CHAPTER TWO
THEORETICAL BACKGROUND

This chapter provides theoretical concepts and framework in relation to fruit and vegetable, which are referred to throughout this current study. With regard to assessment of fruit and vegetable consumption, nutrition concepts and their applications generally used in the area of nutritional epidemiology are introduced. The important aspects include definition of fruits and vegetables, assessment measures and other associated assessment issues. Then, in the section of low fruit and vegetable intake risk quantification of associated disease burden, it describes the conceptual framework, applications and related theoretical aspects, i.e. summary measure of population health (SMPH), disability-adjusted life years (DALYs) and comparative risk assessment (CRA). In addition, an analytical view of risk-factor-disease relationship, a key input for risk estimation, applied to this study, is particularly provided through an approach of systematic review of up-to-date published studies.

2.1 Measuring intake of fruits and vegetables

It is widely accepted that populations have a large variety of food availability and choices, diverse dietary lifestyles, as well as social and cultural preferences towards foods (Pomerleau et al. 2004, Deharveng et al. 1999, Pollard et al. 2002). Despite a common understanding of the terms of “fruits” and “vegetables” and their portion size, there are vast differences in definitions and their portion size, together with measurement methods and errors from country to country; addressing controversial issues, such as inclusion/exclusion of particular vegetable sub-groups (starchy roots, tubers and legumes) (William 1995, Deharveng et al. 1999, WCRF/AICR 1997). However, to attain comparability, standardized methodologies, including definitions and portion sizes, are considerably required (Deharveng et al. 1999, WHO 2003, IARC 2003).

2.1.1 Definition of fruits and vegetables

In general, fruits and vegetables have different meanings depending on the context. In botany, a fruit is the ripened ovary—together with seeds—of a flowering plant. Fruits are the means by which flowering plants disseminate seeds. In relation to food, the fruit refers to the plant's edible parts incorporating the ripened ovary, seeds and surrounding tissues. This term encompasses both fleshy fruits and dry fruits where the ripened ovary wall turns specific characteristics, such as cereal grains, pulses and nuts. Vegetables, botanically speaking, in relation to food encompass all other edible parts of a plant. Given this, vegetables can include stems and stalk (asparagus, celery), roots (carrots), tubers (potatoes), bulbs (onion), leaves (lettuce), flower (broccoli), seeds (beans, peas) and even fruits (cucumber, tomato). With this term, this makes fruits a subset of vegetables (IARC 2003).

In cuisine, the term of fruits simply refers to those plant fruits that are sweet and fleshy, and used as a side-dish, beverage, snack or dissert served at breakfast, lunch, dinner or between meals (IARC 2003). The culinary term of vegetables is broadly similar to the botanical one, only that includes fungi (mushroom, truffles), algae (seaweeds) and sweet corn and hominy. The culinary vegetables, however, exclude cereal grains, nuts and culinary fruits (IARC 2003). Nonetheless, no single terminology truly fits a wide variety that is found among plant fruits. Botanical terminology for fruits is inexact and will remain so, while a culinary term for both fruits and vegetables has less scientific attention and is relatively arbitrary and subjective (IARC 2003).

Fruits and vegetables, apart from botanical and culinary terms, conceivably refer to their nutritive attributes and beneficial effects, such as modulating detoxification enzymes, stimulating immune system, decreasing platelet aggregation, adjusting cholesterol synthesis and hormone metabolism, decreasing blood pressure and possessing antioxidant, antibacterial and antiviral properties (Lampe 1999). Dietetically, fruits and vegetables are low energy-dense diet and are rich sources of diverse nutrients, covering vitamins, trace minerals, dietary fibers and numerous biologically active compounds (Lampe 1999, WCRF/AICR 1997).

In areas of epidemiological studies, variability of fruits and vegetables are mainly determined by the study's aims, definition of variables to be assessed or classification of food categories, as well as their measurement tool and the target population's dietary pattern under assessment (IARC 2003). In this context, IARC refers the terms of fruits and vegetables to "edible plant foods excluding cereal grains, nuts, seeds, tea leaves, coffee beans, cacao beans, herbs and spices. While fruits solely are defined as "edible parts of plants that contain the seeds and pulpy surrounding tissue: have a sweet or tart taste: generally consumed as breakfast beverage, breakfast and lunch side-dishes, snacks and disserts". The term of vegetables refers to "edible plant parts including stems and stalks, roots, tubers, bulbs, leaves, flowers and fruits; usually includes seaweed and sweet corn; may or may not include pulses or mushrooms; generally consumed raw or cooked with main dish, in a mixed dish, as an appetizer or in a salad" (IARC 2003).

From the view of multi-country applications, terms referring to fruits and vegetables are also diverse among countries. These variations are evidently affected by demographic and lifestyle factors (IARC 2003), which normally refer to food choice decision influencing determinants (Pollard et al. 2002). According to the WHO Fruit and Vegetable Promotion Initiative–report of the meeting, Geneva, 25-27 August 2003 (WHO 2003b), the preliminary report from Fruit and Vegetable Survey showed various definitions given to fruits and vegetables by some participating countries (see Table 2.1 and Table 2.2). In this report, it is concluded that the terms are generally more likely similar to those formerly described in botanical and culinary classifications. In spite of their variations, the terms given, however, share some common characteristics of plant-based foods as well as their rich sources of nutrients. It is noted in the report that terms applied for fruits are less heterogeneous than those for vegetables (WHO 2003b).

Table 2.3 illustrates controversial issues over the classification of fruit and vegetable categories. There are some groups of plant-based foods that are usually not considered as vegetables in most classifications (WCRF/AICR 1997, IARC 2003, WHO 2003b). Minor groupings include some herbs or spices, as well as plant products used to make coffee, tea or chocolate. All of these are classified under specific food groups other than vegetables. Likewise, processed vegetables and fruits such as jams, fruit cakes, jellies, vegetable soups, etc. are usually categorized into sweet or dessert groups due to the implausibility to contain sufficient fruit and vegetable ingredients or, even retain their original nutritional quality (William 1995, WCRF/AICR 1997). Also excluded, cereals dietetically contain an average 70% of starch in weight, and they are a major source of complex carbohydrate (non-starchy polysaccharides), mainly in the form of wholegrain cereals. They are consumed as the starchy staples or main carbohydrate sources, and are not used interchangeably with other vegetables (WCRF/AICR 1997).

Table 2.1: Definition of fruits in different countries

Country	Definition
Cambodia	Fruits are foods from a plant source. Fruits are usually consumed after meal or as snacks (not necessary with meal). Fruits are usually consumed raw, but are sometimes cooked. Most fruits taste sweet, but some fruits taste sour or bitter.
Lebanon	Fruits are a rich source of vitamins, mineral salts and dietary fiber. They are rather sweet, refreshing and consumed raw after a meal.
Estonia	Fruits and berries: fresh, frozen, purées, canned, dried or cooked, and fresh juice (not including juice made from concentrate, and jams).
Thailand	Fruits are rich sources of vitamins and minerals in ameliorating body functionalities. They are usually consumed both raw and cooked. They taste sweet and sour. Some fruits should be restricted in consumption amount due to their high content of sugar, such as durians and jackfruits.

Source: extracted from the preliminary report from WHO fruit and vegetable survey (Keller 2003)

Table 2.2: Definition of vegetables in different countries

Country	Definition
Italy	All green and colored edible plants and leaving out dry beans, peas, and cereals.
Latvia	The principle "local products for local consumption"
Turkey	Edible parts of plant food. Cheap and healthy.
Thailand	The leafy plants usually green in color and eaten with rice or with the main dishes. Vegetables are seldom eaten alone. Roots and tubers if consumed with meals are counted as vegetables. But when cooked as a dessert, they, then, are defined not as vegetables.
Northern Mariana Islands	Vegetables provide vitamins and minerals needed to help fight and prevent diseases. There are two types of vegetables: starchy; and green and yellow vegetables.
Republic of Korea	Most edible leafy plants are called vegetables and beans/seaweeds are not included.
Lebanon	Vegetables are a rich source of vitamins and minerals. They are refreshing and consumed raw during breakfast, cooked or as a salad at lunch/dinner.
Ghana	Parts of special and culturally specific plants eaten raw, cooked, dried or any suitable form for the promotion of good health. Usually used in soups and sauces as an accompaniment for the main staples. Cassava, yam, sweet potato and plantains are not classified as vegetables, but as staples.
Guatemala	A vegetable is characterized by a high content of water, cellulose, minerals and vitamins. They are the parts of the plant for human consumption--root, tuber, leaf, and flower. Normally they are eaten for lunch or dinner as salads, mostly cooked.
Chile	The population of lower socio-economic status refers to parsley, basil and other leafy species that are used to give flavor to the dish.

Source: extracted from the preliminary report from WHO fruit and vegetable survey (Keller 2003)

Table 2.3: Controversial issues on exclusions and inclusions of fruits and vegetables

Issues	**Rationale**
Exclude potatoes	Botanically, potatoes are a vegetable, but dietetically are a "starchy staple" as a major source of complex carbohydrate
Exclude other starchy staples, e.g. yams, cassava, plantain, etc.	When they are eaten as a starchy staple or main carbohydrate sources, e.g. bread, pasta or rice. They are not used interchangeably with other vegetables.
Exclude herbs, spices, cocoa and coffee beans, and tea leaves	They are clearly not contributable to or used interchangeably with vegetables.
Exclude fruit drinks, squashes and cordials	Most fruit drinks, squashes and cordials rarely contain sufficient fruit juices.
Exclude nuts	Nuts are usually consumed in small amounts as a snack item.
Exclude some processed foods, e.g. ketchup, processed vegetable soups, fruit cakes, yoghurts, etc.	They are unlikely to contain sufficient fruit or vegetable ingredients, and retain their original nutritional quality.
Include fruit juices (suggested to count only once, so that consumers do not think they can achieve the recommendation by merely drinking liters of fruit juices	As providing almost vitamins and minerals of fresh fruits, they, however, have a disrupted structure of which most of fiber is lost. Also, most of the intrinsic fruit sugar in the fruit will turn extrinsic during extraction and more carcinogenic.
Include root crops, e.g. carrots, Swedes, turnips, etc.	As they are eaten in addition to main starchy staple or side dishes
Include dried fruits	They are clearly fruits and contain dietary fiber and various vitamins and minerals; however, the drying process converts much of the intrinsic sugar to extrinsic and degrades crucial vitamins, e.g. vitamin C. They are also highly energy-dense.
Include frozen and canned fruits and vegetables	They have similar, and sometimes even better, nutritional profiles than fresh fruits and vegetables.
Include composite (recipe) provided that they contain ample fruits or vegetables	To count as a portion, fruits and vegetables are needed to present in a sufficient amount.

Source: Summarized from William 1995, WCRF/AICR 1997, Scarborough et al. 2005

The inclusion of potatoes and tubers, and legumes or pulses (mature beans and peas) as vegetables is more widely controversial (WCRF/AICR 1997, IARC 2003, WHO 2003b). Also included in this group are sweet potatoes, yams, taro, cassavas, plantains and other starchy staples. These plant foods contain variable amounts of starch from 12 to 50%. The potato is the most important starchy food in most developed countries and is often considered as vegetables (Krebs-Smith et al. 2001, Agudo et al. 2002, Painter et al. 2002), whereas many dietary guidelines in other part of the world put this group together with cereals as starchy foods (Painter et al. 2002, WHO 2003b).

Pulses are derived from the fruits and seeds of a number of leguminous plants, including those that have matured and dried (often termed “beans” or “legumes”) and immature pulses such as fresh green peas. Dry legumes are the richest source of protein; however, they also share with vegetables the fact that they are good source of fiber and some bioactive phytochemicals[1], such as isoflavones[2], found particularly in soybeans (Lampe 1999, Munro et al. 2003). In most cases, legumes are included as vegetables, though sometimes dry beans are placed together with meat and fish in the protein-rich foods (Painter et al. 2002). Nevertheless, the WCRF/AICR and IARC excludes potatoes and tubers, legumes or dry pulses from the vegetable category. Besides, in the recent improved Eurocode 2, this vegetable term is

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[1] Phytochemicals, sometimes interchangeably with phytonutrients, are compounds naturally found in plant foods, e.g. fruits, vegetables, grains, nuts and legumes. These compounds have biological effects that are not required for normal functioning of the body but that, however, have a beneficial effect on health or an active role in ameliorating diseases (Lampe 1999).

[2] Isoflavones are a class of organic compounds and biomolecules related to the flavonoids, very strong antioxidants. They act as phytoestrogens in mammals. These phytoestrogens are plant-derived nonsteroidal compounds that possess estrogen-like biological activity, such as antioxidant activity, anticarcinogenic, anti-atherogenic, hypolipidemic and anti-osteoporotic activities. Isoflavones are thought as useful in treating cancer (Munro et al. 2003).

strongly supported for the purposes of assessing fruits and vegetables and developing the nutrient profiling model (William 1995, Scarborough et al. 2005).

Fruit classification is less disputable. Excluded from this category, nuts that are dried fruits often enclosed in hard shells, are consumed in such small quantities as snack items (William 1995). Nuts are energy-dense foods, with most of their energy coming from fat, and they are an important source of unsaturated oil, and of proteins. Nutritionally, they are high in bioactive compounds, including vitamins and minerals such as vitamin E (WCRF/AICR 1997). Fruit juices, only if are they 100% pure juice, can be counted in the fruit category, since they can provide almost all micronutrients presented from the original fresh fruits, but little in fiber, and in some cases, sugar is added (William 1995). Fruit drinks, squashes and cordials are not counted into the fruit group due to the fact that they rarely contain sufficient fruit juices (William 1995, WCRF/AICR 1997). This basically leads to standardized definitions of food groups initiated and recommended by WCRF/AICR (1997) as well as WHO (2003) in achieving the sense of comparability across nations for epidemiological study aims, evidence-base policy formulation and implementation.

In this study, the classification of fruit and vegetable groups, therefore, follows the definition scientifically suggested by WCRF/AICR (1997), and is methodologically applied on the same fashion as other WHO member states for international methodological standardization and comparability. By this, the vegetable term refers to all edible parts of plants commonly considered as vegetables, or vegetables by cuisine of which include foods used as vegetables, such as other fresh green pulses, sprouts and beans, fresh sweet corns (botanically cereals), botanical fruits used as vegetables, such as tomatoes, capsicums, cucumbers, pumpkins, etc., as well as mushrooms and seaweed[3]. The fruit definition basically includes fresh or preserved fruits, except those categorized as vegetables. Exclusions include potatoes, starchy staples, nuts, herbs and spices, as well as fruit drinks. In essence, such exclusion criteria are not a recommendation to avoid eating them, rather not include them in measurements of recommended consumption of fruits and vegetables, in turn, helping promote greater consumption of fruits and vegetables (WCRF/AICR 1997).

2.1.2 Assessing fruit and vegetable intake

The main aim of the dietary measurement in epidemiology or nutritional studies is to attain the best accurate estimates of diet (Margetts et al. 1997, Willett 1998). Like other dietary intake assessments, the prime importance in selecting assessment methods for fruit and vegetable intake lies in the study purposes relative to nutritional surveillances, epidemiologic studies (case-control vs. cohort) and methodological researches, e.g. validation and calibration studies; the need for group specifics versus individual data, e.g. household measures, questionnaire tools and records; the population characteristics; the timeframe of interest; and the resource availability (Margetts et al. 1997, Willett 1998, IARC 2003, Kim et al. 2003). Dietary measures for fruit and vegetable estimation in different settings are summarized in Table 2.4.

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[3] Mushrooms and seaweeds are botanically considered not to be plants according to the classification of living organisms.

Table 2.4: Methods for estimation of dietary fruit and vegetable intake in different settings

Method	Measurement of consumption	National surveillance	Observational epidemiology	Validation for FFQ
Measures at the national or population level for food availability				
Household surveys	Food inventory (disappearance)	Frequently		
Food balance sheets	Food disappearance	Frequently		
Measures at the individual level				
• ***Questionnaires of usual intake***				
Diet history	Usual intake (past, time varies)		Occasionally	
FFQ : long	Usual intake (past, time varies)	Occasionally	Frequently	
FFQ : brief	Usual intake (past, time varies)	Occasionally	Occasionally	
• ***Recording of actual intake***				
24-hour dietary recall	Actual intake (specific time point)	Frequently	Occasionally	Frequently
Food record	Actual intake (specific time point)	Frequently	Occasionally	Frequently

FFQ: food frequency questionnaires

Note: in observational epidemiologic studies include both case-control and cohort approaches.

Source: adopted from the IARC Handbooks of Cancer Prevention Volume 8, 2003.

2.1.2.1 Measures for fruit and vegetable intake at the national or population level

At the national or population levels among greatest concerns to program planners and policy makers are the assessments of measures in the course of monitoring fruit and vegetable consumption trends and conducting even crude comparisons among geographic areas (Margetts et al. 1997, IARC 2003). Food supply data, such as food balance sheets (FBS) provided by the Food and Agricultural Organization of the United Nation (UN/FAO) for 176 countries offer estimates of the amount of various food produce accommodated for human consumption after accounting for post-harvest losses; therefore, they can be of use in reflecting recent fruit and vegetable consumption and availability at the national level. Such data on fruits (excluding wine; FAO code 2919) and vegetables (FAO code 2918) can be directly downloaded from the FAOSTAT database on the FAO Internet website (FAO 2006).

Despite their unique features that can provide average amount of food available per person on a daily basis, the food balance sheets may exaggerate the actual amount consumed due to the fact that they do not include losses of edible food and nutrients at the household level, e.g. during storage, preparation, cooking, plate waste or quantities fed to domestic animals or pets or disposal. These losses may account up to 33 percent (FAO 2006, Joffe and Robertson 2001, WHO 2003b). Another crucial drawback of FBS is that they do not allow breakdown for further levels of information. The "vegetables" category, for example, covers a great deal of specific vegetable produce, in which further retrieval of individual vegetable subtypes is unfeasible (IARC 2003). However, in the 2004 Comparative Risk Assessment project (CRA) as part of the WHO's Global Burden Disease (GBD) study (Ezzati el al. 2004), FBS was of use in performing a crude estimation of the mean daily fruit and vegetable consumption per person designated as the theoretical-minimum risk distribution in calculating risk burden estimates of low fruit and vegetable consumption (see details in 2.2.2.2).

Another measure also widely used in nutritional epidemiology areas, household surveys typically accommodate more detailed information on both fruit and vegetable intake data and non-nutritional characteristics across subgroups of the population. Nonetheless, interpretations from these survey data must be cautious due to the fact that they do not hold information on food distribution among individual household members (Margetts et al. 1997, Willett 1998, IARC 2003).

2.1.2.2 Measures for fruit and vegetable intake at the individual level

At the individual level, main methods in collecting data on fruit and vegetable intake include questionnaires or records (IARC 2003). Questionnaires are of use in collecting data on usual intake either in terms of quantities or frequencies of specific foods consumed during the recent period of time. For assessing the actual dietary intakes, recording methods are basically employed to indicate all amounts of different foods consumed over the last 24 hours or at the time of consumption (Margetts et al. 1997, Willett 1998, IARC 2003).

Across studies the used questionnaires vary considerably in accordance with the food list's length, the quantity of questions, the items of fruits and vegetables covered, the measure's structure, other interested dietary information included, the portion size determining tool, and data quantification (Willett 1998, IARC 2003). In areas of epidemiological studies, the commonly used questionnaires include food frequency questionnaires (FFQs) and diet history questionnaires (DHQs). In general, FFQs or DHQs are used to obtain individual's information pertaining to intake of specific foods, food groups, dietary practices and/or food preparation methods and usual food intake's frequency through interview, self-administration or the combination of both (Margetts et al. 1997, Willett 1998, Subar et al. 2001, IARC 2003).

A diet history is a meal-based report of usual dietary intake gathered for a particular timeframe on the type, recipes, quantity and frequency of consumption, including its preparation method (Margetts et al. 1997, Willett 1998, IARC 2003). Normally equipped with aids to memory and conceptualization, such as food lists and photographs or model, this measure, together with face-to-face interview, can provide the assessed amount of usual foods consumed (Margetts et al. 1997, Willett 1998, IARC 2003). In assessing fruit and vegetable intake, this approach can provide information on specific fruits and vegetables and about seasonal intake, as well as their consumption in mixed dishes for an individual (IARC 2003). Despite its advantageous features, the diet history is less feasible for application in epidemiology, rather plausibly in clinical dietetics. This is because of its complex dietary assessment procedure, very much reliance on skilled interviewers, heavy demands on both participants and investigators due to its potential to over-reporting or double counting, time requirement and ensuing costs (Margetts et al. 1997, Willett 1998).

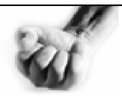
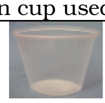
A food frequency questionnaire (FFQ) is a self-administered report, structured with lists of specific foods or food groups that vastly vary across studies (Margetts et al. 1997, Willett 1998). In reflecting individual usual intake, respondents are asked to estimate the frequency of consumption of those listed foods, in some occasions attached with any related instructions and photo atlas, indicating the number of times that the food is typically consumed over a given period of time (day, week, month or year) (Margetts et al 1997, Krebs-Smith et al. 2001, IARC 2003). The semi-quantitative FFQ is a questionnaire specifically equipped with standard or individual portion size or serving estimates for all or selected items of the food list. It can also be quantitative when indicating amounts of food consumed (Margetts et al. 1997). These additional features can enhance accuracy of the dietary assessment (Margetts et al. 1997, Willett 1998, Kim et al. 2003). With its well structured format, ease of application; even in the case that the respondent can complete it without an interviewer, and less cost to administer and process, the FFQ, requiring simply counting the number of items reported as ever consumed, is commonly encouraged to use over other measures in assessing varieties among fruits and vegetables (Krebs-Smith et al. 2001, IARC 2003). However, the extent of variety that can be captured is limited by the number of items included on the list, and this may affect the estimates of mean total intake of fruits and vegetables (Thompson et al. 2000, Krebs-Smith et al. 2001). On the contrary, more questions may lead to a greater tendency to exaggerate intakes (Cox et al. 1997). Subar et al. (2001) suggested that the core essence should be placed on the clarity of design structure and the feasibility of use, instead of the questionnaire length.

Recently, in the context of intervention program evaluation, such as the 5-a-day program, now a global initiative, brief food frequency questionnaires are developed in an attempt to monitor changes in fruit and vegetable intake in response to such programs (Thompson et al. 2000, IARC 2003). The brief FFQs are structured with a much abbreviated list of foods, and the questions may focus on specific food groups of a limited number of food groups or food items. It is notable that the abbreviated tools must be exhaustive enough to capture the foods specified as the major sources of the food group and nutrients of interest (Neuhouser et al. 2001). This, as mentioned earlier, may result in biased reporting owing to the subjects' perceptions of what they should eat, or termed as social desirability bias. This bias, at present, is difficult to quantify the potential for over-reporting of fruits and vegetables, which requires prudent consideration (Kim et al. 2003, Promerleau et al. 2004).

In addition, with FFQs, information on fruits and vegetables consumed in the form of mixed dishes is barely attained (Neuhouser et al. 2001, IARC 2003). Such dishes may be listed as mixed dishes, pasta dishes, soups, stews, ethnic dishes, etc. The actual fruit and vegetable content of these items varies greatly and no estimate of specific fruit and vegetable will be available (William 1995, Krebs-Smith et al. 2001, IARC 2003). However, such mixed dishes may account for up to 13% of total fruits and vegetables (Thompson et al. 2000). Thus, the quality of this measure relies highly on specification whether fruit and vegetables are expressed as groups or single foods in the questionnaires and the number of items included. It is commonly accepted that FFQs, with a caution of cognitive challenge in reporting foods over a wide, defined period, are better suited to ranking subjects by level of intake than producing absolute estimates of intake (Margetts et al. 1997, Thompson et al. 2000, Neuhouser et al. 2001, Schatzkin et al. 2003).

Recording-based measures commonly used in assessing actual dietary intake are the 24-hour dietary recall (24HDR) and food diaries or food records. With open-ended design, the 24HDR or food records provide flexibility in terms of identifying and classifying fruit and vegetable consumption because the investigators will organize the results as desired after the survey is completed (Margetts et al. 1997, Willett 1998, IARC 2003). In the 24 HDR, several types of aids, such as pictures, portion or serving sizes may be used to assist people to provide a detailed description about all fruits and vegetables and other foods typically consumed in the household units or weights if known within 24 hours prior to the interview, in particular about food preparation, brand names and recipes, thereby providing a rich database from which to assess the complexities of the diet (IARC 2003). Table 2.5 demonstrates a baseline minimum number of fruit and vegetable servings recommended for adults as well as the serving size comparison.

Table 2.5: Serving size comparison guide for fruits and vegetables

Food group		Standard Serving	Size comparison
Fruits (2-3 servings)	fresh	1 medium, e.g. apple, orange, banana	 size of a small baseball
	dried	2-3 small pieces of apricot, plums, etc. or ½ cup of cut fruits	 size of a small fist
	juice	½ cup fruit juice (4 oz. or 125 ml)	 a common cup used in house
Vegetables (4-5 servings)	green leafy	1 cup (8 oz or 250 g)	 a common cup used in house
	Cooked, including beans, pea, etc.	½ cup	 a half size of a small tennis ball
	raw	1 cup	 Size of a small base ball

Source: adapted from analysis of food portion size to aid in weight control (Andrew 2003).

Typically recalls are conducted as face-to-face interviews, but they can also be carried out through telephone or self-administered approaches (Margetts et al. 1997, Willett 1998, IARC 2003). Commonly, the 24HDR is particularly suited to assessing the current diet in groups of individuals, and, subsequently, to measuring differences between group means, either cross-sectionally or longitudinally (Margetts et al. 1997, Willett 1998, Schatzkin et al. 2003, IARC 2003). The 24HDR relies on the subject's memory, resulting in fewer tendencies to recall errors than questionnaire methods that refer to usual diet over an extended period in the past. It is also strongly suggested that the 24 HDR may be greater favored to employ if multiple numbers of days are used (Schatzkin et al. 2003, Kim et al. 2003), in considering its shortfalls of day-to-day and season-to-season variations in both the types and amounts of fruits and vegetable consumed (Agudo et al. 2002, IARC, 2003).

Food diaries or food records require the subject to provide all descriptive information of all foods and beverages consumed during a defined period, often 3-7 days. Weighed records or weighed inventory records require, additionally, the weight of all consumed foods (Margetts et al. 1997, Willett 1998, IARC 2003). Normally, these methods are conducted in validation studies in comparing individual results gathered from other measurement tools, such as FFQ. Despite their advantageous characteristics, such methods put a great demand on the respondents and the application is confined to literate respondents who are truly desired to participate, thereby resulting in selection bias, while compliance may encourage changes in usual diet (Margetts et al. 1997, IARC 2003, Schatzkin et al. 2003).

Use of plasma biomarkers has been increasingly extended both in validation studies and as measures of intake (Margetts et al. 1997, Willett 1998, Bogers et al. 2003, Anderson et al. 2005). The biomarker indices are primarily aimed to indicate the amount present in, or available to, the essential and vulnerable tissues of the body, thereby determining nutritional status, whether it is deficient, adequate, or prone to excess, at the tissue level (Margetts et al. 1997, Willett 1998, Schatzkin et al. 2003). To illustrate, plasma carotenoids and plasma ascorbic acids have recently been used as valid biomarkers for fruits and vegetables (Lampe 1999, Bogers et al. 2003, Pollard et al. 2003, Anderson et al. 2005). Some of important biomarkers of nutrient intake used in epidemiologic studies are shown in Table 2.6.

Table 2.6: Main biomarkers of nutrient intake used in epidemiologic studies.

Nutrient	Analytic procedure[a]	Biologic tissue	Reproducibility (Time)[a]	Validity[b,c]
Retinol	HPLC	Plasma	0.58 (6 mo)	0.17
Beta-carotene	HPLC	Plasma	0.45 (6 yr)	0.51
		Adipose	0.50 (4 mo)	0.20
Alpha-carotene	HPLC	Plasma	-	0.58
Beta-cryptoxanthin	HPLC	Plasma	-	0.49
Lutein/zeaxanthin	HPLC	Plasma	-	0.31
Lycopene	HPLC	Plasma	-	0.50
Vitamin E	HPLC	Plasma	0.65 (6 yr)	0.35 (diet)
		Plasma	-	0.53 (+ suppl)
		Adipose	0.78 (4 mo)	0.24
Vitamin D	HPLC	Plasma	-	0.25 (diet)
		Plasma	-	0.35 (+ suppl)
Vitamin C	HPLC	Plasma	0.28 (6 yr)	0.38
		Plasma	-	0.43 (+ suppl)
Vitamin B_6	PLP assay	Plasma	-	0.37
Folacin	Microbiologic assay	Serum	-	0.56
		Erythrocyte	-	0.51
Selenium	Neutron	Serum	0.76 (1 yr)	0.63
	Activation AAS	Toenails	0.48 (6 yr)	0.59
	Glutathione peroxidase activity	Blood	-	Plateaus at 100 μg/day intake
Iron	Ferritin	Serum	-	0.16
Sodium	AAS	Urine (24-hr)	-	0.41
Calcium	AAS	Urine (24-hr)	-	0.16
Potassium	AAS	Urine (24-hr)	-	0.53
Magnesium	AAS	Urine (24-hr)	-	0.34
Cholesterol	Ultracentrifugation	Blood	0.60 (1 yr)	0.46 (low intake)
				0.08 (high intake)
Palmitic acid	HPLC	Plasma	>0.65 (1 yr)	0.23
		Adipose	-	0.27
Oleic acid	HPLC	Plasma	>0.65 (1 yr)	0.03
		Adipose	-	0.13
Linoleic acid	HPLC	Plasma	>0.65 (1 yr)	0.28
		Adipose	-	0.48
Trans fatty acid	HPLC	Adipose	-	0.40
Eicosapentaenoic acid	HPLC	Adipose	0.68 (8 mo)	0.40
Docosahexaenoic acid	HPLC	Adipose	0.93 (8 mo)	0.66
Nitrogen	Kjeldahl	Six 24-hr urines	-	0.69
Sodium	Flame photometry	Six 24-hr urines	-	0.30
Potassium	Flame photometry	Six 24-hr urines	-	0.73
Magnesium	Flame photometry	Two 24-hr urines	-	0.34
Fiber	Hemicellulose	Stool	-	0.54

[a] AAS, atomic absorption spectrophotometry; HPLC, high-performance liquid chromography; PLP, pyridoxol 5-phosphate.
[b] Representative values from the literature; for specific references see text for each nutrient.
[c] Correlations of biochemical indicator values with an appropriate dietary assessment method; for details see text for each nutrient. These are generally underestimates of true validity due to misclassification in measuring dietary intake.

Source: Nutritional Epidemiology, 2nd edition, Willett 1998, pp 228.

Importantly, not any single nutrients, but rather varied nutrients in fruits and vegetables confer protective effects against diseases; it would render greater benefits to have data on the plasma nutrients most affected by fruit and vegetable consumption (Block et al. 2001). Unfortunately, for many other nutrients of interest such valid plasma biomarkers do not yet suffice (Willett 2001). Nonetheless, interpretations require cautions since these biomarkers only represent as surrogates of consumption and are not simply a reflection of true dietary intake (Willett 1998, Pollard et al. 2003, Anderson et al. 2005). The nutrients reflected by these plasma biomarkers, after they have been digested and absorbed, may be affected by complex physiological mechanisms, e.g. homeostatic mechanisms and metabolism in relation to age and diurnal and seasonal variations, as well as other external factors e.g. changes in dietary intake, varying concomitant drug use or the presence of chronic illnesses (Willett 1998, Pollard 2003).

As formerly mentioned, the purpose of the assessment is of prime importance in considering selecting dietary measures. Estimates of fruit and vegetable consumption may be needed, for instance, for the primary prevention of chronic diseases, for the nutritional screening programs, for designing or monitoring of the intervention programs, and for the dietary assessment in epidemiologic studies. Different purposes demand different result estimates, thereby requiring different assessment tools. Therefore, selections of method must be made with great care and under rational considerations.

2.1.3 Related issues on measuring fruit and vegetable intake

Owing to increasing research on assessment of fruit and vegetable consumption in relation to disease outcomes for public heath purposes, estimates of fruit and vegetable intake inevitably center on an aspect of accuracy. In this regard, following are issues related to the validity of dietary estimates, such as mixed dishes or composite foods, frequency of consumption and portion sizes as well as measurement errors and data validity in reflecting the best true intake of fruit and vegetable at the individual level.

2.1.3.1 Composite foods or mixed dishes

In general, most studies on fruit and vegetable consumption are reported in terms of discrete portion, while few include the part of composite foods (O'Brien et al. 2003), which is basically in relation to the food guidance given in terms of a single food pattern or serving (Krebs-Smith et al. 2001). This results in the typical use of dietary assessments to estimate the sufficiency of nutrient intakes (Cleveland et al. 1997). Composite foods, in fruit and vegetable category, refer to mixed foods, mixed dishes or recipes that combine fruits and vegetables with other food components (O'Brien et al. 2003). Conventionally, composite foods or mixed dishes are grouped in accordance with their major ingredients, thereby reporting in such a diverse food group as "meat mixture" or "grain mixture" (Krebs-Smith et al. 2001). As the components of these mixtures are not assembled according to their nutritional equivalents and weighted in gram, this limits exact estimates for food consumption that is directly comparable to dietary recommendation. Cox et al. (1997) suggested that in encouraging greater public consumptions for public health purposes, fruits and vegetables that were part of the mixed dishes were counted as the extra amount recorded by the weighed approach. At present, there still is controversy regarding inclusion of the composite foods in estimating fruit and vegetable consumption.

Several reports demonstrated an importance of composite foods pertaining to the accuracy of the food intake estimation (William 1995, Krebs-Smith et al. 2001, O'Brien et al. 2003, Kim et al. 2003). Underestimation and biases were incurred when composite foods were excluded, which seemed to greater affect vegetable consumption than fruit intake (O'Brien et al. 2003, Kim et al. 2003). In the O'Brien et al (2003)'s analysis, the overall contribution of composite foods to total vegetable intake was 26% (25% in males and 27% in females). For fruit, composite foods accounted for 12% (14% in males and 10% in females). The authors also added that despite large variations among individuals, composite foods were not associated with sex and age, rather than with levels of educational attainment and social class (O'Brien et al. 2003).

2.1.3.2 Frequency of consumption and portion size

Frequency of consumption means the number of times that a food or food group is consumed over a given period of time (Margetts et al. 1997, Willett 1998). This is pertinent when employing questionnaire methods. In many FFQs, this is the only information gathered and it seems to be sufficient to rank subjects according to their intake. However, in order to get a quantitative estimate of fruit and vegetable intake, frequency must be coupled with some measurement of the amount of each food, either assigned as a standard portion or provided by the subjects as part of the information gathered in the questionnaire (Krebs-Smith et al. 2001, IARC 2003). As noted, the structure of the questionnaire is related to validity and precision of fruit and vegetable intake based on the frequency of consumption. In particular, the degree of detail with which fruits and vegetables are specified seems to be very important. In the same way, a review of different models of brief survey instruments concluded that instruments with a moderate number of fruit and vegetable items have a greater validity in comparison to those with short list of foods (Kim et al, 2003). In addition, it is noted that better quality of measurement of fruit and vegetables intake is also attributed to instruments that included questions on portion sizes and on consumption of mixed vegetable dishes (William 1995, Krebs-Smith et al. 2001, O'Brien et al. 2003, Kim et al. 2003).

Normally, summary estimates are prone to be as valid as the sum estimates for fruits, whereas this is not the case for vegetables. For fruits portion size is easier to indicate because, contrary to vegetables, fruits are mostly served in natural units (Krebs-Smith et al. 2001, Bogers et al. 2003). This is because, in general, the public are more likely to be familiar with the food groups presented in the food guides materials and related dietary advice information, in particular for children and teenagers in schools. The public is usually exposed to and has some understanding of several fruit and vegetable groups depicted by color, plant part and/or botanical families (Krebs-Smith et al. 2001, IARC 2003). Therefore, it may be more likely for respondents to estimate consumption frequencies of specific fruits because the number of different kinds of fruits consumed is usually smaller than the number of different vegetables (Bogers et al. 2003).

2.1.3.3 Measurement errors and validity

Many factors affecting accuracy of dietary intake assessment apply to a similar extent to most diet components. Respondent factors and factors associated with the measurement techniques are the two main sources (Margetts et al. 1997, Willett 1998, IARC 2003). Potential errors pertaining to respondents include memory, socio-demographic factors such as age, sex, education, literacy, ethnicity, career, cultural background, disease or health status, knowledge and attitudes (Margetts et al. 1997, Willett 1998, IARC 2003). For fruits and vegetables, respondents may be influenced in their reporting by social desirability. They may over-report consumption simply because high intake of such foods is perceived as a socially desirable habit (Krebs-Smith et al. 2001, IARC 2003). However, it is suggested that consumer knowledge of fruit and vegetable groupings, wordings and placement of questions posed might be used to overcome such drawbacks in designing epidemiological researches, food advice messages, and food choice decisions (Korn and Graubard, 1999, IARC 2003).

Method-related errors are related to both random and systematic errors (Margetts et al. 1997, IARC 2003). They can arise from aspects of sampling methods, questionnaire structure (composition of the food list, specification of portion sizes, grouping of foods into single item, questions' order), interview bias, database and food composition tables (tables use different systems to name, group, and describe foods and different definitions and chemical analytical methods for nutrients) used to calculate nutrients, food coding and fruit and vegetable classifications (Margetts et al. 1997, Willett 1998, Deharveng et al. 1999, IARC 2003). It is not clear whether the format of survey administration plays a substantial role in the validity of measured intakes. Cognitive testing of fruit and vegetable survey instruments would be useful in further assessing the contributions of the method of administration to the validity of intake measurement (Willett 1998). The inclusion of a moderate number of representative fruit and vegetable items and the incorporation of questions on portion size and consumption of mixed vegetable dished may prove beneficial (Kim et al. 2003).

2.2 Attributable risk assessment

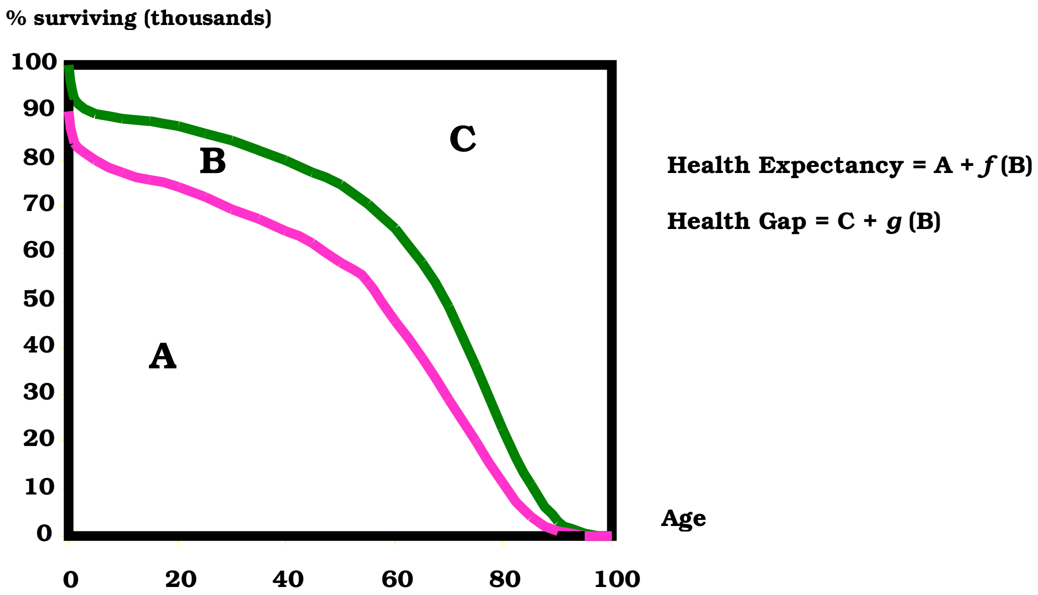
2.2.1 Summary measures of population health

Summary measures of the population health (SMPH) are a combination of information on mortality and morbidity to represent the health of overall population in a single indicator (Field and Gold 1998). Increasing demands of health services, health condition transition, demographic shift to greater ageing population and the introduction of advanced technologies put a challenge to all nations across the world under restricted resource circumstances. An indicator with greater responsive to such environment, in particular, in supporting health policy formulations has been recognized to be urgently needed. The traditional health indicators; namely, morbidity or mortality data, however, insufficiently reflect other states affected by the disease such as disability, impairment and premature death. This has led to many efforts to develop summary measures with the aim to integrate morbidity part into the decision and policy making process, instead of solitary base on mortality (Murray and Lopez 1996).

Since 1940s, SMPH has been originated from ideas of units of lost years of life by applying life expectation and weighting factor concepts (Haenszel 1950) and developed in different health indices, e.g. Health-Adjusted Life Year (HALY), Health-Adjusted Life Expectancy (HALE), Quality-Adjusted Life Year (QALY), Year of Healthy Life (YHL) and Disability-Adjusted Life Year (DALY). Among these measures, QALY and DALY are most frequently used. The QALY indicator has been widely used in areas of health economics, while DALY has been commonly found in the Global Burden of Disease (GBD) study and its affiliated National Burden of Disease (NBD) studies. The key aspects of SMPH involve the selection of health components (mortality vs. morbidity) and the assessment measures selected in those components, estimation of health expectancy or health gap (QALY vs. DALY), and valuation of health states (van der Mass 2003). Other issues also include epidemiological measures (incidence vs. prevalence) and etiological nature and disease progression information (generic vs. specific) (van der Mass 2003). In other words, estimating SMPH includes key inputs; namely, mortality by age, sex and cause; epidemiological data on non-fatal health outcomes (disability) by age, sex and cause; and valuations of health states.

SMPH could be classified into 2 groups; namely, health expectancies and health gaps (Murray et al. 2000). These concepts are illustrated in Figure 2.1.

Figure 2.1: Typology of summary measures of population health



Source: Bulletin of the World Health Organization (Murray et al. 2000)

To describe, the area A+B under the survivorship curve in Figure 2.1 represents life expectancy at birth. The area B between the two curves (full health and worse than full health) corresponds to years lived in health states worse than full health. Health expectancies indicate the area under the survivorship curve and are expressed by the equation of A+f(B), where f(x) is a function that assigns weights to health states less than ideal health using a scale on which full health has a weight of 1. On the other hand, health gaps represent the difference between the actual health of a population and some designated norm or goal for the population health. In Figure 2.1, the health goal is for everyone in the entire population to live in the ideal health until the age of 100. The equation of the health gap is C+g(B), where g(x) is a function that assign weights to health states less than full health, using a scale on which a weight of 1, indicates that time lived in a particular health state is equivalent to time lost due to premature mortality.

Nonetheless, in practice, this single indicator of combined mortality and morbidity information addresses concerns with respect to availability of reliable and comparable data on disease and disability, and value choices of disease and disability in relation to death, which has brought into the most extensive debate, especially on ethical aspects. Valuation of health states vary according to the degree of the aggregate weighting values, which, in turn, directly affect the measure's magnitude of mortality and disability connected to death (van der Mass 2003). Concerns include values given by which population group should be used (patients, professional or general public, and as viewed locally or globally) and the valuation method to be used (Anand and Hanson 1997, Paalman et al. 1998, van der Mass 2003). Despite those critical arguments on such value choices incorporated, summary measures are continuously developed and widely used for the purpose of achieving comparability and best response to different needs (Murray and Lopez 1996).

Main themes of the use of summary measures cover a wide range of applications. Based on World Health Report 2002—Reducing risks, promoting healthy life, the quoted objectives are shown as follows (WHO 2002):

- *To compare the health of one population with another*
- *To analyze the benefits of health interventions for use in cost-effectiveness analysis*
- *To identify and quantify overall health inequalities within populations*
- *To inform debates on health policy*
- *To monitor changes in the health of a given population*
- *To attribute burden from risk factors*

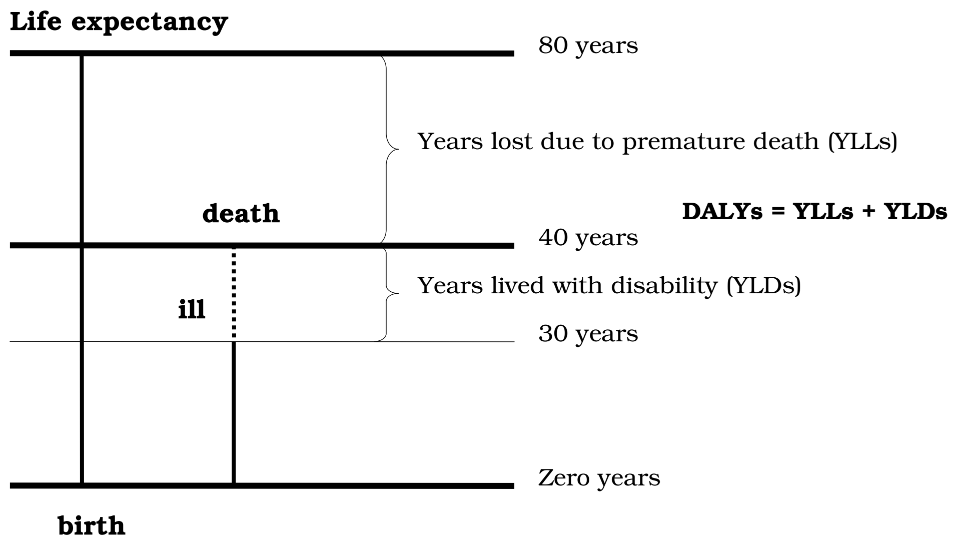
2.2.1.1 Burden of disease concept and estimation: Disability-Adjusted Life Year (DALY) indicator

The Global Burden of Disease and Injury (GBD), a joint study initiated in the early 1990s between the World Bank, the World Health Organization (WHO) and Harvard School of Public Health, purposefully formulated a summary measure reflecting the burden of disease and injury of human populations and the world's main health challenges (Murray and Lopez 1996). The DALY is a health gap measure that combines time lost due to both premature mortality and non-fatal conditions (Murray and Lopez 1996). This measure was used in The World Development Report: Investing in Health (World Bank 1993) in order to define priorities for investments in health. Subsequently, WHO has taken over the responsibility to produce annual estimates of the burden of disease by world regions.

The DALY extends the concept of potential years of life lost due to premature death (PYLL), the number of years of life lost when a person dies prematurely from any cause, to include equivalent years of unhealthy life lost by virtue of being in the states other than good health (Murray and Lopez 1996). A DALY for a disease or health condition is calculated as the sum of the years of life lost due to premature mortality (YLL) in the population and the equivalent unhealthy years living with disability (YLD) for incident cases of the health condition (Murray and Lopez 1996). DALYs are expressed by the following equation and graphically illustrated in Figure 2.2.

$DALY_i = YLL_i + YLD_i$ where i is a given disease/health condition

Figure 2.2: Construction of Disability-Adjusted Life Years (DALYs)



Source: adopted from the Global Burden of Disease, 1996 (Murray & Lopez 1996)

Measure of premature mortality: Year of Life Lost (YLL)

YLLs are the mortality component of DALYs. They are determined by the average life expectancy at age of death. On the equity ground, the standard expected years of life lost (SEYLL) approach is applied to generate the same estimates of a death at the same age in different communities (Murray and Lopez 1996). SEYLL is calculated from the expected remaining years, as specified by a normative survivorship that is derived from a model life table. In the GBD study, the value of 82.5 years for females and 80 years for males has been selected to represent as the standard life expectancy for all population (Murray and Lopez 1996). The value for females was derived by adopting the life expectancy of Japanese women, the current highest national life expectancy observed in the world. The value for males was estimated from the gap difference between sexes at the value of 2.5 years lower in males, based on the assumption of biological differences in life expectancy at birth of both sexes (Murray and Lopez 1996).

There are three approaches to calculating YLL; namely, a) with discounting and age weighting; b) with discounting but no age weighting; and c) without discounting and age weighting (Murray and Lopez 1996). The age weights are applied to capture a greater social responsibility in young and mid adult life for the very young and old in society. When applied to a stream of life lost due to premature mortality, the final resulting effect is that more weight is given to ages between zero and 39 years (Murray and Lopez 1996). Discounting, a common economic practice, is used to adjust the value of a future health benefits to its present value due to unknown uncertainty born in the future (Murray and Lopez 1996). The discount rate incorporated in the YLL measure was suggested at 3% to moderately affect the value of future health benefits (Murray and Lopez 1996).

The simplified formula of YLL without discounting and age weights is:

$$YLL(0,0) = \sum_{x=0}^{l} d_x * e_x \quad ;$$

where l = last age to which people survive;
x = age at death;
d_x = number of deaths in the population at age x;
e_x = expectation of life at age x based on an standard life.

The full formula for non-zero discounting and age weighting is given by Murrey and Lopez (1996) as follows:

$$YLL = \frac{KCe^{ra}}{(r+b)^2}\left[e^{-(r+b)(L+a)}\left[-(r+b)(L+a)-1\right]-e^{-(r+b)a}\left[-(r+b)a-1\right]\right]+\frac{1-k}{r}(1-e^{-rl});$$

where r = discount rate (GBD value at 0.03);
C = age-weighting correction constant (GBD value at 0.1658);
b = parameter for age-weighting function (GBD value at 0.04);
K = age weighting modulation factor;
a = age of onset of disability;
L = duration of disability or time lost due to premature mortality.

Measure of non-fatal health outcomes: Year Lived with Disability (YLD)

Years lost due to disability (YLD) are the morbidity component of DALYs. The loss of healthy life due to non-fatal health conditions requires estimation of the incidence of the health condition (disease or injury) in the specified time period. For each new case, the number of years of healthy life lost is obtained by multiplying the average duration of the condition (to remission or death) by a severity weight that measures the loss of healthy life using an average health state weight (Murray and Lopez 1996). The disability weight concept was developed from the concepts of Health Related Quality of Life (HRQL) and International Classification of Impairments, Disability and Health (ICIDH) (Murray and Acharya 1997). The concept involved individual preference towards time lived in different states that may be expressed meaningfully in cardinal values and those preference values measured through interview or questionnaire approaches (Murray and Acharya 1997). The important issue was the severity of a given health state and the duration spent in a given health state were assumed to be independent. Murray and Acharya (1997) applied the Person Trade-off method (PTO) to define a series of health states for use in the GBD study (Murray and Lopez 1996).

The basic formula for calculating YLD without discounting and age weights is indicated as follows:

$$YLD(0,0) = I*DW*L \quad ;$$

where I = number of incident cases in the reference period;
DW = disability weight;
L = average duration of disability measured in years.

Similar to YLL, calculations are also available with age weights and without discounting (Murray and Lopez 1996). The full formula for non-zero discounting and age weighting is given by Murrey and Lopez (1996) as follows:

$$YLD = D[\frac{KCe^{ra}}{(r+b)^2}[e^{-(r+b)(L+a)}[-(r+b)(L+a)-1]-e^{-(r+b)a}[-(r+b)a-1]] + \frac{1-k}{r}(1-e^{-rl}) \;;$$

where r = discount rate (GBD value at 0.03);
C = age-weighting correction constant (GBD value at 0.1658);
b = parameter for age-weighting function (GBD value at 0.04);
K = age weighting modulation factor;
a = age of onset of disability;
L = duration of disability or time lost due to premature mortality;
D = disability weight.

The study on assessing disease burdens attributable to low fruit and vegetable intake will refer to DALY estimates, as a baseline data for calculation. Such a study provided the DALYs estimates of the population for diseases linked with low intake of fruits and vegetables.

2.2.1.2 DALY and its criticism

There have been extensive debates about the value of DALYs in connection with the decision making process. The criticism centered on the weights incorporated in DALYs; that is, standard life expectancy, age, disability and discount rates used (Anand and Hanson 1997, Paalman et al. 1998, William 1999). Regarding value choices, apart from ethical implications, critics involved the transparency of the approach and responsiveness to local settings (Barker and Green 1996, Anand and Hanson 1997). Arguments were also made upon life expectancy for using the same standard life expectancy applied to all population groups as well as the reduction gap used for generating the value for male (Anand and Hanson 1997, Paalmann et al. 1998). Age-weighting in DALY was also criticized on its unnecessarily complicated application and non-consensus agreement on the assumptions applied (Anand and Hanson 1997, Paalman et al. 1998, William 1999). An often controversial point on disability weights was the issues of values rated by which population group should be used, e.g. patients, professional or general public, and as viewed locally or globally, as well as the approach of valuation used, i.e. Person Trade-off method (Barker and Green 1996, Anand and Hanson 1997, Paalman et al. 1998, William 1999, van der Mass 2003). This also covered failure to cover sufficient determinants to health of the individuals, e.g., social, economic, cultural, infrastructural factors (Barker and Green 1996, Anand and Hanson 1997, Paalman et al. 1998). With respect to discounting, issues included ethical challenges towards justification of future health benefits and its discouraging effect on health investment (Anand and Hanson 1997, Paalman et al. 1998).

However, in spite of those critical arguments, it is apparent that DALY is useful and widely used, in parallel with development of other SMPHs. The DALY has not yet been operationalized as a tool for collecting data alongside experimental or quasi-experimental trials of health interventions. It has been strongly suggested that in applying DALYs for use in cost-effectiveness analysis, relevant cohort life expectancies, local life tables or a population models, including all used assumptions, range of DALY estimates in relation to associate weighting application and sensitivity of cost-effectiveness ratio must be transparently identified (Fox-Rusby and Hanson 2001).

2.2.2 Comparative risk assessment: concept and method

Evolving from its original roots in the environmental sector, risk assessment or exposure assessment acts as a systematic method in comparing environmental problems that pose different kinds and levels of severity of health risk (Spasoff 1999). Importantly, it is increasingly used as a means to help inform policy for further appropriate actions (Spasoff 1999). Technically speaking, a risk assessment process involves a systematic, standard framework; namely, hazard identification, risk assessment in terms of dos-response investigation, exposure assessment and risk characterization (Spasoff 1999, WHO 2002). After the risk has been categorized, risk management can be performed (Spasoff 1999, WHO 2002). Both environmental risk assessment and epidemiological approaches are analogous with respect to their purpose to assess population attributable risks, or, in other words, the proportion of disease in a population that results from a specific hazard (WHO 2002).

In the past, the conducted epidemiological studies in investigating disease determinants or risk factors had limitations regarding their designs, methods and setting specificities, resulting in difficulty in achieving comparison across the studies. This led to development of systematic approach in assessing risk to health (WHO 2002). Comparative Risk Assessment (CRA) involves "a systematic approach to estimate the burden of disease and injury due to different risks, while risk factor is a health determinant of susceptibility with application of a statistical analysis to depict disease and disorder magnitudes" (WHO 2002). Factors that affect disease or injury, however, are not all harmful. Although, as generally perceived, they have a negative implication, ideally a risk assessment includes a range of protective as well as hazardous risk factors (WHO 2002). For instance, fruit and vegetable consumption reflects a protective potential, and would lead to health benefits if the level was increased.

From the epidemiological perspectives, causes of diseases are often described by 3 different means: magnitude of the problem, relative risk and attributable burden measurement (Aday 1996). To quantify the disease burden attributable to risk factor, the comparative risk assessment framework suggested by Murray and Lopez (1996) is principally adopted. The framework provides a clear set of definitions and criteria to distinguish between current burden of disease due to past (and current) exposure (attributable burden), and future burden due to current (and future) exposures (avoidable burdens). Estimates of attributable burden are a necessary step for calculating avoidable burden, but are of much less policy relevance due to rare actions to alter current status (WHO 2002). Moreover, estimates of avoidable burden under different scenarios are required for the further step of cost-effectiveness modeling research. Such crucial terminology is, as identified by World Health Report 2002 (WHO 2002), outlined as follows.

- Risk – a probability of an adverse health outcome, or a factor that raises this probability.
- Prevalence of risk – the proportion of the population who are exposed to a particular risk.
- Relative risk – the likelihood of an adverse health outcome in people exposed to a particular risk, compared with people who are not exposed.
- Hazard – an inherent property that provide the potential for harm.
- Population attributable risk – the proportion of disease in a population that results from a particular risk to health.

- Attributable burden – the proportion of current disease or injury burden that results from past exposure.
- Avoidable burden – the proportion of the future disease or injury burden that is avoidable if current and future exposure levels are reduced to those specified by alternative or counterfactual distribution.

In reality, risk to health does not occur in isolation. The chain of events leading to an adverse health outcome includes both proximal and distal causes (WHO 2002). To clarify, the factors that lead to someone developing a disease on a particular day are likely to have their own roots in a complex chain of environmental events that may have begun years previously, which in turn were shaped by broader socio-economic determinants. It is essential that the whole of causal chain be considered in the assessment of risks to health. In fact, many risks cannot be disentangled in order to be separately considered, due to their effect at different levels and variation over time (WHO 2002). Nonetheless, risk assessment is yet important in demonstrating a wide range of meaningful risk feature to human health as well as in demonstrating its potential for health benefits, thereby helping set agendas for research and policy action (WCRF/AICR 1997, WHO 2002).

For each risk factor the comparator against which the amount of disease burden is calculated is a theoretical minimum level of past exposure. For most risk factor–disease relationships the population attributable fraction (PAF) depends on the prevalence of exposure to the risk factor and a measure of relative risk for the occurrence of disease if exposed (WHO 2002). As fruit and vegetable intake is considered as on the protective benefit side, estimates will be made against a theoretical maximum, the exposure level that would yield the lowest population risk for adverse health outcomes when intake of fruit and vegetable is increased.

In calculating PAF, three inputs are required; namely, prevalence or estimates of the current distribution of exposure to low fruit and vegetable intake (categorized by age, sex), and relative risk (RR) of the disease for all level of exposure and reversibility (WCRF/AICR 1997, WHO 2002, Ezzati et al. 2004).

$$AF_{FV} = \frac{\sum_{i=1}^{n} P_i RR_i - \sum_{i=1}^{n} P'_i RR_i}{\sum_{i=1}^{n} P_i RR_i}$$

AF_{FV} = Attributable fraction of low fruit and vegetable intake among the exposed
P_i = Prevalence of the actual (estimated) exposure, e.g. Thailand
P'_I = Prevalence in reference population (theoretical maximum level)
RR_i = Relative Risk for a specific disease
i = Fruit and vegetable consumption level

2.2.2.1 Choice of exposure variable

Apart from the recognition of their general role in promoting health and well beings, fruits and vegetables have been continuously researched and also suggested to prevent major chronic non-communicable diseases such as cardiovascular diseases and certain types of cancers (WCRF/AICR 1997, Terry et al. 2001, IARC 2003, Riboli and Norat 2003, Heber 2004, Genkinger et al. 2004, Key et al. 2004). This, therefore, results in reduction of premature mortality. Mounting evidence supporting this role has urged national and international bodies to promote an increased consumption of fruits and vegetables up to a minimum level of 400 g/day, excluding potatoes (WCRF/AICR 1997, WHO 2003b, Ezzati et al. 2004).

According to World Health Report 2002, it was estimated that low intake of fruits and vegetables directly contributed to 19% of gastrointestinal cancer, 31% of ischemic heart disease and 11% of stroke worldwide. In addition, the report showed that low fruit and vegetable intake accounted for 1.8% of total

DALY estimates, of which about 85% was resulted from cardiovascular diseases and 15% from cancers (WHO 2002). Ezzati et al. (2004) also reported that in the European Union (EU), about 8.3% of the DALY estimates were diet-related factors, and, interestingly, 3.5% of this being attributed to inadequate intake of fruits and vegetables compared with 3.7% for overweight and 11% for high saturated fat intake. Nevertheless, it was noted that these figures did not include potential interactions with other risk factors for consideration.

Given that, the selected risk factor, as a protective risk, is the mean dietary intake of fruits and vegetables. For common standard reference, the definition of fruits and vegetables is in compliance with the current international recommendations for intake of fruits and vegetables (WCRF/AICR 1997, WHO 2003b). Vegetables refer to parts of plant excluding starchy, tubes, legumes, nuts and seeds, which are eaten cooked or raw with main meals, have different colours, are high in nutritional value and are good for health. Fruits refer to the fresh parts around the seeds of a plant, which have a sweet taste and are often eaten raw as dissert or snack (also see 2.1.1). A term of "intake" is treated as a continuous variable and is measured in grams per person per day.

2.2.2.2 Choice of theoretical-minimum-risk distribution

Based on the CRA conceptual framework, the estimates refer to the risk factor distribution changed towards a counterfactual distribution level (Ezzati et al. 2004). Unlike other exposure variables, fruit and vegetable intake is considered to generate an inverse risk-factor-disease association or the potential protective effect of fruit and vegetable consumption for different disease outcomes (also see 2.3). Therefore, the theoretical-minimum-risk distribution (TM) for fruit and vegetable intake, which technically refers to the distribution of exposure that would yield the lowest population risk, aims to assess an increased consumption that is protective (Ezzati et al. 2004).

The theoretical-minimum-risk distribution level used in the CRA study was established using several evidence-base assumptions (Ezzati et al. 2004). To estimate, the true upper limit of intake as a reference for the counterfactual distribution level was performed with an assumption that the highest groups of fruit and vegetable intake have lower risk compared with those in the lowest consumption groups. Given that, the counterfactual level was, then, based on risk difference studies that mostly conducted in developed countries. The FAO's Food balance sheet data were used to estimate the mean daily intake of fruit and vegetable. The highest levels of fruit and vegetable available for consumers at the national level were from Greece and accounted for about 700-800 g/person. After deduction of 33% of loss at household level, given evidence that the daily mean intake in adult in any given country in the world does not exceed 550 g/day; therefore, it was proposed to locate the daily mean intake level at 600 g/day (Ezzati et al. 2004).

With regard to distribution among age group, The CRA study also assumed that children consume less fruit and vegetable than adults (45% less in children aged 0-4 years and 20% less in children aged 5-14 years) (Ezzati et al. 2004). It was also assumed to apply the margin of 50g/day around the theoretical minimum in respect of population variability (Ezzati et al. 2004). It is also proposed to use set intervals of 80 grams per day of fruit and vegetables (equivalent to one serving) to elaborate the distributional transition (WHO 2002, Ezzati et al. 2004). This amount has been estimated in nutritional studies to equal one serving, which could affect changes for individuals towards the established counterfactual level ((WCRF/AICR 1997, WHO 2002, Ezzati et al. 2004).

Nonetheless, it was noted that for the future estimation as of greater updated evidence, the issues on the threshold effect for fruit and vegetable consumption on disease outcomes (whether the same threshold would apply to all protective effects), as well as relative risks observed from a wider range of intake among different groups of population, particularly outside Western developed countries (Ezzati et al. 2004) were strongly recommended.

The theoretical minimum of fruit and vegetable intake is estimated to be 600 grams per day in adults, 480 grams/day in children aged 5-14 years, and 330 grams/days in children aged 0-4 years, as indicated in Table 2.7. In this current study, however, apart from the theoretical minimum proposed by CRA, it was also decided to apply the mean intake of 400 g/day, the international recommended level for fruit and vegetable consumption, for adults aged over 15 years with the same margin of variation of 50g/day to illustrate different views of burden if Thailand could pursue merely to achieve the currently recommended consumption level.

Table 2.7: Theoretical maximum for fruit and vegetable intakes

Age group (years)	theoretical-minimum-risk distribution and SD (fruit and vegetable intake $g.person^{-1}.day^{-1}$)
0-4	330 ± 50
5-14	480 ± 50
15-29	600 ± 50
30-44	600 ± 50
45-59	600 ± 50
60-69	600 ± 50
70-79	600 ± 50
≥80	600 ± 50

Source: Global and regional burden of diseases attributable to selected major risk factors, volume 2. (Ezzati et al. 2004)

2.3 Relative risk: a systematic review

The associations of low intake of fruits and vegetables and disease outcomes applied in this study are primarily adopted from systematic reviews of the literature conducted in the 2000 revision of the "Global Burden of Disease (GBD) and Comparative Risk Assessment" project (CRA) (Ezzati et al, 2004). The recent and comprehensive report by the World Cancer Research Fund and the American Institute for Cancer Research (WCRF/AICR 1997), which analyzes a wide range of cancers, is also put for consideration. Nonetheless, in advocating a rational use of relative risks derived from the CRA project, apart from the former reviews, an up-to-date additional literature review was systematically performed for risk quantification.

2.3.1 Systematic reviews of literature

The outcomes included in this systematic review, were mainly in accordance with those suggested in the 2000 CRA report. Due to the fact that the methodology applied for estimations of risk of low fruit and vegetable intake within the CRA framework basically required the relative risks that could be converted into the unit of change in relative risks along with changes in each 80-gram-increment in fruits and vegetables (Ezzati et al. 2004). Therefore, the considerations were mainly followed such conditions; namely, an availability of current evidence conducive to drawing valid conclusions on correlation between fruit and vegetable consumption and disease outcomes, the size of the effect and possibility to conversion. For cancers, exclusion covered those cancer sites, as initially reviewed by WCRF/AICR (1997), showing a probable association, such as larynx, pancreas and bladder, or being advocated by scant evidence on an association; such cancers that may be related to hormonal etiology as ovary, endometrium, prostate and thyroid. For cardiovascular disease outcomes, peripheral vascular disorders were excluded from the present study owing to limited current evidence on their relationship with fruit and vegetable intake (Ezzati et al. 2004). So the following disease categories were of further search.

- Cardiovascular diseases: all symptomatic heart, cerebrovascular and total circulatory events, covering ischemic, thrombotic, embolic, hemorrhagic and transient ischemic attack[4] (TIA) were included.
- Cancers: esophagus, stomach, colon-rectum and lung were included.

2.3.1.1. Search strategy

Studies on the association between fruit and vegetable intake and selected disease outcomes were identified; that is, cardiovascular diseases and cancers. The following electronic databases were searched: BASE (Bielefeld Academic Search Engine), MEDLINE, MedPilot (http://medpilot.zbmed.de) and Google™ Scholar BETA using the keywords "fruits" and/or "vegetables". All search terms were linked to medical subject (MeSH) headings and exploded. Searches were confined to human studies in English from 2000 to September 2006.

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[4] A transient ischemic attack (TIA) is a set of symptoms which last a short time and is caused by a temporary obstruction to the blood flow within the brain. Sometimes it is called a mini stroke; however, unlike stroke, the symptoms last only for a short time. (www.bhf.org.uk)

Following were search terms used to identify studies on fruit and vegetable consumption and selected disease outcome

1) "fruits"
2) "fruit"
3) "vegetables"
4) "vegetable"
5) "cancer"
6) "neoplasm"
7) "tumor"
8) "carcinoma"
9) "colon cancer"
10) "rectum cancer"
11) "colorectal cancer"
12) "esophagus cancer"
13) "oral cancer"
14) "stomach cancer"
15) "gastric cancer"
16) "lung cancer"
17) "heart diseases"
18) "cardiovascular diseases"
19) "stroke"
20) "ischemic"
21) "hemorrhagic"

These keywords were combined with appropriate conditional logic of Bolean operators to locate a set of all possible searching keywords.

The following inclusion criteria for the review were applied:

- Studies that measured dietary intake of fruits and/or vegetables;
- Studies were conducted in a cohort or prospective study design, where their results were considered as more reliable evidence of association than those from case-control studies;
- Studies that explored associations of fruit and vegetable intake with diseases. This also included studies that used as their exposure variable proxy measures of intake derived from the measurement of intermediate variables, such as dietary fiber from vegetables or serum biological markers such as carotenoids, folate, flavonoids, vitamin C not due to supplements where there was a high correlation with the specific food type;
- Studies applied the quantitative assessment approach, of which methodology for data collection and analysis was robust and clearly documented; and
- The statistical analyses were adjusted for important potential confounders.
- Studies were published in the year 2000 onwards up to September 2006.

Exclusion criteria were designated as follows:

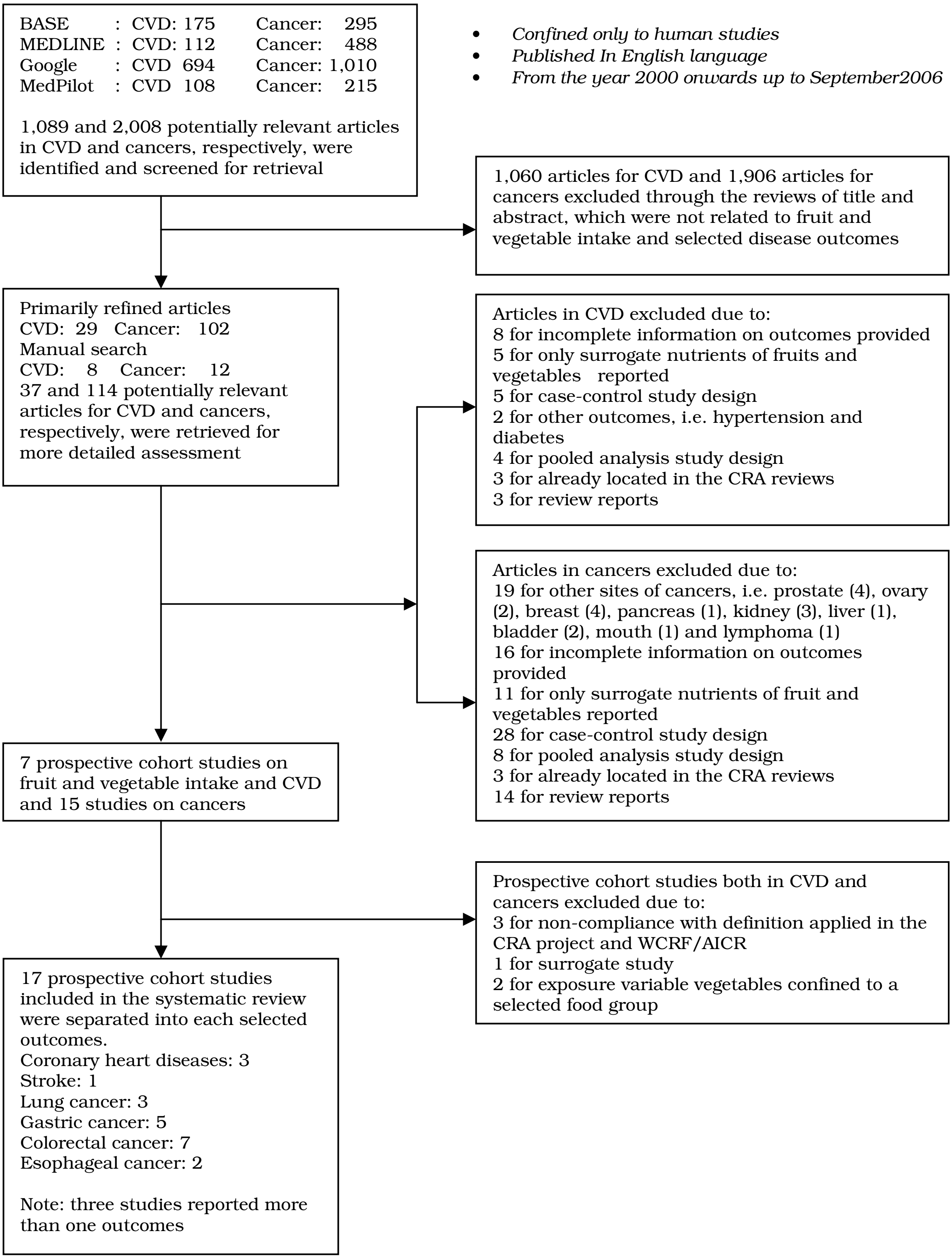
- Studies were conducted in the case-control or ecological study design. Case control studies, where diet is assessed after the onset of disease, may be subject to information (recall) and selection bias, and inaccurate or biased measurements of dietary exposure attributable to dietary changes as a result of disease (Willett, 1998). While ecological studies, which analyze aggregated data at the level of the population, may be subject to confounding and cannot reliably be extrapolated to the individual level (Greenland et al. 1999).
- Exposure variables were total fruit and vegetable intake and not selected groups of fruits and vegetables (e.g. citrus fruit, green leafy vegetables, raw and cooked vegetables).
- The definition of such variables; namely fruits and vegetables, were required to comply with that denoted in the CRA project. Studies with classifications that were not in line with those in the CRA reviews were excluded.
- Results on surrogate nutrients of fruits and vegetables were reported, not on fruits and vegetables themselves. Studies were already included in the 2000 CRA project analysis.

All references that matched the inclusion criteria were retrieved, and references of those articles were further explored for other relevant publications, through the review of title and abstracts. If there was any doubt regarding study relevance, the full text of the study was, then, retrieved.

2.3.1.2 Searching results

A total of 17 studies were identified according to the inclusion criteria (Figure 2.3), of which 3 studies investigated the association of fruit and vegetable intake with coronary heart diseases, 1 for stroke, 2 for esophageal cancer, 3 for lung cancer, 5 for stomach cancer and 7 for colorectal cancer. Details of exclusion were elaborated in each review category of selected outcomes.

Figure 2.3: Summary of study assessment and exclusion stages



As mentioned previously, with regard to a wide range of relative risks estimated in the CRA project, which covered all age groups, and comparability purpose, choices of outcomes for further usage in quantifying risk burden in this study were indicated as follows;

- Cardiovascular diseases: coronary heart disease and stroke
- Cancers sites: lung, stomach, colon-rectum and esophagus

Data extraction for reviews included the first author's name, year of publication, name of the studied group, country of the study conducted, number of participants, participants' age of entry, duration of follow-up, number of events, exposure measure, outcome assessment, relative risks and 95% Confidence Intervals (CI) between the highest and lowest and measurement units (e.g. quantiles) as well as covariates adjustment in the statistical analysis.

2.3.2 Analytical reviews of causality for each selected outcomes

The following section presented the content of the different selected outcomes; namely, cardiovascular disease subtypes of coronary heart disease and ischemic stroke, and cancer sites of lung, stomach, colon-rectum and esophagus. The analytical reviews of risk-factor-disease relationship included the previous review of studies, which covered those studies that conducted and analyzed by the CRA project. Later, the current review of studies illustrated the current work on analytical reviews through systematical search for this study. Then, the current review of recent meta-analysis studies provided additional insights reviewed from up-to-date published meta-analysis or pooled studies. At the end of each disease outcome offered conclusive statement regarding overall reviews.

2.3.2.1 Cardiovascular diseases

2.3.2.1.1 Coronary heart disease

This reviews covered all coronary events, including ischemic, thrombotic, embolic, hemorrhagic and TIA in expanding plausible associations observed as well as the outcomes of ischemic heart disease (ICD-9 codes 410-414 or ICD-10 codes I21.0-I23.9), which is a subtype in the coronary heart disease category (ICD-9 codes 402, 410-414, 429.2 or ICD-10 codes I24.0-I24.9, I25.2, I20.0-I20.9, I25.0-I25.1, I25.3-I25.9, I11.0, I11.9, I51.6).

Previous review of studies

The reviews in the CRA project by Ezzati et al. 2004 included 27 prospective studies investigating the relationship between ischemic heart disease (IHD) risk and fruit and vegetable intake. Most of the reviewed studies were conducted in the industrialized countries, such as Japan, United States and European nations. Such review findings indicated that more than half of the prospective cohort studies in different population settings reported a strong inverse association of fruit and vegetable consumption and cardiovascular disease. After adjustment for potential confounders, the observed association remained generally unchanged. In estimating relative risks derived for CRA, Ezzati et al. (2004) selected 4 cohort studies that most closely met their identified selection criteria. Such pooled studies for the meta-analysis included the European Prospective Investigation into Cancer and Nutrition study (EPIC-Norfolk) (Khaw et al. 2001), the Finnish Mobile Clinic Health Examination study (Knekt et al.1994), the Nurses' Health Study and Health

Professionals' Follow-up Study (NHS/HPFS) (Joshipura et al. 2001) and the Massachusetts Health Care Panel study (Gaziano et al. 1995) (Table 2.8). The authors included the EPIC-Norfolk study despite its results presented in plasma vitamin C. This was considered as an acceptable biomarker available for the whole cohort and well representative for fruit and vegetable intake. Additionally, the high quality of methods used in collecting and analyzing data were recognized.

In NHS/HPFS, the EPIC-Norfolk and Finnish Mobile Clinic studies, fruit and vegetable intake variables, derived for relative risk estimation in meta-analysis, were treated as continuous variables and identified as 80 g/day along with changes in relative risk estimates to generate final estimates expressed as per 80 g/day increase. For the Massachusetts Health Care Panel study, in which fruit and vegetable intake variables were presented in quartiles of intakes and not represented for consumption over the entire population range. Ezzati et al. (2004) [5] applied the relative risks given in the study to estimate the additional gram per day.

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[5] Methods for estimating risk-factor-disease-relationship for CRA (Ezzati et al. 2004)

1) The final RR estimates are expressed as the unit of change in RR associated with 80 grams increase in fruit and vegetable consumption--the amount representing a recognized standard serving size (WCRF &AICR, 1997)
2) Meta-analysis applied the log relative risks and corresponding standard errors, then implemented in Strata 7 ("meta" macro), when more than one study available. Chi-squared statistic was used to test heterogeneity between studies, with pre-specification of condition by the random-effect result. In case of only two studies identified, fixed effect meta-analysis was used; couple with forest plot in showing the results for individual studies.
3) Extrapolation of the RR was made under certain limited conditions. Sub-region was on the ground of assumption of no interaction between the level of intake and sub-region on the associations. Due to limited evidence for separate sexes and age range, the RR estimates were applied to both sexes for each outcome and to all age groups between the age of 15 and 69 years, while attenuations were applied a quarter and by half to ages 70-79 years and above 80, respectively.

Table 2.8: Relative risk estimates for the association between ischemic heart disease and fruit and vegetable consumption

Study population	Country	Age of entry; sex	Outcome	RR	95% CI
Knekt et al. 1994 Finnish Mobile Clinic Health Examination study	Finland	30-69 yrs; m, f	Mortality	0.96	(0.93,0.10)
Khaw et al. 2001 EPIC-Norfolk	United Kingdom	45-79 yrs; m,f	Mortality	0.54	(0.4, 0.74)
Joshipura et al. 2001 NHS/HPFS	USA	34-75 yrs; m,f	MI incidence	0.96	(0.94, 0.99)
Gaziano et al. 1995 Massachusetts Health Care Panel study	USA	> 66 yrs, m, f	Mortality	0.54	(0.35, 0.84)

MI: Myocardial Infraction; RR (95% CI) per 80 grams/day increase in fruit and vegetable intake

Source: Global and Regional burden of diseases attributable to selected major risk factors, volume 2 (Ezzati et al. 2004)

Table 2.9: Summary of relative risks for selected diseases with increase fruit and vegetable consumption by age group.

	Age group							
Outcome	0-4	5-14	15-29	30-44	45-59	60-69	70-79	>= 80
Ischemic heart disease	1.00	1.00	0.90	0.90	0.90	0.90	0.93	0.95
			(0.82-0.99)	(0.82-0.99)	(0.82-0.99)	(0.82-0.99)	(0.85-1.01)	(0.87-1.03)
Ischemic stroke	1.00	1.00	0.94	0.94	0.94	0.94	0.95	0.97
			(0.89-0.99)	(0.89-0.99)	(0.89-0.99)	(0.89-0.99)	(0.91-1.00)	(0.92-1.02)
Lung cancer	1.00	1.00	0.96	0.96	0.96	0.96	0.97	0.98
			(0.93-0.99)	(0.93-0.99)	(0.93-0.99)	(0.93-0.99)	(0.91-1.02)	(0.91-1.02)
Gastric cancer	1.00	1.00	0.94	0.94	0.94	0.94	0.95	0.97
			(0.86-1.03)	(0.86-1.03)	(0.86-1.03)	(0.86-1.03)	(0.87-1.04)	(0.89-1.06)
Colorectal cancer	1.00	1.00	0.99	0.99	0.99	0.99	0.99	1.00
			(0.97-1.02)	(0.97-1.02)	(0.97-1.02)	(0.97-1.02)	(0.97-1.02)	(0.97-1.02)
Esophageal cancer	1.00	1.00	0.94	0.94	0.94	0.94	0.95	0.97
			(0.88-1.01)	(0.88-1.01)	(0.88-1.01)	(0.88-1.01)	(0.89-1.02)	(0.91-1.04)

Note: Unit of change in risk is change per 80 grams/day increase in fruit and vegetable intake, with 95% CI.

Source: Global and Regional burden of diseases attributable to selected major risk factors, volume 2 (Ezzati et al. 2004)

Then, the method of Greenland and Longnecker (1992) was used to estimate the weighted regression slope over the published relative risks, allowing for correlations due to common reference category to generate the final relative risk estimate for inclusion in the meta-analysis. The resulting relative risk estimates for Ischemic heart diseases used for CRA, as indicated in Table 2.9, were methodologically produced in the form of unit of change in relative risks related to each 80-gram increment, an amount recognized as a standard serving size (WCRF/AICR. 1997), in fruit and vegetable consumption. The final relative risk estimates was 0.90 (95% CI: 0.82, 0.99) as demonstrated in Table 2.9.

Current review of studies

Literature and reference searches identified 6 studies. Three studies (Strandhagen et al. 2000, Mozaffarian et al. 2003, Steffen et al. 2003) were excluded because the vegetable category did not comply with the definition used in the CRA project (Ezzati et al. 2004). The final investigation comprised 3 studies; that is, the National Health and Nutrition Examination Survey Epidemiologic Follow-up study (Bazzano et al. 2002), the Prospective Epidemiological Study of Myocardial Infraction (Dauchet et al. 2004) and the Kuopio Ischemic Heart Disease Risk Factor study (Rissanen et al. 2003), which were conducted in the United States and the European settings. Solely one study conducted in both sexes, while the rest studied in men only. The follow-up duration ranged from 5 to 19 years. The exposure measurement tools were different among studies; namely, a 4-day food record and various items of food frequency questionnaires. All studies showed an inverse statistical association of fruit and vegetable intake with cardiovascular and coronary events. However, there was no association observed between fruit and vegetable intake and IHD incidence in the National Health and Nutrition Examination Survey Epidemiologic Follow-up study (Bazzano et al. 2002).

The authors noted that the association between fruit and vegetable consumption and ischemic heart disease was heterogeneous, more marked for IHD mortality [RR=0.76 (95% CI: 0.56, 1.03), *P* for trend 0.07] than for IHD incidence [RR=1.01 (95% CI: 0.84, 1.21), *P* for trend 0.8]. The actual relative risks for the studies in the systematic reviews are demonstrated in Table 2.10.

All the studies, after adjusted for some potential confounding factors, still indicated a significant association with the lower risk of cardiovascular disease and ischemic health disease. However, in the Bazzano et al. (2002) study, only an association between intake of fruits and vegetable and IHD incidence indicated contrast. It was suggested that incident cases may be incorrectly assessed than death as an end-point stage due to definition and method applied in the study and also may fruit and vegetable intake reduce the case-fatality rate after myocardial infraction, leading to stronger relationships with mortality than with incidence.

Table 2.10: Summary of prospective cohort studies reporting a measure of association between intake of fruits and vegetables and cardiovascular diseases

Reference	Country	Age of entry; sex	Years of follow-up	Start of follow-up	No. of cases; No. in cohort	Exposure measure; Quantiles[a]	RR (95% CI), between top and bottom	Outcome	Adjustment
Bazzano et al. 2002 National Health and Nutrition Examination Survey Epidemiologic Follow-up Study	USA	25-74 yrs: m, f	19 yrs	1971	880; 9608	3-item FFQ[b]; Q5	1.01 (0.84, 1.21); P for trend 0.8	IHD[e] (I)	age, race, sex, diabetic history, physical activity, education, alcohol consumption, smoking, vitamin supplement use, total energy intake.
					218; 9608		0.76 (0.56, 1.03); P for trend 0.07	IHD (D)	
					1786; 9608		0.73 (0.58, 0.92); P for trend 0.008	CVD[f] (D)	
Dauchet et al. 2004 Prospective Epidemiological Study of Myocardial Infraction	France, Northern Ireland	50-59 yrs: m	5 yrs	1991	249; 8087	FFQ, 4 categories of FV; Q3	0.78 (0.56, 1.07); P for trend 0.18	CHD[g]	education, smoking, PA, alc, employment, BMI, BP, serum total and HDL-cholesterol
Hissanen et al. 2003 Kuopio Ischemic Heart Disease Risk Factor study	Finland	42-60 yrs: m	mean 12.8	1989	115;2641	4-d food record; Q5	0.66 (0.28, 1.55); P for trend 0.13	CHD	age, examination year, BMI, BP, DM, serum LDL, HDL and triglyceride, dietary factors

[a] Quantiles. Q3 = tertiles; Q5 = quintiles
[b] Food Frequency Questionnaires
[c] Incident cases
[d] Deaths
[e] Ischemic heart disease
[f] Cardiovascular disease
[g] Coronary heart disease
[h] High blood pressure
[i] Diabetes Mellitus
[j] Body Mass Index
[k] Physical Activity

Current review of recent meta-analysis studies

Two recent reviews of the relation between fruit and vegetable consumption and cardiovascular diseases were reported. In a pooled analysis of 10 prospective cohort studies from the United States and Europe, Pereira et al. (2004) investigated associations of dietary fiber intake from different sources and coronary heart disease (CHD) risk, suggesting a strong inverse association of consumption of dietary fiber from fruits and cereals, adjusted for sex, age, baseline body mass index, smoking, history of hypertension, diabetes, hypercholesterolemia. While a null association was found between vegetable fiber intake and coronary events. The study concluded that the risk of coronary heart disease is reduced 10-30% with increase in every 10 grams per day of total, cereal or fruit fiber consumption. Nonetheless, limitations addressed in this study were heterogeneity of dietary assessment and food table methods and incomplete adjustments of all possible covariates and other dietary factors for measurement errors across the studies.

Luc Dauchet and colleagues (2006) performed a meta-analysis of 9 observational cohort studies assessing the association of coronary heart disease (CHD) and intake of fruits and vegetables. The analysis, which covered the studies mostly conducted in the United States, included 91,379 males, 129,701, and 5,007 CHD events under the period of follow-up ranging from 5-19 years. The calculations of pooled RRs were performed for each incremental portion of fruit and/or vegetable intake per day. They estimated that the risk of coronary heart disease was about 4% [RR=0.96 (95% CI: 0.93, 0.99), P =0.003] lower for each incremental portion intake of both fruits and vegetables and about 7% [RR=0.93 (95% CI: 0.89, 0.96), P <0.0001] lower for each increased fruit intake. The association between vegetable intake and

CHD was found to be heterogeneous (*P* =0.004). A significant association was found for cardiovascular deaths [0.74 (0.75, 0.84), *P* < 0.0001] whereas a weaker association was observed for fatal and non-fatal myocardial infarction [0.95 (0.92, 0.99), *P* =0.0058]. The authors noted that publication or selection biases among the pooled studies may affect the causal relations. They, however, concluded that fruit and vegetable consumption yielded a protective effect in reducing the CHD risk.

Conclusion

Despite the slight inconsistency among findings of the National Health and Nutrition Examination Survey Epidemiologic Follow-up study (Bazzano et al. 2002), the pooled studies conducted by Dauchet et al. (2006) and Pereira et al. (2004), the overall literature suggests a strong inverse relationship between fruit and vegetable intake and coronary heart disease. It is noted that a null association between vegetable intake and cardiovascular events in those two pooled studies and the study done by Bazzano et al. (2002) may relate to dietary tool used (3-item FFQ) and duration under observation. A greater scrutiny specific to the effect of vegetable category, numbers and types of items, latency period pertaining to CVD is suggested.

In conclusion, the current review, in general, show the same direction as those analyzed by the CRA project with regard to an increased intake of fruits and vegetables with lower risk of cardiovascular disease (Table 2.9). Therefore, the CRA's RR estimates, which were relatively moderate, were sensibly adopted for risk quantification for this current study.

2.3.2.1.2 Stroke

This reviews covered all events of stroke (ICD-9 codes 430-438, or ICD-10 codes I60.0-I60.9, I61.0-61.9, I62.0, I62.1, I62.9, I63.0-63.9, I64.0, I65.0-65.9, I66.0-I66.9, G45.9, I67.0-I67.9 and I69.0-I69.8).

Previous review of studies

In reviews by Ezzati et al. (2004), the analysis was confined to ischemic stroke on the theoretical assumption that there was inadequate evidence confirming the association of differential types of outcomes with fruit and vegetable consumption and that there was a greater biological plausibility of the association of fruit and vegetable protective effects with ischemic stroke. Twenty-one prospective studies, from Asia, the United States and Europe, investigating the relationship between risk of stroke and fruit and vegetable intake were included in the analysis. More than half of such reviewed studies (13 studies) showed a statistical significance of inverse association of fruit and vegetable intake and stroke. The authors summarized that the association persisted even after adjustment for major potential confounding factors.

In estimating pooled relative risks for the CRA project (Ezzati et al. 2004), only 2 cohort studies met the identified selection criteria for meta-analysis. The assessment included the NHS/HPFS (Joshipura et al. 2001) and the Zutphen study (Keli et al. 1996) as shown in Table 2.11, where the relative risk in terms of one additional portion per day was converted as 80 g/day. The final relative risks for stroke, therefore, were demonstrated in Table 2.9.

Table 2.11: Relative risk estimates for the association between stroke and fruit and vegetable consumption

Study population	Country	Age of entry; sex	Outcome	RR	95% CI
Keli et al. 1996 Zutphen study	Netherlands	50-69 yrs; m	Incidence cerebrovascular accident	0.87	(0.49, 1.53)
Joshipura et al. 2001 NHS/HPFS	USA	34-75 yrs; m,f	Incidence Ischemic stroke	0.96	(0.94, 0.99)

Note: RR (95% CI) per 80 grams/day increase in fruit and vegetable intake

Source: Global and Regional burden of diseases attributable to selected major risk factors, volume 2 (Ezzati et al. 2004)

Table 2.12 Summary of prospective cohort studies reporting a measure of association between intake of fruits and vegetables and stroke

Reference	Country	Age of entry; sex	Years of follow-up	Start of follow-up	No. of cases; No. in cohort	Exposure measure; Quantiles[a]	RR (95% CI), between top and bottom	Outcome	Adjustment
Johnsen et al. 2003 Diet, Cancer and Health study	Danmark	50-64 yrs: m, f	Median = 3.09	1993	266; 54,506	192-item Semi-quantitative FFQ[b]; Q5	0.72 (047, 1.12): P for trend 0.04	Stroke	sex, total energy intake, smoking, BP[c], DM[d] history, BMI[e], alcohol intake, red meat intake, omega-3 intake, PA[f] and education

[a] Quantiles. Q3 = tertiles; Q5 = quintiles
[b] Food Frequency Questionnaires
[c] High blood pressure
[d] Diabetes Mellitus
[e] Body Mass Index
[f] Physical Activity

Current review of studies

Literature and reference searches identified 3 studies. One was excluded owing to exposure variable vegetables confined to a selected food group (yellow/green vegetables), as well as no baseline measurement and information on portion size (Sauvaget et al. 2003). Another one study was excluded as the vegetable category (inclusion of potatoes) did not comply with the definition used in the CRA project (Steffen et al. 2003), leaving one study for a final analysis (Johnsen et al. 2003). The study was conducted in Danish men and women. Periods of follow-up ranged from 0.02 to 5.10 years with median of 3.09 years. The researchers used 192-item food frequency questionnaires for exposure assessment. After adjustment for potential confounders, a risk ratio of ischemic stroke for persons in the top and bottom quintiles of fruit and vegetable intake were 0.72 [(95% CI: 0.47, 1.12), *P* for trend 0.04]. A high inverse association was particularly found for fruit intake with a risk ratio of 0.60 [(95% CI: 0.38, 0.95), *P* for trend 0.02]. The author also pointed out the significant effect on decreased risk of ischemic stroke, notably from citrus fruits (Table 2.12).

Current review of recent meta-analysis studies

He and colleagues (2006) performed the recent meta-analysis of the pooled 8 studies, comprising 9 independent cohorts, in exploring the association of fruit and vegetable consumption and stroke. Eleven to 26 percent reductions in risk of stroke were observed when comparing individuals who have less than three to those with three to five servings per day, and those with three to five servings to those who have more than five servings per day. The results confirmed a significant protective effect of increased intake of fruits and vegetables against both ischemic and hemorrhagic stroke. The study also had several limitations, such as no exclusion of potential biases due to lifestyles, no consideration on types of fruits and vegetables, and no exclusion of potential biases due to misclassification of fruit and vegetable intake as dietary assessment, number of exposure categories, and the reference category varied among individual studies.

The pooled reviews by Dauchet et al. (2005) identified 7 prospective studies investigating fruit and vegetable consumption and risk of stroke. They estimated that the risk of stroke was about 11% lower for each incremental portion intake of fruits per day, about 5% for fruits and vegetables and about 3% for vegetables.

Conclusion

All the studies in this current review suggest consensual findings of a significantly inverse association between fruit and vegetable intake and stroke, in consistence with those reviews in the CRA project (Ezzati et al. 2004) (Table 2.11). It is interesting that the negative association can be observed even in a fairly short period of follow-up (median 3 years). It could be possible that other factors, especially healthy lifestyle factors, such as being a nonsmoker, a moderate alcohol drinker or a consistent physically active person, may enforce stronger effects. It is more likely that people who practice healthy lifestyle have cluster groups of health promoting characteristics.

To conclude, from the current review, most studies indicated the protective effect of increased intake of fruits and vegetables on risk of stroke.

The inverse association was relatively stronger than those proposed by the CRA project (Table 2.9). Therefore, it was decided to adopt the CRA's RR estimates, which was fairly moderate, for estimation of stroke burden attributable to low intake of fruit and vegetable in the current study.

2.3.2.2 Cancers

Fruits and vegetables have long been regarded as key components of diet conferring decreased cancer risks. Considerable evidence from the prospective study designs, for the cancer-preventive effect of fruit and vegetable consumption for each cancer site has been generated. This mainly includes cancers of the mouth (fruits only), esophagus, stomach, colon-rectum, lung, bladder (cruciferous vegetables only), prostate (tomato), kidney (root vegetables) and liver.

For risk estimation in this study, however, the associations of fruit and vegetable consumption with cancer sites are confined to those reviewed and analyzed for the CRA project by reason of availability of conclusive evidence. The selected choices of cancer sites for investigation, therefore, included lung cancer (ICD-9 codes 162 or ICD-10 codes C34.0-C34.9), stomach cancer (ICD-9 codes 151 or ICD-10 codes C16.0-C16.9), colorectal cancer (ICD-9 codes 153, 154 or ICD-10 codes C18.0-C18.9, C20.0) and esophageal cancer (ICD-9 codes 150 or ICD-10 codes C15.0-C15.9).

2.3.2.2.1 Lung cancer

Previous review of studies

The reviews in the CRA project by Ezzati et al. (2004) included 21 cohort and 32 case-control studies investigating the relationship between lung cancer risk and fruit and vegetable intake. Such reviewed studies were conducted across diverse settings, such as geography, age group, religion or lifestyle. None were nationally representative. The report also noted that the reviewed studies were conducted in different analytical methods, follow-up periods, risk factors and expected endpoint outcomes (incidence vs mortality). The reviews of case-control studies showed consistent results with those of the cohort studies in identifying an inverse association of fruit and vegetable intake and lung cancer risk. The authors also pinpointed the benefit conferred through a high consumption of fruits and vegetables significantly appeared in current smokers rather than in non-smokers. This implication was explained by the biological mechanism hypothesis for benefits of fruits and vegetables in lung cancer through late stage modification of carcinogenesis following an initial carcinogen exposure. The authors concluded that some of the reviewed studies' findings suggested an inverse association of fruit and vegetable consumption and lung cancer risk, both incidence and mortality, in spite of insufficient evidence in justifying the result's stratification by smoking status. It was also strongly recommended that further research must be needed to clarify the differential results of current studies, especially with regard to exposure among smokers, non-smokers and non-smokers exposed to environmental tobacco smoke as well as other plausible risk factors to lung cancer.

For meta-analysis, Ezzati et al. (2004) selected 4 cohort studies that most closely met their selection criteria. The analysis included the Finnish Mobile Clinic Health Examination study (Knekt et al.1994), the Netherlands Cohort study (Voorips et al. 2000b), the National Health Interview study (Breslow et al. 2000) and the NHS/HPFS (Feskanich et al. 2000) (Table 2.13). With relative risks derived from the identified studies, the final relative risks were methodologically converted as 80 g/day increase in fruit and vegetable consumption and treated as a continuous variable with the method of Greenland and Longnecker (1992). Owing to no evidence of heterogeneity, the fixed effect meta-analysis approach was applied to generate the pooled relative risk estimate of 0.93 (95% CI: 0.89, 0.97) for an increment of 80 g/day of fruit and vegetable consumption. With a strong consideration on the effects of potential residual confounders, the authors, however, performed adjustments in a conservative manner and gave the final pooled relative risk estimate of 0.96 (95% CI: 0.93, 0.99) for an 80 g/day increase in fruit and vegetable consumption, as presented in Table 2.9.

Current review of studies

In this analysis, 4 studies that examined the association of fruit and vegetable intake with lung cancer risk were primarily identified. One study (Miller et al. 2004) was excluded due to its definition of fruit category not complied with that in the CRA project, leaving 3 prospective studies for the final investigation.

Table 2.13: Relative risk estimates for the association between lung cancer and fruit and vegetable consumption

Study population	**Country**	**Age of entry; sex**	**Outcome**	**RR**	**95% CI**
Knekt et al.1991 Finnish Mobile Clinic Health Examination study	Finland	50-69 yrs; m, f	Incidence	0.92	(0.85, 0.99)
Voorrips et al. 2000b the Netherlands Cohort study	Netherlands	55-69 yrs; m, f	Incidence	0.89	(0.83, 0.96)
Breslow et al. 2000 National Health Interview study	USA	m, f	Mortality (fruit)	0.90	(0.69, 1.17)
Feskanich et al. 2000 NHS/HPFS	USA	34-75 yrs; m, f	Incidence	0.99	(0.91, 1.08)

Note: Unit of change in risk is change per 80 g/day increase in fruit and vegetable intake.

Source: Global and Regional burden of diseases attributable to selected major risk factors, volume 2 (Ezzati et al. 2004)

Table 2.14: Summary of prospective cohort studies reporting a measure of association between intake of fruits and vegetables and lung cancer risk.

Reference	Country	Age of entry; sex	Years of follow-up	Start of follow-up	No. of cases; No. in cohort	Exposure measure; Quantiles[a]	RR (95% CI), between top and bottom	Outcome	Adjustment
Liu et al. 2004 the Japan Public Health Center-based prospective study on cancer and cardiovascular diseases	Japan	40-69 yrs; f, m	10	1990	428; 39993	44-52-item FFQ[b]; Q3	1.10 (0.79, 1.52); P for trend 0.03	Lung (I[c])	age, sex, area, sports in leisure time, BMI[g], consumption of pickled vegetables, alcohol intake, vitamin supplements, smoking status, highly salted fish and meat, PHC[e], cigarettes per day and smoking duration.
Sauvaget et al. 2003 the Hiroshima/Nagasaki Life Span study	Japan	34-103 yrs; f, m	16	1980	563; 38,540	FFQ; Q3	0.80 (0.65, 0.98); P for trend 0.0348 (F)	Lung (D[d])	age, sex, city, radiation dose, education, smoking habits, PA[h], alcohol habits, BMI, smoking status
Holick et al. 2002 the Alpha-Tocopherol, Beta-Carotene Cohort study	Finland	50-69 yrs, m	14	1985	1,644; 27,084	276-item FFQ, Q5	0.73 (0.62, 0.86); P for trend <0.0001	Lung (D)	age, education, smoking history, energy intake, intervention (α-Tocopherol & β-Carotene), supplement use (β-Carotene & vitamin A), alcohol intake, FV[f] intake and cigarettes per day.

[a] Quantiles. Q3 = tertiles; Q5 = quintiles
[b] Food Frequency Questionnaires
[c] Incident cases
[d] Deaths
[e] Public health center
[f] Fruits and vegetables
[g] Body Mass Index
[h] Physical Activity

Two of the selected studies for the final review were conducted in Japan and included both male and female participants (Liu et al. 2004, Sauvaget et al. 2003), while the remaining was carried out only in Finnish males (Hollick et al. 2002). The follow-up duration was relatively long, ranging between 10 to 16 years. In the exposure measurement there was a wide range of food items (44 to 276 items) used in food frequency questionnaires. The results by Liu et al. (2004) indicated no association of fruit and vegetable intake with lung cancer incidence, after adjustment for potential confounders, especially by smoking status. The association between fruit and vegetable intake and lung cancer death seemed to be more evident in the analyses of Sauvaget et al. (2003) and Holick et al. (2002). All studies have considered, apart from smoking status, the intensity of current smoking habits, smoking history and duration of smoking. Holick et al. (2002) highlighted a strong negative association of dietary lycopene with the risk of lung cancer, although this association was slightly weaker when observed for total fruit and vegetable intake. They, however, proposed that high fruit and vegetable consumption, particularly a diet rich in carotenoids, tomatoes, and tomato-based products, may reduce the lung cancer risk (Table 2.14).

It is noted that association of fruit and vegetable consumption with lung cancer mortality appears stronger than that with incidence. This may be related to inadequate follow-up period for observation. Other potential influences may include misclassification biases and unknown residual confounders from tobacco use.

Current review of recent meta-analysis studies

In a pooled analysis of 8 prospective cohort studies, Smith-Warner et al. (2003) examined the associations of fruit and vegetable intake and lung cancer risk, by using the primary data from each cohort and combining study-specific relative risks (RRs). The reviews reported 16-23% lower risks of lung cancer among men and women for quintiles 2 through 5 vs. the lowest quintile of higher intakes of total fruits [RR=0.77 (95%CI: 0.67, 0.87) for quintile 5; *P* for trend <0.001], for total fruits and vegetables [RR=0.79 (95%CI: 0.69,0.90) *P* for trend=0.001]. The association was weaker for total vegetable intake [RR=0.88 (95%CI: 0.78, 1.00) *P* for trend=0.12], when adjusted for age. After adjustment for sex, smoking status and the number of fruit and vegetable questions on the food frequency questionnaires, the association between fruit and vegetable intake and lung cancer risk remained generally unchanged. However, the authors also noted that the findings may be inflated due to the possibility of incomplete control of potential confounding by smoking, residual confounders and misclassifications.

Conclusion

Despite a contrast finding from the Japan Public Health Center-based population study (JPHC) with a notion of shorter duration of observation and the outcome observed (incidence), it may be concluded that, according to the conclusive findings gained from most other studies, an increased intake of fruits and vegetables confers the beneficial effects towards reduction of lung cancer risk. However, owing to lack of current evidence in justifying the results' stratification by smoking, such as cigarette brand (different contents of carcinogenic exposure) or use of filtered versus unfiltered cigarettes, as residual confounders, the results may be overestimated (Ezzati et al. 2004).

In summary, the current review observed an inconsistency of the findings from those studies with regard to the defensive role of an increased intake of fruits and vegetables towards lung cancer risk. However, the RR estimates provided by CRA, as indicated in Table 2.9, seem relatively conservative, given other most studies that supported results on an inverse association. Therefore, this current study applied the RRs derived from CRA for estimation of low intake of fruit and vegetable contributing to lung cancer.

2.3.2.2.2 Stomach cancer

Previous review of studies

In reviews by Ezzati et al. (2004), the analysis identified 14 cohort and 32 case-control studies examining the association of fruit and vegetable intake and stomach cancer, both incidence and mortality. Both prospective and case-control studies reviewed were conducted across a wide range of diverse settings, such as country, geography, ethnicity, and age group. Particularly in the Asian populations, gastric cancer showed high incidence and mortality. H. *pyrori* infection was addressed in several studies as a major potential confounder. In addition, other confounders regarded variations in the findings across studies, such as the varieties of fruits and vegetables consumed in inter-country differences, the consumption methods (raw or cooked), the number of specific fruit and vegetable items included in the questionnaires used or the validity of the dietary assessment methods. The authors concluded that the evidence strongly supported the protective effect of fruit and vegetable intake against gastric cancer, even after adjustment for potential confounders.

The solitary study, the Netherlands Cohort study (Botterbeck et al. 1998), that met the identified selection criteria (Ezzati et al. 2004) (see Table 2.15), gave the relative risk estimates consistent with the effect estimates gathered from the reviews of case-control studies performed by Norat et al. (2001). The authors methodologically analyzed and generated the final relative risk estimate for stomach cancer incidence and mortality of 0.94 (95% CI: 0.86, 1.03) where the relative risk with respect to one additional serving per day was converted as 80 g/day and treated as a continuous variable (Table 2.9).

Current review of studies

The current review of literature identified 7 studies that examined the association of fruit and vegetable consumption with stomach cancer. One study was excluded due to its selected food group variables (citrus fruits and green-leafy vegetables) (McCullough et al. 2001). Another one study was excluded due to no content details or classifications of fruit and vegetable provided (Tran et al. 2005).

Table 2.15: Relative risk estimates for the association between stomach cancer and fruit and vegetable consumption

Study population	Country	Age of entry; sex	Outcome	RR	95% CI
Botterweck et al. 1998 the Netherlands Cohort study	Netherlands	55-69 yrs; m, f	Incidence	0.94	(0.86, 1.03)

Note: Unit of change in risk is change per 80 g/day increase in fruit and vegetable intake.

Source: Global and Regional burden of diseases attributable to selected major risk factors, volume 2 (Ezzati et al. 2004

Table 2.16: Summary of prospective cohort studies reporting a measure of association between fruit and vegetable intake and stomach cancer risk

Reference	Country	Age of entry; sex	Years of follow-up	No. of cases; No. in cohort	Exposure measure; Quantiles[a]	RR (95% CI), between top and bottom	Outcome	Adjustment
Larsson et al. 2006 the Swedish Mammography Cohort study &the Cohort of Swedish Men	Sweden	45-83 yrs; f, m	7.2	139; 82,002	96-item FFQ[b]; Q4	0.37 (0.19, 0.74); P for trend 0.01	Incidence	age, sex, education, DM[d], smoking, energy intake, alcohol, process meat, BMI[e], PA[f], aspirin use, multivitamin supplement use, consumption of red meat, poultry, fish, tea and coffee, excluding 3 years of follow-up
Kobayashi et al. 2002 the Japan Public Health Center-based prospective study	Japan	40-59 yrs; f, m	10	404; 39993	44-52-item FFQ; Q5	0.76 (0.59,0.99); P for trend 0.19 (V) 0.70 (0.49,1.00); P for trend 0.23 (F)	Incidence	age, sex, education, PHC[c] area, smoking, BMI, alcohol, multivitamin supplement use, energy intake, highly salted food, history of peptic ulcer and family history of gastric cancer.

[a] Quantiles. Q3 = tertiles; Q4 = quartiles, Q5 = quintiles
[b] Food Frequency Questionnaires
[c] Public health center
[d] Diabetes Mellitus
[e] Body Mass Index
[f] Physical Activity

Table 2.16: Summary of prospective cohort studies reporting a measure of association between fruit and vegetable intake and stomach cancer risk (cont)

Reference	Country	Age of entry; sex	Years of follow-up	No. of cases; No. in cohort	Exposure measure; Quantiles[a]	RR (95% CI), between top and bottom	Outcome	Adjustment
Gonzalez et al. 2005 the European Prospective Investigation into Cancer and Nutrition	Europe) (28 centers in 10 countries	35-70 yrs; f, m	6.5	348; 418518	88-226 FFQ[b] (self-administered Q); Q3	1.53 (0.49,4.78); P for trend 0.41 (V) 0.72 (0.39,1.33); P for trend 0.013 (F)	Incidence	age, sex, center, date of blood extraction, height, weight, education, smoking status, smoking intensity, PA[f], alcohol intake, energy intake, red meat intake, processed meat inatke, H. pyroli infection.
Nouraie et al. 2005 the α-Tocopherol, β-Carotene Cancer Prevention study	Finland	50-69 yrs, m	12	243; 29,133	276-item FFQ, Q4	0.85 (0.43, 1.68); P for trend 0.45 (V) 0.66 (0.43, 1.02); P for trend<0.001 (F)	Incidence	age, education, smoking, alcohol intake, dietary intake of sodium, nitrates & nitrites, vitamin A or β-Carotene.
Sauvaget et al. 2003 the Hiroshima/Nagasaki Life Span study	Japan	34-103 yrs; f, m	16	617; 38,540	FFQ; Q3	0.80 (0.65, 0.98); P for trend 0.0273(F)	Death	age, sex, city, radiation dose, education, smoking habits, PA, alcohol habits, BMI[e]

[a] Quantiles. Q3 = tertiles; Q4 = quartiles, Q5 = quintiles
[b] Food Frequency Questionnaires
[c] Public health center
[d] Diabetes Mellitus
[e] Body Mass Index
[f] Physical Activity

Five studies were included into the final investigation. Most the studies were conducted in European countries, while 2 studies were carried out in Japan. Most studies included both male and female participants. Only was the Alpha-Tocopherol, Beta-carotene Cancer Prevention (ATRC) study conducted in Finish males. Periods of follow-up ranged from 6 to 16 years. All studies basically used food frequency questionnaires for exposure assessment, but food items were considerably diverse, ranging from simple FFQs to 276 items. All studies performed adjustment for potential confounders. A statistically significant inverse relationship between fruit and vegetable intake and stomach cancer risk ranged from a very strong [RR=0.37 (95% CI: 0.19, 0.74), *P* for trend 0.001] in the Larsson et al. (2006)'s finding to fairly strong for only fruits intake [RR=0.72 (95% CI: 0.39, 1.33), *P* for trend <0.013] in the Gonzalez et al. (2005)'s report. This is probably because H. pylori infection, commonly found in Asian populations, is considered an established risk factor for gastric cancer. This may create distortion of the result interpretation. At present, there has been little evidence providing sufficient information and confirming the tested results (Ezzati et al. 2004). The summary of the review of the 5 studies was provided in Table 2.16.

Current review of recent meta-analysis studies

Lunet and colleagues (2005) performed the recent meta-analysis of previously published studies exploring the association of fruit and vegetable consumption and gastric cancer risk, both incidence and death. The analysis did not observe on the association of total fruit and vegetable consumption and gastric cancer risk. In the analysis, 7 studies observed gastric cancer incidence while another 7 studies examined mortality. The reviews discussed variations across studies, including no consideration on types of fruits and vegetables, and no exclusion of potential biases due to misclassification of fruit and vegetable intake as dietary assessment, number of exposure categories. Also, the reference category varied across studies and disease outcome ascertainment. The pooled relative risks for gastric cancer incidence associated with an increase of consumption of 100 g/day were 0.82 (95%CI: 0.73, 0.93) for fruits and 0.88 (95% CI: 0.69, 1.13) for vegetables. No associations when gastric cancer mortality was considered [RR=1.05 (95%CI: 0.89, 1.25). The author noted that design options, e.g. follow-up duration, may potentially affect the observed association.

Conclusion

Most studies indicated a protective effect of fruit intake against gastric cancer risk (more likely for incidence), regardless of population settings. Some discrepancy of findings were found in two studies (Gonzalez et al. 2005 and Nouraie et al. 2005), which were carried out in the European settings. Such findings' variations among studies could be due to variability of study country settings, study design, types of fruits and vegetables consumed, food preparation methods, numbers of fruit and vegetable items included in the questionnaires used and the validity of the dietary assessment methods, as well as disease etiology (Dekker and Verkerk 2005).

To conclude, most of the studies supported the hypothesis on the protective effect of increased intake of fruits and vegetables against stomach cancer risk. Provided that numerous potential of confounders require further investigation, the relative risks estimated by CRA appeared to be relatively conservative; therefore, it was decided to apply these RRs for quantifying burden of stomach cancer attributable to low intake of fruits and vegetables.

2.3.2.2.3 Colon-rectum cancer

Previous review of studies

In the CRA project by Ezzati et al. (2004), the systematic reviews included 15 cohort and 34 case-control studies investigating the relationship between colorectal cancer risk (both incidence and mortality) and fruit and vegetable intake. The analysis was performed on a combination of studies that observed colon and rectal cancer separately. The reviewed studies were conducted across diverse settings, such as geography, age group, religion or lifestyle. The given analysis also noted that the reviewed studies conducted in different analytical methods, follow-up periods, risk factors and expected outcomes (incidence vs mortality).

The results from the case-control study reviews appeared consistency with those of the cohort studies in identifying an inverse association of fruit and vegetable intake and colon-rectum cancer risk. Note that the authors, however, suggested that pooling of results from different anatomical sites and cell types in many of cohort and case-control studies may have obscured a true relationship for subgroups. In terms of complex biological mechanisms involved in its etiology, the incidence could be expected to reflect a complex combination of genetic factor, diet and hormonal status. The authors made the final conclusion that most of the reviewed studies' findings suggested an inverse association of fruit and vegetable consumption and colorectal cancer risk.

In estimating relative risks derived for CRA, Ezzati et al. (2004) identified 3 cohort studies that most closely met their selection criteria. Such pooled studies for the meta-analysis included the NHS/HPFS (Michels et al. 2000), and the Netherlands Cohort study (Voorips et al. 2000a) and the Swedish Mammography study (Terry et al. 2001), as indicated in Table 2.17. The relative risk results given in these studies were converted to relative risks for an 80 g/day increment and treated as a continuous variable. After testing heterogeneity, the fixed effects model was, then, applied. The relative risk estimate from the pooled studies was 0.99 (95%CI: 0.97, 1.02) for an increment of 80 g/day in fruit and vegetable intake, shown in Table 2.9. The authors stressed the findings given by the Swedish Mammography study on the stronger inverse association and the more evident dose-response among individuals with the lowest amounts of fruit and vegetable consumption. It appeared that individuals with very low amounts of fruit and vegetable consumption were predisposed to the greatest risk of colorectal cancer.

Current review of studies

The systematic review identified 9 studies that investigated the association of fruit and vegetable consumption with colon-rectum cancer risk. Since the vegetable category applied did not comply with the definition given by the CRA project, the study by McCullough et al. (2003) was excluded. Another study was excluded because only surrogate nutrients were reported (Malila et al. 2002).

Table 2.17: Relative risk estimates for the association between colorectal cancer and fruit and vegetable consumption

Study population	Country	Age of entry; sex	Outcome	RR (95% CI)
Voorrips et al. 2000a the Netherlands Cohort study	Netherlands	55-69 yrs; males	Incidence	Colon, 1.00 (0.92, 1.09) Rectum, 0.93 (0.86, 1.02)
		55-69 yrs; females	Incidence	Colon , 0.99 (0.9, 1.09) Rectum, 1.01 (0.89, 1.14)
Terry et al. 2001 Swedish Mammography study	Sweden	females	Incidence	Colorectal, 0.93 (0.87, 0.995)
Michels et al. 2000 NHS/HPFS	USA	34-75 yrs; m,f	Incidence	Colon, 1.02 (0.98, 1.05) Rectum, 1.02 (0.95, 1.09)

Note: Unit of change in risk is change per 80 g/day increase in fruit and vegetable intake.

Source: Global and Regional burden of diseases attributable to selected major risk factors, volume 2 (Ezzati et al. 2004

Table 2.18: Summary of prospective cohort studies reporting a measure of association between intake of fruits and vegetables and colorectal cancer risk.

Reference	Country	Age of entry; sex	Years of follow-up	No. of cases; No. in cohort	Exposure measure; Quantiles[a]	RR (95% CI), between top and bottom	Outcome	Adjustment
Flood et al. 2002 the Breast Cancer Detection Demonstration Project	USA	na, f	17	485; 41323	62-item FFQ[b]; Q5	1.15 (0.86, 1.53); P for trend <0.05 (F[h]) 0.95 (0.71, 1.26); P for trend <0.05 (V[i])	CRC[c] (I[d])	multivitamin supplement, BMI[f], height, use of NSAID, smoking, education, PA[g], intake of grains, red meat, calcium, vitamin D, alcohol intake, energy intake.
Bingham et al. 2003 the European Prospective Investigation into Cancer and Nutrition	Europe (10 countries)	25-70 yrs; f, m	10	1,065; 519,978	country-specific Q; Q5	0.78 (0.64, 0.97); P for trend 0.174 (F) 0.88 (0.70, 1.11); P for trend 0.517 (V)	CRC (I)	age, weight, height, sex, non-fat energy, energy from fat, center

[a] Quantiles. Q3 = tertiles; Q4 = quartiles, Q5 = quintiles
[b] Food Frequency Questionnaires
[c] Colorectal cancer
[d] Incidence
[e] Death
[f] Body Mass Index
[g] Physical Activity
[h] Fruits
[i] Vegetables

Table 2.18:Summary of prospective cohort studies reporting a measure of association between intake of fruits and vegetables and colorectal cancer risk (cont)

Reference	**Country**	**Age of entry; sex**	**Years of follow-up**	**No. of cases; No. in cohort**	**Exposure measure; Quantiles**[a]	**RR (95% CI), between top and bottom**	**Outcome**	**Adjustment**
Sauvaget et al. 2003 the Hiroshima/Nagasaki Life Span study	Japan	34-103 yrs; f, m	16	226; 38,540	FFQ[b]; Q3	0.97 (0.73, 1.29); P for trend 0.814 (F[h])	CRC (D[e])	age, sex, city, radiation dose, education, smoking habits, PA[g], alcohol habits, BMI[f]
Sato et al. 2004 the Miyagi study	Japan	40-64 yrs; f, m	7	165; 47,605 111; 47,605	40-item FFQ; Q4	1.13 (0.73, 1.75); P for trend 0.62 1.12 (0.67, 1.89); P for trend 0.37	Colon (I[d]) Rectum (I)	age, sex, smoking status, alcohol intake, BMI. Education, family history of cancer, time spent for walking, meat intake
Kojima et al, 2004 the Japan Collaborative Cohort study	Japan	40-79 yrs; m, f	9.9	173; 107,824 284; 107, 824	33-item FFQ; Q3 (fruit only)	0.80 (0.46, 1.41); p for trend 0.78 (m) 0.53 (0.22, 1.26); P for trend 0.35 (f) 1.06 (0.64, 1.75); P for trend 0.63 (m) 1.62 (1.02, 2.57); P for trend 0.04 (f)	Rectum (D) Rectum (D) Colon (D) Colon (D)	age, family history of colorectal cancer, BMI, alcohol intake, smoking status, walking time per day, education
Lin et al. 2005 the Women's Health study	USA	over 45 yrs; f	10	233; 36, 976	131-item FFQ; Q5	0.96 (0.58, 1.62); P for trend 0.14	CRC[c] (I)	age, BMI, family history of CRC, smoking, PA, alcohol intake, red meat consumption, aspirin use before trials, menopausal status, use of HT[j], RTA[k], total energy intake, folate intake, multivitamin use
Sanjoaquin et al. 2004 the Oxford vegetarian study	UK	16-89 yrs; f, m	17	95; 10,998	simple FFQ; Q3	0.60 (0.35, 1.02); P for trend 0.067 (F) 0.60 (0.54, 1.38); P for trend 0.415 (V[i])	CRC (I)	age, sex, alcohol intake, smoking

[a] Quantiles. Q3 = tertiles; Q4 = quartiles, Q5 = quintiles
[b] Food Frequency Questionnaires
[c] Colorectal cancer
[d] Incidence; [e] Death
[f] Body Mass Index
[g] Physical Activity
[h] Fruits; [i] Vegetables
[j] Hypertension
[k] Randomized treatment assignment

The final investigation included 7 studies as indicated in Table 2.18) for the, most of which were conducted in Japan, while the rest were carried out in Europe and the United States. Most of the studies included both males and females, whereas there were 2 studies conducted solely in females and both were in the U.S. (Flood et al, 2002 and Lin. et al. 2005). All studies targeted at adults aged over 16 years old. The follow-up period covered a wide range from 7 to 17 years. It is noted that those with longer follow-up period are more likely to show findings of negative association of fruit and vegetable intake with colon-rectum cancer risk. The Food frequency questionnaires are the common exposure measurement tool used among studies, but differences in numbers of food items. It should be also noted that although the majority of colorectal cancers are adenocarcinomas, some studies (Kojima et al, 2004; Sato et al. 2004 and Lin et al. 2005) found differences depending on tumor sites (proximal vs. distal, colon vs rectum). Hence, interpreting findings from these studies requires close consideration regarding these possible potential confounders (Ezzati et al. 2004). Almost all studies performed adjustment for the effect of age and sex. It should be noted that other confounding factors such as dietary habits, variability of food types, as well as etiological and histological pattern of cancers had to be taken into account.

There were two studies (Sato et al. 2004, Kojima et al. 2004) that did not support the role of increased fruit and vegetable consumption against colorectal cancer. The observed drawbacks of this study would be a shorter duration of observation as well as latency of the observed outcome (incidence). Other issues may include the sample size drawn for dietary investigation, a range of fruit and vegetable consumption among subjects and measurement errors. Despite these findings, most other studies supported the protective role of fruit and vegetable consumption against colorectal cancer.

Review of recent meta-analysis studies

Park Yikyung and colleagues (2005) performed a pooled analysis of 13 prospective studies in investigating relationship between dietary fiber from different sources and colorectal cancer risk. The results showed that a significant inverse association was found only in the age-adjusted model [RR=0.84 (95%CI: 0.77, 0.92)]. After adjustment for other confounders, there was no longer an association of high fiber intakes from fruits, vegetables and cereals with colorectal cancer. The analysis, however, did not perform standardization, such as food category or definition of fruits and vegetables among pooled studies. The authors concluded that high intake of dietary fiber was not associated with decreased colorectal cancer risk.

The review by Papas et al. (2004) analyzed 8 studies in examining association of dietary fiber with colorectal neoplasia by source of fiber. The analysis showed a range from inverse associations to no association among observed studies. Given a hypothesized mechanisms of soluble fiber towards insulin and glucose control, the findings suggested an inverse association of fruit fiber (mostly soluble fiber), though with such vast different characteristics among studies as designs, populations and exposure means. The authors, however, did not perform a summary statistic for the association as there were varieties of study design, outcomes of colon-rectum cancer sites, population characteristics, distribution of fiber intake, and potential confounders, but still suggested the protective role against colorectal carcinogenesis.

Conclusion

The uncertainty found among studies of colorectal cancer could be explained through the view of the complex biological mechanisms involved in its etiology, while the incidence could be triggered by a complex combination of genetic factors, diet and hormonal status (Ezzati et al. 2004). Hence, the certain long follow-up period of time may play a crucial role in detecting the association greater accurately, in particular for incidence. In addition, the unknown potential confounders ought not to be disregarded. So this review would make a considerate conclusion that the majority of findings seem to support the protective effects of either fruit or vegetable or both intake against the colorectal cancer risk. However, as new studies appear, the evidence may need to review and update in the near future. It is noted that newer findings have introduced doubt about the role of fruits and vegetables in cancer prevention.

To conclude, despite inconsistency of the findings and reviews with regard to the protective effect of an increased intake of fruits and vegetables against colorectal cancer risk, most other studies yet suggested this role. The RR estimates analyzed by CRA study appeared to be relatively moderate by reason of numerous potential of confounders that are needed further research. Therefore, this study adopted the RRs proposed by CRA to assess the burden of colorectal cancer attributable to low intake of fruit and vegetable in Thailand.

2.3.2.2.4 Esophagus cancer

Previous review of studies

Ezzati et al. (2004) systematically reviewed 4 cohort and 28 case-control studies examining the association of fruit and vegetable intake and esophageal cancer, both incidence and mortality. With an assumption on poor survival rates of esophageal cancer, and incidence highly correlated to mortality, the authors, therefore, considered these outcomes together. The analysis showed non-significant inverse relationships among these reviewed prospective studies. Findings from case-control studies showed an inverse association of fruit and vegetable intake with esophageal cancer risk, both incidence and mortality. However, the authors finally concluded that fruit and vegetable intake may affect esophageal cancer rates, despite being not as strong as those of stomach cancer.

For the CRA project, the final relative risk estimates were adopted from the results of pooled analysis done by Norat et al. (2001) since none of the cohort studies of esophageal cancer met the identified selection criteria. Furthermore, there were very few case-control studies estimating risks for total vegetable and fruit consumption, and none assessing relative risks for quantified levels of fruit and vegetable intake, which allowed the authors performing estimation of a continuous variable. The relative risk estimates for esophageal cancer equaled to 0.94 (95%CI: 0.88, 1.01) and were indicated in Table 2.9.

Current review of studies

This review found two studies meeting the identified criteria for investigating the association of fruit and vegetable intake and esophagus cancer risk; namely, the European prospective investigation into cancer and nutrition (EPIC-EURGAST) (Gonzalez et al. 2005) and the Hiroshima/Nagasaki Lifespan study (Sauvaget et al. 2003), indicated in Table 2.19. Both studies included males and females. The follow-up period of the Japanese study was undertaken longer than that of the multi-center cohort study, 16 years vs. 6.5 years. The items in the food frequency questionnaires, the main assessment tool for exposure assessment in both studies, were discrepant. The EPIC-EURGAST study showed a non significant inverse association of total vegetable intake with esophageal cancer (RR=0.72 (95%CI: 0.32, 1.64), *P* for trend 0.36], and no association with total fresh fruit intake was detected [RR=0.84 (95%CI: 0.60, 1.17, *P* for trend 0.75)]. On the contrary, the findings from the Asian setting showed an inverse association [RR=0.57 (95% CI 0.31, 1.04, *P* for trend 0.071)], but only for fruit intake. The authors of the EPIC-EURGAST study, however, noted that this may be due to its uncommon cancer site found in the European settings, compared to Asian countries, where the protective effect could be higher with regard to their high risk populations. Despite its not significant results, they suggested a probable protective effect of fruit and vegetable consumption against esophageal cancer risk.

Table 2.19 Summary of prospective cohort studies reporting a measure of association between intake of fruits and vegetables and esophagus cancer risk.

Reference	**Country**	**Age of entry; Sex**	**Years of follow-up**	**Start of follow-up**	**No. of cases; No. in cohort**	**Exposure measure; Quantiles[a]**	**RR (95% CI), between top and bottom**	**Outcome**	**Adjustment**
Gonzalez et al. 2005 the European Prospective Investigation into Cancer and Nutrition	Europe) (28 centers in 10 countries	35-70 yrs; f, m	6.5	1991	67; 418518	88-226 FFQ[b] (self-administered Q); Q3	0.72 (0.32, 1.64); P for trend 0.36 (V[f]) 0.84 (0.60, 1.17); P for trend 0.75 (F[e])	Incidence	age, sex, center, height, weight, education, smoking status, smoking intensity, PA[d], alcohol intake, energy intake, red meat intake, processed meat intake.
Sauvaget et al. 2003 the Hiroshima/Nagasaki Life Span study	Japan	34-103 yrs; f,m	16	1980	80; 38,540	FFQ; Q3	0.57 (0.31, 1.04); P for trend 0.071 (F)	Death	age, sex, city, radiation dose, education, smoking habits, PA, alcohol habits, BMI[c]

[a] Quantiles. Q3 = tertiles
[b] Food Frequency Questionnaires
[c] Body Mass Index
[d] Physical Activity
[e] Fruits
[f] Vegetables

Conclusion

In general, the reviewed studies illustrated a non-significant protective effect of fruit and vegetable intake and esophagus cancer, though a significant association was only found between fruit intake and esophageal cancer mortality in the Japanese study. However, there has been little evidence so far from the prospective studies in indicating the protective benefits, which mostly came from case-control approaches. Therefore, it is suggesting that further research with greater scrutiny on unknown residual confounders, variability of study designs, populations or even geographical areas should be done, where this cancer type is commonly found.

In summary, the reviews showed that the defensive role of an increased intake of fruits and vegetables towards esophagus cancer risk was controversial due to scant or inconclusive evidence. In addition, this cancer site is common in Asia, where the resources and researches are relatively limited. However, it was decided to apply the RR estimates provided by CRA, as indicated in Table 2.9, which were relatively conservative, amid no other better evidence, to estimate risk of low intake of fruit and vegetable contributing to esophagus cancer for the Thai population.

2.3.4 Summary of the estimates of risk-factor-disease relationships

It is noted that there is inconsistency of evidence in demonstrating the associations between fruit and vegetable intake and disease outcomes; namely, cardiovascular diseases and cancers. In general, this raises questions towards the accuracy of the data on consumption, variability of data gained, heterogeneity issues, analysis of the multivariate measurement errors and correlations between measurement errors of different variables. Most of these questions lie in the statistical nature. Nonetheless, other points of views should be taken into account.

Dekker and Verkerk (2005) pointed out the underlying rationale for the protective effects of fruit and vegetable intake against chronic diseases. Its statistical significance cannot be reliably assessed with epidemiologic studies as they are currently undertaken. It should be noted that not fruits and vegetables themselves do provide protective effects against chronic diseases, but rather certain components within them. Or, in terms of methodology should the level of such components relatively remain constant or should their variability stay steady by studying a large enough cohort and/or by studying the cohort for a long enough time. Besides, such factors as methods of food preparation (cooked vs. raw), food storage, as well as individual physiological capability in absorbing such nutrients might affect the discrepancy of the findings among cohort studies (Grant 2005).

In addition, Terry et al. (2001) also suggested that cancer is not a single disease with a single etiology, but is rather a general disease category that includes many district diseases with district etiologies. Similarly, fruits and vegetables are not a single exposure. Some categories of fruits and vegetables may be more important in the etiology of certain cancers than in others. This suggests that future research requires more emphasis on study designs, data collections and measuring tools, ranges of exposure and prudent statistical applications.

The relative risk estimates and 95% confidence interval estimated by the CRA project (Ezzati et al. 2004) are shown in Table 2.9. The authors illustrated estimates as a unit of change in relative risk associated with an increment 80-g/day of fruit and vegetable intake. The relative risk were applied to all WHO's sub-regions and to both males and females. With an assumption of age attenuation at the extremes of age, the relative risks, then, apply for individuals with ages of 15-69 years. For older adults, the relative risks are reduced by a quarter for ages 70-79 years, and by half for the age group older than 80 years. Finally, a relative risk of 1 is applied for those aged under 15 years.

However, it should be cautioned that these proposed relative risks for disease outcomes are subject to uncertainty derived from numerous assumptions used. For instance, the theoretical minimum distribution levels which were estimated by technically applying the highest level of fruit and vegetable availability from Food balance sheet data with hypothetical adjustments, are needed to revisit in the near future with more evidence, in particular in areas of risk difference analysis among the consumption categories. It is also suggested that research in investigating the protective effects of fruits and vegetables should be more invested in different specificities where offered a wider range of consumption for investigation, i.e. developing nations, and where some health conditions seem to be more prevalent, e.g. stomach and esophagus cancers among Asian population.

With a sound methodology applied to prevailing data and evidence, as well as the findings relatively consistent to the current review of literature, where evidence is scant or inconclusive, the estimated relative risks of the association of low intake of fruits and vegetables and selected outcomes derived from the CRA project, were adopted for calculating burden of selected diseases attributable to low intake of fruits and vegetable in Thailand's settings. Other advantageous features also include a wide range of RR covering across all age groups allowing possibility to make estimations, as well as to achieve comparability. With other studies applied the same methodology, e.g. CRA, this would allow Thailand to develop research, technology, database and information system as well as policy directions in areas of health for the betterment of Thai as a whole.

Finally, this systematic review of literature has been carried out mainly in line with those outcomes to be assessed conducted for the CRA's project. There would incur biases owing to not fully complete coverage of all studies existed. This is because of the literature searches relied solely on one investigator, as well as no attempt made to contact authors of the articles (Leandro, 2005). Double investigation might be needed for future investigation and should be extended to those outcomes beyond this study's scope.