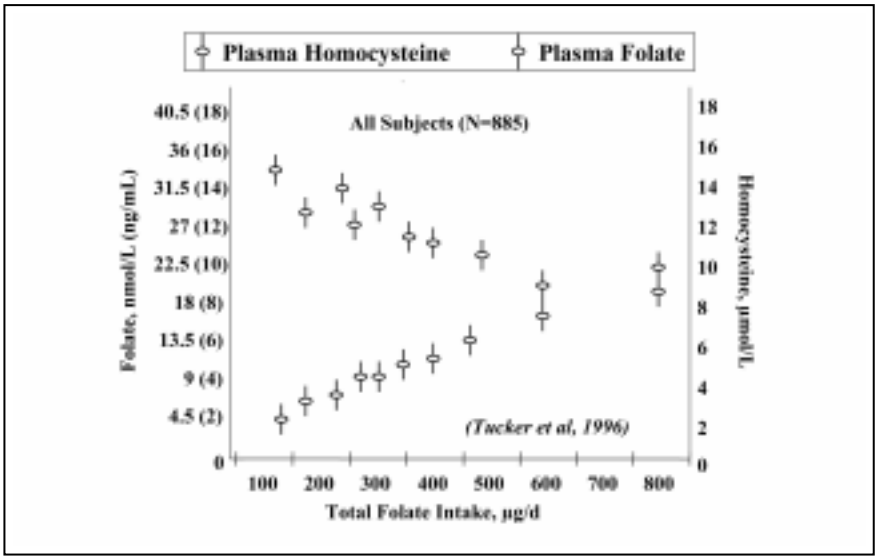


figure 8

We have further shown that the repeated measurements of diet over time improve the measurement of long term dietary intake. Thus, we can be confident that our methods to assess long term diet do provide useful information and can be used to test dietary hypotheses in human populations. This has been the most critical step in the development of nutritional epidemiology.

Findings on diet and disease

In our large studies we have examined many aspects of diet in relation to risks of many diseases, including heart disease, stroke, diabetes, many cancers, kidney stones, gallstones, and degenerative diseases of the nervous system, including decline in cognitive function. Here I will provide just a few examples.

Cardiovascular Disease

Trans fatty acids, or trans fat, have become a common component of many foods worldwide, including fast foods that are sold almost everywhere . Trans fats are created by a process called partial hydrogenation that is used to convert natural liquid vegetable oils to solid fats (figure 9).

figure 9

For example, American fast food companies buy blocks of trans fat to prepare the French fries sold all over the world. In the process of partial hydrogenation, unsaturated fatty acids, which are naturally bent, become straightened out, which can potentially alter their biological function (figure 10). The natural unsaturated fats can reduce blood cholesterol levels,

reduce the chances that clots will form in the coronary arteries, and decrease the probability of fatal heart rhythm disturbances, thereby reducing the risk of heart disease. I became concerned about the effects of partial hydrogenation and the artificial trans fats that it produces , and we began to study trans fats in the late 1970's. After 14 years of follow-up in the Nurses' Health Study, nearly 1000 women had developed coronary heart disease. As shown (figure 11), we found that trans fat was strongly associated with risk of heart disease. On the other hand, and as expected, natural monounsaturated and polyunsaturated fat were related to lower risk of heart disease when compared to the same percentage of calories from carbohydrate. Thus, replacing trans fat in the diet with natural unsaturated fats can have large effect in reducing risk of heart disease. I should note that in this figure and those that follow, all of the relative risks are adjusted for age, smoking, physical activity, and other variables that may affect the outcome.

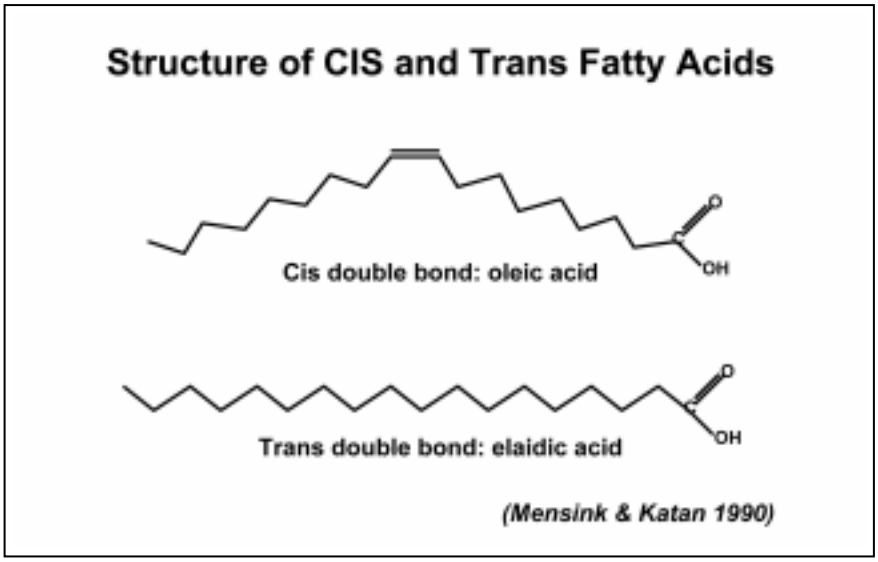


figure 10

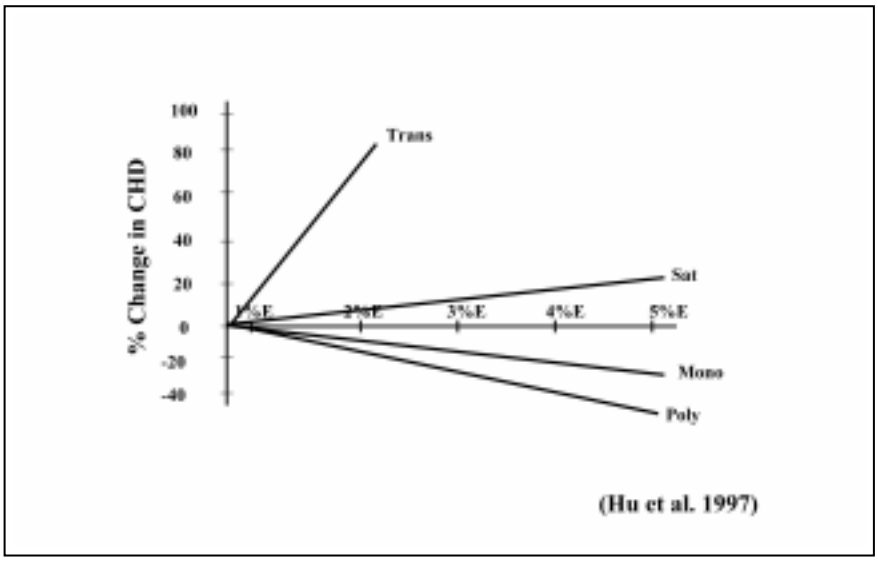


figure 11

In contrast to Western countries, where coronary heart disease has been the leading cause of death, hemorrhagic stroke has been a major reason for death in Japan. Some of my Japanese colleagues have identified very low intake of animal protein and saturated fat, which characterized the Japanese diet in the 1950's, as possible risk factors. Thus, Dr. Iso came to visit us and examine these relationships in our cohorts, which provided confirmation for this hypothesis (figure 12).

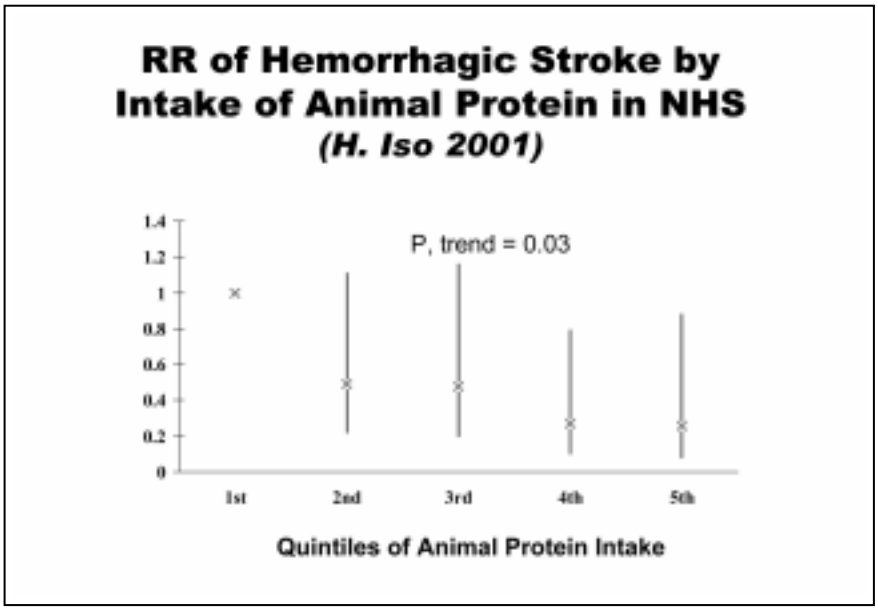


figure 12

Looked at another way, high intake of refined starch, such as white rice, was related to greater risk of hemorrhagic stroke; in contrast, intake of fiber from whole grain products such as whole wheat or brown rice was associated with lower risks of stroke. We have also seen that greater consumption of fish is associated with lower risks (figure 13).

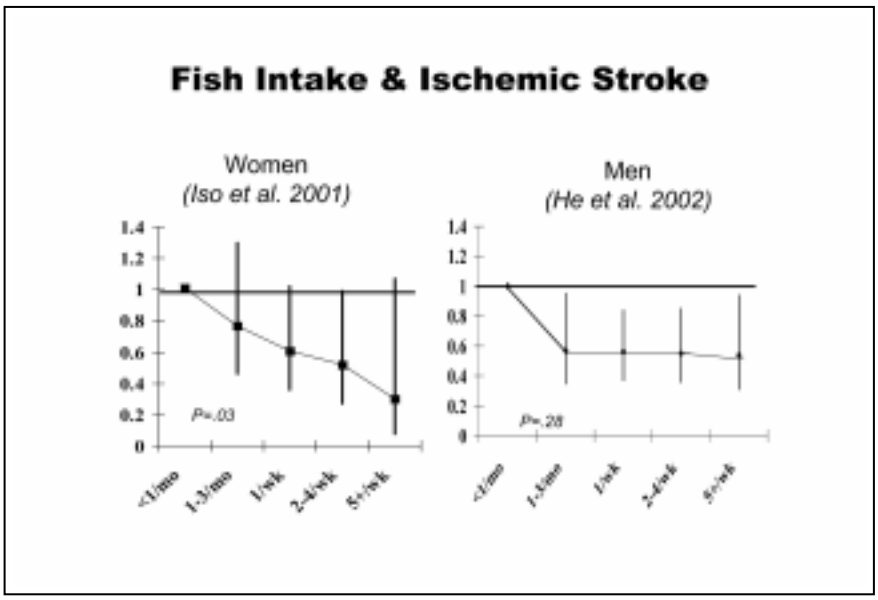


figure 13

Type 2 Diabetes

Rates of type 2 diabetes (the form of diabetes that usually starts in adulthood, but which is increasing seen in overweight adolescents) are increasing rapidly worldwide, including in both the U.S. and Japan. This is turning out to be a particularly serious issue for many Asian populations, which until recently had very low rates of diabetes; for this reason I will focus on this issue for a few minutes. The strongest factor for type 2 diabetes is over weight, which can be expressed as body mass index (figure 14).

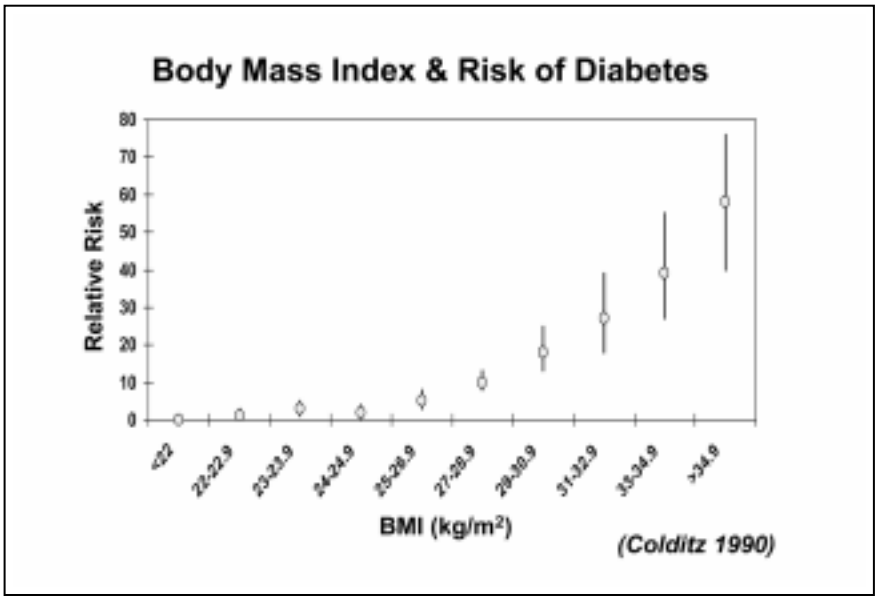


figure 14

In the U.S., the rates of diabetes in Japanese Americans have recently surpassed those of Caucasian Americans, even though Japanese American still weigh less, and I have heard that large increase are also occurring in Japan. There is now convincing evidence that genetic variation, what we have for years called the "thrifty gene", contributes to this higher risk. Some of my Australian colleges conducted a detailed study among healthy young adults from different ethnic groups who were matched for body weight. Even though all appeared perfectly healthy, those from Asia had greatly reduced insulin sensitivity, a precursor of diabetes, compared to those with a European or Arabian background (figure 15). Similarly, in our cohorts we have found a nearly two-fold increase in risk of type 2 diabetes in women with Asian or Hispanic backgrounds after controlling for body weight, diet, physical activity, and other lifestyle factors (figure 16). Because the populations of Asia had low rates of diabetes just a few years ago, we know that diabetes is not inevitable, and we have therefore looked hard to find the responsible nongenetic factors. Trans fat turns out to be one contributing aspect of diet (figure 17), and higher intake of polyunsaturated fat reduces risk, just as these types of fat influence likelihood of developing heart disease (figure 18).

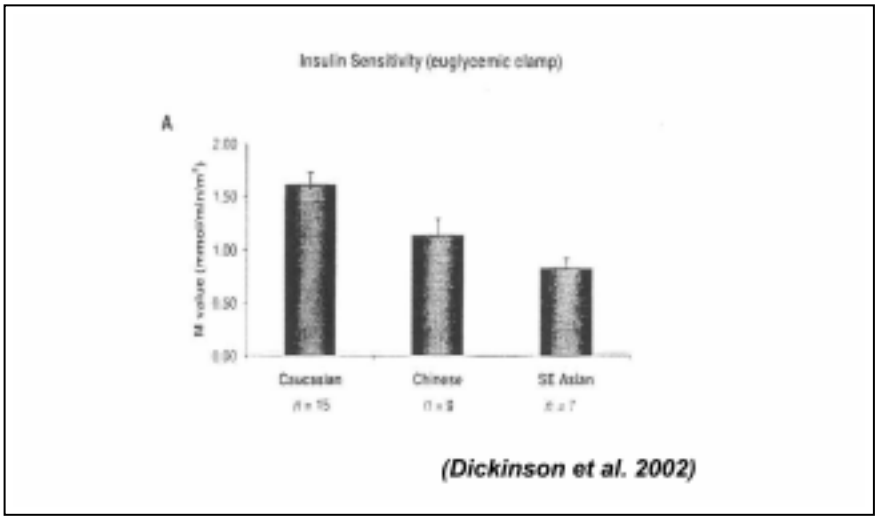


figure 15

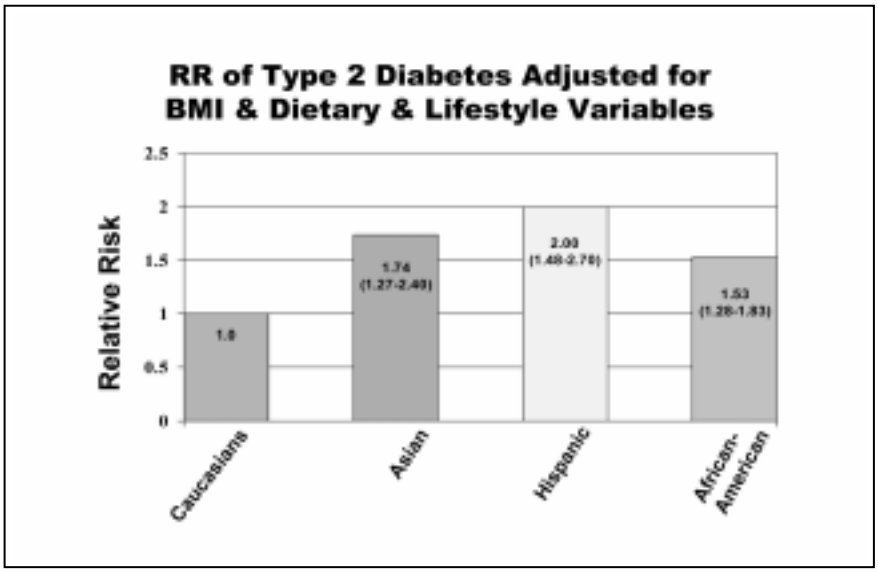


figure 16

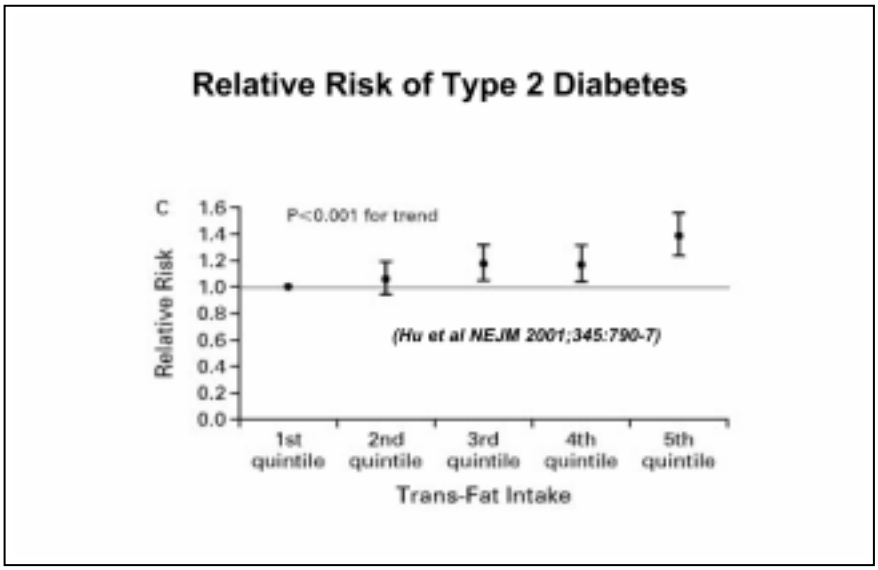


figure 17

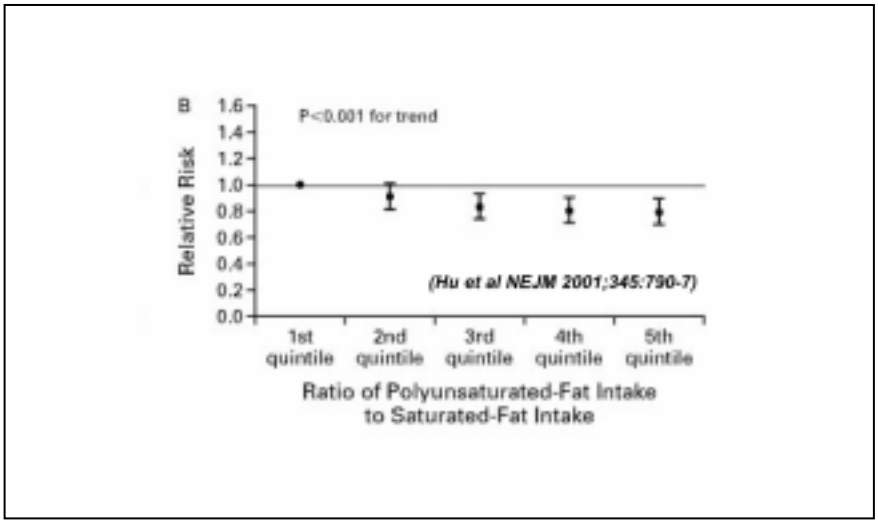


figure 18

Dietary glycemic load, meaning high intake of refined starches and sugar, was also related to higher risk (figure 19) and fiber from cereal products is related to lower risk (figure 20). If we examined intake of cereal fiber intake and glycemic load at the same time, we found that women with high dietary glycemic load and low cereal fiber intake, which would include those who ate large amounts of white bread or white rice, had two and one half times the risk of diabetes compared to women with low glycemic load and high cereal fiber intake (figure 21). Also, women who drank one coke or other sugar sweetened soda beverage daily, a very large source of sugar for many people, had nearly double the risk of type 2 diabetes (figure 22).

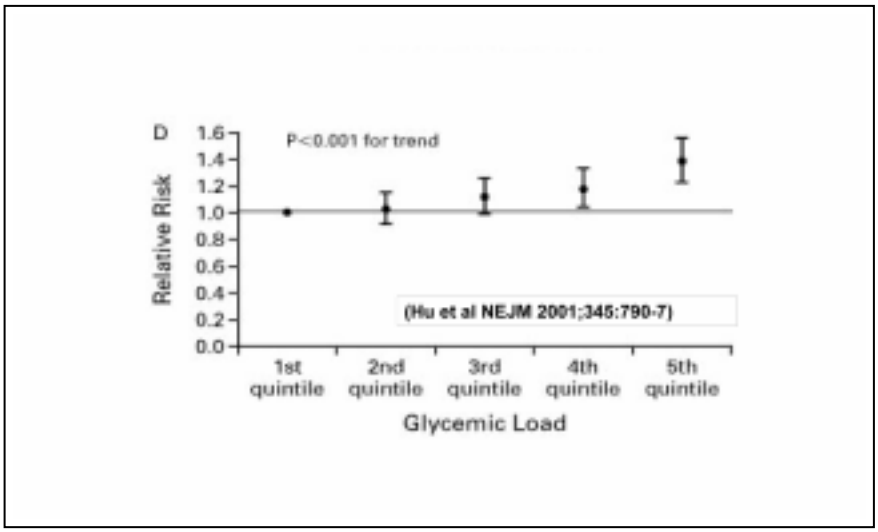


figure 19

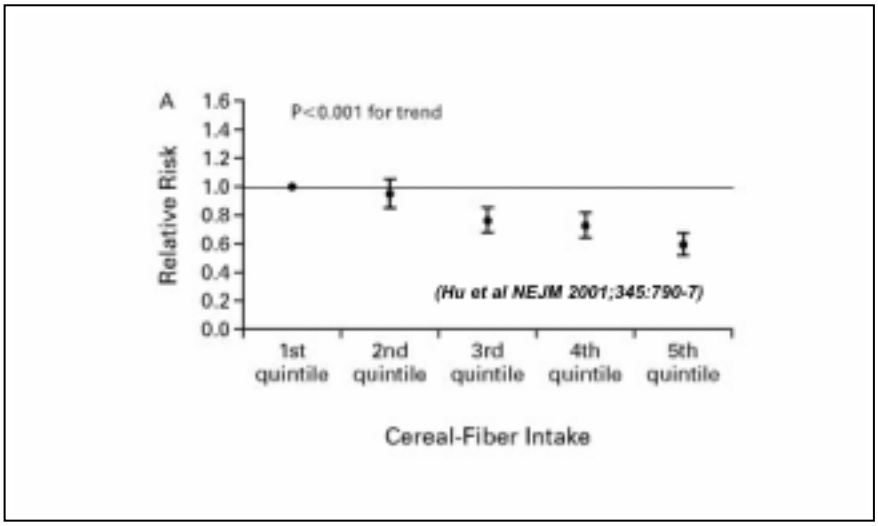


figure 20

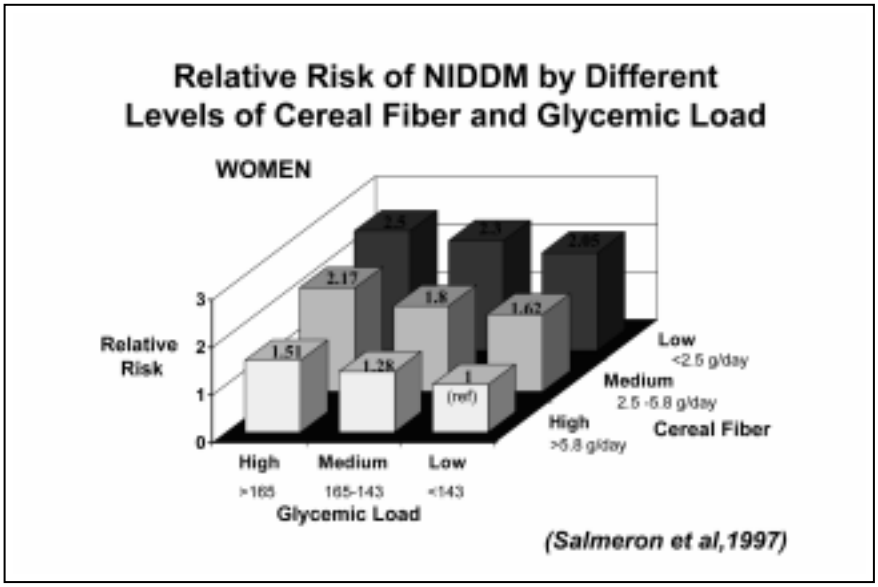


figure 21

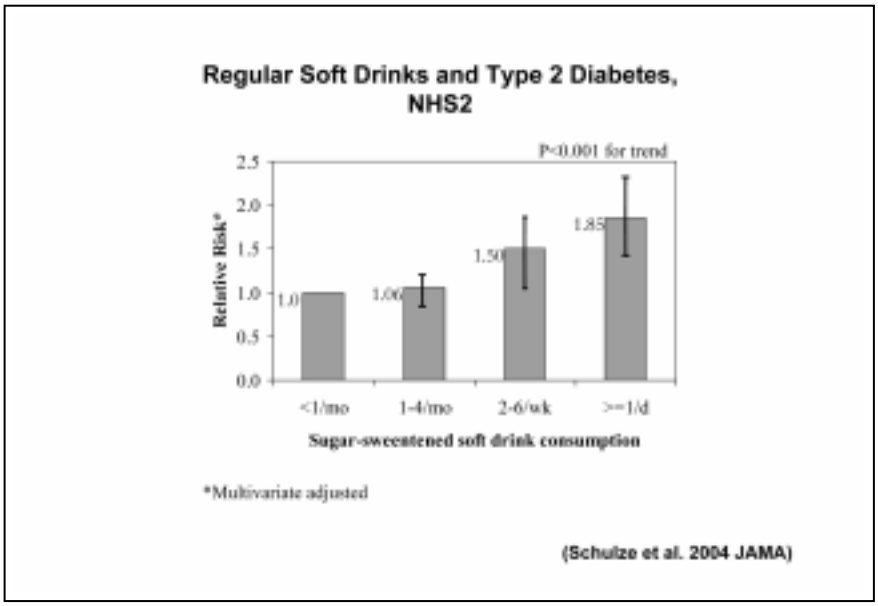


figure 22

One fundamentally important discovery over the last decade has been that the adverse metabolic effects of a high dietary glycemic load are greatly magnified in persons with a greater higher degree of insulin resistance. In other words, large surges of blood glucose due to the ingestion of high intakes of refined starch or sugar have a greater negative effect on blood lipid fractions in persons who cannot move glucose efficiently into cells because of insulin resistance. In our large population studies, we cannot measure insulin resistance directly, so we use body mass index as a surrogate because it is the most important cause of insulin resistance. As an example, as dietary glycemic load increases, we see increasing levels of fasting levels of triglycerides in the blood, which is a sensitive indicator of the adverse metabolic changes that occur with insulin resistance and type 2 diabetes. This increase is seen in women with a BMI of less than 25, but the rise is four times greater among women who have higher insulin resistance due to being overweight (figure 23). Similarly, we saw an overall two-fold increase risk of coronary heart disease with high dietary glycemic load, but in the very leanest women there was little increase in risk (figure 24). These findings have implications for all populations, but especially for those in Asia, both because of the common genetic predisposition to insulin resistance and because traditional diets based on white rice have a high glycemic load. With changes in lifestyle that lead to reductions in physical activity and even small gains in weight, insulin resistance develops, and the same diet that was compatible with low rates of diabetes can then become a cause of high rates of diabetes. This provides an interesting and important example of how nutrition can interact with other aspects of our environment and lifestyle to influence our health and well being.

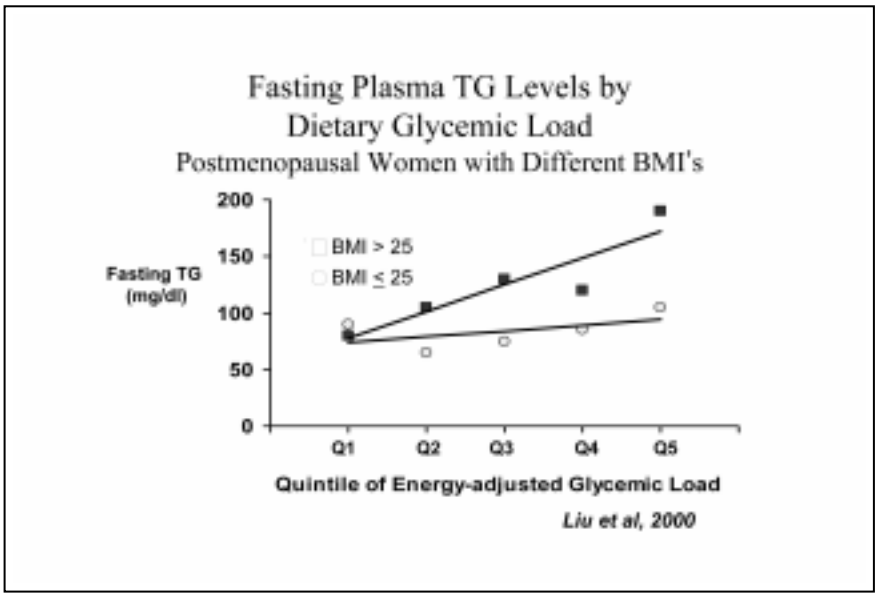


figure 23

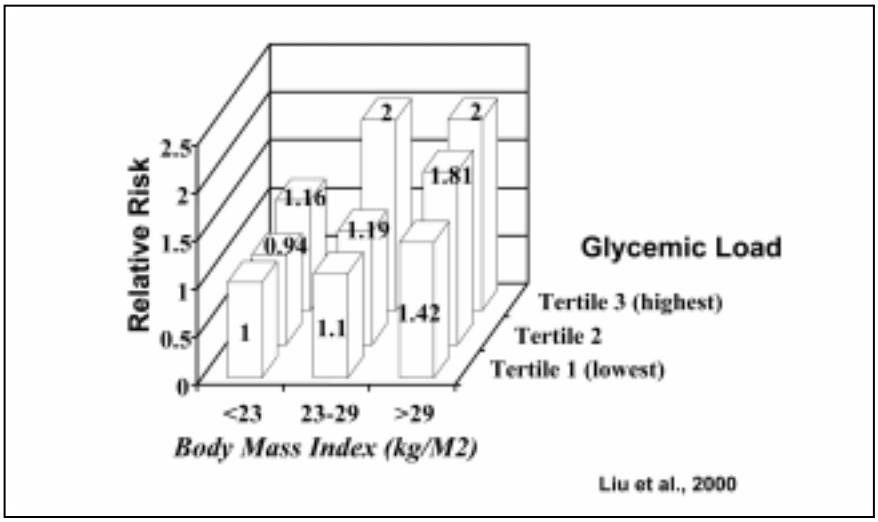


figure 24

Alcohol and Folic Acid

Another important interaction we have observed is that between alcohol consumption and folic acid. Many studies from all regions of the world have shown that persons who consume moderate amounts of alcoholic beverages, but not large amounts, have lower risks of heart disease. That is what we found in our cohort studies as well. Although the evidence is very strong, some people have questioned whether alcohol itself is protective, and have proposed that some other component of these beverages is responsible. However, using DNA samples that we collected and stored, we found that a common variant of the gene for alcohol dehydrogenase-3 (ADH3), an enzyme which metabolizes alcohol, was associated with both blood levels of HDL cholesterol (the good cholesterol) and risk of heart disease, depending on alcohol consumption (figure 25).

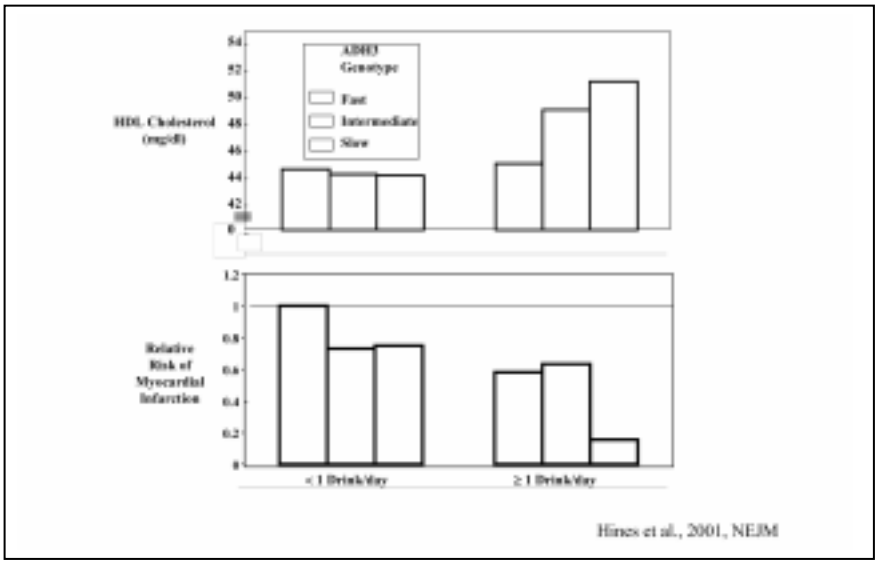


figure 25

Specifically, the form of this gene that leads to slower breakdown of alcohol, and thus longer time for alcohol to circulate, was related to higher HDL among moderate drinkers, but not among nondrinkers. Similarly, the slowly metabolizing form of this gene was related to lower risk of heart disease among alcohol drinkers, but little association was seen among nondrinkers. Because people receive one form or another of this gene from their parents more or less at random, and this gene is specifically involved in alcohol metabolism, these associations provide strong evidence that alcohol itself does reduce risk of heart disease.

When we looked at alcohol consumption and folic acid intake at the same time, we found that there was only a modest benefit of folic acid among nondrinkers (figure 26).

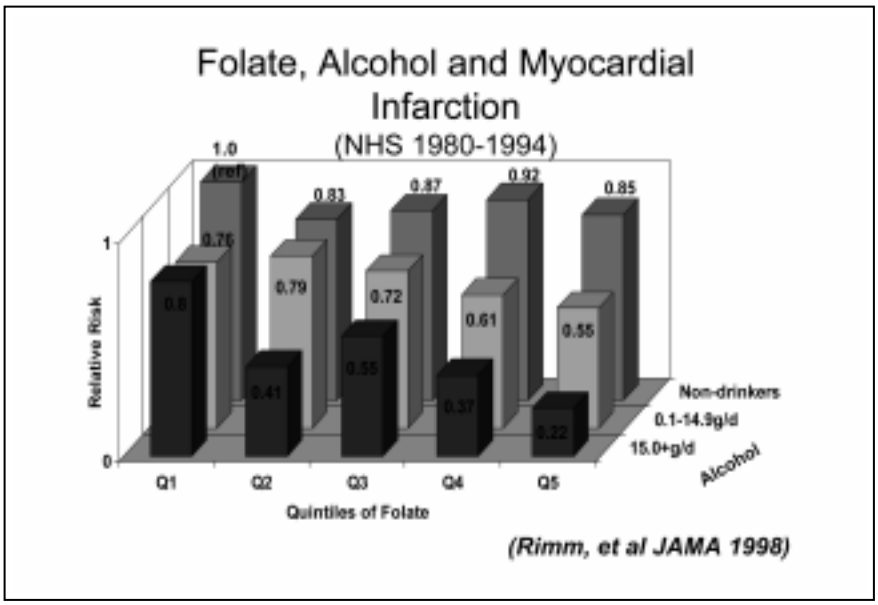


figure 26

However, among drinkers, higher intake of folic acid was associated with a substantially lower risk, probably in part because folic acid reduces blood levels of homocysteine. This is consistent with other data indicating that alcohol consumption can inactivate folic acid and thus increase the requirements of this vitamin. Interestingly, most persons in the highest category of folic acid intake achieved this by taking a multiple vitamin.

In contrast to heart disease, alcohol consumption modestly increases risks of breast and colon cancer (figure 27).

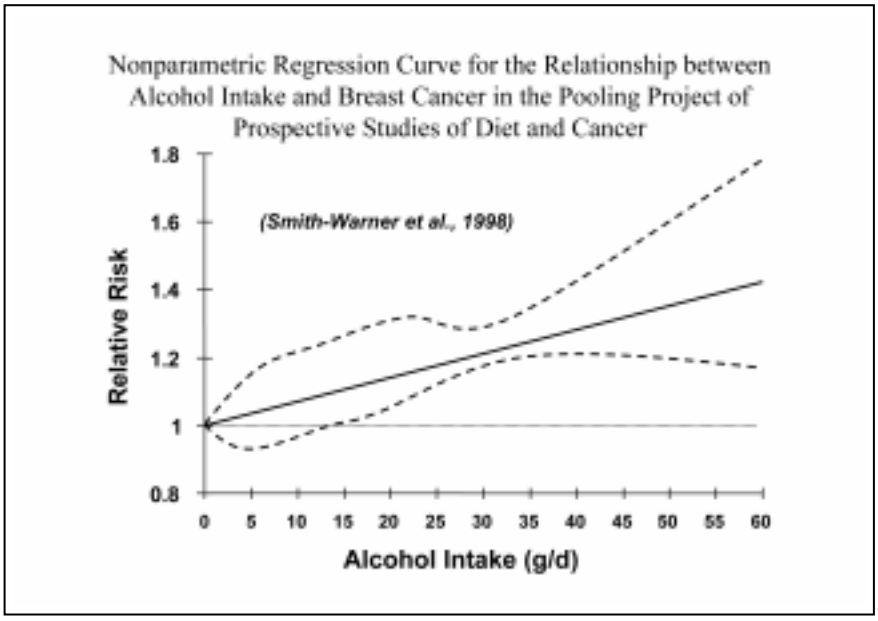


figure 27

Even one drink a day can increase breast cancer risk by about 10 percent. Fortunately, this excess risk appears to be limited to women who have inadequate intake of folic acid (figure 28).

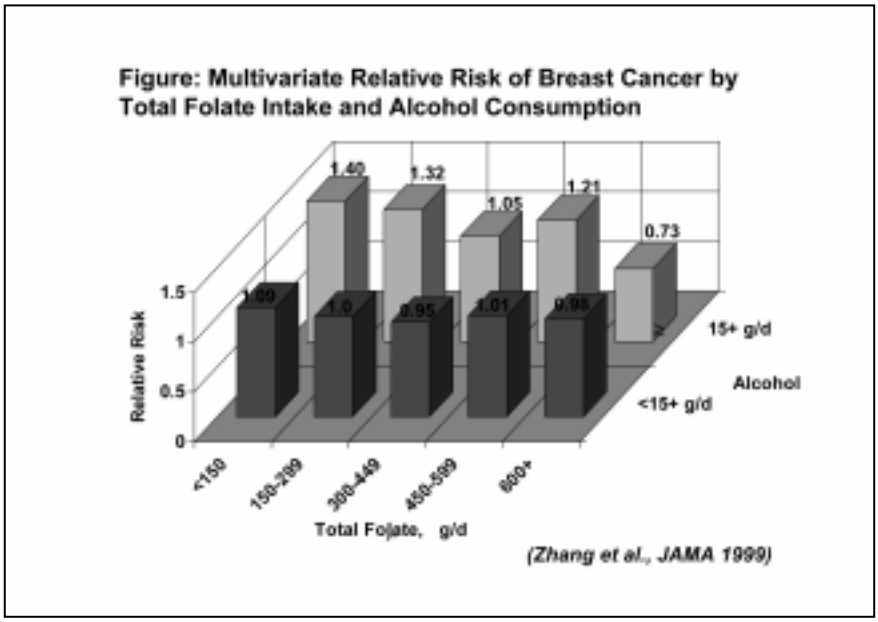


figure 28

Among women with adequate folic acid intake, those who consumed alcohol did not experience an increase in risk of breast cancer. In an analysis led by Dr. Giovannucci, we saw a similar pattern for colon cancer; overall, risk of colon cancer increased with greater alcohol consumption, but if folic acid intake was adequate there was little increase in risk. Thus, adequate folic acid intake is important for everyone, but especially for those who consume alcohol, even if only one drink a day. Although eating many fruits and vegetables will increase intake of folic acid, and has many other health benefits, the most reliable way to assure adequate folic acid intake is to consume a multiple vitamin containing folic acid.

Breast Cancer

Because of the strong correlation among countries between national per capita intake of fat and rate of breast cancer, we have examined this relation in detail within the Nurses' Health Study. In our first report after six years of follow-up, we found no association. Because of the strong belief in this relationship, this finding was controversial. However, with longer follow-up the number of cases of breast cancer has grown rapidly and we have still seen no relation between fat intake in mid life or later and risk of breast cancer, and this lack of association has now been seen in many studies. For example, after fourteen years of follow-up, nearly 3000 women in the Nurses' Healthy Study had developed breast cancer and there was still no association (figure 29).

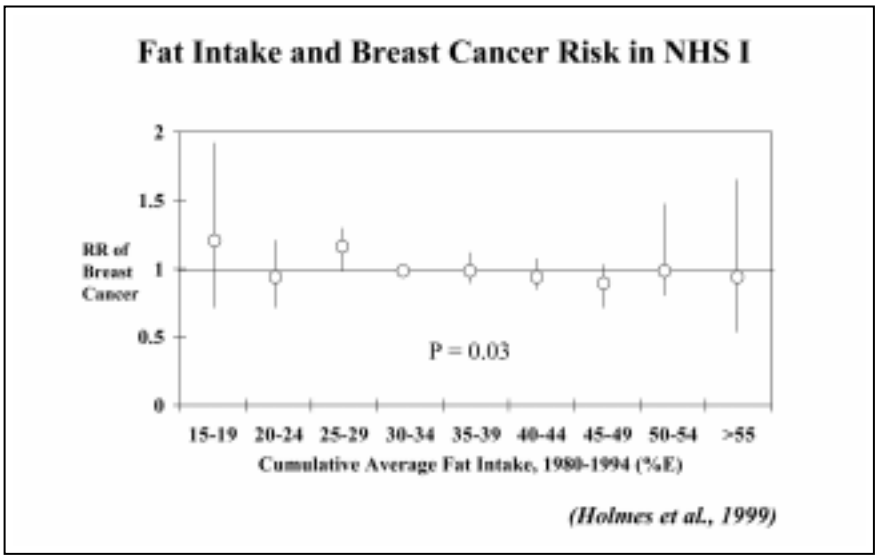


figure 29

If anything, the risk was slightly higher among women with the lowest fat intake. We are now examining the results after twenty years of follow-up, and still there is no hint of a positive association.

This of course leaves unanswered the reason for the large difference in rates of breast cancer between the U.S. and Japan, which have been particularly strong for postmenopausal women. Our findings indicate that much of this difference is due to two factors: weight gain during adult life and the use of postmenopausal hormones, which have been widely used by U.S. women (figure 30).

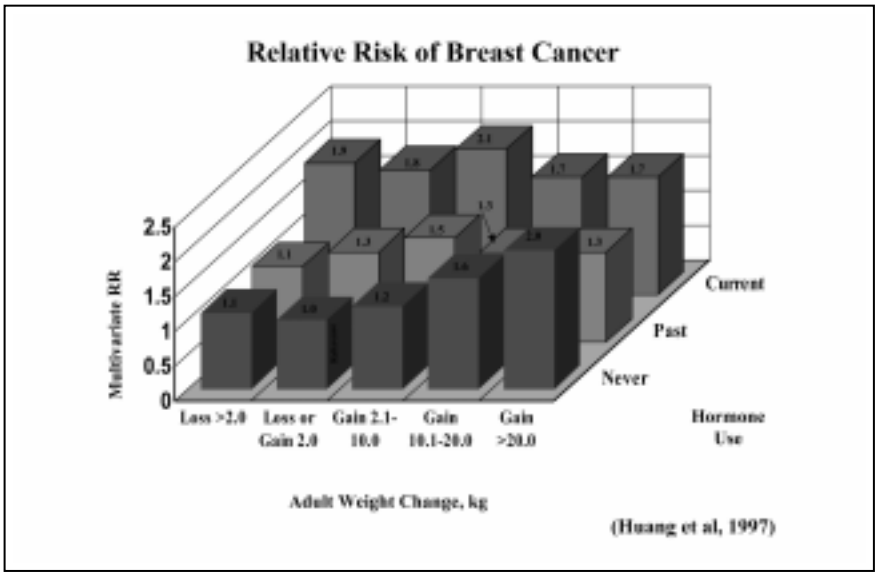


figure 30

As can be seen, all women who used postmenopausal hormones had an elevated risk of breast cancer, and among those who never used them, risk of breast cancer increased steadily with weight gain after age 18. Thus, the only women at relatively low risk were those who never used hormone replacements and who also avoided weight gain during adult life. In our population only about 5% of women fell into this low risk category, but at least until recently most Japanese women were in this low risk group. The combination of hormone replacement therapy and weight gain accounted for about half of breast cancer deaths in our population, and thus the majority of the difference between the U.S. and Japanese rates of breast cancer.

Recently, we have been able to examine dietary factors during early adult life and risk of breast cancer during the premenopausal years within the Nurses' Healthy Study II cohort. These women were 25 to 42 year of age when we enrolled them in 1989. As in the earlier study in somewhat older women, we found little relation between total fat intake and risk of breast cancer. However, when we broke this down into animal fat and vegetable fat, we observed an increasing risk of breast cancer with higher intake of animal fat, but not with vegetable fat (figure 31).

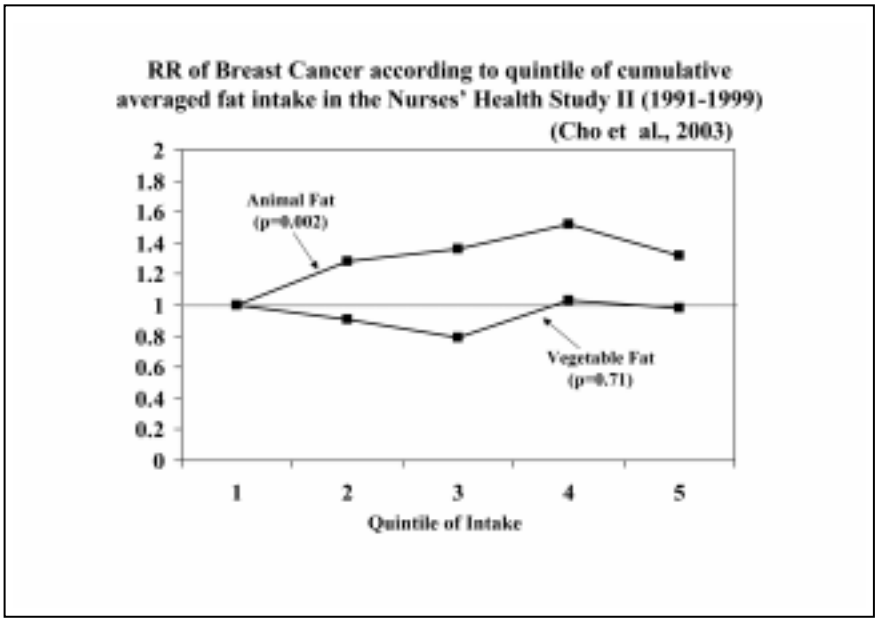


figure 31

This positive association with animal fat was only seen with breast cancers that had estrogen receptors, which suggested a hormonal basis of the relation. When we examined the sources of animal fat separately, we found that the elevated risk was mainly due to high fat dairy products. This has led us to investigate the possibility that hormones in milk products might be contributing to the increase in risk. While this work is ongoing, the topic has become of great interest to us for several reasons. First, the methods of producing milk have changed greatly over the last several decades, which have had a major impact on the hormone content of milk. Presently in the U.S., and in Japan as I understand, to increase production cows are now pregnant most of the time while they are being milked, which is not normal mammalian behavior. Many hormones including estrogens, progesterone, and insulin-like growth factor-1 (IGF-1) are greatly increased during pregnancy, and these are excreted in the milk. Thus, it will be important to know whether these amounts of hormones have physiological effects. In several cross-sectional analyses we found that milk consumption is positively associated with blood levels of IGF-1, which is of concern because IFG-1 levels have been associated with higher risks of premenopausal breast cancer and cancers of the colon and prostate. The effect of milk on IFG-1 levels has now been supported by several randomized trials. IGF-1 has long been known to be a primary factor in promoting growth of children, and height is positively associated with risk of breast cancer, both in comparisons among countries (figure 32) and within populations (figure 33). Thus, increases in milk consumption may in part explain the large increases in both height and breast cancer within Japan during the last several decades. Also, in a recent analysis we found that milk consumption, including intake of low fat milk, was related to higher prevalence of teenage acne, which further supports a possible role for hormones in milk as a contributing factor in human disease.

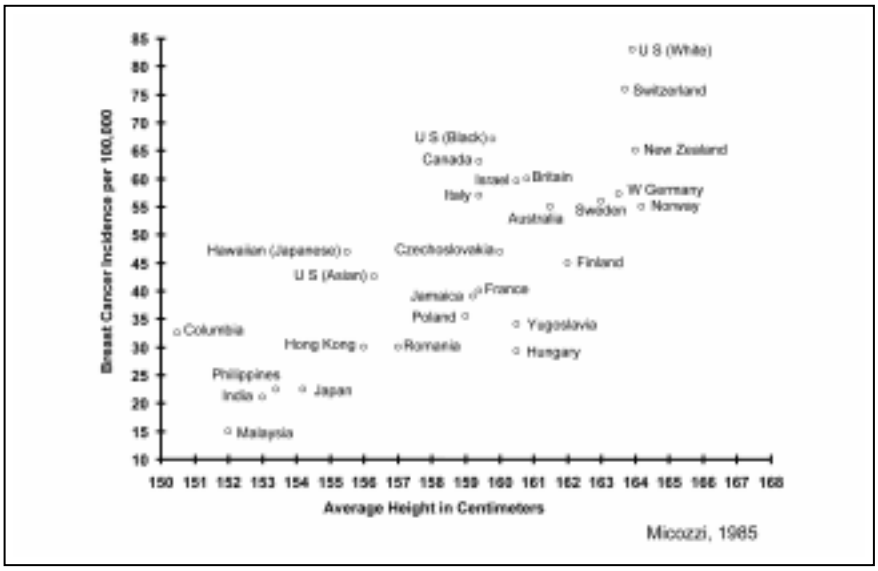


figure 32

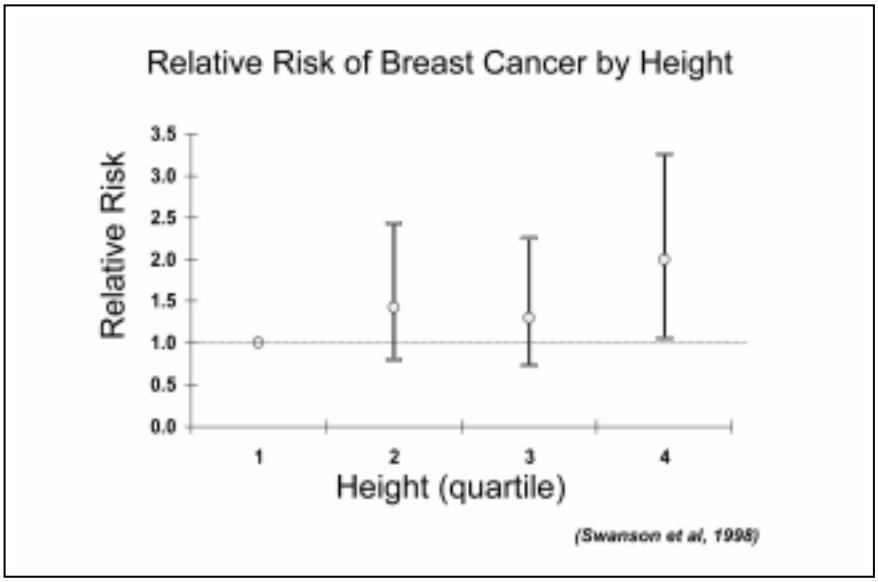


figure 33

Prostate Cancer

Cancer of the prostate has been a leading cause of cancer death in men living in Western countries, and like other "Western" cancers, rates are rising rapidly in Japan. Prospective studies of diet and prostate cancer have been relatively few because most of the early studies included only women, thus research in this area is less well developed. The study of prostate cancer is also complicated by the fact that most men develop a rather benign form of this cancer by the time that they are 60 or 70 years of age, and only a minority become aggressive, spread, and cause death. Thus far, several nutritional factors have emerged as being potentially important. One of the most consistent findings in epidemiologic studies has been

a positive association between milk consumption and risk of prostate cancer, especially the aggressive or fatal forms. For example, in an earlier study by colleagues in California, men who drank large amounts of milk had about three times the risk of death due to prostate cancer compared to those who drank little (figure 34) Initially this was thought to be due to due to the fat content of milk, but in a careful examination, we did not find support for this. As noted above, milk does raise blood levels of IFG-1 levels, which may explain part of the relation. However, the results of our analyses suggest that the large amounts of calcium in milk may be responsible because both calcium supplements and high milk intake appeared to increase the risk of prostate cancer (figure 35). We have also seen that lycopene, the pigment in tomatoes that makes them red, may be a protective factor. Both higher consumption of tomato products, especially tomato sauce, and blood levels of lycopene were associated with lower risk of prostate cancer (figure 36).

Diet and Fatal Prostate Cancer in SDA Men, 1960-1980 (n = 99 cases)

(Snowdon et al, 1984)

Milk		
<1 glass/day	**1.0**	
1-2 glasses/day	**1.8**	**(1.0-3.0)**
3+ glasses/day	**2.4**	**(1.3-4.3)**

p trend = 0.005

figure 34

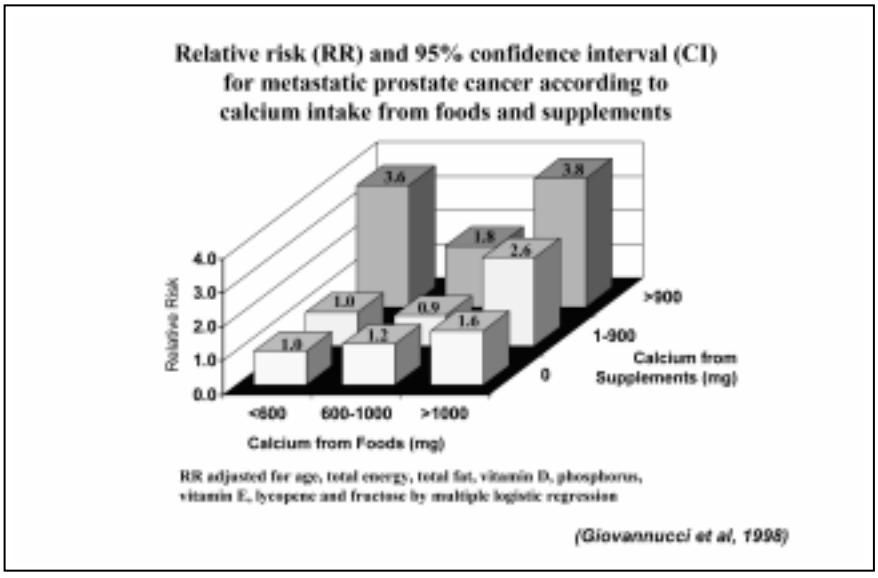


figure 35

Plasma Lycopene Levels & Future Risk of Prostate Cancer (*Gann et al., Cancer Research, 1999)*

	All Cases (n=578)		*Aggressive cases (n=259)*	
Quintile	**RR**	**(CI)**	**RR**	**(CI)**
1	**1.0**		**1.0**	
2	**0.89**	(0.64-1.23)	**0.64**	(0.40-1.03)
3	**0.90**	(0.65-1.24)	**0.71**	(0.44-1.15)
4	**0.87**	(0.63-1.19)	**0.70**	(0.44-1.10)
5	**0.75**	(0.54-1.06)	**0.56**	(0.34-0.92)

figure 36

Vitamin D: ongoing work

At present, vitamin D is one of the most active topics of our research. Vitamin D is different than most other nutrients because the main natural source is from sunlight, which activates vitamin D in the skin. Fatty fish is really the only substantial natural source, but we now also get vitamin D from fortified foods and from supplements. For years we have known that vitamin D is essential for the prevention of rickets in children, and there is now much evidence that the intakes of both adults and children in many parts of the world are suboptimal. Part of the reason for low blood levels of vitamin D is that we have migrated from the warm, sunny climates where we evolved and are now living in areas where sunlight is much less. In fact, in parts of the world close to or above the 40^{th} degree parallel, which includes much of the U.S and Japan, the sun is not high enough above the horizon to activate vitamin D during the winter months, and the blood levels of many people drop to the deficiency range. Levels are also much lower in persons with darker skin simply because the melanin blocks the ultraviolet rays, which leads to lower rates of skin cancer but also lower synthesis of vitamin D. Modern behaviors also lead to lower levels of vitamin D. Instead of spending daylight hours hunting, farming, or walking outdoors as our grandparents did, we spend most of our daylight hours in cars, subways, or inside building, which prevents sunlight from reaching our skin. Even more recently, we have learned to avoid sunlight as a method of reducing the aging of skin and skin cancer.

Many recent lines of evidence indicate that there is a high price for not having enough vitamin D. Not surprisingly, we found that women with low intakes of vitamin D have an elevated risk of bone fractures, as shown in the Nurses' Health Study (figure 37).

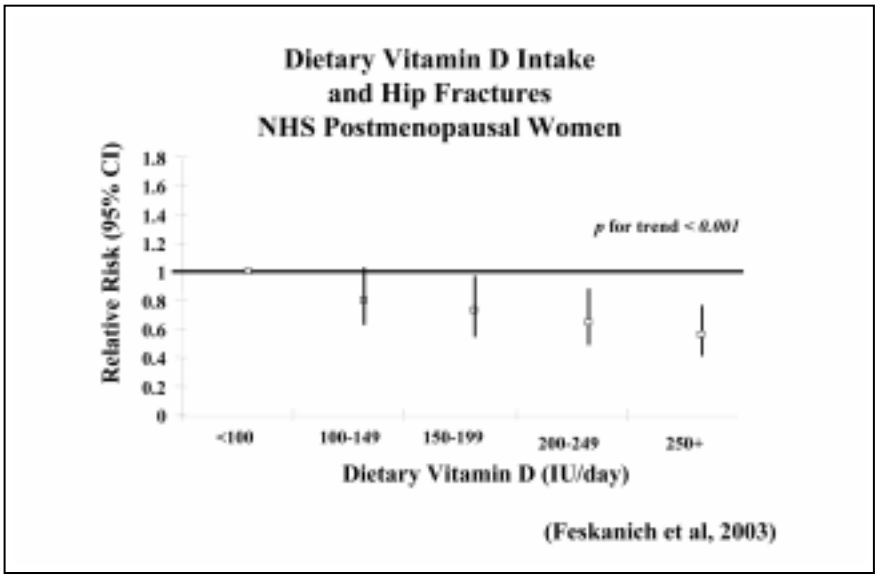


figure 37

Randomized trials have shown that the current recommended amounts, 400 international units per day in the U.S., are not enough to reduce fracture risk; approximately double this amount is required. However, we have also come to appreciate that there are many other consequences of inadequate vitamin D, including elevated risks of cancer, muscle weakness and falls in the elderly, and possibly multiple sclerosis and other conditions. Using blood samples that we collected from participants in the Nurses' Health Study in 1989, we recently reported that women with low blood levels of vitamin D have approximately twice the future risk of colon cancer compared to women with higher levels (figure 38).

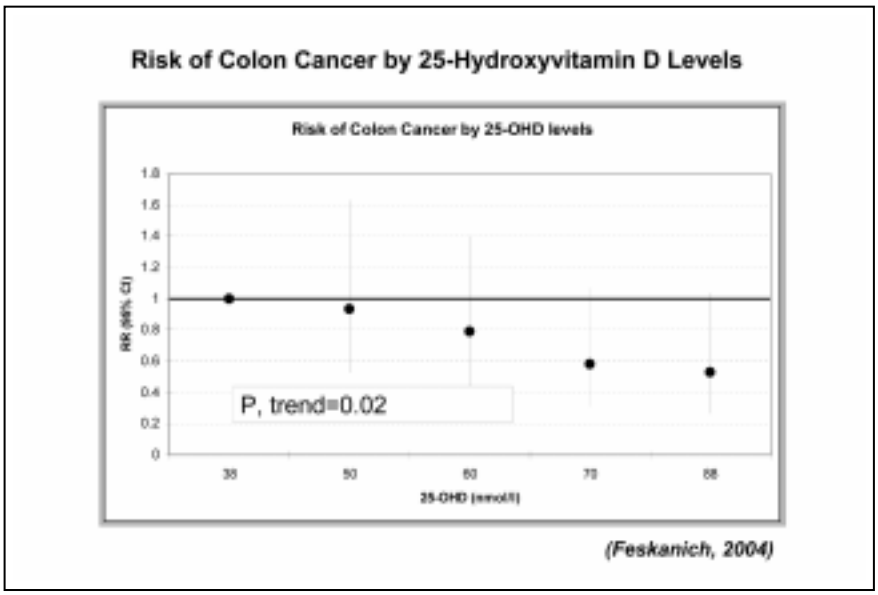


figure 38

Importantly all of these women had blood vitamin D levels that are considered normal by current standards, which suggests that our definition of normal vitamin D status needs to be changed. In our ongoing work, we find that both men and women who have higher intakes of vitamin D from fortified foods and supplements have lower rates of many cancers, including

cancers of the colon, breast, prostate, and lung. Thus it appears that taking adequate amounts of vitamin D, which is higher than the currently recommended intakes, can have enormous health benefits. For most people, the easiest and best way to achieve adequate intake will be as supplements.

A related finding is that too much vitamin A in the form of retinol appears to counteract the beneficial effects of vitamin D. In natural diets, most of the vitamin A comes in the form of beta-carotene, which is obtained from orange and green, leafy vegetables. Vitamin A in the form of retinol is abundant in few natural sources, liver being the primary one. However, many people now consume quite large amounts of vitamin A as retinol because this is used to fortify foods, such as milk and breakfast cereals, and is the form usually used in vitamin supplements. In the Nurses' Health Study we found that women with higher intakes of retinol, even at the amounts that are currently being recommended, had a higher risk of hip fractures than women with lower intakes (figure 39).

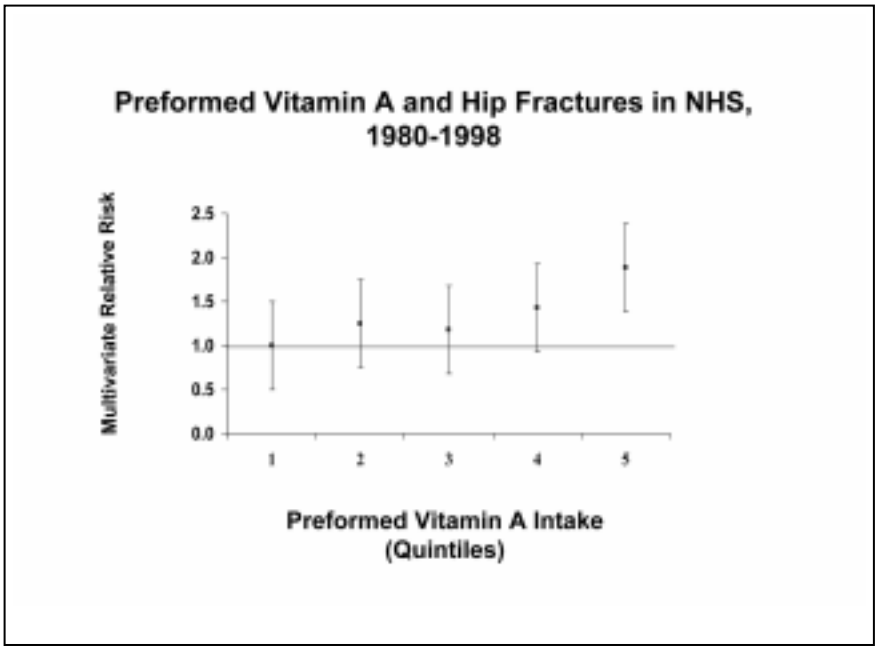


figure 39

Subsequent work by others has shown that retinol can interfere with the action of vitamin D by blocking the receptor for vitamin D in cells. Thus, vitamin A supplements should primarily be in the form of beta-carotene rather than retinol.

The Combined Benefit of Multiple Healthy Behaviors

These few examples indicate how various aspects of diet can impact our wellbeing, either adversely or beneficially. We have recently conducted a series of analyses to estimate the potential combined effect of multiple healthy diet and lifestyle choices on risk of several important health outcomes (figure 40).

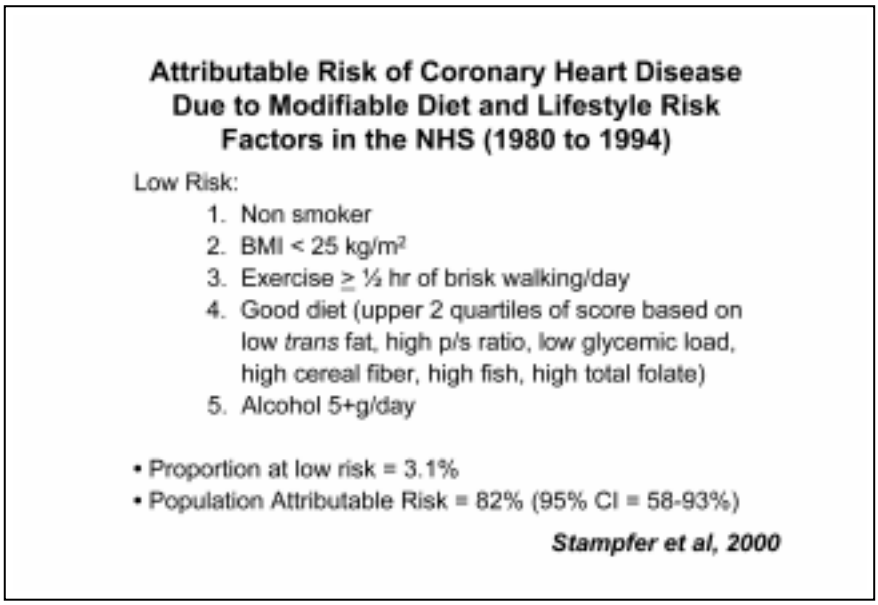


figure 40

To do this for myocardial infarction or death from coronary heart disease, we defined a low risk group, which was characterized by not smoking, BMI below 25, moderate physical activity, healthy diet (defined as low trans fat, high ratio of polyunsaturated to saturated fat, low glycemic load, high cereal fiber, fish intake twice a week or more, and adequate folic acid), and moderate alcohol consumption, which is of course optional. Surprisingly to us, only 3% of the women in the Nurses' Health Study were in this low risk group. However, based on 14 years of follow-up, we found that over 80% of coronary heart disease might have been avoided if everyone had adopted these behaviors. We have also found that almost all these same behaviors, with the exception of folic acid and fish intake, are related to risk of type 2 diabetes. In a similar analysis, we found that over 90% of type 2 diabetes might have been avoided with these healthy behaviors, which again reinforces the conclusion that this disease is not inevitable, even for those with a genetic predisposition (figure 41). Many of these same dietary and lifestyle factors are also related to risks of important cancers. For example, we found that not smoking cigarettes, regular physical activity physical activity, avoidance of overweight, and a dietary pattern with low amounts of red meat and adequate folic acid were related to lower risks of colon cancer (figure 42). We found that over 70% of colon cancer in our population could be avoided by the adoption of these healthy behaviors.

Our recent findings for vitamin D suggest that the avoidable percent can be increased even further by taking 800 to 1000 international units as a supplement.

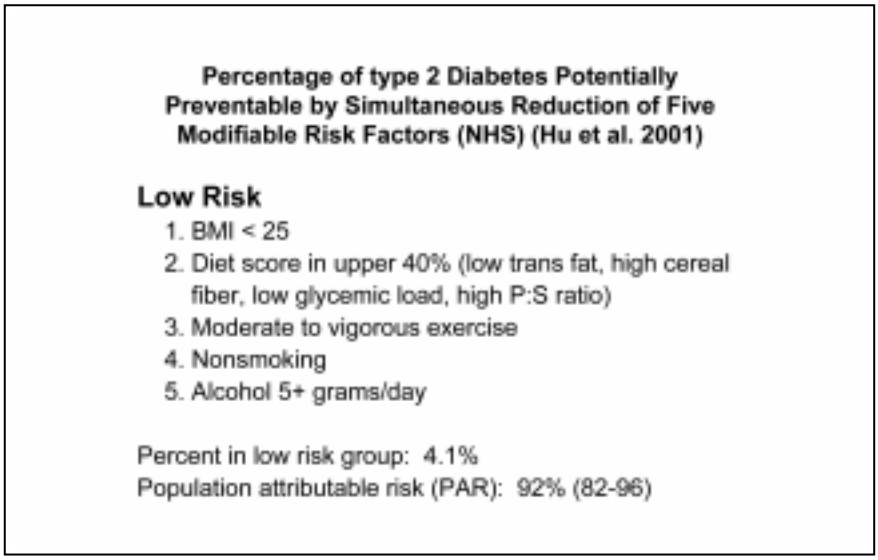


figure 41

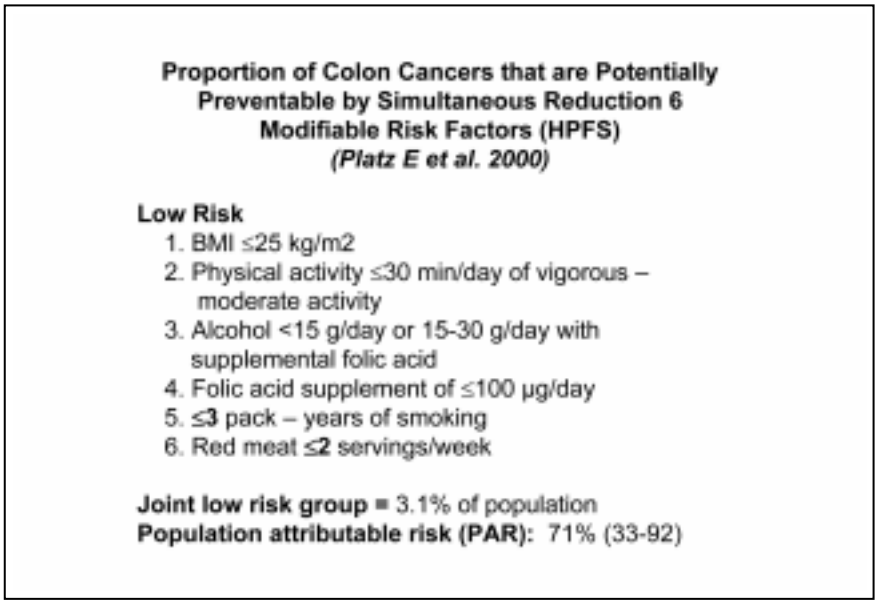


figure 42

This description of our work provides only a small sample of what we have learned over the last 25 years. Because much of this can be directly beneficial to those who are interested in improving their health, with the help of my colleagues I have written a nontechnical book for a general audience called “Eat, Drink, and Be Healthy: The Harvard Medical School Guide to Healthy Eating”. My technical book, meant as a textbook for those who want to conduct this type of research, or to interpret findings from such studies, is called “Nutritional Epidemiology” (figure 43). I am deeply honored and grateful that my Japanese colleagues, Drs. Tanaka and Maeda, who are themselves leading scientists, have translated these books into Japanese so that they are available to readers in this country (figure 44).

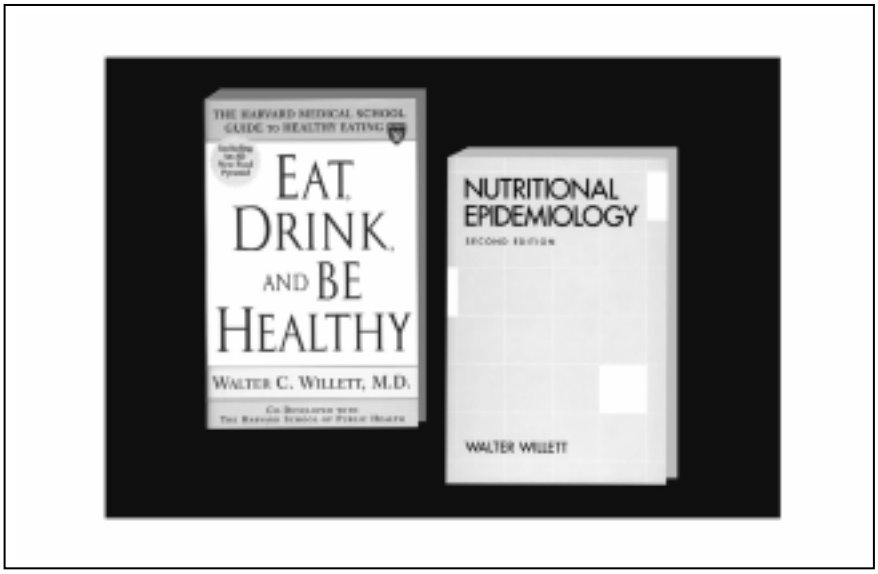


figure 43

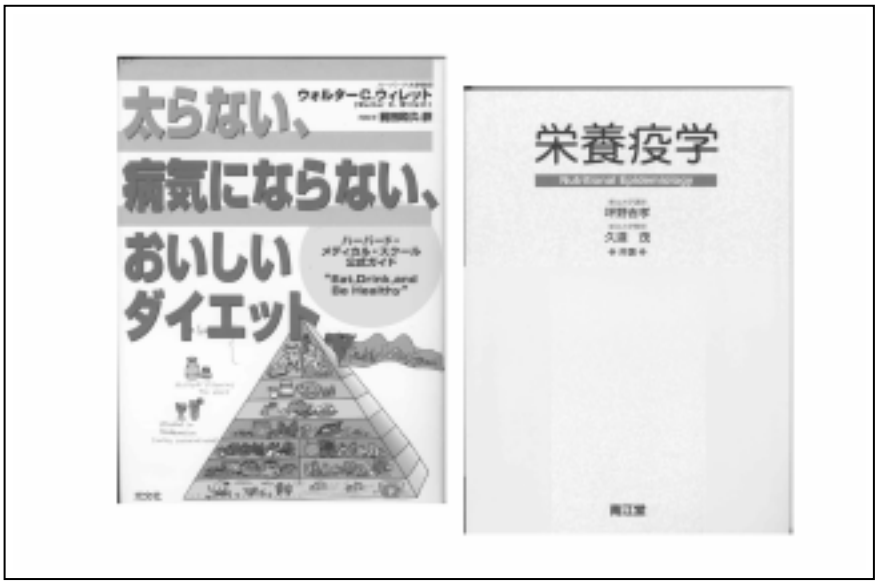


figure 44

Of course, it is reasonable to ask why anyone in Japan would want to read about a book about diet and health based largely on data from the U.S. because Japan at present has the best life expectancy of any large country. Indeed, we in the West can benefit by learning about nutrition and health in Japan, including the great appreciation for the quality and presentation of food. However, it is a reality that many people in Japan are incorporating Western foods into their diets, and it will be important to understand that some of these can have adverse effects, whereas some of these foods can be both enjoyable and healthy.

Nutritional Epidemiology and Eco-technology

When I first learned that I would be receiving an award from the Honda Foundation for eco-technology, I was very surprised because I had not thought of my work as eco-technology. However, upon learning more about the world vision of Mr. Honda, I have come to appreciate the breadth of his understanding and goals. Human health and well being certainly fits within his goals, and it is interesting to consider how our work has used technology to achieve them. The results that I have described this evening are completely dependent on many forms of technology, including sophisticated biochemical methods to define and measure components of diets, and also modern methods of genetic analysis. From the beginning, our research has been completely dependent on powerful computing hardware and software, and our demands have grown enormously as the amount of data has multiplied many times and our statistical methods have become more complex. Thus, in a very direct way, we have used many forms of modern technology to understand the consequences of simple human acts, such as choices among the foods we put in our mouths.

Our research has also emphasized the importance of the environment in human health and disease, with the food aspect of the environment being a critical component. Until very recently, humans were obligated to eat primarily what could be produced by their local environment. Thus, northern Europe was heavily dependent on dairy foods, which allowed survival in a cold and hostile climate, fish became a dominant part of the diet of Japan, which is surrounded by the sea, and olive oil was a key element of the Mediterranean cuisine because the olive tree provided a reliable source of food energy in a arid and rugged countryside. Not all of these were equally conducive to long term health, and we have learned much from these natural experiments. Today, because of improved transportation and better preservation technology, we have choices that were unknown to earlier generations. It is my hope that through better information about the consequences of these options, individuals and the food industry will be able to make more informed decisions that will enhance human well being.

Finally, healthy food can only be produced from a healthy environment. Thus, all the efforts of Soichiro and Benjiro Honda to sustain our global environment are ultimately linked with the issues that I have described today. In closing I again want to thank the Honda Foundation and all those who have made this event possible for their continuing efforts to make the world a better place in which to live.